

# **Draft Screening Assessment**

## **Ketones Group**

### **Chemical Abstracts Service Registry Numbers**

**78-93-3, 107-87-9, 108-10-1, 110-12-3, 123-42-2, 513-86-0, 123-54-6, 431-03-8, 600-14-6, 141-79-7**

**Environment and Climate Change Canada  
Health Canada**

**January 2019**

## 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 ten substances referred to collectively as the Ketones Group. Substances in this group 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 human health concerns. The Chemical Abstracts Service Registry Numbers (CAS RN<sup>1</sup>), their *Domestic Substances List* (DSL) names and their common names and acronyms are listed in the table below.

### Substances in the Ketones Group

<b>CAS RN</b>	<b>Subgroup</b>	<b>Domestic Substances List name</b>	<b>Common name (acronym)</b>
78-93-3	1	2-Butanone	Methyl ethyl ketone (MEK)
107-87-9	1	2-Pentanone	Methyl propyl ketone (MPK)
108-10-1	2	4-Methyl-2-pentanone	Methyl isobutyl ketone (MIBK)
110-12-3	2	2-Hexanone, 5-methyl	Methyl isoamyl ketone (MIAK)
123-42-2	2	4-Hydroxy-4-methyl-2-pentanone	Diacetone alcohol (DAA)
431-03-8	3	2,3-Butanedione	Diacetyl
513-86-0	3	2-Butanone, 3-hydroxy	Acetoin
600-14-6 <sup>a</sup>	3	2,3-Pentanedione	2,3-Pentanedione (2,3-PD)
123-54-6 <sup>a</sup>	Individual	2,4-Pentanedione	2,4-Pentanedione (2,4-PD)
141-79-7	Individual	4-Methyl-3-penten-2-one	Mesityl oxide (MO)

<sup>a</sup>This substance 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.

All ten substances in the Ketones Group are commercially produced and are also naturally present in the environment in various plants and/or food items or produced by microbes and other organisms. Several of the ketones are also produced endogenously in humans including MEK, diacetyl and acetoin. MEK, MPK and MIBK have been detected in breast milk. According to information reported in response to surveys under section 71 of CEPA, only DAA (23 000 kg) and 2,3-PD (1200 kg) were reported to be manufactured in Canada in 2011. Reported imports in Canada for these ketones ranged

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between 100 kg (for acetoin) and 6 000 000 kg (for MEK) in 2011. In the same year, no Canadian manufacturing or importing activities were reported for MO above the reporting threshold of 100 kg.

In general, ketones are primarily used as solvents in various products including products available to consumers such as paints, coatings and adhesives, and in numerous industrial applications as chemical intermediates and solvents among others. They may also be used as food flavouring agents, in cosmetics and as formulants in pest control products.

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

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from MEK, MPK, MIBK, MIAK, DAA, diacetyl, acetoin, 2,3-PD, 2,4-PD, and MO. It is proposed to conclude that MEK, MPK, MIBK, MIAK, DAA, diacetyl, acetoin, 2,3-PD, 2,4-PD, and MO 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.

Several of these ketones have been previously reviewed internationally; these reviews and assessments were used to inform the health effects characterization in this screening assessment.

For the human health risk assessment, eight of the substances in this group have been addressed under three subgroups with the remaining two substances addressed individually. For subgroup 1, the critical health effects include developmental effects for MEK and decreased body weight gain for both MEK and MPK. The general population in Canada is exposed to MEK and MPK from air and from food (primarily natural occurrence), and from products available to consumers including cosmetics, paints and do-it-yourself products for MEK and paint products for MPK. A comparison of levels of MEK and MPK that Canadians can be exposed to in environmental media and food with levels associated with adverse effects in laboratory studies results in margins that are considered adequate to address uncertainties in exposure and health effects data used to characterize risk. However, the margins between exposures to MEK in some

products available to consumers, namely lacquer and adhesive remover, paint products and PVC cement/primer and critical health effect levels are considered potentially inadequate to account for uncertainties in the exposure and health data used to characterize risk. Given the low acute toxicity of MPK and absence of developmental effects via inhalation, there are no concerns related to the presence of MPK in products available to consumers.

For subgroup 2 (MIBK, MIAK and DAA), the International Agency for Research on Cancer (IARC) considers MIBK to be in group 2B (“possibly carcinogenic to humans”), with “sufficient evidence” of carcinogenicity in laboratory animals. For non-cancer effects, effects on the liver and kidney as well as developmental effects were observed in laboratory studies. The general population of Canada may be exposed to MIBK, MIAK and DAA from environmental media and food (primarily from their natural occurrence), and from the use of products available to consumers, including cosmetics, markers, paints and do-it-yourself products. A comparison of estimated levels of exposure to MIAK and DAA and critical effect levels results in margins that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk. However, for MIBK, the resulting margins associated with the use of various paint and wood lacquer products are considered to be potentially inadequate.

For subgroup 3 (diacetyl, 2,3-PD and acetoin), diacetyl was carcinogenic in laboratory studies. Non-cancer effects have also been observed such as effects on the respiratory tract for diacetyl. The general population of Canada is primarily exposed to diacetyl, 2,3-PD and acetoin from food (due to natural occurrence and use as a flavouring agent), and to diacetyl and 2,3-PD from use of a limited number of products available to consumers including cosmetics and air fresheners, respectively. A comparison of estimated levels of exposure to diacetyl, 2,3-PD and acetoin and critical effect levels results in margins that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk.

The available health effects information on 2,4-PD indicates general systemic toxicity and developmental effects. 2,4-PD has shown some potential for genotoxicity but is not expected to be carcinogenic. The general population of Canada may be exposed to 2,4-PD from food (natural occurrence), and from the use of a limited number of products available to consumers, such as specialty coating products. Margins for levels of 2,4-PD in food are considered adequate. A comparison of estimated levels of exposure to 2,4-PD from use of a coating applied to a large surface area such as a trailer or a boat, and critical effect levels results in margins that are considered potentially inadequate to address uncertainties in exposure and health effects data used to characterize risk.

Canadians may be exposed to MO from its presence in air and food. MO is not expected to be carcinogenic or genotoxic. General systemic toxicity has been associated with exposure to MO in laboratory studies. Comparison of estimated levels of exposure to MO in environmental media and food and critical effect levels results in

margins that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk.

Therefore, on the basis of the information presented in this draft screening assessment, it is proposed to conclude that MEK, MIBK, and 2,4-PD meet the criteria under paragraph 64(c) of CEPA as they are 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.

However, it is proposed to conclude that MPK, MIAK, DAA, diacetyl, 2,3-PD, acetoin and MO 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 MEK, MIBK, and 2,4-PD meet one or more of the criteria set out in section 64 of CEPA.

Therefore, it is proposed to conclude MPK, MIAK, DAA, diacetyl, 2,3-PD, acetoin and MO do not meet any of the criteria set out in section 64 of CEPA.

MEK, and 2,4-PD are proposed to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

MIBK is proposed to not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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## 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 ten substances referred to collectively as the Ketones Group to determine whether these substances present or may present a risk to the environment or to human health. The substances in this group 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 human health concerns (ECCC, HC [modified 2017]).

The ecological risks of the substances in the Ketones Group were characterized using the ecological risk classification of organic substances (ERC) (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity and considers the possible exposure of organisms in the aquatic and terrestrial environments based on 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.

Some substances are assessed in subgroups due to similarities in chemical structure, properties and/or toxicity. Given the potential for these substances to be used in similar ways and applications, the potential for risk to human health is assessed using similar exposure assumptions across the group.

Some substances in the Ketones Group currently being evaluated have been reviewed internationally through the Organisation for Economic Cooperation and Development (OECD) Cooperative Chemicals Assessment Programme. OECD assessments undergo rigorous review (including peer-review) and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in this process, and consider these assessments reliable. Some of the substances have also been reviewed by the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (US EPA), the International Agency for Research on Cancer (IARC), and the US National Toxicology Program (NTP). Reviews conducted by these institutions are used to inform the health effects characterization in this screening assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to April 2017. Additional data were submitted up to September 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.

Diacetyl, 2,3-PD and acetoin have been detected in measurable quantities in vaping products. Vaping products (also known as electronic cigarettes) may represent an additional source of exposure to these substances. The assessment of risk to the general population from this use, including risk relative to that associated with conventional cigarettes, and possible options to mitigate risk associated with these products is being addressed through a separate legislative and regulatory framework.

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 human health portions of this assessment have undergone external review and/or consultation. Comments on the technical portions relevant to human health were received from Theresa Lopez, Jennifer Flippin and Joan Garey (TetraTech Inc.), and from D.L. Morgan (National Toxicology Program, National Institute of Environmental Health Sciences, USA). The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was peer-reviewed and subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

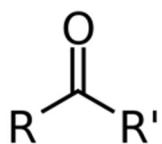
This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution<sup>2</sup>. This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

## 2. Identity of substances

The ten substances assessed in this screening assessment are ketones with a general formula shown in Figure 1. The ketones in this assessment have been divided into three subgroups based on their chemical structure, properties and/or toxicity and two individual assessments.

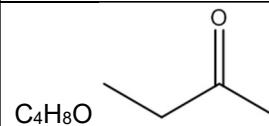
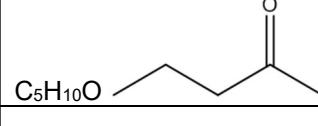
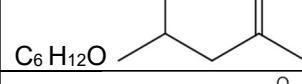
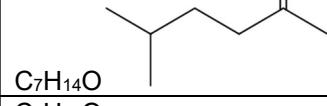
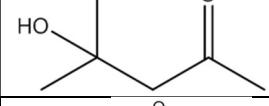
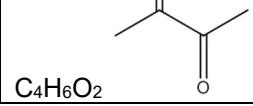
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<sup>2</sup>A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, 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.

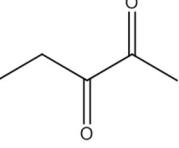
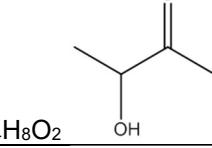
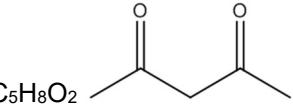
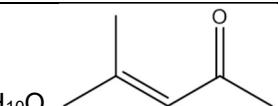
**Figure 1. General formula for ketones.**

The Chemical Abstracts Service Registry Numbers (CAS RN<sup>3</sup>), *Domestic Substances List* (DSL) names and common names and/or acronyms for the individual substances in the Ketones Group are presented in Table 2-1. A list of additional chemical names (e.g., trade names) is available from the National Chemical Inventories (NCI 2015).

**Table 2-1. Substance identities for the Ketones Group**

Subgroup	CAS RN	DSL name (common name or acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)
1	78-93-3	2-butanone (methyl ethyl ketone; MEK)	 C <sub>4</sub> H <sub>8</sub> O	72.11
1	107-87-9	2-pentanone (methyl propyl ketone; MPK)	 C <sub>5</sub> H <sub>10</sub> O	86.13
2	108-10-1	4-methyl-2-pentanone (methyl isobutyl ketone; MIBK)	 C <sub>6</sub> H <sub>12</sub> O	100.16
2	110-12-3	2-hexanone, 5-methyl- (methyl isoamyl ketone; MIAK)	 C <sub>7</sub> H <sub>14</sub> O	114.19
2	123-42-2	4-hydroxy-4-methyl-2-pentanone (diacetone alcohol; DAA)	 C <sub>6</sub> H <sub>12</sub> O <sub>2</sub>	116.16
3	431-03-8	2,3-butanedione (diacetyl)	 C <sub>4</sub> H <sub>6</sub> O <sub>2</sub>	86.09

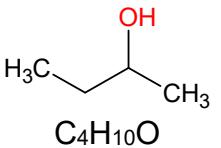
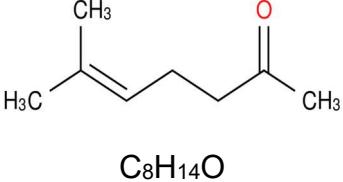
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Subgroup	CAS RN	DSL name (common name or acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)
3	600-14-6	2,3-pentanedione (2,3-PD)	 C <sub>5</sub> H <sub>8</sub> O <sub>2</sub>	100.12
3	513-86-0	2-butanone, 3-hydroxy- (acetoin)	 C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>	88.11
Individual	123-54-6	2,4-pentanedione (2,4-PD)	 C <sub>5</sub> H <sub>8</sub> O <sub>2</sub>	100.12
Individual	141-79-7	4-methyl-3-penten-2-one (mesityl oxide; MO)	 C <sub>6</sub> H <sub>10</sub> O	98.14

## 2.1 Selection of analogues and use of (Q)SAR models

A read-across approach using data from analogues and the results of (quantitative) structure-activity relationship ((Q)SAR) models, where appropriate, have been used to inform the human health assessments. Analogues were selected that were structurally similar and/or functionally similar to substances within this group (similar physical-chemical properties, toxicokinetics) and that had relevant empirical data that could be used to read across to substances with limited empirical health effects data. Details of the read-across data chosen to inform the human health assessments of each subgroup and individual are further discussed in the relevant sections of this report. Information on the identities and chemical structures of the analogues used to inform this assessment is presented in Table 2-2. The applicability of (Q)SAR models was determined on a case-by-case basis.

**Table 2-2. Analogue identities**

Subgroup or substance being assessed	CAS RN	DSL or other name (common name or acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)
Subgroup 1	78-92-2	2-butanol	 <chem>C4H10O</chem>	74.1
MO	110-93-0	6-methyl-5-heptene-2-one (MHE)	 <chem>C8H14O</chem>	126.2

### 3. Physical and chemical properties

A summary of physical and chemical property data for the substances in the Ketones Group are presented in Table 3-1 to 3-4. Additional physical and chemical properties are presented in ECCC (2016b).

**Table 3-1. Physical and chemical properties (at standard temperature) for subgroup 1 of the Ketones Group (experimental values unless indicated otherwise)**

Property	MEK	MPK	Reference
Physical state	colourless liquid	colourless liquid	HSDB
Melting point (°C)	-85.9	-76.9	OECD 1997a, ChemIDplus 1993-
Vapour pressure (Pa)	10 332	4720	OECD 1997a, ChemIDplus 1993-
Henry's law constant (Pa·m <sup>3</sup> /mol)	5.85	8.47	ATSDR 1992, ChemIDplus 1993-
Water solubility (mg/L)	276 000	43 000	OECD 1997a, ChemIDplus 1993-
Log K <sub>ow</sub> (dimensionless)	0.29	0.91	OECD 1997a, ChemIDplus 1993-
Log K <sub>oc</sub> (dimensionless)	0.55	1.87 [estimated]	ATSDR 1992, HSDB 1983-

Abbreviations:  $K_{ow}$ , octanol–water partition coefficient;  $K_{oc}$ , organic carbon–water partition coefficient

**Table 3-2. Physical and chemical properties (at standard temperature) for subgroup 2 of the Ketones Group (experimental values unless indicated otherwise)**

Property	MIBK	MIAK	DAA	Reference
Physical state	colourless liquid	colourless, clear liquid	colourless liquid	OECD 1996, HSDB 1983-
Melting point (°C)	-84.7	-74	-44	OECD 1996, ChemIDplus 1993-
Vapour pressure (Pa)	2653	769	228	ChemIDplus 1993-
Henry's law constant (Pa·m <sup>3</sup> /mol)	14.0 [estimated]	16.2 [estimated]	0.026 [estimated]	ChemIDplus 1993-
Water solubility (mg/L)	19 000	5 400	1 000 000	ChemIDplus 1993-
Log $K_{ow}$ (dimensionless)	1.31	1.88	-0.34 [estimated]	ChemIDplus 1993-
Log $K_{oc}$ (dimensionless)	2.08 [estimated]	2.40 [estimated]	1.32 [estimated]	HSDB 1983-

Abbreviations:  $K_{ow}$ , octanol–water partition coefficient;  $K_{oc}$ , organic carbon–water partition coefficient

**Table 3-3. Physical and chemical properties (at standard temperature) for subgroup 3 of the Ketones Group (experimental values unless indicated otherwise)**

Property	Diacetyl	2,3-PD	Acetoin	Reference
Physical state	greenish-yellow liquid	Dark yellow to green yellow liquid	Slightly yellow liquid or crystals	HSDB 1983-, CDC 2016
Melting point (°C)	-2.40	-29.38 [estimated]	15.0	ChemIDplus 1993-, EPI Suite
Vapour pressure (Pa)	7572	4146 [estimated]	359 [estimated]	ChemIDplus 1993-, EPI Suite
Henry's law constant (Pa·m <sup>3</sup> /mol)	1.35	0.674 [estimated]	1.04 [estimated]	ChemIDplus 1993-, EPI Suite
Water solubility (mg/L)	200 000	66 700 (at 15 deg C)	1 000 000	ChemIDplus 1993-
Log $K_{ow}$ (dimensionless)	-1.34	-0.85 [estimated]	-0.36 [estimated]	ChemIDplus 1993-
Log $K_{oc}$ (dimensionless)	-0.28 [estimated]	-0.004 [estimated]	0.3 [estimated]	EPI Suite; HSDB 1983-

Abbreviations:  $K_{ow}$ , octanol–water partition coefficient;  $K_{oc}$ , organic carbon–water partition coefficient

**Table 3-4. Physical and chemical properties (at standard temperature) for 2,4-pentanedione and mesityl oxide of the Ketones (experimental values unless indicated otherwise)**

Property	2,4-PD	MO	Reference
Physical state	colourless or slightly yellow liquid	oily, colourless to light-yellow liquid	HSDB 1983-
Melting point (°C)	-23.0	-59.0	ChemIDplus 1993-
Vapour pressure (Pa)	395	1095	ChemIDplus 1993-
Henry's law constant (Pa·m <sup>3</sup> /mol)	0.238 [estimated]	3.72 [estimated]	ChemIDplus 1993-
Water solubility (mg/L)	166000	28 900	ChemIDplus 1993-
Log $K_{ow}$ (dimensionless)	0.34 – 0.4	1.2 – 1.7	ChemIDplus 1993-, OECD 2001, OECD 1997b
Log $K_{oc}$ (dimensionless)	1.54 [estimated]	1.04	EPI Suite; OECD 1997b

Abbreviations:  $K_{ow}$ , octanol–water partition coefficient;  $K_{oc}$ , organic carbon–water partition coefficient

## 4. Sources and uses

All ten substances in the Ketones Group are naturally present in the environment in various plants and/or food items or produced by microbes and other organisms but may also be synthetically produced (Burdock 2010, VCCEP 2003, O'Donoghue 2012a,b). MEK, diacetyl and acetoin are also produced endogenously in humans (VCCEP 2003, WHO 1999a, NTP 2007a).

All of the substances in the Ketones Group, except MEK, have been included in a recent survey issued pursuant to section 71 of CEPA (Environment Canada 2012). Methyl ethyl ketone was surveyed pursuant to a CEPA section 71 in 2001. Reported manufactured quantities for MEK ranged between 1 million and 10 million kg in the year 2000; however, manufacturing of this substance in Canada ceased in 2002 (Environment Canada 2001). Reported import quantities of MEK into Canada from the year 2000 were greater than 10 million kg. According to the Canadian International Merchandise Trade Database (CIMT), between 2011 and 2016, annual average imports of MEK into Canada were approximately 4.9 million kg (CIMT 2017). Table 4-1 presents a summary of the reported total manufacture and total import quantities for the Ketones Group.

**Table 4-1. Summary of information on Canadian manufacturing and imports of Ketones Group submitted pursuant to a section 71 survey under CEPA**

Common name	Total manufacture <sup>a</sup> (kg)	Total imports <sup>a</sup> (kg)
MEK	-	6 042 865 (data for 2011; CIMT)
MPK	-	1 097 844
MIBK	-	1 241 783
MIAK	-	35 906
DAA	23 000	265 529
Diacetyl	-	1 430
2,3-PD	1 200	-
Acetoin	-	100 – 1 000
2,4-PD	-	100 000 – 1 000 000
MO	-	-

<sup>a</sup> Values reflect quantities reported in response to surveys conducted under section 71 of CEPA (Environment Canada 2012) except for MEK. See survey for specific inclusions and exclusions (Schedules 2 and 3).

Table 4-2 presents a summary of the major uses of Ketones Group according to information reported pursuant to section 71 surveys under CEPA (Environment Canada 2001, 2013) and Table 4-3 presents additional uses identified in Canada.

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

Major Uses	Subgroup 1 <sup>a</sup>	Subgroup 2	Subgroup 3	Individual
Paints and Coatings	MEK, MPK	MIBK, MIAK, DAA	N/A	2,4-PD
Food and Beverage	N/A	N/A	2,3-PD, Acetoin	N/A
Agricultural Products, mixtures or manufactured items (non-pesticidal)	MEK	N/A	Diacetyl	N/A
Adhesives and Sealants	MEK, MPK	MIBK, DAA	N/A	2,4-PD
Ink, Toner and Colourants	MEK, MPK	MIBK, DAA	N/A	N/A
Automotive, Aircraft and Transportation	MEK, MPK	MIBK, DAA	N/A	N/A
Plastic and Rubber materials not	N/A	MIBK	N/A	2,4-PD

otherwise covered				
Electrical and Electronics	N/A	MIBK, DAA	N/A	N/A
Floor Coverings	MEK	MIBK	N/A	N/A
Cleaning and Furnishing Care	MEK	DAA	N/A	N/A
Personal Care	N/A	DAA	2,3-PD, Acetoin	N/A
Toys, Playground and Sporting Equipment	N/A	DAA	N/A	N/A
Other <sup>b</sup>	MEK, MPK	MIBK, DAA	Diacetyl	N/A

Abbreviations: N/A, Not Applicable.

<sup>a</sup> Results for MEK are from uses in 2000 and may no longer be relevant.

<sup>b</sup> Other refers to minor uses and/or uses that cannot be disclosed as a result of confidentiality claims.

**Table 4-3. Additional uses in Canada for each of the substances in the Ketones Group.**

Use	Subgroup 1	Subgroup 2	Subgroup 3	Individual
Food additive <sup>a</sup>	MEK	N	N	N
Food packaging materials <sup>a</sup>	MEK, MPK	MIBK, DAA	N	2,4-PD
Incidental additive <sup>a</sup>	MEK	N	N	N
Internal Drug Product Database as medicinal or non-medicinal ingredients in final Pharmaceutical, Disinfectant or Veterinary drug products in Canada <sup>b</sup>	N	N	N	N
Natural Health Products Ingredients Database <sup>c</sup>	MEK, MPK	MIBK, DAA	Diacetyl, Acetoin, 2,3-PD	MO
Licensed Natural Health Products Database as medicinal or non-medicinal ingredients in natural health products in Canada <sup>d</sup>	MEK	MIBK	N	N
List of Prohibited and Restricted Cosmetic Ingredients <sup>e</sup>	N	N	N	N

Use	Subgroup 1	Subgroup 2	Subgroup 3	Individual
Notified to be present in cosmetics, based on notifications submitted under the <i>Cosmetic Regulations</i> to Health Canada <sup>a</sup>	MEK	DAA	N	N
Formulant in pest control products registered in Canada <sup>g</sup>	MEK	MIBK, MIAK, DAA	Diacetyl, Acetoin, 2,3-PD	N

Abbreviations: N, No

<sup>a</sup> Personal communication, e-mail from Food Directorate (FD), Health Canada (HC) to Existing Substances Risk Assessment Bureau (ESRAB), Health Canada (HC), dated Aug. 18, 2016; unreferenced)

<sup>b</sup> DPD [modified 2016]; Personal communication, e-mail from Therapeutic Products Directorate (TPD), HC to ESRAB, HC, dated August 3, 2016; unreferenced)

<sup>c</sup> NHPID [modified 2018]

<sup>d</sup> LNHPD [modified 2018]

<sup>e</sup> Health Canada [modified 2015a]

<sup>f</sup> Personal communication, e-mail from Consumer Product Safety Directorate (CPDS), HC to ESRAB, HC, dated August 5 and 8, 2016; unreferenced)

<sup>g</sup> Personal communication, e-mail from Pest Management Regulatory Agency (PMRA), HC to ESRAB, HC, dated July 28, 2016; unreferenced)

In general, ketones are primarily used as solvents in various products including products available to consumers, and in numerous industrial applications as chemical intermediates and solvents among others (O'Donoghue 2012a,b, Kirk-Othmer). MEK is listed as a permitted food additive in natural extractives and in spice extracts as prescribed in Health Canada's *List of Permitted Carrier or Extraction Solvents*, incorporated by reference in its respective Marketing Authorization issued under the *Food and Drugs Act*. MEK, MPK, MIBK, DAA, and 2,4-PD may be used in non-food contact food packaging applications in Canada. MEK is also used as a solvent in non-food contact cleaners in the food industry. In addition, 7 of the ketones in this group were identified as potentially being used as food flavouring agents (personal communication, email from FD, HC to ESRAB, HC, dated Aug 18, 2016; unreferenced).

MEK and MIBK are listed in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline as class 3 residual solvents (solvent with low toxic potential) used in the manufacture of pharmaceuticals. The final drug product is permitted to contain up to 5000 ppm of residual solvent (personal communication, e-mail from Biologics and Genetic Therapies Directorate, HC to ESRAB, HC, dated 2016 Aug 5; unreferenced).

MEK is classified as a natural health product (NHP) substance, with a medicinal role, falling under Schedule 1, item 2 (an isolate) to the *Natural Health Products Regulations*, as well as with a non-medicinal role for topical use as a denaturant or oral use as a flavour enhancer. MPK, 2,3-PD, and MO are also listed with a non-medicinal role for oral use as flavour enhancers; MIBK is listed with a non-medicinal role for oral use as a flavour enhancer or topical use as a denaturant; DAA is listed with a non-medicinal role for topical use as fragrance ingredient or solvent. Acetoin is listed with a non-medicinal

role for oral use as flavour enhancer or for topical use as a fragrance ingredient. Only MEK and MIBK are listed in the Licensed Natural Health Products Database as being present in a limited number of currently licensed topical NHPs in Canada (NHPID [modified 2018]; LNHPD [modified 2018]; personal communication, e-mail from Natural and Non-prescription Health Products Directorate, HC to ESRAB, HC, dated Aug 16, 2016, unreferenced).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, MEK and DAA are used in certain cosmetics in Canada, primarily in nail care products (personal communication, e-mail from CPSD, HC to ESRAB, HC, dated August 5 and 8, 2016, unreferenced). According to publicly available sources, diacetyl was identified in cosmetics in Canada (SDS 2008a), but there are no products notified with this ingredient.

MEK, MPK, MIBK, MIAK, DAA and 2,4-PD are used in products available to consumers including liquid and spray paints and coatings, automotive care products, do-it-yourself (DIY products) such as paint removers, adhesives and pipe sealants (Environment Canada 2012, Health Canada 2016, HPD 1993-). MEK, MPK and MIBK have been identified in emissions from various building materials (e.g., wood, carpet, insulation) and products available to consumers (e.g., paint, automotive cleaners, caulking) in Canada by the National Research Council of Canada (Won and Lusztyk 2011, Don and Yeng 2012, Won et al. 2013, Won et al. 2014, Won 2015).

MEK was identified in several different children's products including tents/tunnels (Hansen et al. 2004), slimy toys (Svendsen et al. 2005), rubber figures and speed markers (Glensvig and Ports 2006) in Denmark. Under the state of Washington's Children's Product Safety Act (WSDE 2016), MEK was detected in various products intended for children 12 years and younger including kids' crafts, baby furniture, baby bibs, pacifiers/teething rings, children's toys and games, baby and children's bedding and clothing as well as footwear and camping gear (WSDE 2016). MEK's presence in these products was primarily as a contaminant but was also present as an adhesive, binding agent, coloration/pigment/dye/ink, component of plastic resin or polymer process, hardening, manufacturing additive, preservative, protective coating, reinforcement/strength, and as a solvent (WSDE 2016). MEK has also been measured in animal care products (Nylén et al. 2004), and adult toys (Nilsson et al. 2006) in Denmark.

Other sources of these ketones include vehicle exhaust (MEK, diacetyl) (IPCS 1993), cigarette smoke (MEK, diacetyl, 2,3-PD), as well as flavoured e-cigarette liquids (diacetyl, 2,3-PD, acetoin) (personal communication e-mails from Tobacco Control Directorate, HC to ESRAB, HC, dated Aug. 15-18, 2016 and Nov 16, 2017 unreferenced) .

MO was not reported to be manufactured or imported into Canada in 2011 (Environment Canada 2013). Two of the ten substances, MEK and MIBK, are reportable under the National Pollutant Release Inventory (NPRI). Table 4-4 summarizes the various types of releases from 2011 to 2015 (NPRI 2011-2015a,b).

**Table 4-4. Range of releases (tonnes per year) of MEK and MIBK reported under the NPRI from 2011 to 2015 (NPRI 2011-2015 a,b).**

Substance	On-site releases to air	On-site releases to water	On-site releases to land	Disposal on-site	Disposal off-site	Off-site recycling
MEK	1105 – 1362	5.4 – 20	0 – 0.149	0.802 – 46	863 – 1563	1441 – 2616
MIBK	199 – 243	0.025 – 1.9	0 – 0.049	1.3 – 20	105 – 207	243 – 316

## 5. Environmental fate and behaviour

### 5.1 Environmental persistence

MEK, DAA, diacetyl, 2,3-PD, and 2,4-PD may be persistent in air, but are not expected to be persistent in water, sediment or soil according to models used in ERC (ECCC 2016b). MPK, MIBK, MIAK, acetoin and MO are not expected to be persistent in air, water, sediment or soil according to models used in ERC (ECCC 2016b).

### 5.2 Potential for bioaccumulation

Based on low Kow and low bioconcentration factors (ECCC 2016b) MEK, MPK, MIBK, MIAK, DAA, diacetyl, acetoin, 2,3-PD, 2,4-PD, and MO are not expected to significantly bioaccumulate in organisms.

## 6. Potential to cause ecological harm

### 6.1 Characterization of ecological risk

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

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and in response 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 as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

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

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

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

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

The hazard and exposure classifications for the substances in the Ketones Group are summarized in Table 6-1.

**Table 6-1. Ecological Risk Classification results for the substances in the Ketones Group.**

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
MEK	low	high	low
MPK	low	low	low
MIBK	low	low	low
MIAK	low	low	low
DAA	low	high	low
Diacetyl	low	low	low
Acetoin	low	low	low
2,3-PD	low	low	low
2,4-PD	low	low	low
MO	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, MPK, MIBK, MIAK, diacetyl, acetoin, 2,3-PD, 2,4-PD, and MO 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.

According to information considered under ERC, MEK and DAA have a high exposure potential due to high reported use quantities in combination with a long half life in air. MEK and DAA were classified as having a low hazard potential and a low potential for ecological risk. It is therefore unlikely that these substances will result in concerns for the environment in Canada.

## 7. Potential to cause harm to human health

### 7.1 Assessment of subgroup 1 (MEK, MPK)

#### 7.1.1 Exposure assessment of subgroup 1 (MEK, MPK)

##### Environmental media

MEK was monitored by the National Air Pollution Surveillance (NAPS) program, where mean concentrations measured between 2006 and 2010, from various sites across

Canada ranged from 0.20 to 5.7  $\mu\text{g}/\text{m}^3$  with 95<sup>th</sup> percentile concentrations ranging from 0.53 to 19.3  $\mu\text{g}/\text{m}^3$  (ECCC 2017c). Ambient air concentrations for MEK and MPK were also measured in five Canadian air studies conducted in Windsor, Regina, Halifax, Edmonton and Ottawa (Health Canada 2010a, b, 2012, 2013, Zhu et al. 2005).

MEK concentrations in ambient air from these Canadian studies ranged from < 0.03 to 39.06  $\mu\text{g}/\text{m}^3$  with geometric mean and 95<sup>th</sup> percentile concentrations ranging from 0.41 to 1.77  $\mu\text{g}/\text{m}^3$  and from 0.78 to 5.53  $\mu\text{g}/\text{m}^3$ , respectively (Zhu et al. 2005; Health Canada 2010a, b, 2012, 2013). Ambient air concentrations for MPK from the five Canadian studies ranged from 0.002 to 14.38  $\mu\text{g}/\text{m}^3$  with geometric mean and 95<sup>th</sup> percentile concentrations ranging from 0.055 to 0.49  $\mu\text{g}/\text{m}^3$  and from 0.22 to 1.25 (Health Canada 2010a, b, 2012, 2013). The highest 95<sup>th</sup> percentile concentrations were used to estimate general population exposures (5.53  $\mu\text{g}/\text{m}^3$  for MEK from the Windsor study, and 1.25  $\mu\text{g}/\text{m}^3$  for MPK from the Regina study).

MEK and MPK were measured in the national Canadian indoor air study conducted in 2009-2011 as part of cycle 2 of the Canadian Health Measures Survey (CHMS). MEK was detected in 99% of the samples with a geometric mean concentration of 1.14  $\mu\text{g}/\text{m}^3$  (weighted data at the household level) and a 95<sup>th</sup> percentile concentration of 9.76  $\mu\text{g}/\text{m}^3$ . MPK was detected in 97% of the samples with a geometric mean concentration (weighted data at the household level) of 0.36  $\mu\text{g}/\text{m}^3$  and a 95<sup>th</sup> percentile concentration of 1.58  $\mu\text{g}/\text{m}^3$  (Zhu et al. 2013).

Indoor air concentrations for MEK and MPK were also measured across the same five Canadian studies referred to above. Geometric mean concentrations of MEK in indoor air ranged from 1.51 to 9.81  $\mu\text{g}/\text{m}^3$  with 95<sup>th</sup> percentile values ranging from 9.9 to 51.63  $\mu\text{g}/\text{m}^3$  (Zhu et al. 2005; Health Canada 2010a, b, 2012, 2013). Geometric mean MPK concentrations in indoor air ranged from 0.089 to 2.77  $\mu\text{g}/\text{m}^3$  with 95<sup>th</sup> percentile values ranging from 1.34 to 12.77  $\mu\text{g}/\text{m}^3$  (Health Canada 2010a, b, 2012, 2013).

As a conservative approach, the highest 95<sup>th</sup> percentile concentrations of MEK and MPK across all indoor air studies were used to estimate general population exposures (51.63  $\mu\text{g}/\text{m}^3$  for MEK from the Windsor study, and 12.77  $\mu\text{g}/\text{m}^3$  for MPK from the Regina study).

MEK and MPK were also measured in personal air in the Windsor, Ontario air study (Health Canada 2010a). Personal air samples take into account exposures to MEK from both indoor and outdoor air from various locations including the home, office and during transit. The geometric mean and 95<sup>th</sup> percentile concentrations for MEK in the summer were 8.79  $\mu\text{g}/\text{m}^3$  and 28.22  $\mu\text{g}/\text{m}^3$ , respectively which were higher than the samples collected during the winter (geometric mean of 4.24  $\mu\text{g}/\text{m}^3$  and 95<sup>th</sup> percentile of 11.44  $\mu\text{g}/\text{m}^3$ ). The geometric mean personal air concentration of MPK in the summer and winter were 2.91  $\mu\text{g}/\text{m}^3$  and 1.44  $\mu\text{g}/\text{m}^3$ , respectively. The 95<sup>th</sup> percentile concentrations for MPK were 12.65  $\mu\text{g}/\text{m}^3$  and 6.30  $\mu\text{g}/\text{m}^3$  in the summer and winter, respectively (Health Canada 2010a).

MEK and MPK have very high water solubilities, but, based on their high vapour pressures and moderate Henry's Law Constants, they are expected to rapidly volatilize from water (HSDB 1983-). In addition, MEK and MPK are expected to biodegrade in water making water unlikely to be a major source of human exposure (VCCEP 2003, HSDB 1983-). In 2000, MEK was not detected above the limit of detection of 0.99 µg/L in potable water (sample size not known) from Montreal, QC (Bernier 2000). No other Canadian data on the presence of MEK in water were identified. MEK was detected in a limited number of studies in the U.S. with low detection frequencies (0.5-0.8% of samples) and concentrations ranging from 0.6 to 340 µg/L (Grady and Casey, 2001, Delzer and Ivahnenko 2003, Grady 2003). No data were identified on the presence of MPK in water in Canada. MPK was detected in drinking water in Ottumwa, Iowa at a concentration of 0.1 µg/L (0.1 ppb) and was identified but not quantified in drinking water from 5 other US cities, and in England (HSDB 1983-). As a conservative approach, in order to estimate potential drinking water exposures to MEK and MPK, the detection limit of 0.99 µg/L from the Montreal study and the data from Iowa (0.1 µg/L) for MEK and MPK, respectively, were used.

For soils, one Canadian study was identified in which Golder Associates (1987) surveyed levels of MEK in soil in two parkland areas in the vicinity of southern Ontario petroleum refineries. A mean concentration of 5.78 µg/g (maximum: 25 µg/g) was found in 19 of 30 soil samples in which MEK was detected. Using the maximum concentration of MEK in soil resulted in general population exposures below 1 ng/kg-bw per day for all age groups; therefore exposure to MEK from soil is considered to be negligible. No information on the presence of MPK in soil or sediment was identified for Canada or elsewhere. ChemCAN was used to derive potential soil concentrations of MPK using the volume data from Table 4-1 (i.e., 1 097 844 kg). The estimated concentration of MPK in soil was 1.1 ng/kg and resulted in intakes less than 1 ng/kg-bw per day for the general population of Canada, which are considered to be negligible.

Estimates of exposure for MEK and MPK from environmental media ranged from 9.1 µg/kg-bw per day for adults (60 years and older) to 27.6 µg/kg-bw per day for toddlers (6 months to 4 years) and 2.3 µg/kg-bw per day for adults (60 years and older) to 6.8 µg/kg-bw per day for toddlers (6 months to 4 years), respectively (Health Canada 2018).

## Food

MEK and MPK in food or as volatiles derived from food have been measured in most food groups primarily as a result of their natural occurrence in plants or from the production by microbes (i.e., fermentation). In addition, MEK and MPK are noted to be used as flavouring agents in food including baked goods, fats/oils, frozen dairy, gelatins/puddings, non-alcoholic beverages, and soft candy (Burdock 2010). In Canada, MEK is used as a food additive in natural extractives and in spice extracts; however, it is expected to be a minor contributor of MEK compared to the natural occurrence in foods. MEK (5 out of 12 samples) and MPK (4 out of 12 samples) were detected but not quantified in breast milk (Pellizari et al. 1982).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated a group of 39 saturated aliphatic acyclic secondary alcohols, ketones and related saturated and unsaturated esters used as flavouring substances including MEK and MPK (WHO 1999b). As part of that evaluation, the Committee estimated the per capita intake of MEK and MPK from their use as a food flavouring agent to be 0.6 and 0.7 µg/kg bw per day respectively for the US population and 2 µg/kg bw per day respectively for the European population (see Appendix A for more details).

Estimates of exposure for MEK and MPK based on their natural occurrence in food<sup>4</sup> ranged from 66 µg/kg-bw per day for 14-18 year olds to 185 µg/kg-bw per day for 1 year olds and 68 µg/kg-bw per day for 14-18 year olds to 216 µg/kg-bw per day for 1 year olds, respectively (see Appendix A for more details).

## Products available to consumers

### MEK

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, MEK is used in certain cosmetic products in Canada such as face moisturizer and in various nail care products including base-coats, top-coats, nail polish, nail polish remover, nail adhesive, nail brush cleaner, nail hardener, nail cream, products to reduce drying time, and nail repair (personal communication, e-mail dated from CPSD, HC to ESRAB, HC, dated Aug. 2016 and April 2017,unreferenced). The function of MEK in these products is as a solvent or as a perfuming agent (European Commission 2017).

Inhalation exposure concentrations were derived for certain sentinel products (top-coat, nail polish and nail polish remover) which represent the highest exposures when compared to similar products using ConsExpo Web (2016). Table 7-1 summarizes the range of MEK concentrations for the various products along with the associated inhalation exposure estimates. Only exposure estimates for adults and toddlers are shown; however, they represent the range of potential exposures for all age groups. Details on the method and parameters used to estimate inhalation and dermal exposures to MEK from cosmetics are available in Appendix B.

**Table 7-1. Estimated inhalation exposures to MEK from the use of cosmetics**

Product scenario	Max Concentration <sup>a</sup>	Mean event concentration (mg/m <sup>3</sup> )	Mean concentration on day of exposure (mg/m <sup>3</sup> )	7-hr TWA <sup>b</sup> (mg/m <sup>3</sup> )
Top-coat	55.7%	140	1.8	6.0

<sup>4</sup> Infants 0 to 6 months old are assumed to be exclusively breast-fed or formula-fed.

Product scenario	Max Concentration <sup>a</sup>	Mean event concentration (mg/m <sup>3</sup> )	Mean concentration on day of exposure (mg/m <sup>3</sup> )	7-hr TWA <sup>b</sup> (mg/m <sup>3</sup> )
Nail polish (adult/teen)	35%	190	4.6	15.8
Nail polish (toddler)	35%	65	1.6	5.4
Nail polish remover (adult/teen)	84% <sup>c</sup>	280	1.6	5.3
Nail polish remover (toddler)	76.4%	220	1.2	4.1

Abbreviations: N/A, Not Applicable

<sup>a</sup> Personal communication, emails from CPSD, HC to ESRAB, HC, Aug. 2016 and April 2017; unreferenced.

<sup>b</sup> Seven-hour time-weighted average (TWA) concentrations were derived for all product scenarios to match up with the exposure durations of the critical effects study used to characterize risk. 7-hr TWA = mean event concentration (mg/m<sup>3</sup>) x exposure duration (min) / (7 x 60 min)

<sup>c</sup> Product not anticipated to be used by young children (personal communication, emails from CPSD, HC to ESRAB, HC, dated April 2017; unreferenced)..

Although dermal exposure would be expected to contribute to the overall exposure during use of products available to consumers, the primary route is considered to be inhalation. Wilkinson and Williams (2001) measured a dermal absorption of less than 1% for MEK in a non-occluded human in vitro study. Given the high volatility and low dermal absorption of MEK, dermal exposure is considered to be minimal in comparison to that of inhalation; therefore, only inhalation estimates are presented.

### Children's products

MEK was identified in several different children's products in the United States and Denmark including pacifiers and teething rings (WSDE 2016), as well as slimy toys (Svendsen et al. 2005). Only oral and inhalation exposure estimates are presented since they resulted in the highest exposures and would account for any possible dermal exposures.

The potential oral exposure from mouthing toys or children's objects containing MEK was estimated using a pacifier and teether as sentinel exposure scenarios. MEK was identified as a contaminant in pacifiers/teethers by the WSDE (2016) with concentrations ranging from equal to or greater than 100 ppm to less than 500 ppm. Estimated oral exposures using the approach outlined in Appendix B ranged from 110 to 232 µg/kg-bw/day for toddlers (6 months to 4 years old) and from 91 to 300 µg/kg-bw/day for infants (0 to 6 months old).

Limited data were available regarding the migration of MEK from products. According to Svendsen et al. (2005), MEK did not migrate into artificial sweat and saliva from slimy toys with concentrations of 2.3% and 9%. The breathing zone concentration for the slimy toys was estimated to be 0.079 and 0.098 µg/m<sup>3</sup> (Svendsen et al. 2005), lower than indoor air concentrations presented in the environmental media section. Nilsson et al. (2006) analyzed MEK in adult toys in headspace analyses and artificial sweat (pH of 4.5 and 6.5). Concentrations of MEK ranged 174 – 13016 ng/180 min in headspace analyses, from 12 – 49 µg/dm<sup>2</sup> in artificial sweat with a pH of 4.5, and 17 µg/dm<sup>2</sup> in artificial sweat with a pH of 6.5.

#### *Other products*

MEK is found in a limited number of currently licensed topical natural health products in Canada with a non-medicinal role including hand antiseptics meant primarily for use in medical facilities and in a facial cleanser (LNHPD modified 2016). The sentinel scenarios for cosmetics are considered to address any exposures to MEK from use of natural health products.

MEK is also used in numerous products available to consumers. Only product scenarios that result in the highest levels of potential exposure to MEK by the inhalation routes are presented in Table 7-2. Potential inhalation exposures were estimated using ConsExpo Web (ConsExpo 2016). Appendix B summarizes the details on the parameters used in each model.

**Table 7-2. Estimated exposures to MEK from the use of products**

Product scenario	MEK conc.	Mean event conc. (mg/m <sup>3</sup> )	Mean conc. on day of exposure (mg/m <sup>3</sup> )	7-hr TWA <sup>a</sup> (mg/m <sup>3</sup> )
Lacquer removal	10 – 40%	920 – 3600	38 – 150	131 – 514
Adhesive removal	100%	3600	530	1843
Paint Thinner (floor coating)	100% diluted to 3% in coating	840	35	120
Liquid paint (solvent-rich) for truck bed	20%	210	20	176
Spray paint	1 – 52%	56 – 2800	0.98 – 48	3 – 167
PVC cement/primer	5 – 100%	9.3 – 190	1.5 – 31	5 – 109
Multipurpose adhesive	15 – 80%	44 – 230	2.4 – 13	8 – 44

Abbreviations: conc., concentration

<sup>a</sup> Seven-hour time-weighted average (TWA) concentrations were derived for all product scenarios to match up with the exposure durations of the critical effects study used to characterize risk. 7-hr TWA = mean event concentration (mg/m<sup>3</sup>) x exposure duration (min) / (7 x 60 min)

## MPK

MPK was not identified in cosmetics or children's products but was identified in several paint products. Table 7-3 summarizes inhalation exposure estimates for products available to consumers containing MPK using ConsExpo Web (ConsExpo 2016). Similar to MEK, although dermal exposure could contribute to the overall exposure during use of products available to consumers, the primary route is considered to be inhalation; therefore, only inhalation estimates are presented.

**Table 7-3. Estimated exposures to MPK from the use of products**

Product scenario	MPK conc.	Mean event conc. (mg/m <sup>3</sup> )	Mean conc. on day of exposure (mg/m <sup>3</sup> )	6-hr TWA <sup>a</sup> (mg/m <sup>3</sup> )
Liquid paint for steel (high-solid)	1 – 10%	87 – 870	8 – 80	32 – 319
Spray paint	2 – 13%	90 – 570	1.2 – 8	8 – 49

Abbreviations: conc., concentration

<sup>a</sup> Six-hour time-weighted average (TWA) concentrations were derived for all product scenarios to match up with the exposure durations of the critical effects study used to characterize risk. 6-Hr TWA = Mean event conc. x exposure duration / 6 x 60 min

## 7.1.2 Health effects assessment of subgroup 1 (MEK and MPK)

MEK and MPK are structurally similar monoketones differing in the chain length by only one carbon. Based on the similarity in the effects of exposure to MEK and 2-butanol, as well as the finding that 2-butanol is rapidly metabolized to MEK in rats, 2-butanol is used as an analogue to inform assessment of this group. Toxicity data on 2-butanol have been used to read-across to MEK or MPK where required (see Table 7-4).

### 7.1.2.1 MEK

MEK has been reviewed by OECD (1997a) and US EPA IRIS (2003a). These reviews provide a basis for the health effects characterization in this draft screening assessment. Literature searches were conducted from a year prior to the US EPA IRIS (2003a) report to April 2017. No health effect studies that would impact the risk characterization (i.e. result in different critical endpoints or lower points of departure than those stated in US EPA IRIS 2003a) were identified.

## Toxicokinetics

Orally administered MEK has been found to be extensively absorbed from the GI tract of rodents and rapidly eliminated (Dietz et al. 1981; reviewed in EPA IRIS 2003a). Due to its high blood/air solubility ratio it is also well-absorbed in both humans and rats upon inhalation exposure. Similarly, it was found to be rapidly absorbed upon dermal exposure (Munies and Wurster, 1965; reviewed in EPA IRIS 2003a). The available information indicates that the metabolism of MEK is similar in humans and laboratory animals with 2-butanol and 2,3-butanediol as the major metabolites (Perbellini et al., 1984; Liira et al., 1988, 1990a; reviewed in EPA IRIS 2003a). In humans, MEK appears to form endogenously, as it has been identified as a minor but normal constituent of urine, as a constituent in the serum and urine of diabetics, and in expired air (WHO 1992; reviewed in EPA IRIS 2003a).

## Carcinogenicity and genotoxicity

For MEK, the US EPA (IRIS 2003a) did not identify concerns related to carcinogenicity or genotoxicity for MEK.

## Repeated dose toxicity

The reported health effects of MEK were primarily related to absolute and/or relative organ weight increases (most frequently the liver) at high concentration (Nilson and Toftgard, 1980; Cavender et al., 1983; Toxigenics Inc., 1981; reviewed in US EPA IRIS 2003a).

## Reproductive and Developmental toxicity

There are no studies that evaluated reproductive toxicity potential of MEK by any route of exposure (Cox et al., 1975; reviewed by US EPA IRIS 2003a; ECHA c2007-2017f, US EPA AcToR 2015).

In an inhalation developmental toxicity study, groups of 10 virgin Swiss CD-1 mice and 33 sperm plug-positive (GD 0) females were exposed to mean concentrations of 0, 398, 1,010 and 3,020 ppm (0, 1174, 2980 and 8909 mg/m<sup>3</sup>) MEK by inhalation for 7 hours/day on GD 6–15 (Schwetz et al., 1991, as reviewed in EPA IRIS 2003a). A slight but statistically significant dose-related increase absolute liver weight was observed in dams at 3,020 ppm (increase of approximately 7% when compared with the control). There was a statistically significant decrease in mean foetal weight (5%, per litter) at 3,020 ppm in males and a 4% decrease for all foetuses combined. There was also a positive trend for an increased incidence of foetuses with misaligned sternebrae with increasing exposure level (incidences were 31/310, 27/260, 49/291, and 58/323 for the control through 3,020 ppm (8909 mg/m<sup>3</sup>) exposure groups, respectively). Other non-significant developmental effects (cleft palate, fused ribs, missing vertebrae and syndactyly) were observed in exposed groups but not in controls. The NOAEC for both maternal and developmental adverse effects was considered to be 1,010 ppm (2980

mg/m<sup>3</sup>), while the developmental and maternal LOAECs were established at 3,020 ppm (8909 mg/m<sup>3</sup>), based on the decreased foetal weight among males, increased incidence of misaligned sternebrae, and an increased relative liver weight in dams. Similarly, Deacon et al. (1981, as cited in US EPA IRIS 2003a) reported foetal toxicity (increased incidence of extra ribs) and maternal toxicity (decreased body weight gain) at 3005 ppm (8865 mg/m<sup>3</sup>) (considered to be the LOAEC) in a rat developmental study, with a NOAEC of 1002 ppm (2955 mg/m<sup>3</sup>). Based on the data for misaligned sternebrae, the US EPA (2003) derived a LEC<sub>10<sup>5</sup></sub><sup>5</sup> (95% lower confidence on the concentration associated with a 10% extra risk) of 5202 mg/m<sup>3</sup> for intermittent exposure (7 hours per day) and LEC<sub>HEC</sub><sup>6</sup> (human equivalent concentration adjusted for continuous exposure) of 1517 mg/m<sup>3</sup>.

Similarly, a more recent inhalation developmental toxicity study in rats also showed developmental toxicity with a NOAEC of 2949 mg/m<sup>3</sup>; decreased foetal body weight was observed at 2000 ppm (5899 mg/m<sup>3</sup>), while decreased maternal body weight was also noted at 11797 mg/m<sup>3</sup> and above (Saillenfait et al. 2006). Other developmental study reported developmental effects in the absence of maternal toxicity at 7723 mg/m<sup>3</sup> with a NOAEC of 1126 ppm (3322 mg/m<sup>3</sup>) (Schwetz et al. 1974, as cited in US EPA IRIS 2003a).

No oral developmental toxicity studies were reported for MEK hence, a read-across from the oral reproductive and developmental toxicity study with 2-butanol to MEK was used. In this multigeneration drinking water study, male and female Wistar rats were exposed to 2-butanol concentrations of 0, 0.3, 1.0, or 3.0% (equivalent to doses of 0, 538, 1644, and 5089 mg/kg bw per day (male rats) and 0, 594, 1771, and 4571 mg/kg bw per day (female rats) for 8 weeks before mating. Because increased mortality and decreased body weight occurred in the F1A litters at the 3% dose level, the high-dose was reduced to 2% (average daily intake of 3384 mg/kg-bw/day in males and 3122 mg/kg-bw/day in females for the remaining of the study). F0 females were mated again and F1A pups mated to produce litters F2. A NOAEL of 1771 mg/kg bw per day for 2-butanol for both maternal and developmental effects was established based on decreased F1B foetal weights and decreased F1A and F2 pup body weights and decreased body weight gain in dams at 3122 mg/kg bw per day (Cox et al. 1975; reviewed in US EPA IRIS 2003a). The US EPA (2003) estimated a lowest effective dose (LED)<sub>05</sub> (95% lower confidence limit on the effective dose, ED) of 639 mg/kg bw per day for MEK (adjustment based on the molecular weights from the LED<sub>05</sub> of 657 mg/kg bw per day for 2-butanol).

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<sup>5</sup> Concentration derived from benchmark concentration for developmental effects associated with a 10% extra risk in mice exposed to MEK and exposed for 7 hours/day on GD6-15 (as cited in US EPA IRIS 2003a).

<sup>6</sup> Human equivalent derived from LEC<sub>(ADJ)</sub> (5202 mg/m<sup>3</sup> x 7h/24h) for continuous exposure (as cited in US EPA IRIS 2003a).

No dermal developmental toxicity studies were identified for MEK or the analogue 2-butanol.

### **7.1.2.2 MPK**

MPK has not been assessed by other agencies. The following health assessment is based on the information identified from ECHA registration dossier (ECHA c2007-2017c) and US EPA HPVIS (US EPA 2001a).

#### **Toxicokinetics**

No quantitative information on the absorption of MPK via any route of exposure was identified. MPK is structurally similar to MEK and its metabolite 2-butanol, therefore absorption of MPK is expected to be similarly rapid and extensive.

#### **Carcinogenicity and genotoxicity**

No oral, dermal or inhalational carcinogenicity studies were reported for MPK. No positive (Q)SAR model predictions or presence of structural alerts for genotoxicity or carcinogenicity were found. In addition, MPK was not genotoxic in several in vitro assays (i.e., Ames tests, chromosomal aberration test and mouse lymphoma assay; ECHA c2007-2017c).

#### **Repeated dose toxicity**

In an oral repeat dose toxicity study, CD male rats were administered MPK in the drinking water at concentrations of 0, 0.25%, 0.5% and 1.0% MPK (equivalent to doses of 0, 144, 250 and 454 mg/kg bw per day) for a period of 13-months). The only effect reported was a slight decreased body weight gain (9%) at 1.0% at the highest dose tested (454 mg/kg bw per day). There were no effects on clinical signs, organ weights or histology and no pathological changes were observed in the central or peripheral nervous systems (Bingham et al., 2001 as cited in HSDB 1983-).

With respect to inhalation exposure, the critical effect levels were derived from inhalation studies in rats, in which NOAECs of 5000 and 5300 mg/m<sup>3</sup> were identified after 35-21 days and 13 weeks exposure, respectively (Anonymous 1999a, Eastman Chemical Company 1999; ECHA c2007-2017c). In the combined inhalation reproductive/developmental toxicity study, SD rats were exposed up to 5000 mg/m<sup>3</sup> MPK 6h/d for 35-48 days (females) until GD19 and for 51-days (males) (ECHA c2007-2017c, EPA AcToR 2015). Although slight neurotoxicity in dams was observed at a lower concentration (2500 mg/m<sup>3</sup>), this effect appears to be transient and similar effects were not observed at similar concentrations in other studies. No other significant effects were reported. The other short-term study revealed only a slight enlargement of hepatocytes in one animal after two 16-hour periods and two 20-hour periods on 4

consecutive days at a dose of 1074 mg/m<sup>3</sup> (Eastman Kodak Company 1977, as cited in US EPA 2001a).

For the dermal route, no suitable study was identified.

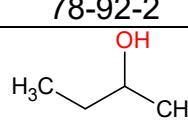
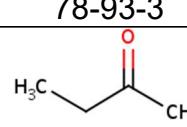
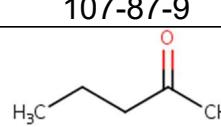
### Reproductive and developmental toxicity

In a prenatal developmental toxicity study female SD rats were exposed to concentrations 0, 250, 750 and 1500 ppm (equivalent to 0,880, 2650, 5300 mg/m<sup>3</sup>) of MPK from GD 6-19 (ECHA c2007-2017c). No effects on mean body weights, body weight gains, net body weights, net body weight gains, gravid uterine weights, or food consumption in any test substance-exposed group were observed. No adverse effects on maternal animals or effects on intrauterine growth, survival, and foetal morphology were observed at any exposure level. Based on these observations, the study authors identified a NOAEC of 1500 ppm (5300 mg/m<sup>3</sup>) (the highest exposure level evaluated) for maternal toxicity and embryo/foetal development.

Similarly, no developmental toxicity was reported up to the highest concentration tested (i.e. NOAEC of 5000 mg/m<sup>3</sup>) in the combined inhalation reproductive/developmental toxicity study described above. The results of these studies would suggest that MPK is not a developmental toxicant. In addition, based on OECD toolbox in silico prediction tools, there is no structural alert, indicating that MPK has any potential for inducing developmental toxicity.

No oral or dermal reproductive or developmental toxicity data are available for MPK.

**Table 7-4. Read-across within Ketones Subgroup 1 (MEK, MPK).**

Chemical name	2-Butanol	MEK	MPK
Role	Analogue	Target chemical	Target chemical
CAS#	78-92-2	78-93-3	107-87-9
Chemical structure	 MW: 74.12 Log Kow: 0.61	 MW: 72.11 Log Kow: 0.29	 MW: 86.13 Log Kow: 0.91
Toxicokinetics & metabolism	Rapidly converted to MEK	Rapidly absorbed via oral route	NA
Acute toxicity	N/A	Oral LD50 = 3460 mg/kg bw Dermal LD50 >6400-8000 mg/kg bw	Oral LD50 = >1600-<3200 mg/kg bw Dermal LD50 = 8000 mg/kg bw
Short term inhalation studies	N/A	NOAEC = 590 mg/m <sup>3</sup> (human study)	NOAEC = 1074 mg/m <sup>3</sup> (No effect after 4 exposures)

		LEC <sub>5</sub> = 5202 mg/m <sup>3</sup> (intermittent exposure)/ LEC <sub>HEC</sub> =1517 mg/m <sup>3</sup> (continuous exposure) (from developmental study)	NOAEC = 5300 mg/m <sup>3</sup> (14-d developmental study)
Repeat dose toxicity (Oral)	NOAEL = 1771 mg/kg bw per day (8-week; decreased BW gain in dams)	NOAEL = 1723 mg/kg bw per day (read-across from 2-butanol <sup>a</sup> )	NOAEL/LOEL = 454 mg/kg bw per day (13-month; 9% decreased body weight gain)
Repeat dose toxicity (Inhalation)	N/A	NOAEC = 14870 mg/m <sup>3</sup> (decreased body weight gain, increased liver, kidney weights, decreased brain weight; absence of central/peripheral neural histopathology) (90-day)	NOAEC = 5300 mg/m <sup>3</sup> (13-week) NOAEC = 5000 mg/m <sup>3</sup> (35-51-day)
Repeat dose toxicity (Dermal)	NA	NA	NOAEL = 454 mg/kg bw/d (from MPK oral study)
Reproductive and/or developmental toxicity (oral)	LED <sub>05-dev</sub> = 657 mg/kg bw per day (multigeneration 8-week; NOAEL <sub>dev-mat</sub> = 1771 mg/kg bw/d; decreased foetal weight, with evidence of retarded skeletal maturation; decreased body weight in dams)	LED <sub>05</sub> = 639 mg/kg bw per day (NOAEL = 1723 mg/kg bw per day) (read-across from 2-butanol <sup>a</sup> )	LED <sub>05</sub> = 763 mg/kg bw per day (read-across from 2-butanol <sup>a</sup> )

Reproductive and/or developmental toxicity (inhalation)	N/A	NOAEL <sub>dev-mat</sub> = 2955 mg/m <sup>3</sup> (GD6-15; decreased foetal weight among males, increased incidence of misaligned sternebrae and increased relative liver weight in dams) LEC <sub>10</sub> = 5202 mg/m <sup>3</sup> (intermittent exposure)/ LEC <sub>HEC</sub> =1517 mg/m <sup>3</sup> (continuous exposure)	NOAEC <sub>dev</sub> = 5000 mg/m <sup>3</sup> NOAEC <sub>mat</sub> = 5000 mg/m <sup>3</sup> (35-51-day until GD19) NOAEC <sub>dev</sub> = 5300 mg/m <sup>3</sup> (GD6-19)
Reproductive and/or developmental toxicity (dermal)	N/A	LED <sub>05</sub> = 639 mg/kg bw per day (read-across from 2-butanol oral study <sup>a</sup> )	LED <sub>05</sub> = 763 mg/kg bw per day ( read-across from 2-butanol oral study <sup>a</sup> )
Genotoxicity	Not genotoxic	Not genotoxic	Not genotoxic
Carcinogenicity	N/A	Negative/ Inconclusive (EPA 2003). However, unlikely based on structural alerts, (Q)SAR.	Not expected to be carcinogenic (read across from MEK)

Abbreviations: NA, Not Available; N/A, Not Applicable; Log Kow, octanol-water partition coefficient; MW, molecular weight (g/mol)

<sup>a</sup> molar adjustment calculated from read-across value. Molecular weights are 74.12 g/mol for 2 butanol, 72.11 g/mol for MEK and 86.13 g/mol for MPK.

### 7.1.3 Risk characterization of subgroup 1 (MEK and MPK)

#### MEK

In the range of adverse effects in animals resulting from repeated inhalation exposure to MEK, there is consistent evidence in studies in rats and mice that developmental effects are the critical health effect, which occurred mostly in the presence of slight maternal toxicity. Based on the available studies, the US EPA (2003a) selected the study in mice by Schwetz et al (1991) with a LEC<sub>10</sub> for intermittent exposure (7h/day) of 5,202 mg/m<sup>3</sup> and a LEC<sub>HEC</sub> for continuous exposure of 1517 mg/m<sup>3</sup>, based on the incidence of

misaligned sternebrae (US EPA IRIS 2003a). Therefore, these values were considered to be the most appropriate points of departure to use for risk characterization for MEK.

In the absence of oral repeat dose toxicity studies for MEK, the reproductive and developmental drinking water toxicity study of 2-butanol in rats (Cox et al., 1975 as cited in US EPA IRIS 2003a) was selected to characterize risk by the oral and dermal routes. The US EPA (2003) estimated a LED<sub>05</sub> (95% lower confidence limit on the effective dose, ED) of 639 mg/kg-bw/day for MEK (adjustment based on the molecular weights from the LED<sub>05</sub> of 657 mg/kg-bw/day for 2-butanol) based on decreased pup survival and decreased neonatal body weight in presence of maternal toxicity.

The predominant source of exposure to MEK from environmental media and food for the general population is through the diet and to a lesser extent from indoor air. Based on the available data, it is expected that the majority of the dietary exposure to MEK results from its natural occurrence in foods.

The general population of Canada may also be exposed to MEK when using various products available to consumers containing the substance including nail products, paints and do-it-yourself products, primarily through inhalation. Table 7-5 provides relevant exposure values and effect levels for critical health effects as well as the resultant margins of exposure (MOEs) for the characterization of risk for MEK.

**Table 7-5. Relevant exposure and hazard values for MEK, as well as margins of exposure, for characterization of risk<sup>a</sup>.**

Exposure Scenario	Exposure	Critical effect level	Critical health effect	MOE
Total exposure from environmental media	9.1 – 27.6 µg/kg-bw/day	LED <sub>05</sub> = 639 <sup>b</sup> mg/kg-bw/day	Developmental study for 2-butanol; decreased foetal and pup weights, and body weight gain in dams	> 22 986
Food flavouring agent	0.6 – 2.0 µg/kg-bw/day	LED <sub>05</sub> = 639 <sup>b</sup> mg/kg-bw/day	Developmental study for 2-butanol; decreased foetal and pup weights, and body weight gain in dams	> 319 500
Nail products (inhalation)	7-hr TWA <sup>a</sup> = 4.1 – 15.8 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	increased incidence of misaligned sternebrae in foetus	329 – 1 269

Pacifiers and teethingers (oral)	0.09 – 0.30 mg/kg-bw/day	LED <sub>05</sub> = 639 <sup>b</sup> mg/kg-bw/day	Developmental study for 2-butanol; decreased foetal and pup weights, and body weight gain in dams	2 130 – 7 100
Lacquer remover (inhalation)	7-hr TWA = 131 – 514 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	10 – 40
Adhesive remover (inhalation)	7-hr TWA = 1843 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	3
Paint thinner, floor coating (inhalation)	7-hr TWA = 120 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	43
Liquid paint (solvent-rich) for truck bed (inhalation)	7-hr TWA = 176 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	30
Spray paint (inhalation)	7-hr TWA = 3 – 167 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	31 – 1 743
PVC cement/primer (inhalation)	7-hr TWA = 5 – 109 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	48 – 10 40
Multipurpose adhesives	7-hr TWA = 8 – 44 mg/m <sup>3</sup>	LEC <sub>10</sub> = 5 202 mg/m <sup>3</sup> (Intermittent exposure)	Increased incidence of misaligned sternebrae in foetus	118 – 650

Abbreviations: TWA, time-weighted average

<sup>a</sup> Seven-hour time-weighted average (TWA) concentrations were derived for all product scenarios to match up with the exposure durations of the critical effects study used to characterize risk.

<sup>b</sup> Molar adjustment calculated from read-across value. Molecular weights are 74.12 g/mol for 2 butanol, 72.11 g/mol for MEK and 86.13 g/mol for MPK.

MOEs for exposure to MEK in environmental media and food (flavouring agent) are considered adequate to address any uncertainties in the health effects and exposure databases. Additional intake of MEK from its natural occurrence in food was not identified as a concern for human health. Furthermore, the JECFA (WHO 1999b) concluded "No safety concern with the estimated levels of intake as flavouring substances" based on the dietary exposure estimates for MEK.

The calculated MOEs for exposure to pacifiers and teethers, nail products and multipurpose adhesives are considered adequate; however, inhalation exposure to MEK from the other products available to consumers (i.e., lacquer remover, adhesive remover, paint thinner, liquid paint and spray paint), are considered potentially inadequate to account for uncertainties in the databases.

## MPK

No carcinogenicity studies were identified for MPK. However, there were no positive (Q)SAR model predictions or presence of structural alerts for carcinogenicity. In addition, MPK was not genotoxic in several in vitro assays. In the only available oral toxicity study, minimal effects (slight decreased body weight gain) was reported in rats at the highest dose of MPK administered in the drinking water for 13 months (Bingham et al., 2001, HSDB 2015b); the NOAEL/LOEL is considered to be 454 mg/kg bw per day). With respect to inhalation exposure, no adverse effects, other than slight transient neurotoxicity in dams during exposure, were observed in studies in which NOAECs of 5000 and 5300 mg/m<sup>3</sup> were identified (ECHA c2007-2017c).

The predominant source of exposure to MPK from environmental media and food for the general population is through the diet. Based on the available data, it is expected that the majority of the dietary exposure to MPK results from its natural occurrence in foods.

The only consumer uses identified for MPK were for paint products. Comparison of the estimates of exposure to MPK from environmental media (2.3 – 6.8 µg/kg bw/day) and from its use as a flavouring agent in food (0.7 – 2.0 µg/kg bw/day) with the NOAEL/LOEL of 454 mg/kg-bw per day resulted in MOEs greater than 66 765, which are considered adequate to address any uncertainties in the health effects and exposure databases. Additional intake of MPK from its natural occurrence in food was not identified as a concern for human health. Furthermore, the JECFA (WHO 1999b) concluded "no safety concern with the estimated levels of intake as flavouring substances" based on the dietary exposure estimates for MPK. Given the low hazard potential of MPK via inhalation, risk to human health related to the presence of MPK in products available to consumers is considered to be low.

### 7.1.4 Uncertainties in evaluation of risk to human health for MEK and MPK

The key sources of uncertainty are presented in the table below. There is some uncertainty in the estimates of inhalation exposure from use in products available to consumers, with respect to the range of concentrations in the various products, the location of the activity as well as the defaults used in the ConsExpo Web (ConsExpo 2016). Confidence is high that use of the maximum concentrations and the high end of the range of product amounts from these types of products does not underestimate potential population exposures.

There is some uncertainty regarding the toxicity of MEK following long term oral exposure, since no data are available; however, the use of 2-butanol, a major metabolite of MEK, was considered an appropriate analogue for use in risk characterization.

**Table 7-6. Sources of uncertainty in the risk characterization.**

Key sources of uncertainty	Impact
Assumption that dermal exposures are minimal in comparison to inhalation exposures, given the high volatility of the substances; however,	-
Lack of chronic oral or inhalation study for MEK or MPK.	-
The use of 2-butanol as read-across to assess repeated dose toxicity and reproductive/developmental toxicity for MEK	+/-
Selection of a conservative effect level from a repro/devo study for risk characterization of an acute inhalation exposure scenario for MPK (paint products).	+

+ = 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.

## 7.2 Assessment of subgroup 2 (MIBK, MIAK, and DAA)

### 7.2.1 Exposure assessment of subgroup 2 (MIBK, MIAK, and DAA)

#### Environmental media

MIBK was monitored by the National Air Pollution Surveillance (NAPS) program. Mean concentrations of MIBK between 2006 and 2010 from various sites across Canada ranged from 0.014 to 0.29 µg/m<sup>3</sup> with 95<sup>th</sup> percentile concentrations ranging from 0.08 to 1.05 µg/m<sup>3</sup> (ECCC 2017). Geometric mean ambient air concentrations of MIBK from the five Canadian air studies referred to in section 7.1.1 ranged from <0.016 to 0.185 µg/m<sup>3</sup>, and 95<sup>th</sup> percentile concentrations ranging from 0.086 to 0.470 µg/m<sup>3</sup> (Zhu et al. 2005; Health Canada 2010a, b, 2012, 2013). The highest 95<sup>th</sup> percentile concentration (0.470 µg/m<sup>3</sup> from the Windsor 2005 study) was used to estimate general population exposures. No information or data on MIAK and DAA in ambient air were identified in Canada or elsewhere.

MIBK was measured in the CHMS Cycle 2 Indoor Air Study and was detected in approximately 96% of the samples. The geometric mean concentration of MIBK from this study was 0.235 µg/m<sup>3</sup> with a 95<sup>th</sup> percentile concentration of 1.62 µg/m<sup>3</sup> (weighted data at the household level) (Zhu et al. 2013). Geometric mean MIBK concentrations from the five Canadian air studies ranged from 0.14 to 1.33 µg/m<sup>3</sup> with 95<sup>th</sup> percentile concentrations ranging 0.33 to 13.82 µg/m<sup>3</sup> (Zhu et al. 2005; Health Canada 2010a, b, 2012, 2013). The highest 95<sup>th</sup> percentile concentration was used to estimate general population exposures (13.82 µg/m<sup>3</sup> from the Windsor 2005 study). MIAK was also measured in the CHMS Cycle 2 Indoor Air study but was only detected in 1.45% of samples (limit of detection of 0.19 µg/m<sup>3</sup>). The geometric mean and 95<sup>th</sup> percentile MIAK concentration in indoor air was 0.10 µg/m<sup>3</sup> and 0.11 µg/m<sup>3</sup>, respectively (weighted data at the household level). (Zhu et al. 2013). MIAK was also measured in 24 indoor air samples from a Quebec field study with a geometric mean concentration of 0.23 µg/m<sup>3</sup> and a maximum concentration of 1.51 µg/m<sup>3</sup> (Won and Lustyk 2011). This maximum indoor air concentration was used to estimate general population exposures. No empirical data on DAA in indoor air were identified in Canada or elsewhere. Based on the very high water solubility and low Henry's Law Constant, air is not expected to be a significant source of population exposure for DAA.

Personal air samples were also measured for MIBK in the Windsor study (Health Canada 2010a). The geometric mean personal air concentration of MIBK in the summer and winter were 1.04 µg/m<sup>3</sup> and 0.23 µg/m<sup>3</sup>, respectively. The 95<sup>th</sup> percentile concentrations for MIBK were 7.96 µg/m<sup>3</sup> and 0.99 µg/m<sup>3</sup> in the summer and winter, respectively (Health Canada 2010a).

No concentrations for MIBK, MIAK and DAA in drinking water in Canada were identified. No further information on the presence of MIAK in water elsewhere was identified; however, MIBK was detected in 3 out of 646 samples in a study conducted in the US with measured concentrations ranging from 16-20 µg/L (Grady and Casey 2001). MIBK was also measured in several surface water studies (Benfenati et al. 1992, Hall, 1987, Sheldon and Hites, 1978, Bianchi and Varney, 1998, U.S. EPA 2002). In addition, elevated concentrations of MIBK were found in groundwater, effluent and leachate in the vicinity of landfill sites, oil reprocessing facilities and sewage treatment plants (Mutch et al., 1983; Sawhney and Kozloski, 1984; Sabel and Clark, 1984; Canter and Sabatini, 1994; Paxeus, 1996; U.S. EPA, 1998). The maximum value of 20 µg/L measured in the US was used to estimate general population exposures to MIBK from drinking water and resulting general population intakes ranged from 0.1 µg/kg-bw per day (adults 60 years and older) to 2.1 µg/kg-bw per day (formulat fed infants 0 to 6 months old). ChemCan was used to derive concentrations of MIAK and DAA in water using volume data from Table 4-1. Drinking water concentrations for MIAK and DAA were 0.15 ng/L and 46.6 ng/L, respectively resulting in general population intakes.

No information or data on MIBK, MIAK and DAA in soil were identified in Canada. DAA was qualitatively detected in sediment in a lake in Saskatchewan, Canada (HSDB 1983). ChemCan was used to derive concentrations of MIBK, MIAK and DAA in soil using volume data from Table 4-1. Soil concentrations for MIBK, MIAK and DAA were

1.9 ng/kg, 0.3 ng/kg, and 7 pg/kg respectively; therefore, exposure to these substances from soil is considered to be negligible (intakes less than 1 ng/kg-bw per day).

Estimates of exposure for MIBK, MIAK and DAA from environmental media ranged from 2.5 µg/kg-bw per day for adults (60 years and older) to 7.5 µg/kg-bw per day for toddlers (6 months to 4 years), 0.3 µg/kg-bw per day for adults (60 years and older) to 0.9 µg/kg-bw per day for toddlers (6 months to 4 years), and 0.001 µg/kg-bw per day for adults (60 years and older) to 0.005 µg/kg-bw per day for formula fed infants (0 to 6 months old), respectively (Health Canada 2018).

## Food

MIBK was detected in various food items as a result of its natural occurrence including in beer, brandy, chicken, fruit, olive oil, eggs, coffee and cow's milk (Nijssen et al. 1963-2016, studies, Burdock 2010). MIBK is also cited as being used as a flavouring ingredient in baked goods, frozen dairy, gelatins/puddings, meat products, non-alcoholic beverages and soft candy (Burdock 2010). MIBK was detected (2 out of 12 samples) but not quantified in breast milk (Pellizari et al. 1982).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated a group of 39 saturated aliphatic acyclic secondary alcohols, ketones and related saturated and unsaturated esters, including MIBK, used as flavouring substances (WHO 1999b). As part of that evaluation, the Committee estimated the per capita intake of MIBK from its use as a food flavouring agent to be 0.03 µg/kg bw per day for the US population, and 0.12 µg/kg bw per day for the European population (see Appendix A for more details).

MIAK was identified in a few food items including coffee (0.5 µg/g) and papaya (0.001 µg/g) (Nijssen et al. 1963-2016), in roasted filberts, fried bacon, cooked beef and cooked pork (HSDB 1983-). DAA was detected in various food items including fruit, vegetables, dairy, honey, nuts, eggs, chicken and alcoholic beverages (Nijssen et al. 1963-2016, study).

Quantitative exposure estimates for MIBK, MIAK and DAA from its natural occurrence in food<sup>7</sup> ranged from 0.4 µg/kg-bw per day for 4 to 8 year olds to 32 µg/kg-bw per day for adults 19 years and older for MIBK, from 0.001 µg/kg-bw per day for 1 year olds to 3 µg/kg-bw per day for adults 19 years and older for MIAK, and from 0.04 µg/kg-bw per day for 6 to 12 month olds to 4 µg/kg-bw per day for 2-3 year olds for DAA.

## Products available to consumers

### *MIBK*

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<sup>7</sup> Infants 0 to 6 months old are assumed to be exclusively breast-fed or formula-fed.

MIBK was identified as being present as a non-medicinal ingredient in rubbing alcohol, licensed as an NHP, meant for topical use with a concentration of 0.98% (personal communication, e-mail from Natural and Non-Prescription Health Products Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada, dated Aug 16, 2016 unreferenced). ConsExpo Web (2016) was used to estimate inhalation exposures to MIBK from use of this product for toddlers and adults. Parameters used in the model are outlined in Appendix B. The mean event concentration, regardless of age group for this exposure scenario was estimated to be 0.19 mg/m<sup>3</sup> and the mean concentration on the day of exposure was estimated to be 2.7E-4 mg/m<sup>3</sup>. Although dermal exposure could contribute to the overall exposure during use of products available to consumers, the primary route is considered to be inhalation in light of the high volatility of MIBK; therefore, only inhalation exposure estimates are presented.

MIBK is used in a variety of products available to consumers that may result in exposure to the general population of Canada. Only product scenarios that result in the highest levels of potential exposure to MIBK by the inhalation are presented in Table 7-7. Incidental oral as well as inhalation exposures for toddlers and children (representing highest exposed age groups) from use of dry erase markers were also estimated (see Table 7-7). Per event incidental oral exposure estimates from the use of dry erase markers were 0.48 and 0.97 mg/kg bw for children and toddlers, respectively. Potential exposures were estimated using ConsExpo Web (ConsExpo 2016) or relevant algorithms; see Appendix B for details.

**Table 7-7. Estimated exposures to MIBK from the use of products**

Product scenario	MIBK conc.	Mean event conc. (mg/m <sup>3</sup> )	Mean conc. on day of exposure (mg/m <sup>3</sup> )	6-hr TWA <sup>a</sup> (mg/m <sup>3</sup> )
Wood lacquer	1 – 10%	270 – 2600	11 – 110	45 – 433
Liquid paint (solvent-rich) for truck bed liners, appliances	13%	130	12	48
Spray paint	0.1 – 30%	5.3 – 1200	0.09 – 21	0.4 – 83
Filler/putty from tube (automotive)	1 – 8%	6.7 – 38	0.3 – 1.6	1 – 6
Dry erase marker	30%	3.6	0.11	0.45

<sup>a</sup> Six-hour time-weighted average (TWA) concentrations were derived for all product scenarios to match up with the exposure durations of the critical effects study used to characterize risk. 6-Hr TWA = Mean event conc. x exposure duration / 6 x 60 min.

**MIAK**

MIAK was identified in several brands of spray paints, and in automotive repair coating pen (Health Canada 2016, HPD 1993-). Use of spray paints containing 1 - 10% MIAK represents the sentinel scenario. The mean event concentration derived from ConsExpo Web (ConsExpo 2016) for an adult using a spray paint containing MIAK ranged from was 41 - 280 mg/m<sup>3</sup> while the mean event concentration on the day of exposure ranged from 0.7 to 4.8 mg/m<sup>3</sup>. Six-hour TWA concentrations ranged from 3 – 19 mg/m<sup>3</sup> (see Appendix B for more details). Although dermal exposure could contribute to the overall exposure during use of products available to consumers, the primary route is considered to be inhalation in light of the high volatility of MIAK, only inhalation estimates are presented.

#### DAA

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, DAA is used as a solvent or as an odour masking agent in certain cosmetic products in Canada such as eyeliner stickers and in various nail care products including base-coats, top-coats, nail polish, nail polish remover, and nail hardener (personal communication, emails from CPSD, HC to ESRAB, HC, dated Aug. 2016 and April 2017, unreferenced).

Inhalation exposure estimates were derived for certain sentinel products (base-coat, top-coat, nail polish and nail polish remover) which represent the highest exposures when compared to similar products. Table 7-8 summarizes the concentration range for the various product scenarios along with the associated inhalation exposure estimates. Only exposure estimates for adults and toddlers are shown; however, they represent the range of potential exposures for all age groups. Details on the method and parameters used to estimate inhalation exposures to cosmetics are available in Appendix B.

Dermal exposure to DAA from use of these products is also possible and unlike the other ketones described thus far, is more likely given its lower vapour pressure and high water solubility. A human in vitro dermal absorption study was identified and found that the amount of DAA that penetrated the skin after 10-, 60-minutes, and 24 hours was 0.04%, 0.15%, and 5.71% of a 25 mg/cm<sup>2</sup> dose, respectively (Fasano and McDougal 2008; ECHA c2007-2017a). Table 7-8 includes the estimated systemic dermal exposures assuming 6% dermal absorption through the skin.

**Table 7-8. Estimated inhalation and dermal exposures to DAA from the use of cosmetics.**

Product scenario	Maximum concentration <sup>a</sup>	Mean event concentration (mg/m <sup>3</sup> )	6-Hr TWA (mg/m <sup>3</sup> )	Systemic dermal exposure (mg/kg-bw/event)
Nail polish (adults/teens)	10%	3.5	0.34	0.014 – 0.016

Product scenario	Maximum concentration <sup>a</sup>	Mean event concentration (mg/m <sup>3</sup> )	6-Hr TWA (mg/m <sup>3</sup> )	Systemic dermal exposure (mg/kg-bw/event)
Nail polish (toddler)	10%	3.1	0.30	0.023
Eyeliner sticker (adults/teens)	30%	0.67	1.3	0.007 – 0.008

<sup>a</sup> Personal communication, emails from CPSD, HC to ESRAB, HC, dated Aug. 2016 and April 2017, unreferenced.

DAA was identified in pipe thread sealants, spray products including paints, cleaners, and automotive products, and paint thinners (used to dilute lacquers and clean brushes). Table 7-9 summarizes inhalation and dermal exposure scenarios for paint and DIY products available to consumers containing DAA using ConsExpo Web (ConsExpo 2016).

**Table 7-9. Estimated inhalation exposures to DAA from the use of products.**

Product scenario	DAA conc.	Mean event conc. (mg/m <sup>3</sup> )	Internal inhalation dose on day of exposure (mg/kg-bw/day)	Sytemic dermal exposure (mg/kg-bw/day)
Pipe thread sealant	20 – 30%	35 – 51	1.7 – 2.5	0.012 – 0.018
Automotive choke cleaner (spray)	1 – 30%	13 – 110	0.04 – 0.32	0.013 – 0.38
Paint/marker remover (spray)	10%	81	0.32	0.13
Spray paint	1 – 5%	21 – 72	0.11 – 0.36	0.007 - 0.066
Paint thinner (for epoxy paint)	5 – 10%	55 – 71	0.46 – 0.60	0.09 – 0.17

DAA was also identified in permanent markers (Health Canada 2016, HPD 1993-). These products may be used by young children, and therefore, incidental oral and dermal exposures were estimated. A concentration of 100% was assumed based on limited data available on the quantity of DAA in markers (SDS 2008b, SDS 2012a, SDS 2014). Per event incidental oral exposure estimates from the use of permanent markers

were per event incidental oral exposure estimate from the use of permanent markers was 1.6 and 3.2 mg/kg bw for children and toddlers, respectively. The daily systemic dermal exposure estimates, assuming dermal absorption of 6%, ranged from 0.002 mg/kg-bw/day for adults to 0.005 mg/kg-bw/day for a child (toddlers assumed to not use permanent markers on a daily basis). Any inhalation exposures to DAA from use of permanent markers are considered to be included in the conservative oral or dermal exposure estimates (details in Appendix B).

## **7.2.2 Health effects assessment of subgroup 2 (MIBK, MIAK, and DAA)**

MIBK and MIAK are structurally similar molecules, differing in chain length by only one methyl group. Biologically they are likely to have similar interactions and metabolites in the body. DAA has been included in this subgroup as it is a primary metabolite of MIBK. It is likely to have similar metabolic clearance and is possibly responsible for some of the biological effects seen following MIBK exposure. Effects common to all three chemicals included decreased body weight, increased kidney and liver weights, and central nervous system (CNS) depression. While no data on the metabolism of MIAK was identified, the structural similarities to MIBK suggest it would have analogous metabolites and metabolic rates.

### **7.2.2.1 MIBK**

MIBK has been reviewed by OECD (1996), IPCS (1996), US EPA IRIS (2003b), IARC (2013) and NICNAS (2017). These reviews provide a basis for the health effect characterisation in this draft screening assessment. A literature search has been conducted from a year prior to the OECD SIAR report (1996) and updated to January 2017. Based on a 2-year inhalation carcinogenicity study by NTP (2007b) in two mammalian species (rat and mouse), IARC classified MIBK as group 2B (“possibly carcinogenic to humans”) with sufficient evidence of carcinogenicity in experimental animals (IARC Monograph Vol. 101, 2013). Whereas the IARC report was the basis for characterization of cancer effects, the US EPA IRIS document was the basis for characterization of non-cancer effects of MIBK

### **Toxicokinetics and metabolism**

MIBK is rapidly absorbed following oral, inhalation and dermal exposure (Duguay and Plaa, 1995; Hjelm et al., 1990; Hjelm et al., 1991 as cited in EPA IRIS 2003b and NTP 2007b). The major metabolite detected in plasma of rats administered MIBK by gavage was DAA, with somewhat lesser amounts of 4-methyl-2-pentanol (DiVincenzo et al., 1976; Duguay and Plaa, 1995 as cited in NTP 2007b and EPA IRIS 2003b). However, 4-methyl-2-pentanol was the major metabolite (about twice as much as DAA) detected in the lung of rats following inhalation exposure. In humans, inhalation exposure to concentrations of 10, 100, or 200 mg/m<sup>3</sup> MIBK for 2 hours resulted in a pulmonary retention of about 60% with mean blood clearance of 1.6L/h/kg and about 0.04% of the

total dose was excreted unchanged in the urine within 3 hours post-exposure (Hjelm et al., 1990 as cited in NTP 2007b). With respect to dermal exposure, the percutaneous uptake rate of MIBK in exposed guinea pigs ranged from 0.11 to 2.0  $\mu\text{mol}/\text{min}/\text{cm}$  and averaged 1.1  $\mu\text{mol}/\text{min}/\text{cm}$  (Hjelm et al., 1991 as cited in EPA IRIS 2003b).

## **Carcinogenicity and genotoxicity**

In a 2-year inhalation study in male and female mice and rats, MIBK increased the incidences of hepatocellular adenoma, and hepatocellular adenoma and carcinoma combined in male and female mice, as well as that of renal tubule adenoma and renal tubule adenoma and carcinoma combined in male rats, and caused two rare renal malignant mesenchymal tumours in high-dose female rats at a concentration of 7374 mg/m<sup>3</sup> (NTP 2007b, IARC 2013). Two rare renal malignant mesenchymal tumours and increased incidence of mononuclear cell leukemia were also observed at the highest dose in rats. In rats, the incidence of renal effects, including chronic nephropathy, was significantly increased, with an increasing trend in severity. Although the pathological changes in male rats were consistent with the spectrum of  $\alpha$ 2u-globulin induced nephropathy and hyaline droplet formation has been reported in MIBK exposed male rats in shorter term studies (e.g., Phillips et al, 1987 and Nemec et al, 2004, as cited in NTP, 2007b), in light of the observation of nephropathy also in female rats, the NTP (2007b) stated that the renal tumours may arise independently of a  $\alpha$ 2u-globulin mechanism. Further, IARC (2013) determined that the relevance of the kidney tumours in rats to humans could not be excluded. The chronic inhalation LOAEC non-cancer effects for MIBK was established at 1843 mg/m<sup>3</sup>, based on minimal to mild nephropathy in the 2-year bioassay (NTP 2007b).

Subsequent to the publication of the NTP (2007b) report and the IARC (2013) Monograph, recent studies have suggested that the MIBK-induced kidney and liver tumors occurred in rodents by mechanisms such as alpha2u-globulin nephropathy and constitutive androstane receptor (CAR)-mediated mode of action, respectively that are not relevant to humans (Hughes et al. 2016; Borghoff et al. 2015). In a review of these data, NICNAS (2017) has concluded that, while the evidence supports the liver tumours in mice arising from activation of the CAR, a mechanism other than that involving  $\alpha$ 2u-globulin may be responsible for the renal tumours in rats; this information, along with the observation of mononuclear leukaemia in male rats and the renal mesenchymal tumours in female rats, support that the conclusion that the tumours in rats are relevant to humans and are sufficient to classify MIBK as a Category 2 carcinogen according to the GHS.

Based on numerous *in vivo* and *in vitro* studies MIBK is not considered genotoxic (NTP 2007b; IARC 2013).).

## **Repeated dose toxicity**

Repeated inhalation exposure to MIBK has been associated with effects on liver and kidney weights, biochemical parameters or central nervous system in rats and/or mice

at concentrations starting to 410 mg/m<sup>3</sup> (Phillips et al 1987; MacEwen et al. 1971; David et al. 1999, all as cited in EPA IRIS 2003b). However, according to the US EPA IRIS (2003b), there were no clear toxicological continuum of severity and/or marked progression of response with increasing concentration or any treatment-related corroborative gross pathologies or histopathological lesions and the observed effects were not considered to be clearly adverse and were therefore considered to be of uncertain relevance to effects in humans after chronic exposures.

In an oral subchronic toxicity study, male and female rats were administered a dose of 0, 50, 250 or 1000 mg/kg-bw/day MIBK by gavage for 13 weeks (MAI, 1986 as cited in US EPA IRIS 2003b and WHO 1990). Alterations in a range of clinical chemistry parameters suggestive of hepatic and renal effects were observed in males and/or females at the highest dose; increased absolute and relative kidney weights were also observed in both sexes at 250 mg/kg bw/day and above. There was an increased incidence of mild nephropathy in males at 1000 mg/kg bw/day. No effects were noted at 50 mg/kg-bw/day, which the WHO (1990) and IARC (2013) considered to be the NOEL. However, the US EPA (US EPA IRIS 2003b) considered 1000 mg/kg bw/day to be a NOAEL, suggesting that the effects observed were difficult to interpret and may not be biologically adverse in light of the absence of clear histopathological changes. The NOAEL for an oral drinking water study was also considered by the US EPA to be around 1000 mg/kg-bw/day, based on uncertainty regarding biological adversity of the observed renal effects (Carnegie-Mellon Institute of Research, 1977a, b as cited in US EPA IRIS 2003b).

In light of the uncertainties regarding the adversity of the effects observed in the subchronic oral studies, for characterization of risk following longer term oral exposure, the LOAEC of 1843 mg/m<sup>3</sup> from the more recent, comprehensive inhalation study by the NTP (2007b) is extrapolated to an oral dose of 101 mg/kg bw/day; route to route extrapolation is considered appropriate for the critical internal effects in the kidneys of male and female rats. In addition, NICNAS (2017) recently determined the renal effects observed in the 2 year study in rats to be relevant to humans.

In a dermal study, MIBK was applied to the tails (lower 2/3) of an unspecified number of male white rats daily (4 h/day) in doses of 300 or 600 mg/kg for 4 months. These doses induced morphological changes to the skin, brain, liver, adrenal gland, spleen and testes and a reduction in the number of spermatocytes, spermatids and spermatozoa (Malysheva, 1988 as cited in NTP 2007b).

### **Short-term and acute toxicity**

Short-term inhalation studies were conducted in rats and mice. Effects observed were limited to the liver and kidney. The lowest NOAEL was considered to be 410 mg/m<sup>3</sup> based on increased relative kidney weight and hyaline droplet-related tubular nephrosis in males animals (Hazleton Laboratories, Inc. 1968 as cited in EPA IRIS 2003b; Dodd et al., 1982; Phillips et al., 1987 as cited in NTP 2007b and IPCS 1990; MacEwen et al., 1971; Vernot et al., 1971 as cited in EPA IRIS 2003b). Similarly to the longer term

studies, the observed effects were not considered to be clearly adverse and were therefore considered to be of uncertain relevance to effects in humans.

MIBK has been shown to be of low toxicity following acute oral, dermal, and inhalation exposure (Smyth et al., 1951 & 1956; Batyrova, 1973; RTECS, 1987; Zakhari, 1977). Neurological effects (principally behavioural changes) were observed in several of the studies described above; however, effects were generally transient or attenuated with prolonged exposure and occurred at concentrations higher than those associated with liver and kidney endpoints. In several studies with human volunteers exposed to up to 200 ppm, MIBK caused reversible irritation and CNS symptoms (US EPA IRIS 2003b).

## **Reproductive and developmental toxicity**

In an inhalation reproductive and developmental toxicity study, groups of 35 pregnant F344 rats and 30 CD-1 mice were exposed GD 6-15 to airborne MIBK concentrations of 0, 300, 1000 or 3000 ppm (0, 1229, 4106 and 12292 mg/m<sup>3</sup>) (Tyl et al., 1987, as cited in EPA IRIS 2003b and IPCS 1990). In rats, signs of maternal toxicity were observed at 12292 mg/m<sup>3</sup>, including decreased body weight gain and food consumption (which returned to normal upon cessation of exposure) and increased relative kidney weight. Maternal body weight was not affected in mice although there was increased mortality and absolute and relative liver weights in dams exposed to 12292 mg/m<sup>3</sup> MIBK. Other maternal effects, including hypoactivity, ataxia and lacrimation, were observed at 12292 mg/m<sup>3</sup>. In rats, foetal body weights were decreased at 1229 and 12292 mg/m<sup>3</sup>, but not at 4106 mg/m<sup>3</sup>; the study authors attributed this observation to differential litter size and not exposure related. Foetal body weights were also reduced in mice at the highest concentration. At 12294 mg/m<sup>3</sup>, delays in some skeletal ossification parameters were noted in both rats and mice. Based on this study, the EPA IRIS (2003b) established a NOAEC of 4106 mg/m<sup>3</sup> and LOAEC of 12292 mg/m<sup>3</sup> for maternal effects and delayed foetal skeletal ossification in rats and mice. A NOAEL<sub>HEC</sub> of 1026 mg/m<sup>3</sup> was also derived for continuous exposure (LOAEL<sub>HEC</sub> = 3073 mg/m<sup>3</sup>). In a 2 generation study in SD rats, signs of CNS depression in pups and transient decreased body weight and food consumption in parents were observed at 8200 mg/m<sup>3</sup>, with a NOAEC of 4100 mg/m<sup>3</sup> (Nemec et al., 2004, as cited in IARC, 2013).

### **7.2.2.2 MIAK**

MIAK has not been assessed by other agencies. The following hazard assessment is based on the information identified from ECHA registration dossier (ECHA c2007-2017b) and US EPA HPVIS (US EPA 2001b).

### **Toxicokinetics**

It has been reported that clearance of MIAK following oral administration is slower than that following inhalation exposure. Results of an *in vitro* dermal absorption study (OECD TG 428) indicate that dermal absorption is moderate (ECHA c2007-2017b).

### **Carcinogenicity and genotoxicity**

No chronic studies were identified for MIAK. MIAK was not genotoxic in a variety of *in vitro* studies.

### **Repeated dose toxicity**

In a sub-chronic inhalation study, SD rats were exposed to MIAK vapour at concentrations of 0, 200, 1000 and 2000 ppm (equivalent to 0, 934, 4670 and 9340 mg/m<sup>3</sup>), for a total 69 exposures spanning 96 days. There were no significant changes in body weight, hematology, serum clinic chemistry or gross pathology. Dose-dependent statistically significant increases of absolute and relative liver weights were seen in males and females at concentrations of 4670 and 9340 mg/m<sup>3</sup>. Absolute and relative kidney weights were also increased in males at both these concentrations, and relative kidney weights were elevated in females at the highest dose. Histopathology revealed hyaline droplet formation in the kidneys of male rats, hepatocytic hypertrophy in livers and tubular epithelium regeneration in kidneys in both males and females exposed to MIAK at the two highest concentrations. Overall, the NOEC was determined to be 200 ppm (934 mg/m<sup>3</sup>) based on organ weight changes and histological changes observed in the livers and kidneys of both males and females at 4670 mg/m<sup>3</sup> or higher (Katz et al. 1986; ECHA c-2007-2017b).

With respect to oral exposure, in the only repeated dose oral study identified, only a very high dose was tested (2000 mg/kg-bw/day), which was associated with a wide range of effects (mainly kidney and liver effects) (ECHA c-2007-2017b).

In light of the limitations of the only repeated dose oral study, an oral NOEL of 52 mg/kg bw/day<sup>8</sup> was derived using route-to-route extrapolation from the inhalation study, based on the similar effects on liver and kidney by both routes of exposure.

No dermal repeat dose toxicity study was reported for MIAK.

### **Short term and acute toxicity**

Exposure of male and female SD rats to 1000 or 2000 ppm (4670 or 9340 mg/m<sup>3</sup>) MIAK via the inhalation route for a total of 12 exposures over 16 days resulted in slight, dose-dependent increase in absolute and relative liver weights in rats with no corresponding effects on serum clinical chemistries or histopathology. At 9340 mg/m<sup>3</sup>, renal hyaline

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<sup>8</sup> See Appendix D for calculation parameters

droplet formation was noted in males as was mineralization involving the heart in females (Anonymous 1983; Katz et al. 1986 as cited in ECHA c-2007-2017b). Based on these observations, the authors determined a NOAEC of 1000 ppm (4670 mg/m<sup>3</sup>).

Systemic effects were also observed in the developmental study described below at lower doses. dams exposed to MIAK for 14 days at 3503 mg/m<sup>3</sup> and above, showed significant body weight changes and neurological effects (i.e., reduced reactivity to stimuli). The NOAEC for systemic toxicity was considered to be 380 ppm (1775 mg/m<sup>3</sup>) (ECHA c-2007-2017b).

### **Reproductive and developmental toxicity**

In a reproductive/developmental toxicity screening test, MIAK did not affect a range of parameters investigated in parents or offspring; the substance was therefore not considered to be a reproductive toxicant at up to the highest test concentration of 5000 mg/m<sup>3</sup> (ECHA c-2007-2017b).

In a prenatal developmental toxicity test on MIAK, Groups of bred female SD rats were exposed to MIAK via whole body inhalation at concentrations of 0, 380, 750 or 1500 ppm (equivalent to 0, 1775, 3503 or 7005 mg/m<sup>3</sup>) from GD 6 through 19. In the 1500 ppm group, significant decreases of mean body weights, mean body weight gains and corresponding mean food consumption were observed in dams throughout the exposure period, while reduced reactivity to a noise stimulus was noted at concentrations of 750 or 1500 ppm. The NOAEC for maternal toxicity was considered to be 380 ppm (1775 mg/m<sup>3</sup>). No exposure related external, visceral, skeletal malformations or developmental variations were seen in foetuses up to doses of 1500 ppm (7005 mg/m<sup>3</sup>). However, significantly reduced foetal weights were seen in the 1500 ppm group compared with the control group. Therefore, the NOAEC for developmental toxicity was considered to be 750 ppm (3503 mg/m<sup>3</sup>) (ECHA c-2007-2017b).

#### **7.2.2.3 DAA**

DAA has been reviewed by OECD (2000). This review provides the basis for the health effects characterization in this draft screening assessment. A literature search has been conducted from a year prior to the OECD SIAR report (2000) until January 2017.

### **Toxicokinetics and metabolism**

The low molecular weight, log Kow value, and physical state of DAA favour its absorption via various routes of exposure (oral, dermal, and inhalation); available data suggest that absorption by the oral and inhalation routes is extensive. In an in vitro dermal absorption study the skin penetration was found to be 0.04, 0.15 and 5.71 % of the dose (25mg/cm<sup>2</sup>) after 10 min, 60 min and 24 h, respectively (Fasano and McDougal 2008).

### **Carcinogenicity and genotoxicity**

No carcinogenicity studies on DAA have been identified. DAA was reported to be non-genotoxic in various in vitro Ames tests, mammalian gene mutation assays and mammalian chromosome aberration tests (OECD 2000, ECHA c-2007-2017a).

### **Repeated dose toxicity**

In a combined repeat dose-reproductive/developmental toxicity screening test, DAA was administered daily for 45 days by gavage to male and female SD rats at doses of 0, 30, 100, 300, or 1000 mg/kg bw/day (MHW, 1997 as cited in OECD 2000). Decreased locomotor activity and stimulation response were observed at 300 and 1000 mg/kg bw/day in both sexes while altered haematological and blood chemistry parameters were noted in males at 1000 mg/kg bw/day. In males, renal effects were observed, including hyaline droplet formation at 100 mg/kg bw/day or greater, basophilic tubules at 300 mg/kg bw/day or more and dilatation of distal tubules at 1000 mg/kg bw/day. At 300 and 1000 mg/kg bw/day, females showed dilatation of the distal tubules and fatty degeneration of the proximal tubular epithelium in the kidneys. The OECD considered to NOAELs for repeat dose toxicity to be 30 mg/kg bw/day in males and 100 mg/kg bw/day in females. However, given the hyaline droplet formation considered to be specific to male rats, the NOAEL for male rats was considered to be 100 mg/kg bw/day. In an inhalation study, Wistar rats were exposed to DAA daily for 6 weeks to concentrations of 0, 233, 1041 and 4685 mg/m<sup>3</sup> (Butterworth et al. 1980 as cited in ECHA c2007-2017a). The authors identified a NOAEC of 4685 mg/m<sup>3</sup> and a NOEC of 1041 mg/m<sup>3</sup>. Only liver weight changes, not associated with histological alterations, were observed at 1041 mg/m<sup>3</sup>. At 4685 mg/m<sup>3</sup>, increased liver and kidney weights as well as rat-specific eosinophilic hyaline droplets in the proximal tubular cells were observed in males. OECD considered the middle concentration to be a NOAEC (reported as 1035 mg/m<sup>3</sup>) (SHELL Research Ltd, as cited in OECD 2000).

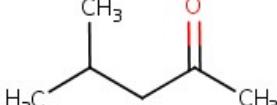
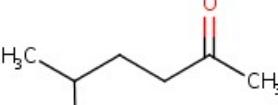
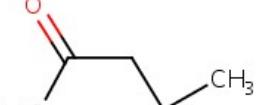
No repeated-dose dermal studies were available for DAA. Therefore, the oral NOAEL of 100 mg/kg-bw/day will be used to inform the risk from dermal exposure..

### **Reproductive and developmental toxicity**

In the combined repeat dose toxicity study with the reproduction/developmental toxicity screening test described above, there was a non-statistically significant decrease in reproductive parameters (fertility index, number of implantations and implantation index) and in developmental parameters (number of pups born, delivery index, live birth index, number of pups alive and viability index) at the highest dose of 1000 mg/kg bw/day. Although all of these changes were not statistically significant, it was considered that DAA could cause reproductive /developmental effects at 1000 mg/kg bw/day. Based on this the authors considered a NOAEL of 300 mg/kg bw/day for reproductive and developmental effects, with a parental NOAEL of 100 mg/kg bw/day as described above (MHW 1997 as cited in OECD 2000). No effect was observed in another developmental rat study up to dose of 1000 mg/kg-bw/day in rats (ECHA c2007-2017a).

In the absence of inhalation and dermal reproductive/developmental studies on DAA, the oral NOAEL of 300 mg/kg bw/day for reproductive/developmental effects was used.

**Table 7-10. Hazard information for Ketones Subgroup 2 (MIBK, MIAK, DAA).**

Chemical name	MIBK	MIAK	DAA
Role	Target chemical	Target chemical	Target chemical
CAS#	108-10-1	110-12-3	123-42-2
Chemical structure	 MW = 100.16	 MW = 114.18	 MW = 116.16
Acute toxicity Oral	Rat LD <sub>50</sub> = 2080 to 4570 mg/kg-bw Mice LD <sub>50</sub> = 1900-2850 mg/kg bw	Rat LD <sub>50</sub> = 5657 mg/kg bw	Rat LD <sub>50</sub> = 3002 mg/kg bw
Acute toxicity Inhalation	Rat LC <sub>50</sub> = 8200 to 16 400 mg/m <sup>3</sup> Mice LC <sub>50</sub> (1.25h) = 20 500 to 74 200 mg/m <sup>3</sup>	Rat LC <sub>50</sub> (6h) = 17806 mg/m <sup>3</sup> NOEC for non-lethal effects = 7486 mg/m <sup>3</sup>	Rat LC <sub>0</sub> (4h) = 7600 mg/m <sup>3</sup> Rat (6 h) = 7230 mg/m <sup>3</sup> air based (no effects up to)
Acute toxicity Dermal	Rabbit LD <sub>50</sub> = >20 000 mg/kg bw	NA	Rat LD <sub>50</sub> (24h) > 1875 mg/kg bw
Short-term (14d) Inhalation	NOAEC = 410 mg/m <sup>3</sup> (increased relative kidney weight and hyaline droplet-related tubular nephrosis)	NOAEC = 1775 mg/m <sup>3</sup> (maternal toxicity in developmental toxicity study)	NOAEC = 968 mg/m <sup>3</sup> (from oral 15-day developmental study)
Short-term dermal (14d)	NA	NOEL = 137 mg/kg bw/day (from inhalation developmental study)	NOEL = 1000 mg/kg bw/day (from oral 15-day developmental study)
Repeat dose toxicity (Oral)	LOEL/NOAEL = 250 mg/kg bw / day	NOEL = 52 mg/kg bw/day	NOAEL = 100 mg/kg/day

	(13-week; Hepatic and renal effects at 1000 mg/kg-bw/d)  LOAEL = 101 mg/kg-be/day (2-year; chronic nephropathy in females)	(from inhalation NOAEC)	(45-day; kidney changes and altered hematological and blood chemistry)
Repeat dose toxicity (Inhalation)	LOAEC = 410 mg/m <sup>3</sup> (increased incidence in renal tubule hyperplasia and chronic nephropathy (female) and mineralization of renal papilla (male))  LOAEC = 1843 mg/m <sup>3</sup> (2-year; chronic nephropathy in females)	NOAEC = 934 mg/m <sup>3</sup> (96-day; increased liver and kidney weight and hepatocytic hypertrophy in liver and tubular epithelium regeneration in kidneys in both males and females at 4670 mg/m <sup>3</sup> )	NOAEC = 1035 mg/m <sup>3</sup> (6-week; liver weight changes without histopathological alterations at 4685 mg/m <sup>3</sup> )
Repeat dose toxicity (Dermal)	LOAEL = 300 mg/kg bw (4-month; lowest dose tested; morphological changes in several tissues)  LOEL/NOAEL = 250 mg/kg bw/day (from MIBK oral)	NOEL = 52 mg/kg bw/day (from inhalation NOAEC)	NOAEL = 100 mg/kg/day (from oral NOAEL)
Developmental and/or Reproductive toxicity (Oral)	NOAEL = 259 mg/kg bw / day (read-across from DAA)	NOAEC <sub>dev</sub> = 271 mg/m <sup>3</sup> (R2R from inhalation NOAEC) NOAEC <sub>mat</sub> = 137 mg/m <sup>3</sup> (from inhalation NOAEC)	NOAEL <sub>devo</sub> = 300 mg/kg/day (reproductive and developmental effects at 1000 mg/kg-w/d) NOAEL <sub>mat</sub> = 100 mg/kg/day (kidney changes and altered hematological and blood chemistry)

Developmental and/or Reproductive toxicity (Inhalation)	NOAEC <sub>dev/mat</sub> of 4106 mg/m <sup>3</sup> (based on transient decreased body weight and food consumption and changes to reproductive organs weights in parents and on acute CNS depressive effects in pups)	NOAEC <sub>dev</sub> = 3503 mg/m <sup>3</sup> (reduced foetal weight at 3503 mg/m <sup>3</sup> ) NOAEC <sub>mat</sub> = 1775 mg/m <sup>3</sup> (decreases body weight gain and corresponding food consumption at 3505 mg/m <sup>3</sup> )	NOAEC <sub>devo</sub> = 968 mg/m <sup>3</sup> (from oral 45-day NOAEL)  NOAEC <sub>devo/mat</sub> = 3182 mg/m <sup>3</sup> (from oral study GD6-20)
Developmental and/or Reproductive toxicity (dermal)	NOAEL = 259 mg/kg bw / day (read-across from DAA)	NOAEC <sub>dev</sub> = 271 mg/m <sup>3</sup> (from inhalation NOAEC) NOAEC <sub>mat</sub> = 137 mg/m <sup>3</sup> (from inhalation NOAEC)	NOAEL <sub>devo</sub> = 300 mg/kg/day NOAEL <sub>mat</sub> = 100 mg/kg/day
Genetic toxicity	Negative	Negative/	Negative
Carcinogenicity	Positive	Possible	Possible

Abbreviations: MW, molecular weight (g/mol); NA, not available

### 7.2.3 Risk characterization of subgroup 2 (MIBK, MIAK, and DAA)

#### MIBK

MIBK is classified as a Category 2B carcinogen (“possibly carcinogenic to humans”) by IARC (2013), based on increased incidences of tumors in 2 year studies in rats and mice. Although some evidence suggested that the liver and kidney tumors may not be relevant to human, recent analyses by NICNAS (2017) have concluded that, while the evidence supports the liver tumours in mice arising from activation of the constitutive androstane receptor (CAR), a mechanism other than that involving  $\alpha$ 2u-globulin may be responsible for the renal tumours in rats. This information, along with the observation of mononuclear leukaemia in male rats and the renal mesenchymal tumours in female rats, support the conclusion that the tumours in rats are relevant to humans and are sufficient to classify MIBK as a Category 2 carcinogen according to the GHS (NICNAS 2017). However, MIBK is not expected to be genotoxic (NTP 2007b; IARC 2013).

The chronic inhalation LOAEC for non-cancer effects was established at 1843 mg/m<sup>3</sup>, based on minimal to mild nephropathy in the 2-year bioassay (NTP 2007b).

The available data from short-term MIBK inhalation studies in animals indicate that developmental effects were the critical health effects. A NOAEC of 4106 mg/m<sup>3</sup> was identified for developmental effects in mice and rats (Tyl et al. 1987 as cited in US EPA IRIS 2003b). The corresponding calculated NOAEC<sub>HEC</sub> for developmental effects was 1026 mg/m<sup>3</sup> for continuous exposure.

For the oral route, in light of the uncertainties regarding the adversity of the effects observed in the subchronic oral studies, for characterization of risk following longer term oral exposure, the LOAEC from the more recent, comprehensive inhalation study by the NTP (2007) is extrapolated to an oral dose of 101 mg/kg bw/day; route to route extrapolation is considered appropriate for the critical effects in the kidneys of male and female rats. In addition, NICNAS (2017) recently determined the renal effects observed in the 2 year study in rats to be relevant to humans.

In the only dermal study available, MIBK induced morphological changes to the skin and multiple organs in rats administered doses of 300 mg/kg-bw/day and higher for four months (Malysheva, 1988 as cited in NTP 2007b). Although only limited details were available for this study, the critical effect level of 300 mg/kg bw/day is supported by the effects observed in rats administered 250 mg/kg bw/day the 13 week oral study.

The predominant source of exposure to MIBK from environmental media and food for the general population is through the diet. Based on the available data, it is expected that the majority of the dietary exposure to MIBK results from its natural occurrence in foods.

MIBK is used in a number of products available to consumers, including rubbing alcohol, dry erase markers and a range of paint and do-it-yourself products. Table 7-11 provides all the relevant exposure values and the critical health effects as well as the resultant MOEs for the characterization of risk for MIBK.

**Table 7-11. Relevant exposure and hazard values for MIBK, as well as margins of exposure, for characterization of risk.**

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Environmental media	2.5 – 7.5 µg/kg-bw/day	LOEL/NOAEL = 101 mg/kg/day	Renal effects in rats (hyperplasia, nephropathy, mineralization) in 2 year study (R2R from inhalation study)	13 467 – 40 400
Food flavouring	0.03 – 0.12 µg/kg-bw/day	LOEL/NOAEL = 101 mg/kg/day	Renal effects in rats (hyperplasia, nephropathy, mineralization) in 2 year study	≥ 850 000

			(R2R from inhalation study)	
Rubbing alcohol (inhalation)	6-hr TWA <sup>a</sup> = 0.001 mg/m <sup>3</sup>	NOAEC = 4106 mg/m <sup>3</sup>	Skeletal variations in mice and rats and reduced foetal body weight and increased foetal death in mice	4 106 000
Wood lacquer (inhalation)	6-hr TWA <sup>a</sup> = 45 – 433 mg/m <sup>3</sup>	NOAEC = 4106 mg/m <sup>3</sup>	Skeletal variations in mice and rats and reduced foetal body weight and increased foetal death in mice	9 – 91
Liquid paint (solvent-rich) for trucks (inhalation)	6-hr TWA <sup>a</sup> = 48 mg/m <sup>3</sup>	NOAEC = 4106 mg/m <sup>3</sup>	Skeletal variations in mice and rats and reduced foetal body weight and increased foetal death in mice	86
Spray paint (inhalation)	6-hr TWA <sup>a</sup> = 0.4 – 83 mg/m <sup>3</sup>	NOAEC = 4106 mg/m <sup>3</sup>	Skeletal variations in mice and rats and reduced foetal body weight and increased foetal death in mice	49 – 10 265
Filler/putty from tube (inhalation)	6-hr TWA <sup>a</sup> = 1 – 6 mg/m <sup>3</sup>	NOAEC = 4106 mg/m <sup>3</sup>	Skeletal variations in mice and rats and reduced foetal body weight and increased foetal death in mice	684 – 4 106
Dry erase markers (per event) [oral]	0.48 mg/kg-bw (child) 0.97 mg/kg-bw (toddler)	LOEL = 300 mg/kg/day	Morphological changes in several tissues at lowest dose tested in a 4-month dermal study.	309 – 625

		LOEL/NOAEL = 250 mg/kg/day	Hepatic and renal effects at 1000 mg/kg-bw/d in a 13-week oral study.	258 – 520
Dry erase markers [inhalation]	6-hr TWA <sup>a</sup> = 0.45 mg/m <sup>3</sup>	NOAEC = 4106 mg/m <sup>3</sup>	Skeletal variations in mice and rats and reduced foetal body weight and increased foetal death in mice	9 124

<sup>a</sup>Six-hour TWA concentrations were derived for all product scenarios to match up with the exposure durations of the critical effects study used to characterize risk.

Calculated MOEs for exposure to MIBK in environmental media and food (flavouring agent) are considered adequate to address any uncertainties in the health effects and exposure databases. Additional intake of MIBK from its natural occurrence in food was not identified as a concern for human health. Furthermore, the JECFA (WHO 1999b) concluded "No safety concern with the estimated levels of intake as flavouring substances" for MIBK used as a flavouring agent based primarily on it being "metabolized to innocuous products". The MOEs for inhalation exposure to MIBK in some products available to consumers, namely wood lacquer, liquid paint, and spray paints are considered potentially inadequate in light of the severity of the observed effects (i.e., developmental toxicity) and uncertainty regarding the adversity of effects observed at lower concentrations.

## MIAK

No chronic studies were identified for MIAK. MIAK was not genotoxic in a variety of studies.

Subchronic exposure to MIAK induced liver and kidney effects (organ weight and histological changes) in rats exposed to concentrations of 4670 mg/m<sup>3</sup> or higher. The NOEC was determined to be 934 mg/m<sup>3</sup> (Katz et al. 1986; ECHA c-2007-2017b). With respect to oral exposure, in the only repeated dose oral study identified only a very high dose was tested (2000 mg/kg-bw/day), which was associated with a wide range of effects. Therefore, an oral NOEL of 52 mg/kg bw/day was derived using route-to-route extrapolation from the inhalation study, given the similarity effects on liver and kidney by both routes of exposure.

With respect to short-term inhalation exposure to MIAK, a NOAEC of 1775 mg/m<sup>3</sup> was used to characterize the risk based on maternal systemic effects observed at 3503 mg/m<sup>3</sup> and above in a developmental toxicity study (reduced reactivity to noise stimulus concentrations, decreased body weights, body weight gains and food consumption ) (ECHA c-2007-2017b).

The predominant source of exposure to MIAK from environmental media and food is from its natural presence in certain foods, and to a lesser extent in indoor air.

MIAK is also used in a few paint products available to consumers. Table 7-12 provides all relevant exposure estimates and critical effect values, as well as resulting MOEs.

**Table 7-12. Relevant exposure and hazard values for MIAK, as well as margins of exposure, for characterization of risk.**

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Environmental media	0.3 – 0.9 µg/kg-bw/day	NOEL = 52 mg/kg/day	Route-to-route extrapolation from NOEC = 934 mg/m <sup>3</sup>	≥ 57 778
Spray paint (inhalation)	6-hr TWA <sup>a</sup> = 3 – 19 mg/m <sup>3</sup>	NOAEC = 1775 mg/m <sup>3</sup>	Significant decreases of mean body weights, mean body weight gains and corresponding mean food consumption in dams at 7005 mg/m <sup>3</sup> , while reduced reactivity to a noise stimulus at 3503 mg/m <sup>3</sup>	93 – 592

<sup>a</sup>Six-hour TWA concentrations were derived for the spray paint scenario to match up with the exposure durations of the critical effect study used to characterize risk.

Calculated MOEs for exposure to MIAK in environmental media are considered adequate to address any uncertainties in the health effects and exposure databases. Additional intake of MIAK from its natural occurrence in food was not identified as a concern for human health. The MOEs for inhalation exposure to MIAK in spray paints available to consumers is considered adequate to address uncertainties in the health effects and exposure databases.

## DAA

No chronic studies were identified for DAA. An oral NOAEL of 100 mg/kg-bw/day for the systemic toxicity (kidney changes and altered hematological and blood chemistry in rats), from the reproductive/developmental study, is used to address the risk to chronic exposure to DAA (MHW, 1997 as cited in OECD 2000; ECHA c-2007-2017a). In the

absence of dermal studies, route-to-route extrapolation using the oral NOAEL is used to characterize the risk to dermal exposition of DAA.

In the only inhalation study in animals identified, only liver weight changes not associated with histological alterations were observed at 1041 mg/m<sup>3</sup> (reported as 1035 mg/m<sup>3</sup> by OECD 2000) in a 6-week inhalation study (Butterworth et al. 1980 as cited in ECHA c2007-2017a).

The reproductive and developmental NOAEL was established at 300 mg/kg-bw/day based on effects on numerous reproductive and developmental parameters at 1000 mg/kg-bw/day. In order to be protective of the developing foetus and children, a critical effect level of 300 mg/kg-bw/day is used to characterize risk for short-term use of products available to consumers. In the absence of dermal or inhalation reproductive/developmental studies on DAA, the oral NOAEL of 300 mg/kg bw/day was used.

The primary source of exposure to DAA from environmental media and food is from its natural occurrence in various food items.

DAA is used in a range of products available to consumers, including nail care products and permanent markers, pipe thread sealant, floor coatings, thinner, and spray products including paint removers and automotive cleaners.

Table 7-13 provides all relevant exposure estimates and critical effect values, as well as resulting margins of exposure (MOEs). Although limited, available dermal absorption data suggest that DAA is not extensively absorbed through the skin (less than 1% to approximately 6% in humans); therefore, the dermal estimates below incorporate a 6% dermal absorption value. Given that the same oral health effects study is being used to characterize risks from both potential dermal and inhalation exposures to DAA from use of products available to consumers, these exposure estimates were combined.

**Table 7-13. Relevant exposure and hazard values for DAA, as well as margins of exposure, for characterization of risk.**

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Cosmetics (inhalation)	6-hr TWA = 0.3 – 1.3 mg/m <sup>3</sup>	NOAEC = 1035 mg/m <sup>3</sup>	Liver weight changes without histopathological alterations at 4685 mg/m <sup>3</sup>	796 – 3450
Cosmetics (dermal)	0.007 – 0.016 mg/kg-bw/day	NOAEL = 100 mg/kg/day	Kidney changes and altered hematological and blood chemistry	6 250 – 14 286

Paint/DIY products (inhalation and dermal)	0.053 – 2.5 mg/kg-bw/day	NOAEL = 300 mg/kg/day	Reproductive and developmental effects	120 – 5 660
Permanent markers (per event) [oral]	1.6 mg/kg-bw (child) 3.23 mg/kg-bw (toddler)	NOAEL = 300 mg/kg/day	Reproductive and developmental effects at 1000 mg/kg-bw/day	93 – 188
Permanent markers (daily) [dermal]	0.00244 – 0.05 mg/kg-bw/day	NOAEL = 100 mg/kg/day	Kidney changes and altered hematological and blood chemistry	1 250 – 2 500

Calculated MOEs for exposure to DAA in environmental media, and from use of products available to consumers, including the assumption of 100% DAA in permanent markers and the non-statistically significant changes in reproductive and developmental parameters used to characterize the risk associated with use of markers and paint/DIY products, calculated margins of exposure are considered adequate to address uncertainties in the health effects and exposure databases. Additional intake of DAA from its natural occurrence in food was not identified as a concern for human health.

#### 7.2.4 Uncertainties in evaluation of risk to human health for MIBK, MIAK and DAA

The key sources of uncertainty are presented in the table below. Confidence is high that use of the maximum concentrations and the high end of the range of product amounts from these types of products do not underestimate general population exposures.

For MIBK, although the MOEs for chronic exposures are based on non-cancer effects, confidence is high that they are also protective of the carcinogenicity of MIBK in light of a likely non-genotoxic mode of action.

For MIAK, the MOE for use of spray paints is considered adequate in light of the minimal maternal effects in the critical developmental toxicity effects study and the conservativeness of exposure estimate.

In terms of the risk from use of products available to consumers for DAA, confidence in the adequacy of the margins is high in light of the conservativeness associated with the dermal absorption value and the non-statistically significant effects on reproductive and developmental parameters at the critical effect level.

**Table 7-14. Sources of uncertainty in the risk characterization.**

Key sources of uncertainty	Impact
Assumption that dermal exposures are minimal for MIBK and MIAK in comparison to inhalation exposures, given the high volatility of the substances; however, confidence is high that exposure is overestimated in light of the conservative nature of the exposure models.	+
Assumption that DAA is present in permanent markers at a concentration of 100%	+
Lack of chronic studies for MIAK or DAA.	-
There are uncertainties associated with the selection of effect levels for characterization of risk of MIBK from inhalation and oral exposure.	-
Use of route-to-route extrapolation 96-day inhalation study for both oral and dermal exposure scenario for MIAK.	+/-
No short-term inhalation study was available for DAA. Route-to-route from oral study was applied.	+/-

+ = 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.

## 7.3 Assessment of subgroup 3 (diacetyl, 2,3-PD, and acetoin)

### 7.3.1 Exposure assessment of subgroup 3 (diacetyl, 2,3-PD, and acetoin)

#### Environmental media

No empirical data were identified for diacetyl, 2,3-PD or acetoin in air, water and soil in Canada.

Diacetyl has been identified as a by-product of ozone disinfection, and was detected in drinking water and in surface water (HSDB 1983-). No data were identified regarding the presence of diacetyl in soil or sediment; however, based on its low log Koc, diacetyl is not expected to be present in this media.

Only one ambient air study was identified that detected 2,3-PD in air in Roseville, California, in the summer and winter at concentrations of 11.1 and 8.1 ng/cm<sup>3</sup>, respectively (HSDB 1983-). No other environmental concentration data were identified elsewhere.

Based on its physical and chemical properties, acetoin may be present in air and water but is not likely to be present in soil and sediment. Based on its moderate Henry's Law Constant, acetoin is expected to volatilize from water. The half-life in air is approximately 37 hours (HSDB 1983-).

ChemCAN was run to derive potential environmental concentrations of diacetyl, 2,3-PD, and acetoin for Canada using the upper-end volume data from Table 4-1. These concentrations were used to estimate exposure to diacetyl, 2,3-PD, and acetoin from environmental media for the general population of Canada. All resulting exposures were

less than 2.5 ng/kg-bw/day. Based on the the information presented above, exposure to these substances from environmental media is not expected.

## Food

Diacetyl, 2,3-PD and acetoin are naturally present in various food items and may also be used as flavouring ingredients (Nijssen et al. 1963-2016, Burdock 2010). Diacetyl is being replaced in some products by 2,3-PD, acetoin and other diketones with a similar “butter” aroma and taste (Gaffney et al. 2015, Doepper et al. 2012, CDC 2016).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated a group of aliphatic acyclic and alicyclic alpha-diketones and related alpha-hydroxyketones including diacetyl, 2,3-PD and acetoin (WHO 1999a). As part of that evaluation, the Committee estimated the per capita intake for diacetyl, 2,3-PD and acetoin from their use as food flavouring agents. For the U.S. population, per capita intake estimates are 133 µg/kg-bw/day, 1 µg/kg-bw/day, and 29 µg/kg-bw/day, respectively. For the European population, per capita intake estimates are 56 µg/kg-bw/day, 4 µg/kg-bw/day, and 46 µg/kg-bw/day, respectively (WHO 1999a) (see Appendix A for more details).

Quantitative exposure estimates for diacetyl, 2,3-PD and acetoin from its natural occurrence in food<sup>9</sup> ranged from 281 µg/kg-bw per day for 14 to 18 year old to 1625 µg/kg-bw per day for 1 year olds for diacetyl, from 6.5 µg/kg-bw per day for 6 to 12 month olds to 208 µg/kg-bw per day for adults 19 years and older for 2,3-PD, and from 161 µg/kg-bw per day for 14 to 18 year olds to 369 µg/kg-bw per day for 2-3 year olds for acetoin (see Appendix A for details).

The estimates of daily intake for diacetyl from its natural occurrence in food are based primarily on the high level in pasteurized milk identified in the literature (approximately 30 µg/g) (De Leonardis et al. 2013). Higher levels of diacetyl have been reported in raw milk and ultra-high temperature milk (UHT) (Macciola et al. 2008, De Leonardis et al. 2013). However, other studies reported diacetyl concentrations in milk ranging from 0.0002 to 0.024 µg/g (Nijssen et al. 1963-2016, Toso et al. 2002, Shimoda et al. 2000, Valero et al. 2001, Imhof et al. 1995). Assuming levels of diacetyl in milk in Canada are similar to those in Europe, the highest value in pasteurized milk (semi-skim) from the De Leonardis et al. (2013) study was selected. The authors explain that the analytical method that was used in this study extracts the diacetyl that is linked primarily to the proteins and lactose found in the milk. The other studies used headspace techniques which only capture the volatile portion of the substance in the food (De Leonardis et al. 2013).

In addition to oral exposures to these substances, it is possible that, for certain food items such as microwaved popcorn, inhalation exposures may also be important.

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<sup>9</sup> Infants 0 to 6 months old are assumed to be exclusively breast-fed or formula-fed.

According to Rosati et al. (2007), diacetyl and acetoin were measured in a chamber air study with concentrations in the chamber air ranging from 0.02 to 5.8 mg/m<sup>3</sup> and 0.01 to 4.2 mg/m<sup>3</sup> for diacetyl and acetoin, respectively. The average amount of diacetyl emitted from a bag of microwaved popcorn was 778.9 µg/bag (Rosati et al. 2007). Based on information from Rosati et al. (2007) and an approach outlined in Zhu et al. (2001), for diacetyl, this converts to approximately 0.03 mg/m<sup>3</sup> in a standard room 1 hour after popping the popcorn (maximum of 0.04 mg/m<sup>3</sup> during the first hour after popping) (see Appendix C). Diacetyl and 2,3-PD have also been measured in coffee roasting plants (McCoy et al. 2017) and diacetyl was measured in a study designed to simulate exposures that could occur in a small coffee shop (Pierce et al. 2015)

### Products available to consumers

Diacetyl was not listed in any cosmetics notified to Health Canada; however, it was identified in a hair styling product available in Canada at 0.1-1% (SDS 2008a). 2,3-PD was identified in certain air fresheners for home care, and in fragrant oils which can be used as an air freshener (SDS 2016a, 2015 a,b). Table 7-15 summarizes the estimated inhalation exposures for products available to consumers containing diacetyl or 2,3-PD. Although dermal exposure could contribute to the overall exposure during use of products available to consumers, the primary route is considered to be inhalation; therefore, only inhalation estimates are presented. Acetoin was not identified in any other products available to consumers in Canada.

**Table 7-15. Estimated exposures to diacetyl and 2,3-PD from the use of products available to consumers.**

Product scenario	Concentration range	Mean event concentration (mg/m <sup>3</sup> )	Mean concentration on day of exposure (mg/m <sup>3</sup> )
Hair styling product (diacetyl)	0.1 – 1%	0.24 – 2.4	0.002 – 0.016
Air freshener <sup>a</sup> (2,3-PD)	0.1-5%	0.0031 – 0.064	0.0011 – 0.035

<sup>a</sup> Includes use of essential oils as air fresheners, as well as plug-in and gel type air fresheners.

### 7.3.2 Health effects assessment of subgroup 3 (diacetyl, 2,3-PD, and acetoin)

Diacetyl and 2,3-PD are alpha-diketones and their structures are identical except for an additional methyl group on 2,3-PD. Diacetyl, 2,3-PD and acetoin are all used in the food flavouring industry. The similarity in the structures and functional groups in diacetyl and 2,3-PD is reflected in their comparable physicochemical properties and similar buttery flavour and sensory sensation. 2,3-PD is expected to be similarly readily bioavailable via the oral, dermal, and inhalation routes as diacetyl and the impact of the additional

methyl group in 2,3-PD is expected to be minimal. Both chemicals exhibit portal-of-entry effects to respiratory tract following inhalation exposure. Following oral exposure diacetyl is rapidly metabolized in liver to acetoin and 2,3-butanediol. For 2,3-PD the OECD QSAR Toolbox v4 *in vivo* and *in vitro* rat liver metabolism simulator predicted metabolites 2-hydroxy-3-pentanone, 3-hydroxy-2-pentanone and 2,3-pentanediol (among others) that were similar in structure to metabolites of diacetyl. Based on this information, diacetyl, acetoin and 2,3-PD were treated as a group and toxicity data for these substances were used to read-across within the group.

### 7.3.2.1 Diacetyl

Diacetyl has been reviewed by IPCS (1999), EFSA (2004), SCOEL (2014), CDC (2016). These reviews provide a basis for the health effect characterisation in this draft screening assessment. A literature search has been conducted from a year prior to the CDC report (2016) up to July 2017 and significant new information is included to support risk characterisation.

#### Toxicokinetics

Diacetyl can be generated endogenously and is a metabolite of acetaldehyde in mammals (IPCS 1999; SCOEL 2014). It is anticipated that methyl ketones are principally metabolized by oxidation of the terminal methyl group at low concentrations. At higher levels, diacetyl is reduced to acetoin, 2,3-butanediol and then conjugated with glucuronic acid and excreted. A computational fluid dynamics-physiologically based pharmacokinetic model has been developed to compare diacetyl absorption and tissue concentrations in the rat and human respiratory tracts (Gloede et al. 2011). The model estimated that the bronchiolar tissue concentrations of diacetyl in the human during light exercise exceeded those in the rat by 20 to 40 fold. Further dosimetry modeling indicated that rat inhalation toxicity studies under-predict the risk of bronchiolar injury in the human (Cichocki and Morris 2017).

#### Carcinogenicity and chronic toxicity

Diacetyl has not been classified by any agency on the basis of carcinogenicity or other health effects. However, recent NTP studies (NTP 2017a) demonstrated some evidence of carcinogenic activity in 2-year inhalation studies. Groups of Wistar Han rats and B6C3F1/N mice were exposed to diacetyl vapor by whole body inhalation at concentrations of 0, 12.5, 25, or 50 ppm (0, 45, 90, 179 mg/m<sup>3</sup>) 6 hours per day, 5 days per week for 105 weeks. In rats, there were increases in the incidences of squamous cell carcinomas of the nasal cavity in males and females and in the combined incidence of squamous cell carcinomas and papilloma in the nasal cavity of males at 179 mg/m<sup>3</sup>. In mice, the incidence of adenocarcinoma of the nose was increased in females at this concentration. NTP concluded that “There was *some evidence of carcinogenic activity* of diacetyl in male and female rats. There was *no evidence of carcinogenic activity* of diacetyl in male B6C3F1/N mice exposed to 12.5, 25, or 50 ppm. There

was equivocal evidence of carcinogenic activity of diacetyl in female B6C3F1/N mice based on the occurrences of adenocarcinoma of the nose" (NTP 2017a).

Exposure to diacetyl also resulted in increased incidences of non-cancer effects in the nose, larynx, trachea and lung of mice at all concentrations tested and in rats at 25 and 50 ppm, with more severe effects on the respiratory system occurring at higher concentrations in mice and rats. In rats, the nasal lesions with significantly increased incidences included suppurative inflammation, respiratory epithelium hyperplasia and squamous metaplasia, olfactory epithelium atrophy, respiratory metaplasia, and necrosis (males), turbinate hyperostosis, and fibrosis of the lamina propria. Significantly increased incidences of chronic active or suppurative inflammation and epithelium hyperplasia were also observed in the larynx, trachea, lung and eye at 50 ppm. At 25 ppm, significantly increased incidences were observed for squamous epithelium hyperplasia in larynx (male and female), epithelium regeneration in trachea (male) and epithelium hyperplasia in lung (female). In mice, similar effects were observed at 12.5 ppm and also included metaplasia of the respiratory epithelium, atrophy of olfactory epithelium and turbinate atrophy in the nose, and squamous epithelium hyperplasia in the larynx. Survival rate was moderately decreased in females at 25 ppm and significantly decreased in males at 50 ppm. At the end of the study, mean body weights were decreased for both males and females at 50 ppm compared with controls. Thus a chronic inhalation LOAEC of 12.5 ppm (45 mg/m<sup>3</sup>) is considered based on these observations of non-cancer effects observed at 12.5 ppm in mice and 25 ppm in rats (NTP 2017a).

Available information indicated that diacetyl is mutagenic in a variety of in vitro test (More et al. 2012, Kato et al. 1989, Bjeldanes and Chew 1979; Marnett et al. 1985; Shane et al. 1988; Dorado et al. 1992; Aeschbacher et al. 1989, reviewed in EFSA 2004 and NTP 2017a). However, diacetyl was negative in the SOS-chromotest in *E. coli* (Von der Hude et al. 1988) and did not induce chromosome aberration in *S. cerevisiae* (Zimmermann and Mohr 1992).

### **Repeat dose toxicity**

A profile of effects similar to that seen in the chronic bioassay was observed in subchronic inhalation studies in Wistar Han rats and B6C3F1/N mice. A NOAEC of 12.5 ppm (45 mg/m<sup>3</sup>) was derived based on significant increase in incidence of nonneoplastic lesions in the respiratory tracts (nose, larynx, trachea and lung) of mice and rats, primarily in the 50 and 100 ppm group after 14 weeks. At 25 ppm, increased incidences of squamous metaplasia of the respiratory epithelium were observed in male and female rats along with increased degeneration of the olfactory epithelium in female rats. In mice, there were increased incidences of necrosis in respiratory epithelium in males and females at 25 ppm; increased hyperplasia and chronic active inflammation were also observed in larynx in females (NTP 2017a). Similar effects were reported in an earlier study in mice exposed diacetyl for 6 or 12 weeks to 25 ppm or more; the lowest concentration tested (25 ppm or 90 mg/m<sup>3</sup>) was considered to be the LOAEC,

based on the significant epithelial injury and peribronchial lymphocytic inflammation (Morgan et al. 2008).

In an oral repeat dose toxicity study, male and female CFE rats were administered 0, 10, 30, 90 or 540 mg/kg-bw/day of diacetyl in water by oral intubation for 90 days. At the highest dose of 540 mg/kg-bw/day, rats had decreased body weight gain and increased water consumption. Effects observed included anaemia, an increased leucocyte counts and an increase in relative weights of brain, liver, kidney, adrenals and pituitary glands (organ weight increases were greater than changes likely to be associated with decreased body weight). Ulcers in both squamous and glandular parts of the stomach mucosa were observed. No adverse effects were noted in lower dose groups. However, slight, but not statistically significant, anaemia and increased relative weights of some organs were noted at lower doses in the absence of histopathological changes in the stomach. The authors concluded that the NOAEL of diacetyl in this study was 90 mg/kg-bw/day, although it is not clear whether the effects observed at 540 mg/kg-bw/day may have been secondary to the ulcer formation (Colley et al. 1969; reviewed in IPCS 1999; SCOEL 2014).

The results of another repeated-dose oral study suggest that diacetyl may induce neurological and reproductive effects (Bawazir 2016). Daily administration of 25 mg/kg-bw/day diacetyl to rats via oral tube during 4-week study resulted in changes in levels of several neurotransmitters in different areas of the brain as well as a decrease in serum testosterone levels. Histological changes in the testes, associated with a significant decrease in mature sperm and tubular deficit. However, the published account of this study was very limited and only one dose was tested.

### **Short term and acute toxicity**

Acute and short-term exposures to diacetyl vapour caused a wide range of nasal and olfactory lesions in rodents (Morgan et al 2008, Hubbs et al. 2002; Larsen et al. 2009; Morris and Hubbs 2009), affected sensory neurons (Goravanahally et al. 2014) and led to airway hyporeactivity (Zaccone et al. 2013).

Hubbs et al. (2008), exposed male Hla:(SD)CVF rats (6/exposure group) to diacetyl at concentrations over a 6 hour period as continuous exposure at time weighted average (TWA) concentrations of 0, 99.3, 198.4, or 294.6 ppm (0, 355, 710 or 1055 mg/m<sup>3</sup>), as 4 brief, intense exposures at TWA concentrations of 0, 122, 225, or 365 ppm (0, 437, 806 or 1307 mg/m<sup>3</sup>) or as a single 15 minute pulse exposure to a TWA concentration of 92.9 ppm (333 mg/m<sup>3</sup>). Both pulsed and continuous exposure patterns caused epithelial injuries including epithelial necrosis and suppurative/fibrinosuppurative inflammation in the nose, larynx, trachea, and bronchi. The most severe effect was observed in the nose. The larynx and trachea were affected at diacetyl concentrations of 225 ppm or higher and bronchi were affected at concentrations of 294.6 ppm or more. In rats exposed to the single 15 minute pulse exposure (TWA of 92.9 ppm), there were significant histological changes (i.e., necrosis) in the nose. The authors concluded

that the NOAEC for acute inhaled diacetyl was less than 93 ppm (333 mg/m<sup>3</sup>), considered here to be the LOAEC.

### **Reproductive and developmental toxicity**

In groups of CD-1 mice and albino Wistar rats administered diacetyl by gavage on days 6-15 of gestation at doses of up to 1600 mg/kg-bw/day, no effects were seen on maternal survival, weight, or reproductive parameters or on foetal survival or microscopic appearance of external, skeletal, or soft tissues. Similarly, no maternal or developmental effects were observed in hamsters administered doses up to 1600 mg/kg-bw/day on gestation days 6-10 (US FDA 1973; reviewed in WHO 1999a; EFSA 2004).

### **Human studies**

In several epidemiological studies, inhalation of diacetyl vapours and other ketones by workers at a microwave popcorn manufacturing plant or in the flavouring manufacturing companies has been consistently associated with the development of diverse respiratory impairment conditions such as obliterative bronchiolitis (OB), a rare disease of airway epithelial injury and airway fibrosis (Kreiss et al. 2002; Parmet and Von Essen 2002; van Rooy et al. 2007; CDC 2016). Several case reports, case series and cross-sectional studies have also been reviewed by EU (SCOEL 2014) and CDC (2016).

#### **7.3.2.2 2,3-Pentanedione**

2,3-Pentanedione (2,3-PD) has been reviewed by WHO/IPCS (1999), EFSA (2004) and CDC (2016). These reviews provide a basis for the health effect characterisation in this draft screening assessment. A literature search has been conducted from a year prior to the CDC (2016) up to July 2017 and significant new information is included to support risk characterisation.

### **Toxicokinetics**

Zaccone et al. (2015) showed that 2,3-PD could be metabolized to acetoin and 2,3-hydroxy-3-pentanone, respectively, by human airway epithelium.

### **Carcinogenicity and genotoxicity**

No carcinogenicity data were identified for 2,3-PD. Two studies showed that 2,3-PD was not mutagenic in *Salmonella* (Kim et al. 1987; Aeschbacher et al. 1989; reviewed in WHO1999 and EFSA 2004, 2016). 2,3-PD did not cause the formation of micronuclei in either rats or mice of both sexes (NTP 2017b).

### **Repeated dose toxicity**

In a repeated dose inhalation study, male and female Wistar Han rats and B6C3F1 mice were exposed to 2,3-PD by inhalation at concentrations of 0, 6.25, 12.5, 25, 50, or 100 ppm (0, 26, 51, 102, 205 or 409 mg/m<sup>3</sup>) 6 hours/day, 5 days/week for 14 weeks. Similar results to those reported in the subchronic study with diacetyl were observed. At 50 and 100 ppm, clinical observations were noted including abnormal breathing, sneezing and eye abnormality. Significantly increased incidences of non-neoplastic lesions occurred in the respiratory tracts of male and female rats, including epithelium hyperplasia in the nose and metaplasia in the larynx. At 25 ppm and above, the incidences of respiratory epithelium hyperplasia in the nose were significantly increased in males, while the incidences of respiratory epithelium metaplasia in the larynx were significantly increased in females. In mice, there were significant decreased body weight gain and changes in internal organ weights of both sexes (in the absence of histopathological alterations) at 50 ppm (205 mg/m<sup>3</sup>) and higher, along with increased incidences of non-neoplastic lesions of the respiratory tract. At 25 ppm, incidences of respiratory epithelium metaplasia and regeneration were significantly increased in male mice. The NTP considered the NOAEC for respiratory tract effects in both rats and mice to be 12.5 ppm (51 mg/m<sup>3</sup>) and the NOAEC for non-respiratory tract effects in mice to be 25 ppm (102 mg/m<sup>3</sup>) (NTP 2017b).

No oral repeat dose toxicity study was reported for 2,3-PD. Therefore, route-to-route extrapolation of the NOAEC for non-respiratory tract effects was carried out from the subchronic inhalation study on 2,3-PD to obtain a NOAEL of 24 mg/kg bw/day (see appendix D). The NOAEL from the oral subchronic study with diacetyl was also used in a read-across manner to estimate a NOAEL of 105 mg/kg-bw/day for 2,3-PD, as support for hazard characterization .

### **Acute and short term repeated dose toxicity**

Acute and short-term exposure to 2,3-PD for up to two weeks induced a range of histopathological lesions (including necrotizing rhinitis, tracheitis, mucosal inflammation, squamous metaplasia and regenerative changes, epithelial atrophy, exudate and lymphoid deposits) in nose, larynx, trachea and/or lungs of mice and rats at all concentrations tested. (Morgan et al. 2012; Hubbs et al. 2012; Zaccone et al. 2013; NTP 2017a).

#### **7.3.2.3 Acetoin**

Acetoin has been reviewed by WHO/IPCS (1999), EFSA (2004, 2016). These reviews provide a basis for the health effect characterisation in this draft screening assessment. A literature search has been conducted from a year prior to EFSA (2016) up to July 2017 and some information was identified in NTP draft technical report on carcinogenicity of diacetyl (NTP 2017a).

### **Toxicokinetics**

Acetoin is metabolised primarily via oxidation at low concentration *in vivo* and by reduction to 2,3-butanediol at high concentration (EFSA 2004; NTP 2007a).

### **Carcinogenicity and chronic toxicity**

In a screening test for pulmonary carcinogenicity of food additives, in which a limited number of tissues were evaluated, no increase in lung tumors was observed in strain A mice administered acetoin by intraperitoneal injection 3 times per week for 7 weeks (Stoner et al. 1973).

### **Genotoxicity**

Several studies indicated that acetoin was not mutagenic in *Salmonella* or *E. coli* (EFSA 2004; WHO 1999a; NTP 2017b).

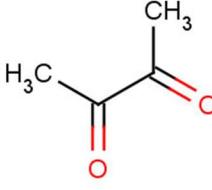
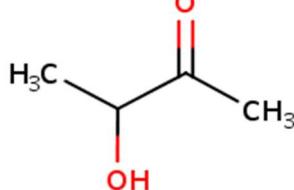
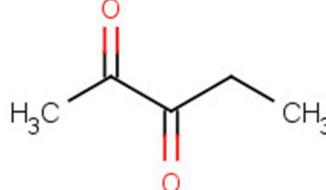
### **Repeat dose toxicity**

In an oral study, male and female CFE rats (15/group) were administered acetoin in the drinking water at concentrations of 0, 750, 3000, or 12000 ppm (equivalent to 0, 85, 330, or 1300 mg/kg-bw/day) for 13 weeks (Gaunt et al. 1972). At concentrations of 750 and 3000 ppm, no significant effects were observed with respect to body weight gain, haematological findings, serum chemistry, renal cell excretion, urinary concentration tests, organ weights or histopathology. At the highest concentration, body weights were significantly decreased in males from week 5 and relative liver weight was significantly increased at weeks 2, 6, and 13; females showed these effects after 13 weeks. These effects were not accompanied by any histopathologic changes and probably due to metabolic load from acetoin intake. Small but statistically significant decreases in hemoglobin concentration and erythrocyte counts were also observed at the high dose in both sexes. The authors concluded that the NOAEL was 3000 ppm in the drinking water (equivalent to 330 mg/kg-bw/day), based on the effects of decreased body weight gain and haematologic effects (Gaunt et al. 1972, reviewed in IPCS 1999).

Male and female Wistar Han rats and B6C3F1/N mice were exposed to acetoin by whole body inhalation at concentrations of up to 800 ppm (2883 mg/m<sup>3</sup>) 6 hours per day, 5 days/week for 14 weeks. No exposure related effects on survival, body weights, organ weights, clinical pathology, or histopathology were observed in either species following exposure to acetoin concentrations up to the highest concentration tested (i.e.c 800 ppm or 2883 mg/m<sup>3</sup>) (NTP 2017b).

**Table 7-16. Hazard information for Ketones Subgroup 3 (diacetyl, acetoin, 2,3-PD).**

Chemical name	Diacetyl	Acetoin	2,3-PD
Role	Target chemical	Target chemical	Target chemical
CAS#	431-03-8	513-86-0	600-14-6

Chemical structure			
	MW = 86.09	MW = 88.10	MW = 100.12
Acute toxicity (Lethality)	Oral LD <sub>50</sub> = 3000 mg/kg in rats	Oral LD <sub>50</sub> > 5000 mg/kg	Oral LD <sub>50</sub> = 3000 mg/kg in rats
Short term toxicity (inhalation, 6h, systemic effects)	LOAEC = 92.9 ppm (333 mg/m <sup>3</sup> )	NA	NOAEC = 112 ppm (459 mg/m <sup>3</sup> ) (respiratory & olfactory cytotoxicity).
Repeated dose toxicity (inhalation, < 2 wks)	LOAEC = 100 ppm (358 mg/m <sup>3</sup> ) the lowest test concentration in rats. LOAEC = 50 ppm (176 mg/m <sup>3</sup> ) (read across from 2,3-PD)	NA	LOAEC = 50 ppm (205 mg/m <sup>3</sup> ) (histopathological changes in rats and mice, 10-12 days).
Subchronic toxicity (90-day oral)	NOAEL = 90 mg/kg-bw/d	NOAEL= 330 mg/kg-bw/d (drinking water, (decreased body weight and anemia)	NOAEL = 105 mg/kg bw/d (read-across from diacetyl)  NOAEL = 24 mg/kg-bw/day (from non-respiratory tract effects in 90-day inhalation study)
Subchronic toxicity (90-day inhalation)	NOAEC = 12.5 ppm (45 mg/m <sup>3</sup> )	NOAEC = 800 ppm (2883 mg/m <sup>3</sup> ) the highest test concentration (NTP 2017b)	NOAEC = 12.5 ppm (51 mg/m <sup>3</sup> ) (histopathological effects in respiratory system in rats and mice; 14 weeks)
Subchronic toxicity (dermal)	NOAEL = 90 mg/kg bw/d (from oral exposure)	NOAEL = 330 mg/kg bw/d (Extrapolation from oral)	NOAEL = 105 mg/kg bw/d (read-across from diacetyl)
Chronic toxicity (inhalation)	LOAEC =12.5 ppm ( 45 mg/m <sup>3</sup> ) (squamous epithelium	NA	NA

	hyperplasia in larynx, trachea and lung)		
Developmental toxicity (Oral)	NOAEL = 1600 mg/kg bw/d	NOAEL = 1640 mg/kg bw/d (read-across from diacetyl)	NA
Genetic toxicity	Likely to be genotoxic	Genotoxic potential is low	Likely to be genotoxic (read across from diacetyl)
Carcinogenicity	Some evidence for carcinogenicity in chronic animal studies	Low potential	Some evidence for carcinogenicity in chronic animal studies (read across from diacetyl)

Abbreviations: NA, Not available; MW, molecular weight (g/mol)

### 7.3.3 Risk characterization of subgroup 3 (diacetyl, 2,3-PD, and acetoin)

#### Diacetyl

Although diacetyl has not been classified by any agency on the basis of carcinogenicity or other health effects, recent NTP studies (2017a) demonstrated some evidence of carcinogenic activity in 2-year inhalation studies in mice and rats, with significant increases in incidences of nasal tumours at 179 mg/m<sup>3</sup>. Evidence also indicates that diacetyl is likely genotoxic. Chronic exposure to diacetyl also resulted in increased incidences of non-cancer effects in the nose, larynx, trachea and lung of mice at all concentrations tested (LOAEC of 45 mg/m<sup>3</sup>), with more severe effects on the respiratory system occurring at higher concentrations in mice and rats. A similar spectrum of respiratory tract effects were also observed in subchronic, short term and acute studies in rodents. Both pulsed and continuous exposure to diacetyl for as short a duration as 15 minutes caused epithelial injuries, with the NOAEC for acute inhaled diacetyl considered to be less than 333 mg/m<sup>3</sup> (Hubbs et al. 2008).

The available database in regards to the toxicity of oral exposure to diacetyl is more limited. In a subchronic study in rats, effects on haematological parameters and several organ weights were noted at 540 mg/kg bw/day (NOAEL of 90 mg/kg bw/day), which may have been secondary to the observed stomach ulceration (Colley et al. 1969; reviewed in IPCS 1999; EFSA 2004; SCOEL 2014). In light of the limitations of the other oral studies identified (Bawarzi 2016; US FDA 1973; reviewed in IPCS 1999; EFSA 2004) and the systemic oral NOAEL of 330 mg/kg-bw/day reported for acetoin (a metabolite of diacetyl which has been demonstrated to be less potent than diacetyl in studies involving similar protocols), in a drinking water study (Gaunt et al., 1972), it is suggested that the true NOAEL for diacetyl could potentially be between 90 and 330 mg/kg-bw/day.

Several lines of evidence demonstrate that the effects observed in inhalation studies in laboratory animals are relevant to humans and support the conclusion of the epidemiologically based quantitative risk assessment for diacetyl (CDC 2016), based on reports of the development of diverse respiratory impairment in workers at a microwave popcorn or flavouring manufacturing plants<sup>10</sup> (Kreiss et al. 2002; Parmet and Von Essen 2002; van Rooy et al. 2007). However, dosimetry modelling estimates suggest that tissue concentrations of diacetyl in the respiratory tract of humans might be 20 to 40-fold greater than those in exposed rodents (Gloede et al. 2011) and that bioassay data might underestimate the risk to humans (Cichocki and Morris 2017).

The predominant source of exposure to diacetyl for the general population is through the diet. The estimated intake from the use of diacetyl as a possible flavouring agent in foods (56 – 133 µg/kg-bw/day) is less than intakes that have been estimated from natural occurrence (–281 - 1625 µg/kg-bw/day) for this substance. The JECFA (WHO 1999a) concluded "No safety concern at current levels of intake when used as a flavouring agent; secondary components do not raise a safety concern" based on the dietary exposure estimates for substances in this flavouring grouping. Considering the true NOAEL for diacetyl is likely between 90 and 330 mg/kg-bw/day and effects are likely linked to ulcer formations in the stomach, the calculated margins of exposure ( $\leq$  54 and 199 and higher) are considered adequate to account for uncertainties in the databases.

Given the wide use of diacetyl as a flavoring agent including in microwave popcorn, potential inhalation exposures were calculated. Diacetyl was also found in a hair styling product that can be purchased in Canada. Table 7-17 provides all relevant exposure values and the critical health effects for diacetyl as well as the resulting MOEs for the characterization of risk.

**Table 7-17. Relevant exposure and hazard values for diacetyl, as well as margins of exposure, for characterization of risk.**

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Inhalation of microwave popcorn	Conc. After 15 min. = 0.04 mg/m <sup>3</sup>	LOAEC = 333 mg/m <sup>3</sup>	Nasal and laryngeal effects (necrosis/inflammation in epithelium)	8325
Cosmetics (inhalation)	6-hr TWA = 0.008 – 0.064 mg/m <sup>3</sup>	LOAEC = 45 mg/m <sup>3</sup>	Nasal effects (exudate and atrophy of the olfactory epithelium)	703 – 5625

<sup>10</sup> Based on the epidemiological studies, NIOSH recommended a REL of 5 ppb as a time-weighted average for up to 8 hours/day and a short-term exposure limit (STEL) of 25 ppb for a 15 minute time period in occupational settings (CDC 2016).

The MOEs for inhalation exposure to diacetyl from microwave popcorn and from its use in a hair styling product available to consumers, are considered adequate to account for uncertainties in the databases.

## 2,3-PD

No carcinogenicity data were identified for 2,3-PD..

Based on preliminary results of a subchronic inhalation study in rats and mice (NTP 2017b), similar to observations with diacetyl, the respiratory tract (the nasal passage and larynx in particular) is the target of 2,3-PD induced toxicity. The incidences of non-neoplastic lesions were significantly increased in rats and mice at concentrations of 102 mg/m<sup>3</sup> and above (NOAEC = 51 mg/m<sup>3</sup>). Similar results were reported in shorter term studies with a LOAEC of 205 mg/m<sup>3</sup>, the lowest concentration tested (Morgan et al., 2012).

Although effects observed in mice and rats exposed to 2,3-PD were located mainly to the respiratory tract, systemic effects (decreased mean body weight gain and organ weights) were also observed at 205 mg/m<sup>3</sup> and higher in the absence of histopathological alterations. Therefore, with respect to oral exposures, route-to-route extrapolation from the subchronic inhalation study, resulting in a NOAEL of 24 mg/kg-bw/day for non-respiratory tract effects, and read-across from the subchronic oral study with diacetyl, resulting in a NOAEL of 105 mg/kg-bw/day, were used to characterize the risk of ingested 2,3-PD.

The predominant source of exposure to 2,3-PD for the general population is through the diet primarily from its natural occurrence in foods. The estimated intake from the use of 2,3-PD as a possible flavouring agent in foods (1 – 4 µg/kg-bw/day) is less than intakes that have been estimated from natural occurrence for this substance (6.5 – 208 µg/kg-bw/day). Although the MOE associated with an oral NOAEL of 24 mg/kg-bw/day based on route-to-route extrapolation is low, in light of the absence of the histopathological changes in internal organs and the conservative approaches used in estimating exposure to 2,3-PD naturally occurring in food, the calculated MOEs, ranging from 115 to 16 154, are considered adequate to address uncertainties in the health effects and exposure databases. The MOEs would be slightly lower, but still considered adequate, if the estimated intake from the use of 2,3-PD as a possible flavouring agent in foods was combined with the natural occurrence in food. Furthermore, the JECFA (WHO 1999a) concluded "No safety concern at current levels of intake when used as a flavouring agent; secondary components do not raise a safety concern" based on the dietary exposure estimates for 2,3-PD.

2,3-PD was also identified in products available to consumers, including certain continuous air fresheners for home care, and in fragrant oils which can be used as an air freshener. Comparison of the 6-hr TWA estimated exposures from use of air

fresheners containing 2,3-PD (0.004 – 0.14 mg/m<sup>3</sup>) with the NOAEC of 51 mg/m<sup>3</sup> resulted in MOEs ranging from 364 – 12 750 which are considered adequate to account for uncertainties in the databases.

## Acetoin

A limited number of toxicity studies were available for acetoin. Acetoin did not promote lung tumors in a limited screening test for carcinogenicity of food additives in mice (Stoner et al. 1973). Acetoin is not expected to be genotoxic.

To characterize the risk associated with oral exposure to acetoin, a NOAEL of 330 mg/kg-bw/day was used, based on changes in body weight and hematological parameters in a 13-week study (Gaunt et al. 1972, reviewed in IPCS 1999).

Based on a preliminary account of the results of an inhalation study, acetoin did not induce any effects in mice exposed to concentrations of up to 800 ppm (2883 mg/m<sup>3</sup>) for 14 weeks (NTP 2017b), which is considered to be the NOAEC.

The predominant source of exposure to acetoin for the general population is through the diet primarily from its natural occurrence in foods. The estimated intake from the use of acetoin as a possible flavouring agent in foods (29 – 46 µg/kg-bw/day) is less than intakes that have been estimated from natural occurrence for this substance (0.5 – 3.2 mg/kg-bw/day). On the basis of the conservative approaches used in estimating exposure to acetoin in food, calculated margins of exposure, ranging from 102 – 11 379, are considered adequate to address uncertainties in the health effects and exposure databases. Furthermore, the JECFA (WHO 1999a) concluded "No safety concern at current levels of intake when used as a flavouring agent; secondary components do not raise a safety concern" based on the dietary exposure estimates for substances in this flavouring grouping. In addition, potential inhalation exposures to acetoin in microwave popcorn were considered. Comparison of the conservative estimates of air concentrations of acetoin from popping microwave popcorn (10 – 4200 µg/m<sup>3</sup>) with the NOAEC of 2883 mg/m<sup>3</sup> resulted in MOEs ranging from 686 – 288 300 which are considered adequate to account for uncertainties in the databases.

### 7.3.4 Uncertainties in evaluation of risk to human health for diacetyl, 2,3-PD and acetoin

The key sources of uncertainty are presented in the table below. For diacetyl and 2,3-PD, while there is confidence that they induce adverse health effects following inhalation exposure, there is greater uncertainty regarding the toxicity of these substances following long term oral exposure, since ingestion in food is an important source of population exposure due to the natural occurrence of these diketones in food and their use as food flavouring agents. For acetoin, although the hazard database is limited, there is sufficient evidence to indicate that it is of lower toxicity than diacetyl; therefore there is confidence that risks to human health in Canada are likely to be low.

There is uncertainty on the natural presence of diacetyl in milk consumed by Canadians as well as the estimated daily intake derived for diacetyl based on a higher end concentration given the wide range in diacetyl concentrations in milk reported in the literature.

**Table 7-18. Sources of uncertainty in the risk characterization.**

Key sources of uncertainty	Impact
Absence or limited Canadian monitoring data in foods.	+/-
For the natural occurrence of diacetyl, 2,3-PD and acetoin in food, where a range of concentrations were available from the literature, maximum values were chosen except in the case of outliers.	+
The potential inhalation exposures to diacetyl when cooking with foods containing the substance, both natural sources and as a food flavouring agent.	-
Assumption that dermal exposures are minimal for diacetyl in comparison to inhalation exposures, given the high volatility of the substance;	-
Although direct evidence is limited, it was considered that hair styling products containing diacetyl may be available to the general population in Canada.	+
There are no chronic toxicity studies for acetoin and 2,3-PD and the overall database on acetoin is limited.	-
The database on the oral toxicity of diacetyl, 2,3-PD and acetoin is limited.	+/-
Uncertainties related to the relevance to humans of diacetyl-induced carcinogenicity and other respiratory toxicity in rats and mice via inhalation and the potential greater sensitivity of humans.	-
There are no dermal or inhalation absorption data identified.	+/-
<b>The use of diacetyl as read-across to assess data gap for 2,3-PD</b>	+/-

+ = 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.

## 7.4 Assessment of individual substance 2,4-PD

### 7.4.1 Exposure assessment

#### Environmental media

No data were identified on the presence of 2,4-PD in indoor or outdoor air, drinking water, or soil, in Canada or elsewhere. Based on its physical and chemical properties, if released into the environment, 2,4-PD is expected to be distributed mainly to water (~90%), and to a lesser extent into air (~10%); however, its moderate Henry's Law Constant and vapour pressure, indicate that 2,4-PD is likely to volatilize from water (HSDB 1983-, OECD 2001). 2,4-PD is likely to have high mobility in soil and not likely to adhere to sediment or suspended particles in water (HSDB 1983-).

The level III fugacity model known as ChemCAN (2003) was run to derive potential environmental concentrations of 2,4-PD for Canada using the upper-end volume data from Table 4-1 (i.e., 1 000 000 kg). The estimated concentration from air, water, soil and sediment was 5.4 ng/m<sup>3</sup>, 48.9 ng/L, 0.007 ng/g, and 0.003 ng/g, respectively. These concentrations were used to estimate exposure to 2,4-PD from environmental media for the general population of Canada. Concentrations of 2,4-PD derived from ChemCAN for soil and sediment were all in the nanogram range with resulting exposures less than 1 ng/kg/day and are therefore considered to be negligible.

Estimates of exposure for 2,4-PD from environmental media ranged from 0.002 µg/kg-bw per day for breast fed infants (0 to 6 months old) to 0.007 µg/kg-bw per day for formula fed infants (0 to 6 months old) (Health Canada 2018).

## Food

2,4-PD was identified as a volatile in a few food items including beef, chicken, coffee, mushrooms, papaya and passion fruit (Nijssen et al. 1963-2016). Quantitative data were only available for roasted chicken (0.004 ppm) and passion fruit juice (<0.01 ppm) and was used to estimate potential exposures to 2,4-PD from food for the general population of Canada. Quantitative exposure estimates for 2,4-PD from its natural occurrence in food<sup>11</sup> ranged from 0.02 µg/kg-bw per day for adults 19 years and older to 0.14 µg/kg-bw per day for 2 to 3 year olds (see Appendix A for details).

## Products used by consumers

2,4-PD is used as an additive in paints and coatings (OECD 2001, Environment Canada 2012, SDS 2012b). Most of these products were identified as being for commercial or industrial use only; however, some may be used by consumers (Environment Canada 2012, SDS 2012b). Inhalation and dermal exposure estimates were derived using ConsExpo Web (ConsExpo 2016) for coating a large surface such as a truck trailer or a boat containing 1 – 5% 2,4-PD (SDS 2012b, 2016b). Mean event concentrations ranged from 75 – 320 mg/m<sup>3</sup>, mean event concentrations on the day of exposure ranged from 3 – 13 mg/m<sup>3</sup>, and 6-hr TWA concentration ranged from 13 – 53 mg/m<sup>3</sup>. Dermal exposure estimates were 0.04 – 0.2 mg/kg-bw/day.

### 7.4.2 Health effects assessment

2,4-PD has been reviewed by OECD (2001) and EFSA (2004). These reviews provide a basis for the health effect characterisation in this draft screening assessment. A

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<sup>11</sup> Infants 0 to 6 months old are assumed to be exclusively breast-fed or formula-fed.

literature search has been conducted from a year prior to the OECD (2001) SIAR report up to June 2017 and significant new information is included to support risk characterisation.

## Toxicokinetics

, EFSA (2004) noted that the substance was expected to be readily absorbed from the gastrointestinal tract and widely distributed and metabolized, based on the structure and physicochemical characteristics. No toxicokinetic information was identified for dermal exposure of 2,4-PD.

## Carcinogenicity/chronic toxicity

In a two-year inhalation carcinogenicity study, F344 rats and B6D2F1 mice were exposed to 2,4-PD vapors at target concentrations of 0, 100, 200 or 400 ppm (0, 417, 834 or 1668 mg/m<sup>3</sup>) for 6 hours/day, 5 days/week for 2 years (JBRC, 2010a,b). In rats, non-neoplastic lesions were mainly located in the nasal cavity in both sexes at 200 ppm and above, including squamous metaplasia of the respiratory epithelium, inflammation hyperplasia of the transitional epithelium, and atrophy of the olfactory epithelium. Similarly, nasal cavity effects observed in mice included squamous metaplasia, eosinophilic change, ulcer, necrosis and transitional cell hyperplasia in the respiratory epithelium; atrophy, respiratory metaplasia, eosinophilic change, necrosis in the olfactory epithelium; and respiratory metaplasia in the sub-mucosal gland at 200 and 400 ppm, while exudate and atrophy in the olfactory epithelium occurred at all concentrations. Alterations in biochemical parameters were also noted in males and females at 200 and 400 ppm. Based on the nasal lesions, the study authors identified 100 ppm (417 mg/m<sup>3</sup>) to be the NOAEC in rats and the LOAEC in mice (JBRC 2010a,b). There were no significantly increased incidences of neoplastic lesions in the extensive range of tissues examined from exposed animals.

## Genotoxicity

The potential genotoxicity of 2,4-PD has been reviewed in OECD (2001) and EFSA (2004). Overall, 2,4-PD was not consistently mutagenic *in vitro* but showed a clastogenic potential (chromosomal aberrations and sister chromatid exchanges) notably in the absence of metabolic activation (Ballantyne and Cawley 2001; OECD 2001). *In vivo*, a clastogenic potential (micronuclei) was observed in mice exposed via *i.p.* administration, but not in rats or mice exposed via inhalation, suggesting a route dependence (Ballantyne and Cawley 2001; OECD 2001). Oral administration of 2,3-PD did not induce DNA damage in tissues of rats (ECHA c2007-2017d) or chromosomal aberrations in spermatogonia of mice (OECD 2001), although inhalation exposure resulted in a slight transient dominant lethal effect in rats (Tyl et al. 1989). However, EFSA (2004) concluded that the use of 2,4-PD as a flavouring substance is not acceptable due to its genotoxic (clastogenic) potential.

## Repeated dose toxicity

In a dermal study, New Zealand White rabbits were exposed to 2,4-PD at doses of 0, 244, 975 and 1463 mg/kg bw/day by occluded contact daily for 9 days (Ballantyne 2001, as cited in OECD 2001). In the high dose group (1463 mg/kg bw/day) approximately 50% of animals of either sex died. At the middle and high doses, 2,4-PD caused signs of hypoactivity, prostration, salivation, tremors, gasping, convulsions, cyanosis (as derived from blue cutis of the nasal area), reduced body weight gain and food consumption, hemorrhages and neuronal degeneration. Based on systemic effects, the author established a NOAEL of 244 mg/kg bw/day and a LOAEL of 975 mg/kg bw/day.

With respect to oral exposure, based on limited data, gavage administration of doses of 500 mg/kg bw/day to rats for 2 weeks resulted in a range of systemic effects in the bladder, lungs, eyes, thymus, liver, kidneys, heart and lymph nodes, while all animals administered 1000 mg/kg bw/day died; the NOAEL was considered to be 100 mg/kg bw/day (Eastman Kodak 1979, as cited in OECD 2001). Other gavage studies by these investigators are cited in EFSA (2004) include a 126 day study in rats (NOAEL < 200 mg/kg bw/day) and a 14 day study in rabbits (NOAEL = 250 mg/kg bw/day); however, details provided are insufficient for evaluation.

Inhalation exposure of rats to 0, 100, 300 or 650 ppm (0, 417, 1217 or 2711 mg/m<sup>3</sup>) 2,4-PD for 14 weeks induced a wide range of systemic effects at 300 ppm and above and high mortality at 2711 mg/m<sup>3</sup>. Based on hematological, clinical and urinary chemical effects in the 1217 mg/m<sup>3</sup> group and severe effects at 2711 mg/m<sup>3</sup>, including histopathological effects in the brain and thymus, the authors established a NOAEC of 417 mg/m<sup>3</sup> for this study (Dodd et al. 1986, as cited in OECD 2001). In a two week study by the same authors, the NOAEC and LOAEC were determined to be 200 ppm (834 mg/m<sup>3</sup>) and 400 ppm (1668 mg/m<sup>3</sup>), respectively, based on reduced organ weights and nasal necrosis or inflammation at higher concentrations (OECD 2001).

Since no long-term oral study were available, a route-to-route extrapolation from the inhalation NOAEC of 417 mg/m<sup>3</sup> from the study above was carried out to obtain an oral NOAEL of 23 mg/kg-bw/day (see appendix D).

### **Reproductive and developmental toxicity**

In the sub-chronic inhalation study in male and female F344 rats exposed to 2,4-PD at concentrations of up to 2711 mg/m<sup>3</sup>, no significantly pathological findings were noted in testes and epididymis of males or in uterus, cervix and ovaries of females (Dodd et al. 1986, as cited in OECD 2001). No studies were identified in which potential effects of exposure to 2,4-PD on reproductive performance were investigated.

In an inhalation developmental toxicity study, pregnant F344 rats were exposed to concentrations of 0, 53, 202 or 398 ppm (0, 217, 827 or 1629 mg/m<sup>3</sup>) 2,4-PD for 6 hours/day through gestation days 6-15 (Tyl et al. 1990). No effects were observed on number of corpora lutea, viable implants per litter, pre- or post-implantation losses or foetal sex ratio. Significantly reduced foetal body weights per litter (approximately 10%)

were reported for males, females and all foetuses at 398 ppm (1,629 mg/m<sup>3</sup>). At this concentration, a consistent pattern of reduced foetal ossification, skeletal variations and reduced maternal weight was also reported. At 202 ppm (827 mg/m<sup>3</sup>), there was a slight but statistically significant reduction (approximately 3%) in foetal body weights per litter in males only. The authors concluded the NOEC to be 53 ppm for both maternal and developmental toxicity (Tyl et al. 1990). Likewise, the OECD (2001) considered 53 ppm (217 mg/m<sup>3</sup>) to be the developmental NOAEC. However, in light of the minimal decrease in body weight in male foetuses only, which is unlikely to be considered adverse, the NOAEC for developmental and maternal toxicity is considered in this assessment to be 202 ppm (827 mg/m<sup>3</sup>).

#### **7.4.3 Risk characterization of 2,4-PD**

2,4-PD was not carcinogenic in rats and mice exposed via inhalation. Non-carcinogenic lesions were mainly located in the nasal cavity (JBRC 2010a, b). However, clastogenic effects were reported for 2,4-PD, leading EFSA to conclude that the use of 2,4-PD as a flavouring substance is not acceptable (2004).

Systemic and developmental toxicities are identified as critical health effects for characterizing risk for shorter term inhalation exposure to 2,4-PD. The NOAEC for systemic and developmental toxicity in rats was established at 827 mg/m<sup>3</sup>. A NOAEC of 200 ppm (834 mg/m<sup>3</sup>) from a 14-day study (Dodd et al., 1986, as cited in OECD 2001) supports the selection of this critical effect concentration for risk characterization. With respect to longer term exposure, various systemic effects were observed in the 14-week study and the NOAEC was established at 417 mg/m<sup>3</sup> (Dodd et al. 1986, as cited in OECD 2001).

With respect to oral exposure, based on limited data, the short-term gavage study with a NOAEL of 100 mg/kg bw/day (Eastman Kodak 1979, as cited in OECD 2001) and a route-to-route extrapolation from the developmental inhalation study for longer term exposure, resulting in a NOAEL of 23 mg/kg-bw/day, were considered.

Dermal exposure to 2,4-PD also produced a range of effects in rabbits administered 500 mg/kg-bw/day; therefore, a NOAEL of 244 mg/kg-bw/day (Ballantyne 2001, as cited in OECD 2001) was used to characterize the risk associated with dermal exposure to 2,4-PD.

The general population of Canada is exposed to 2,4-PD in small amounts through environmental media and the diet as a result of its natural occurrence in foods.

2,4-PD is also used as an additive in paints and coatings primarily for commercial or industrial use; however, some are available to consumers. Table 7-19 provides all relevant exposure values and the critical health effects for 2,4-PD as well as the resulting MOEs for the characterization of risk.

**Table 7-19. Relevant exposure and hazard values for 2,4-PD, as well as margins of exposure, for characterization of risk.**

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Environmental media	0.002 – 0.007 µg/kg-bw/day	NOAEL = 100 mg/kg-bw/day NOAEL = 23 mg/kg-bw/day	Systemic toxicity in a 2-week oral study Route-to-route extrapolation from 14-week inhalation study	> 3 million
Coating for large surface (inhalation)	6-hr TWA = 13 – 53 mg/m <sup>3</sup>	NOAEC = 827 mg/m <sup>3</sup>	Developmental effects (reduced foetal weight in foetuses and reduced foetal ossification, skeletal variations) and reduced maternal weight.	16 – 64
Coating for large surface (dermal)	0.04 – 0.2 mg/kg-bw/day	NOAEL = 244 mg/kg-bw/day	Distended bladder, congested lungs, clouding of cornea, thymic necrosis, hepatocyte swelling and congestion, nephrosis, lymphadenitis of mesenteric lymph nodes and inflammation of the heart from a 9-day dermal study.	1 220 – 6 100

Calculated MOEs for exposure to 2,4-PD from environmental media are considered adequate to address uncertainties in the health effects and exposure databases. Additional intake of 2,4-PD from its natural occurrence in food was not identified as a concern for human health. However, the MOEs for exposure to 2,4-PD in products available to consumers, namely floor coating, is considered potentially inadequate to account for uncertainties in the exposure and health effects databases.

#### 7.4.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below. In light of the evidence of the genotoxicity of 2,4-PD, additional data from longer term studies would be helpful to increase confidence that potential risks from prolonged exposures would be low.

**Table 7-20. Sources of uncertainty in the risk characterization.**

Key source of Uncertainty	Impact
Absence or limited Canadian monitoring data in foods.	+/-
Details on the specific types of products available to consumers that contain 2,4-PD ; however, use of high-end product amounts and maximum concentrations likely overestimates exposures to products available to consumers.	+
There are no chronic oral or dermal studies or subchronic oral studies for 2,4-PD	+/-

+ = 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.

### 7.5 Assessment of MO

#### 7.5.1 Exposure assessment

##### Environmental media

Mesityl oxide was measured in the CHMS Cycle 2 indoor air study and in a smaller indoor air study from Quebec (personal communication, e-mail from EHSRB, HC to ESRAB, HC, dated 2012 December, unreferenced; Won and Lusztyk 2011). MO was detected in less than 12% of samples (limit of detection  $0.16 \mu\text{g}/\text{m}^3$ ) in the CHMS study with a geometric mean concentration of  $0.10 \mu\text{g}/\text{m}^3$  and a 95<sup>th</sup> percentile concentration of  $0.26 \mu\text{g}/\text{m}^3$  (weighted data at the household level) (Zhu et al. 2013). The geometric mean concentration of MO from 12 samples from the Quebec field study was  $0.30 \mu\text{g}/\text{m}^3$  with a maximum of  $4.15 \mu\text{g}/\text{m}^3$  (Won and Lusztyk 2011).

No Canadian data were identified on the presence of MO in water. MO was qualitatively detected in drinking water from Cincinnati, Ohio as well as in a river in Switzerland (HSDB 1983-). Based on the moderate Henry's Law Constant and high vapour pressure, MO is likely to volatilize from water (HSDB 1983-); therefore, drinking water is not expected to be a significant source of population exposure.

No data were identified on the presence of MO in soil in Canada or elsewhere. Based on its low Log K<sub>oc</sub>, MO is likely to have high mobility in soil and is not likely to adhere to sediment or suspended particles in water (HSDB 1983-); soil is therefore not expected to be an important source of exposure.

Estimates of exposure for MO from environmental media ranged from 0.8 µg/kg-bw per day for adults (60 years and older) to 2.5 µg/kg-bw per day for toddlers (6 months to 4 years) (Health Canada 2018).

## Food

Mesityl oxide is naturally occurring in various food items including nectarines, bell pepper, tomatoes, crisp bread, parmesan cheese, milk, coffee, tea, peanuts, basil and shrimp to name a few (Nijssen et al. 1963-2016, Burdock 2010). It can also be used as a food flavourant in baked goods, frozen dairy, gelatins/puddings, milk products and soft candy (Burdock 2010). Quantitative exposure estimates for MO from its natural occurrence in food<sup>12</sup> ranged from 0.3 µg/kg-bw per day for 1 year olds to 1.5 µg/kg-bw per day for toddlers 2 – 3 years old (see Appendix A for details).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated a group of aliphatic secondary alcohols, ketones and related esters used as flavouring substances, including MO (WHO 2003). As part of that evaluation, the Committee estimated the per capita intake of MO from its use as a food flavouring agent to be 0.0067 µg/kg bw per day for the European population (no intake data reported for the US) (see Appendix A for details).

## Products available to consumers

MO was not identified in any products available to consumers in Canada.

### 7.5.2 Health effects assessment of individual substance (MO)

MO has been reviewed by OECD (OECD 1997b, updated in 2010) and EFSA (EFSA 2012). These reviews provide a basis for the health effects characterization in this assessment. A literature search has been conducted from one year prior to the OECD publication until May 2017. No new information was identified on the health effects associated with exposure to MO.

Limited toxicological information is available for MO; therefore, route-to-route extrapolation for MO is supported by read-across from the analogue 6-methyl—5-heptene-2-one (MHE, CAS RN 110-93-0). MHE was the only analogue identified for the read-across of MO, based on structural similarity and data availability (TERA 2017). Both MO and MHE are unsaturated ketones; MO contains an alkene group and a ketone group on adjacent carbon atoms, while MHE contains an additional two carbons in the chain between the alkene and ketone group. This structure difference suggests

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<sup>12</sup> Infants 0 to 6 months old are assumed to be exclusively breast-fed or formula-fed.

that MO may be more reactive (therefore more toxic) than MHE due to the presence of  $\alpha$ ,  $\beta$ -unsaturated carbonyl. Toxicity data on MHE has been used to read-across to MO where required.

### **Carcinogenicity and genetic toxicity**

No carcinogenicity data were identified for MO. The predictive model OncoLogic® identified a structural alert of alpha-beta unsaturated carbonyl function group in the molecule of MO for carcinogenic potential (TERA 2017).

MO was not mutagenic in *Salmonella*, *E. coli* or in the mouse lymphoma assay, nor did it induce micronuclei in cultured human lymphocytes or in mice administered MO by intraperitoneal injection (ECHA c2007-2017e).

### **Repeated dose toxicity**

Two studies are available for repeated dose inhalation toxicity for MO and no data are available by either oral or dermal route.

A combined repeated dose and reproductive/developmental toxicity study was conducted in groups of SD rats exposed to MO at concentrations of 0, 31, 103 and 302 ppm (0, 124, 413 and 1211 mg/m<sup>3</sup>) for 6 hours/day, 7 days/week for a total 49 exposures for male rats and a total of 36 to 49 exposures for female rats. There were no effects on mortality, haematological or urinalysis parameters, or in gross pathology for the parental animals. However, significant reductions in feed consumption, body weight, and body weight gain, along with clinical abnormalities and nasal passage pathology, were observed in the all test groups in a concentration-dependent matter. The clinical abnormalities included increased incidence of post-exposure porphyrin nasal discharge and sialorrhea. Histopathological findings included the presence of sero-cellular exudates, chronic focal inflammation and focal metaplasia of the respiratory and olfactory epithelium of the nasal passage. These changes are considered a common response to an irritating vapour (Bernard and Faber 1992, reviewed in OECD 1997b). Thus an inhalation LOAEC of 31 ppm (124 mg/m<sup>3</sup>) was determined based on the effects on feed consumption, body weights, body weight gain and nasal passage histopathology (OECD 1997b; ECHA c2007-2017e). No inhalation NOAEC has been identified in this study.

Groups of male Wistar rats and guinea pigs of both sexes were exposed to MO at concentrations of 0, 50, 100, 250 or 500 ppm (0, 200, 400, 1000 or 2000 mg/m<sup>3</sup>) for 8 hours/day, 5 days/week for 6 weeks. Chronic conjunctivitis, nasal irritation and mild albuminuria were observed at 250 and 500 ppm. Significant concentration-related increases pathological effects were observed in kidney, lung and/or liver at 100 ppm and higher doses. The pathological changes included poor growth, congestion of the liver, dialated Bowman's capsules, swollen convoluted tubular epithelium in the kidney and congestion of the lungs. No effects were seen at 50 ppm. The authors considered

the NOAEC to be 50 ppm (200 mg/m<sup>3</sup>) on the basis of pathological changes in lung, liver and/or kidney (Smyth et al. 1942; ECHA c2007-2017e).

### Reproductive and developmental toxicity

In the combined repeated dose and reproductive/developmental toxicity study described above in which groups of SD rats were exposed to MO for a total 49 days for male rats and a total of 36 to 49 days for female rats (through Day 20 of gestation), no significant effects on reproductive organs or performance or on gestation length were observed at any concentration tested. However, a reduced number of litters produced by the mating pairs was observed at 302 ppm (1211 mg/m<sup>3</sup>). No external malformations were noted; no histopathological examination was conducted in pups. The NOEC for reproductive toxicity was 103 ppm (413 mg/m<sup>3</sup>) (Bernard and Faber 1992, reviewed in OECD 1997b; ECHA c2007-2017e).

No information has been identified on the potential reproductive and developmental toxicity from oral or dermal exposure to MO.

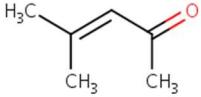
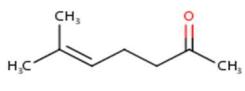
### Route to route extrapolation and read-across for hazard characterization

In light of the lack of data on the toxicity of orally administered MO, observations from inhalation studies are considered in a route-to-route extrapolation approach. In the combined repeated dose and reproductive/developmental toxicity study in rats, the critical effects mainly occurred in nasal passage (i.e., the site of contact) which the OECD (1997b) attributed to the irritative property of MO. Therefore, it is considered to be more appropriate to use the NOAEC of 50 ppm (200 mg/m<sup>3</sup>) from the 6 week inhalation study in rats in which systemic effects in the lung, liver and kidney were observed to derive an oral NOAEL for MO. The adjusted oral NOAEL for repeated dose toxicity is 15.0 mg/kg-bw/d (see appendix D).

MHE (CAS RN 110-93-0) was identified as an analogue that could be used for read-across of MO, based on the structural similarity and data availability (TERA 2017). A NOAEL of 39 mg/kg-bw/day for MO can be derived by read-across from the oral NOAEL of 50 mg/kg-bw/day from MHE (based on alterations in haematological and clinical chemistry parameters in a 90 day study with rats (OECD 2003) by adjusting for molecular weight (Table 7-21). This read-across based NOAEL for MO is similar to the route-to-route extrapolation based NOAEL (i.e., only about 2.5-fold greater, as may be expected, based on the longer chain).

**Table 7-21. Read-across for MO.**

Chemical name	MO	6-methyl-5-heptene-2-one (MHE)
Role	Target chemical	Analogue
CAS#	141-79-7	110-93-0

Chemical structure	 MW = 98.1 Log Kow: 1.2 – 1.7	 MW = 126.2 Log Kow: 2.06
Repeat dose toxicity (Inhalation, 49-day exposure)	LOAEC=124 mg/m <sup>3</sup> (reductions in body weight and body weight gain, and histopathology in nasal passage); No NOAEC was identified.	NA
Repeat dose toxicity (Inhalation, 6 weeks)	NOAEC=200 mg/m <sup>3</sup> (histopathological effects in kidney, lung and liver)	NA
Repeat dose toxicity (Oral)	NOAEL=15.0 mg/kg-bw/d (R2R from inhalation 6-week study*);  NOAEL = 39 mg/kg-bw/d (read-across from MHE by adjusting the molecular weight)	NOAEL = 50 mg/kg-bw/d (increases in platelet counts in female rats in a 90-day study)  LOAEL=200 mg/kg bw/d
Developmental toxicity (Inhalation)	No developmental toxicity was noted up to 1211 mg/m <sup>3</sup>	NA
Developmental toxicity (Oral)	No developmental toxicity was noted up to 95.2 mg/kg-bw/d (R2R from inhalation study*);  NOAEL = 165 mg/kg-bw/d (read-across from MHE by adjusting the molecular weight)	NOAEL=200 mg/kg-bw/d (maternal and prenatal developmental toxicity); LOAEL=1000 mg/kg-bw/d. No developmental up to 1000 mg/kg-bw/d
Genetic toxicity	Negative	Negative
Carcinogenicity	NA	NA

Abbreviations: NA, not available; MW, molecular weight (g/mol); Log Kow, octanol-water partition coefficient

\*This concentration was converted to oral dose using parameters from Health Canada (1994), with rat average body weight of 0.35kg and inhalation rate of 0.11m<sup>3</sup>/day. i.e. 200 mg/m<sup>3</sup> X 0.11 m<sup>3</sup>/day X 8h/24h X 5 days/7 days / 0.35 kg = 15.0 mg/kg-bw/d for repeated dose toxicity; or 413 mg/m<sup>3</sup> X 0.11 m<sup>3</sup>/day X 6h/24h / 0.35 kg = 32.5 mg/kg-bw/d for reproductive toxicity.

### 7.5.3 Risk characterization of MO

No carcinogenic studies on MO have been identified.

The LOAEC of 124 mg/m<sup>3</sup> for the systemic toxicity in dams was used to characterize the risk associated with inhalation exposure to MO (OECD 1997b; ECHA c2007-2017e). Although no oral toxicity studies on MO have been identified, route to route extrapolation of the NOAEC from a 6 week inhalation study (Smyth et al. 1942; ECHA c2007-2017e) is considered appropriate to characterize potential hazards associated with ingestion of the substance. The equivalent oral NOAEL was determined to be 15 mg/kg-bw/day. This value is supported by reading across from toxicity data for an analogous substance, MHE.

The predominant source of exposure to MO for the general population is through air and the diet as a result of its natural occurrence in foods.

MO was not identified in any products available to consumers in Canada.

Comparison of the estimates of exposure to MO from environmental media (1.2 – 2.5 µg/kg bw/day) and from its use as a flavouring agent in food (0.0067 µg/kg bw/day) with the NOAEL of 15 mg/kg-bw per day resulted in MOEs greater than 6 000 which are considered adequate to address uncertainties in the health effects and exposure databases. Additional intake of MO from its natural occurrence in food was not identified as a concern for human health. Furthermore, the JECFA (WHO 2003) concluded "No safety concern at current levels of intake when used as a flavouring agent" based on the dietary exposure estimates for MO.

### 7.5.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below. Although the database for MO is limited, in light of the large MOEs, confidence is high that risk to general population of Canada from this substance is low.

**Table 7-22. Sources of uncertainty in the risk characterization.**

Key source of Uncertainty	Impact
Limited environmental monitoring data for MO.	+
Limited hazard database for MO (especially long term data)	-

+ = 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.

## 8. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from MEK, MPK, MIBK, MIAK, DAA, diacetyl, 2,3-PD, acetoin, 2,4-PD and MO. It is proposed to conclude that these 10 substances 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 MEK, MIBK, and 2,4-PD meet the criteria under paragraph 64(c) of CEPA as they are entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that MPK, MIAK, DAA, diacetyl, 2,3-PD, acetoin and MO 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 MEK, MIBK, and 2,4-PD meet one or more of the criteria set out in section 64 of CEPA but that MPK, MIAK, DAA, diacetyl, 2,3-PD, acetoin and MO do not meet any of the criteria set out in section 64 of CEPA.

MEK and 2,4-PD are proposed to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

MIBK is proposed to not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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## Appendices

### Appendix A. Ketones in food

**Table A-1. JECFA per capita intake estimates for food flavouring uses for the U.S. and European populations (WHO 1999a,b, 2003).**

Substance Name	U.S per capita intake (µg/day)	U.S per capita intake (µg/kg-bw/day)	Europe per capita intake (µg/day)	Europe per capita intake (µg/kg-bw/day)
MEK	36	0.6	110	2
MPK	42	0.7	140	2
MIBK	2	0.03	7	0.12
Diacetyl	8000	133	3300	56
2,3-PD	1800	1	2800	4
Acetoin	80	29	220	46
MO	NA	NA	0.40	0.0067

Abbreviations: NA, not applicable

The JECFA per capita intake estimates (µg/day) were derived using the maximized survey-derived daily intake (MSDI) approach, assuming that the reported annual production amount for the various substances in the U.S. 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. A body weight of 60 kg was used to derive intake estimates in µg/kg-bw/day (International Organization of the Flavor Industry, 1995, US National Academy of Sciences, 1989, both cited in WHO 1999b).

Quantitative exposure estimates for all 10 substances were derived based on consumption data for comparable food categories from the Canadian Community Health Survey (CCHS) 2.2 Food Consumption Table (Health Canada 2015b). A summary of the data identified for each of the substances in foods from the literature, and from the Volatile Compounds in Food (VCF) database (Nijssen et al. 1963-2016) can be found in the Table A-2, Table A-3, Table A-4, and Table A-5. Quantitative data for all food items were not available; therefore, maximum reported values from the VCF database, and the literature were used for various food items to estimate potential high-end exposures to all substances from food for the general population of Canada. Estimated exposures for all ten substances from their natural occurrence in food are presented in Table A-6.

**Table A-2. Levels of MEK and MPK naturally occurring in food<sup>a</sup>.**

Food category	MEK (µg/g)	MPK (µg/g)
Beers and coolers	0.06	0.02
Spirits and liquors	2.00	1.20
Fruit juices	0.20	0.10
Coffee, powder items are reconstituted	NA	4.70

Tea, including iced tea	8.00	NA
Milks	NA	0.10 <sup>b</sup>
Creams	0.07	0.05
Cheeses	67.10	14.71
Yoghurts	7.00	0.01
Bananas	NA	27.00
Cherries	NA	0.01
Pears	1.00	2.40
Pineapple	NA	0.01
Plums and prunes	NA	2.00
Strawberries	NA	3.10
Other fruits (blueberries, dates, kiwis, fruit salads)	0.02	3.30
Vegetables, excluding potatoes	6.00	20.00
Potatoes, fried	0.13	0.07
Chicken, turkey and other birds	0.10	0.23
Pork, fresh and ham	0.72 <sup>c</sup>	NA
Fish	0.60	NA
Shellfish	NA	0.12
Eggs	0.01	NA
Nuts, seeds and peanut butter	0.10	7.60
Legumes	0.05	NA
Butter	0.16	0.95
Other fats and spreads	1.51	0.03
Sugars, syrups and preserves	0.08	0.03
Savory snacks	0.13	NA

Abbreviations: NA, not available

<sup>a</sup> Data from the Volatile Compounds in Food (VCF) Database (Nijssen et al. 1963-2016) unless specified otherwise.

<sup>b</sup> Yue et al. 2015

<sup>c</sup> Sánchez-Peña et al. 2005

**Table A-3. Levels of MIBK, MIAK and DAA naturally occurring in food<sup>a</sup>.**

Food category	MIBK (µg/g)	MIAK(µg/g)	DAA (µg/g)
Beers and coolers	0.12	NA	NA
Coffee, powder items are reconstituted	6.50	0.50	NA
Milks	0.016 <sup>b</sup>	NA	0.00015 <sup>c</sup>
Plums and prunes	0.01	NA	NA
Other fruits (blueberries, dates, kiwis, fruit salads)	0.02	0.001	0.408
Chicken, turkey and other birds	0.0004	NA	0.07
Eggs	0.003	NA	NA
Other fats and spreads	0.38	NA	NA
Sugars, syrups and preserves	NA	NA	2.70
Other ingredients for recipes (e.g., spices, baking ingredients)	NA	NA	28.50

Abbreviations: NA, not available

<sup>a</sup> Data from the Volatile Compounds in Food (VCF) Database (Nijssen et al. 1963-2016) unless specified otherwise.

<sup>b</sup> Yue et al. 2015

<sup>c</sup> Toso et al. 2002

**Table A-4. Levels of diacetyl, 2,3-PD, and acetoin naturally occurring in food<sup>a</sup>.**

Food category	Diacetyl (µg/g)	2,3-PD (µg/g)	Acetoin (µg/g)
Beers and coolers	0.20	0.30	9.00
Spirits and liqueurs	9.77 <sup>b</sup>	0.60	335.00

Wines	4.10	NA	234.00 <sup>l</sup>
Fruit juices	3.15 <sup>c</sup>	NA	0.35
Coffee, powder items are reconstituted	58.70	39.60	4.90
Tea, including iced tea	1.00	2.00	NA
Milks	29.3 <sup>d</sup>	0.20 <sup>j</sup>	NA
Creams	30.00	NA	NA
Cheeses	4.20	NA	40.00
Yoghurts	43.00 <sup>e</sup>	NA	28.00
Pasta, rice, cereal grains and flours	0.19	0.25	0.75
White breads	0.92	0.14	NA
Wholemeal breads	1.52	0.14 <sup>k</sup>	1.22 <sup>m</sup>
Other breads	0.33	0.04	NA
Apples	0.40	NA	3.50
Cherries	NA	NA	4.70
Pears	NA	NA	0.11
Strawberries	0.20	NA	0.49
Other fruits (blueberries, dates, kiwis, fruit salads)	0.60 <sup>f</sup>	NA	22.63
Vegetables, excluding potatoes	0.79 <sup>g</sup>	NA	6.40
Potatoes, fried	0.31	NA	NA
Beef	23.00	6.50	8.40
Veal	23.00	6.50	8.40
Chicken, turkey and other birds	0.90	NA	2.40
Livers and liver pates	27.81	NA	NA
Luncheon meats, canned and cold cuts	27.81	NA	NA
Pork, fresh and ham	0.36	NA	NA
Fish	0.0017	0.69	0.31
Shellfish	0.10 <sup>h</sup>	NA	0.16
Nuts, seeds and peanut butter	0.09	0.23	NA
Butter	21.00 <sup>e</sup>	0.05 <sup>e</sup>	2.00
Margarines, tub	NA	0.01	NA
Margarines, block	NA	0.01	NA
Other fats and spreads	0.60	0.01	0.04
Confectionary, chocolate bars	0.40	NA	17.00
Sugars, syrups and preserves	2.60	NA	26.00
Savory snacks	NA	0.20	NA
Soups without vegetables	0.00056 <sup>i</sup>	0.42 <sup>i</sup>	NA
Gravies	0.09	NA	NA
Seasonings, salt, pepper, vinegar	197.00	NA	1020
Other ingredients for recipes (e.g., spices, baking ingredients)	238.00	109.00	951.00

Abbreviations: NA, not available

<sup>a</sup> Data from the Volatile Compounds in Food (VCF) Database (Nijssen et al. 1963-2016) unless specified otherwise.

<sup>b</sup> Cardoso et al. 2003

<sup>c</sup> Lawson et al. 1995

<sup>d</sup> De Leonardis et al. 2013

<sup>e</sup> Macciola et al. 2008

<sup>f</sup> Mujic et al. 2014

<sup>g</sup> Annan et al. 2005

<sup>h</sup> Yu and Chen 2010

<sup>i</sup> Giri et al. 2010

<sup>j</sup> Imhof et al. 1994

<sup>k</sup> Rychlick and Grosch 1996

<sup>l</sup> Garcia-Martinez et al. 2013

<sup>m</sup> Birch et al. 2013

**Table A-5. Levels of 2,4-PD and MO naturally occurring in food<sup>a</sup>.**

Food category	2,4-PD (µg/g)	MO (µg/g)
Wines	NA	0.00005
Fruit juices	0.01	NA
Other fruits (blueberries, dates, kiwis, fruit salads)	NA	0.01
Vegetables, excluding potatoes	NA	0.04
Chicken, turkey and other birds	0.004	NA
Other fats and spreads	NA	3.00
Other ingredients for recipes (e.g., spices, baking ingredients)	NA	2.40

Abbreviations: NA, not available

<sup>a</sup> Data from the Volatile Compounds in Food (VCF) Database (Nijssen et al. 1963-2016) unless specified otherwise.**Table A-6. Estimated exposures to Ketones Group from natural occurrence in food (µg/kg-bw per day).**

Substance	0-6 mo <sup>a</sup>	6-12 mo	1 yr	2-3 yrs	4-8 yrs	9-13 yrs	14-18 yrs	19+ yrs
MEK	0	112	185	174	130	82	66	67
MPK	0	146	216	192	137	86	68	98
MIBK	0	0.5	0.9	0.7	0.4	0.8	5	32
MIAK	0	0	0.001	0.001	0.0004	0.04	0.4	3
DAA	0	0.04	3	4	4	3	2	2
Diacetyl	0	996	1625	1118	671	370	281	445
2,3-PD	0	6.5	22	22	20	16	40	208
Acetoin	0	173	346	369	293	189	161	308
2,4-PD	0	0.04	0.1	0.1	0.08	0.04	0.03	0.02
MO	0	0.3	1	2	1	0.9	0.7	0.6

<sup>a</sup> Infants 0 to 6 months old are assumed to be exclusively breast-fed or formula-fed.

## Appendix B. Parameters used to estimate exposures.

Cosmetic exposures were estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights of 70.9 kg, 59.4 kg, 15.5 kg, and 7.5 kg for adults (20 years and older), adolescents (12 to 19 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (Health Canada 1998). The estimated inhalation and dermal exposure parameters for cosmetics are described in Table B-1. Dermal intakes are only presented for DAA and 2,4-PD. Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

**Table B-1. Exposure parameter assumptions for inhalation and dermal cosmetic scenarios**

Product (substance)	Assumptions <sup>a</sup>
Top coat (assume put on finger and toe nails) (MEK)	<p>Concentration of MEK: 55.7%</p> <p><i>Inhalation</i> – Exposure to vapour, evaporation model, Exposure duration: 18 minutes</p> <p>Product amount: 0.33 g (Ficheux et al. 2014)</p> <p>Room volume: 1 m<sup>3</sup> (close to the face)</p> <p>Ventilation rate: 1 change per hour</p> <p>Mass transfer coefficient: 6.401 m/hr (Sparks method)</p> <p>Release area mode: constant</p> <p>Release area: 26.2 cm<sup>2</sup> (based on data from Ficheux et al. 2014 and assumption that both finger- and toenails are painted)</p> <p>Molecular weight matrix: 124 g/mol</p>
Nail polish (2 coats on finger and toe nails) (MEK)	<p>Concentration of MEK: 35%</p> <p><i>Inhalation</i> – Exposure to vapour, evaporation model</p> <p>Exposure duration: 35 minutes</p> <p>Product amount: 0.8 g for adults and teens, and 0.27 g on toddlers (Ficheux et al. 2014)</p> <p>Room volume: 1 m<sup>3</sup> (close to the face)</p> <p>Ventilation rate: 1 change per hour</p> <p>Mass transfer coefficient: 6.401 m hr (adults), 9.082 m hr (toddler) (Sparks method)</p> <p>Release area mode: constant</p> <p>Release area: 26.2 cm<sup>2</sup> (adults and teens), 8.8 cm<sup>2</sup> (toddlers) (based on data from Ficheux et al. 2014 and assumption that both finger- and toenails are painted)</p> <p>Molecular weight matrix: 124 g/mol</p>
Nail polish (2 coats on finger and toe nails) (DAA)	<p>Concentration of DAA: 10%</p> <p><i>Inhalation</i> – Exposure to vapour, evaporation model</p> <p>Exposure duration: 35 minutes</p>

	<p>Product amount: 0.8 g for adults and teens, and 0.27 g on toddlers (Ficheux et al. 2014)</p> <p>Room volume: 1 m<sup>3</sup> (close to the face)</p> <p>Ventilation rate: 1 change per hour</p> <p>Mass transfer coefficient: 5.043 m hr (adults), 7.029 m hr (toddler) (Sparks method)</p> <p>Release area mode: constant</p> <p>Release area: 26.2 cm<sup>2</sup> (adults and teens), 8.8 cm<sup>2</sup> (toddlers) (based on data from Ficheux et al. 2014 and assumption that both finger- and toenails are painted)</p> <p>Molecular weight matrix: 124 g/mol</p> <p><b>Dermal:</b></p> <p>Amount on the skin (g/use): 0.16 for adults and teens and 0.06 for toddlers (Ficheux et al. 2014)</p> <p>Frequency (use/day): 0.18 for adults, 0.2 for teens, 0.13 for toddlers (Ficheux et al. 2014)</p> <p>Surface area: area around the nails = 2.7 cm<sup>2</sup> (adults), 0.9 cm<sup>2</sup> (toddlers) (Ficheux et al. 2014)</p>
Nail polish remover (MEK)	<p>Concentration of MEK: 84% (adults), 76.4% (toddlers)</p> <p><i>Inhalation</i> – Exposure to vapour, evaporation model</p> <p>Exposure duration: 8 minutes</p> <p>Product amount: 5.36 g (adults and teens) and 1.82 g (toddlers)</p> <p>Room volume: 1 m<sup>3</sup> (close to the face)</p> <p>Ventilation rate: 1 change per hour</p> <p>Mass transfer coefficient: 5.080 m hr (adults), 7.209 m hr (toddler) (Sparks method)</p> <p>Release area mode: constant</p> <p>Release area: 34 cm<sup>2</sup> (adults and teens) and 11.6 cm<sup>2</sup> (toddlers) (based on data from Ficheux et al. 2014 and assumption that both finger- and toenails are painted)</p> <p>Molecular weight matrix: 124 g/mol</p>
Rubbing alcohol (MIBK)	<p>Concentration of MIBK: 0.98%</p> <p>No scenario identified in ConsExpo, used professional judgement</p> <p><i>Inhalation</i> – Exposure to vapour, instantaneous release model</p> <p>Exposure duration: 5 minutes</p> <p>Product amount: 0.02 g</p> <p>Room volume: 1 m<sup>3</sup> (close to the face)</p> <p>Ventilation rate: 1 change per hour</p>

	<p>Dermal: Surface area: assumed an area of 5 cm x 5 cm = 25 cm<sup>2</sup> is covered Amount on the skin (g/use): adjust product amount of hand sanitizer 0.7 g (Health Canada 2015c) for 910 cm<sup>2</sup> surface area to an area of 25 cm<sup>2</sup> = 0.02 g</p>
Eyeliner stickers (DAA)	<p>Concentration of DAA: 30%</p> <p><i>Dermal:</i> Product amount (g/use): 27 mg (P95 from Ficheux et al. 2016) Surface area: 5 cm<sup>2</sup> (professional judgement, based on 3.2 cm<sup>2</sup> in ConsExpo and that stickers appear to cover a larger surface area)</p> <p><i>Inhalation</i> – Exposure to vapour, evaporation model Exposure duration: 12 hours Product amount: 27 mg/use (Loretz et al. 2005) Room volume: 1 m<sup>3</sup> (close to the face) Mass transfer coefficient: 6.844 m/hr (Sparks method) Release area mode: constant Release area: 5 cm<sup>2</sup> (professional judgement) Ventilation rate: 1 change per hour Molecular weight matrix: 124 g/mol</p>
Hair styling product (Diacetyl)	<p>Concentration of diacetyl: 0.1 – 1%</p> <p>Frequency of use: 1 /day (professional judgement)</p> <p><i>Inhalation</i> – Exposure to vapour, evaporation model Exposure duration: 10 minutes Product amount: 0.25 g (according to product label, apply 2 or more drops. One drop is assumed to be 0.05 mL (reference) and assuming a density of 1 g/mL results in 0.05 g/drop. Assumed 5 drops would be used, therefore, 0.25 g) Room volume: 1 m<sup>3</sup> Ventilation rate: 0.6 per hour Mass transfer coefficient: 5.421 m/hr (Sparks method) Release area mode: constant Release area: 637.5 cm<sup>2</sup> (half the area of the head) Emission duration: 10 minutes Molecular weight matrix: 330 g/mol</p>

<sup>a</sup> Unless specified, a retention factor of 1 was used

**Table B-2 Oral exposures to MEK in toys**

Product (substance)	Assumptions <sup>a</sup>
Mouthing pacifier and/or teether	<p>Concentration of MEK residue: 500 ug/g (WSDE 2016)</p> <p>Oral:</p> $E_{toy} = q_{product} \times f_{time} \times f_{surface} / bw$ <p>where,</p> $E_{toy} = \text{exposure from mouthing toy (}\mu\text{g/kg-bw per day)}$ <p>Pacifier:</p> <p><math>q_{product}</math> = amount of substance that leaches from product over 24 hours (ug) = 22500 ug (500 ug/g x 45 g)<sup>b</sup></p> <p><math>f_{time}</math> = fraction of the day that the product is mouthed (i.e., sucking time) = 0.2 (infants) and 0.32 (toddler) (Juberg et al. 2001 as cited in EFSA 2015)</p> <p><math>f_{surface}</math> = fraction of the product surface that is mouthed = 0.5 (Lassen et al. 2011 as cited in EFSA 2015)</p> <p>Teether:</p> <p><math>q_{product}</math> = amount of substance that leaches from product over 24 hours (ug) = 68000 ug (500 ug/g x 136 g)<sup>b</sup></p> <p><math>f_{time}</math> = fraction of the day that the product is mouthed (i.e., sucking time) = 0.02 (Juberg et al. 2001) to 0.05 (Van Engelen et al. 2008 (infants and toddler))</p> <p><math>f_{surface}</math> = fraction of the product surface that is mouthed = 0.5 (RIVM 2002)</p>

<sup>a</sup> Approach from EFSA (2015), body weights of 7.5 kg and 15.5 kg for infants (0 – 6 months old) and toddlers (6 months to 4 years old), respectively (Health Canada 1998).

<sup>b</sup> Assume all of the MEK (500 ug/g) could be released. Weight of pacifier and teether from examining product weights based on product labels.

## Other products

Sentinel exposure scenarios were used to estimate the potential exposure to substances in the Ketones Group. Exposures were estimated based on the assumed weight, 70.9 kg of an adult (Health Canada 1998), and use behaviours of an adult. Exposures were estimated using ConsExpo Web (ConsExpo 2016) or algorithms (see below for more details). Scenario-specific assumptions are provided in Table B-3. The PARAMs model was used to estimate mass transfer coefficients (Sparks method) (US EPA 2005). Refer to Table B-4 for defaults used in the PARAMs model.

**Table B-3. Dermal and inhalation exposure parameter assumptions for paint and do-it-yourself (DIY) products.**

Exposure scenario	Assumptions
Lacquer removal (MEK)	<p>Concentration of MEK: 10 – 40%</p> <p>Scenario: paint remover in DIY Fact Sheet (RIVM 2007a). Assume work would be done in garage.</p> <p>Inhalation – Exposure to vapour, evaporation model</p> <p>Exposure duration: 60 minutes</p> <p>Product amount: 1000 g</p> <p>Room volume: 34 m<sup>3</sup> (garage)</p> <p>Ventilation rate: 1.5 change per hour</p> <p>Mass transfer coefficient: 2.758 m/hr (Sparks method)</p> <p>Release area mode: increasing</p> <p>Release area: 2 m<sup>2</sup></p> <p>Molecular weight matrix: 3000 g/mol</p>
Adhesive removal (MEK)	<p>Concentration of MEK: 100%</p> <p>Scenario: adhesive remover used in the house based DIY Fact Sheet (RIVM 2007a) and US EPA 2011 defaults.</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 215 minutes (application duration + time exposed after duration of use ~94 minutes from US EPA 2011)  Application duration: 121 minutes (mean value for adhesive removers from US EPA 2011)  Product amount: 200 g [based on mean amount of product used per year, 34.46 oz/yr (~1019 mL/yr) x density of MEK 0.8 g/mL divided by mean uses/year (4.22) = 193 g] (US EPA 2011)  Room volume: 30 m<sup>3</sup>  Ventilation rate: 1.5 change per hour  Mass transfer coefficient: 3.743 m/hr (Sparks method)  Release area mode: increasing  Release area: 5 m<sup>2</sup>  Molecular weight matrix: 3000 g/mol</p>
Paint thinner (dilute lacquer or other coating) (MEK)	<p>Concentration: MEK = 100% (3% diluted in product)  Scenario: general coating (floor) in Do-It-Yourself Fact Sheet (RIVM 2007a). Assume work done in garage.  The final concentration of MEK in the product was based on product information stating that lacquers should be diluted with pure MEK at no more than 4oz per gallon (3%)  4oz = 118mL  1 gallon = 3785 mL</p> <p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 60 minutes  Product amount: 3000 g  Room volume: 34 m<sup>3</sup>  Ventilation rate: 1.5 change per hour  Mass transfer coefficient: MEK = 2.595 m/hr, (Sparks method)  Release area mode: increasing  Release area: 15 m<sup>2</sup>  Molecular weight matrix: 3000 g/mol</p>
Liquid paint (solvent-rich paint for truck bed) (MEK, MIBK)	<p>Concentration: MEK = 20%, MIBK = 13%  Scenario: Brush or roller paint with solvent-rich paint (truck bed paint) in Paint Fact Sheet (RIVM 2007b). Assume work done in garage.</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 132 minutes  Product amount: 420 g (adjusted product amount based on surface area covered. 1000 g for 12-15 m<sup>2</sup> to 420 g for 5 m<sup>2</sup>)  Room volume: 90 m<sup>3</sup> (garage, would need larger garage if truck being painted) (US EPA 2017)</p> <p>Ventilation rate: 1.5 change per hour  Mass transfer coefficient: MEK = 2.595 m/hr, MIBK = 2.115 m hr (Sparks method)  Release area mode: increasing  Release area: 5 m<sup>2</sup>  Application duration: 120 minutes  Molecular weight matrix: 300 g/mol</p>
Liquid paint for steel (high-solid paint) (MPK)	<p>Concentration of MPK: 1-10%</p> <p>Scenario: Brush or roller paint with high-solid paint in Paint Fact Sheet (RIVM 2007b). Assume work done in garage.</p> <p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 132 minutes  Product amount: 1300 g  Room volume: 34 m<sup>3</sup> (garage)  Ventilation rate: 1.5 change per hour  Mass transfer coefficient: Thibodeaux (only very slight change if use Sparks method)  Release area mode: increasing  Release area: 10 m<sup>2</sup>  Application duration: 120 minutes  Molecular weight matrix: 550 g/mol</p>
Spray Paint (MEK, MPK, MIBK, MIAK, DAA)	<p>Concentration: MEK = 1 – 52%, MPK = 2 – 13%, MIBK = 0.1 – 30%, MIAK = 1 – 10%, DAA = 1 – 5%</p> <p>Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b), but used exposure to vapour – evaporation model since substances are volatile.  Assume work done in garage. Some aerosol spray cans are ~400 g in size, therefore adjusted product amount to 400 g and increased application and exposure duration by 5 minutes each.</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 25 minutes  Product amount: 400 g  Room volume: 34 m<sup>3</sup> (garage)  Ventilation rate: 1.5 change per hour  Release area mode: increasing  Release area: 2 m<sup>2</sup>  Application duration: 20 minutes  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: MEK = 3.743 m/hr, MPK = 3.346, MIBK = 3.051 m hr, MIAK = 2.820, DAA = 2.949 (Sparks method)</p>
PVC cement/ primer (MEK, DAA)	<p>Concentration: MEK = 10 – 100%, DAA = 20 – 30%  Scenario: universal / wood glue in a bottle as per DIY Fact Sheet (RIVM 2007a)</p> <p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 240 minutes  Product amount: 10 g  Room volume: 20 m<sup>3</sup>  Ventilation rate: 0.6 change per hour  Release area mode: increasing  Release area: 0.04 m<sup>2</sup>  Application duration: 20 minutes  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: MEK = 8.064 m hr, DAA = 5.043 (Sparks method)</p>
Multipurpose adhesives (MEK)	<p>Concentration of MEK: 70%  Scenario: tube glue (contact glue) in Do-It-Yourself Fact Sheet (RIVM 2007a)</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 80 minutes (based on mean minutes exposed after duration of use, ~ 70 minutes, from US EPA 2011)  Product amount: 9 g  Room volume: 20 m<sup>3</sup>  Ventilation rate: 0.6 change per hour  Release area mode: increasing  Release area: 200 cm<sup>2</sup>  Application duration: 10 minutes  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: MEK = 8.064 m/hr (Sparks method)</p>
Wood lacquer (MIBK)	<p>Concentration: MIBK = 1 – 10%</p> <p>Scenario: general coating on a floor (in a garage) in DIY Fact Sheet (RIVM 2007a)</p> <p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 60 minutes  Product amount: 3000 g  Room volume: 34 m<sup>3</sup>  Ventilation rate: 1.5 change per hour  Release area mode: increasing  Release area: 15 m<sup>2</sup>  Application duration: 60 minutes  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: MIBK = 2.115 m hr (Sparks method)</p>
Filler/putty from tube (automotive) (MIBK)	<p>Concentration of MIBK: 1 – 8%</p> <p>Model: filler/putty from tube (in a garage) in DIY Fact Sheet (RIVM 2007a). Assume work done in garage.</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 60 minutes  Product amount: 100 g (adjusted from 40 g based on product size and additional info from US EPA 2017)  Room volume: 34 m<sup>3</sup> (garage)  Ventilation rate: 1.5 change per hour  Release area mode: increasing  Release area: 200 cm<sup>2</sup>  Application duration: 60 minutes  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: MIBK = 8.28 m/hr (Sparks method)</p>
Automotive choke cleaner (DAA)	<p>Concentration of DAA: 30%</p> <p>Model: spray paint (in a garage) in Paint Fact Sheet (RIVM 2007b). Assume work done in garage.</p> <p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 15 minutes (13.67 min rounded up to 15 min, US EPA 2011)  Product amount: 165 g (US EPA 2011)  Room volume: 34 m<sup>3</sup> (garage)  Ventilation rate: 1.5 change per hour  Release area mode: increasing  Release area: 1 m<sup>2</sup>  Application duration: 15 minutes (US EPA 2011)  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: DAA = 10 m/hr (new default from RIVM)</p>
Paint/marker remover, spray (DAA)	<p>Concentration of DAA: 10%</p> <p>Model: spray paint (in unknown room) in Paint Fact Sheet (RIVM 2007b).</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 20 minutes  Product amount: 300 g  Room volume: 20 m<sup>3</sup> (garage)  Ventilation rate: 0.6 change per hour  Release area mode: increasing  Release area: 1 m<sup>2</sup>  Application duration: 15 minutes (US EPA 2011)  Molecular weight matrix: 3000 g/mol  Mass transfer coefficient: DAA = 2.95 m/hr (Sparks method)</p>
Paint thinner (for epoxy paints)	<p>Concentration: DAA = 5 - 10% (SDS 2017)</p> <p>Scenario: epoxy thinner, to clean brushes or surfaces. Assume this could be done where epoxy being used in the home (unspecified room)</p> <p>Inhalation – Exposure to vapour, evaporation model  Exposure duration: 30 minutes (Versar 1986)  Product amount: 400 g (500 mL (TDS 2015)/container x 0.8 g/ml, density of paint thinner) (Versar 1986)  Room volume: 20 m<sup>3</sup>  Ventilation rate: 0.6 change per hour  Mass transfer coefficient: 10 m/hr (new RIVM default)  Release area mode: constant  Release area: 0.078 m<sup>2</sup>  Molecular weight matrix: 3000 g/mol</p> <p>Dermal – instant application  Product amount on skin = 2.07 g (Versar 1986)</p>
Markers (MIBK, DAA)	<p>Concentration: MIBK = 10 - 30% in dry erase markers, DAA = 60 - 100% in permanent markers</p> <p>Scenario: markers (dry erase or permanent)</p> <p>Inhalation: used scenario from Children's Products Fact Sheet (RIVM 2002) – for MIBK only  Product amount: 300 mg  Duration: 45 minutes  Room volume: 20 cm<sup>3</sup>  Ventilation Rate: 0.6 per hour  Release area: 450 cm<sup>2</sup>  Molecular weight matrix: 450 g/mol</p>

Exposure scenario	Assumptions
	<p>Mass transfer coefficient: MIBK = 4.843 m/hr (Sparks method)</p> <p>Dermal or oral (ink scenario from the Arts &amp; Creative Materials Institute (ACMI) approach<sup>a</sup>)</p> <p>Acute or per event scenario:</p> <p>Intake (mg/kg-bw/event) = (Concentration of substance in marker (w/w) x estimated amount of ink per exposure (50 mg) x fraction absorbed) / body weight (kg)</p> <p>Amount of ink per exposure = 50 mg (Hansen et al. 2008)</p> <p>Chronic scenario:</p> <p>Intake (mg/kg-bw/day): ((Concentration of substance in marker (w/w) x ink laydown rate (µg/cm) x 25 cm ink line/day)/1000 µg/mg) / body weight (kg)</p> <p>Ink laydown rate = 100 µg/cm (90<sup>th</sup> percentile level for ink laydown of writing instruments<sup>b</sup>)</p>
Specialty coating (2,4-PD)	<p>Concentration: 2,4-PD = 1 – 5%</p> <p>Scenario: general coating on a truck or boat (applied in a 2-car garage) in DIY Fact Sheet (RIVM 2007a)</p> <p>Inhalation – Exposure to vapour, evaporation model</p> <p>Exposure duration: 60 minutes</p> <p>Product amount: 3000 g</p> <p>Room volume: 90 m<sup>3</sup></p> <p>Ventilation rate: 1.5 change per hour</p> <p>Release area mode: increasing</p> <p>Release area: 15 m<sup>2</sup></p> <p>Application duration: 60 minutes</p> <p>Molecular weight matrix: 3000 g/mol</p> <p>Mass transfer coefficient: 2,4-PD = 2.266 (Sparks method)</p>
Essential oil as air freshener (inhalation) (2,3-PD)	<p>Concentration of 2,3-PD: 0.1 – 1%</p> <p>Scenario: essential oil as air freshener (in a living room) in Cosmetics Fact Sheet (RIVM 2006)</p>

Exposure scenario	Assumptions
	<p>Inhalation – Exposure to vapour, constant rate model  Exposure duration: 240 minutes  Product amount: 1.08 g  Room volume: 58 m<sup>3</sup>  Ventilation rate: 0.5 changes per hour  Emission duration: 180 minutes</p>
Plug-in air freshener (inhalation) (2,3-PD)	<p>Concentration of 2,3-PD: 0.1 – 1%  Scenario: plug-in air freshener  Inhalation - exposure to vapour - instantaneous release scenario  Frequency: all day, every day  Exposure duration: 24 hour/day  Product amount: 1 plug-in contains ~26 mL of product and can last up to 30 days (P&amp;G c2017a<sup>a</sup>). Assume same amount emitted each day (26mL/30 days = ~0.9 mL or 0.9 g/day)  Room volume: 20 m<sup>3</sup>  Ventilation rate: 0.6/hr</p>
Gel air freshener (inhalation) (2,3-PD)	<p>Concentration of 2,3-PD: 1 – 5%  Scenario: gel air freshener  Inhalation: exposure to vapour - instantaneous release scenario  Frequency: all day, every day  Exposure duration: 24 hour/day  Product amount: 1 gel ~5.5 mL of product and can last up to 30 days (P&amp;G c2017b). Assume same amount emitted each day (5.5 mL/30 days = ~0.2 mL or 0.2 g/day)  Room volume: 20 m<sup>3</sup>  Ventilation rate: 0.6/hr</p>

<sup>a</sup> ACMI approach (personal communication, 2009 from ACMI to ESRAB, HC; unreferenced)

<sup>b</sup> personal communication, 2009 from Duke Medical Centre to ESRAB, HC; unreferenced

**Table B-4. Defaults used in PARAMs model to estimate mass transfer coefficients (Sparks method)**

Parameter	Value	Additional Information
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Density of air (g/cm <sup>3</sup> )	0.0011774	At 25 degrees Celsius, atmospheric pressure of 760 mmHg, and relative humidity of 50%
Viscosity of air (g/cm/s)	1.86E-04	At 25 degrees Celsius
Velocity of air (cm/s)	10	(McGready and Fontaine 2010 and Sparks et al. 1996)
Diffusivity in air (cm <sup>2</sup> /s)	MEK: 9.19E-02 MPK: 8.22E-02 MIBK: 7.49E-02 MIAK: 6.92E-02 DAA: 7.24E-02 Diacetyl: 8.91E-02 2,3-PD: 8.02E-02 2,4_PD: 8.02E-02	At 25 degrees Celsius
Length of surface for various scenarios	Nail polish: 20 cm (adult), 7 cm (toddler) Nail polish remover: 40 cm (adult), 14 cm (toddler) Lacquer remover: 2.5 m Adhesive remover: 1 – 5 m Paint thinner (floor coating): 3 – 5 m Truck bed paint: 3 – 5 m Spray paint: 1 – 2 m Multi-purpose adhesive: 10 – 20 cm Wood finish (floor): 3 – 5 m Markers: 25 cm Graffiti remover (spray): 1 – 2 m Eyeliner stickers: 8 cm General coating: 3 – 5 m Filler/putty: 2 – 5 cm	Values estimated taking into account release area listed in ConsExpo Fact Sheets for each specific scenario (if scenario not available in ConsExpo, used professional judgement)

## Appendix C. Inhalation exposures to diacetyl from microwave popcorn

The approach used in Zhu et al. (2001) and the Priority Substances List Assessment for 2-butoxyethanol (Environment Canada, Health Canada 2002) was used to convert the data from Rosati et al. (2007) on the emission of diacetyl from a bag of microwaved popcorn based on chamber studies to a concentration in air in a standard room. Details on the assumptions used are outlined below.

It was assumed that the emission of diacetyl from microwave popcorn follows first order decay and that there are no sink effects in the chamber. Given these assumptions, the concentration of substance in an emission chamber (or a room) is related to the emission factor as follows:

$$C = [(EF_0 \times A) / (V \times (N - k))] \times [\exp(-kt) - \exp(-Nt)] \quad (\text{equation 1})$$

where: C = the concentration of diacetyl in the chamber at any time [mg/m<sup>3</sup>]

EF<sub>0</sub> = the initial emission factor for diacetyl from the product sample [mg/m<sup>2</sup>/h]

A = the emitting surface area of the product sample [m<sup>2</sup>]

N = the number of air changes per hour in the chamber [h<sup>-1</sup>]

V = the volume of the chamber [m<sup>3</sup>]

t = the duration of the emission [h]

and k = emission decay constant [h<sup>-1</sup>]

For a slowly depleting or nearly constant emission source, the decay constant k approaches zero. When the test time t becomes infinite or a steady-state equilibrium is reached, equation 1 can be rewritten as:

$$C = (EF_0 \times A) / (V \times N) \quad (\text{equation 2})$$

Assumed steady-state equilibrium was achieved during product testing. For calculating the initial emission factors, equation 2 was rearranged to:

$$EF_0 = (C \times N \times V) / A \text{ [mg/m}^2\text{/h]} = [\text{mg/m}^3] \text{ [h-1][m}^3\text{]} / [\text{m}^2] \quad (\text{equation 3})$$

where N is the number of air changes per hour in the chamber, V is the cell volume and A is the emitting surface area, and the average concentrations of diacetyl emitted from the bag of 778.9 µg/bag (Rosati et al. 2007).

Step 1: Calculate the initial emission factor using equation 3 (data from Rosati et al. 2007).

Range of concentration (mg/m <sup>3</sup> )	N = ACH (h <sup>-1</sup> )	V = volume of chamber (m <sup>3</sup> )	A - emitting SA <sup>a</sup> (m <sup>2</sup> )	EF <sub>0</sub> (mg/m <sup>2</sup> /h)
5.8	2.3	0.515	0.1	<b>68.70</b>
0.02	2.3	0.515	0.1	<b>0.237</b>

<sup>a</sup> Assume emitting surface area is surface area of a popcorn bag, 1000 cm<sup>2</sup> (Borkowski 2007)

Step 2: Calculate the emission decay constant using  $k = EFO \cdot A/W$ , where W is the total evaporable amount of the substance in the source (W = average amount emitted from microwave popcorn bag 0.779 mg)

EF <sub>0</sub> (mg/m <sup>2</sup> /h)	A (m <sup>2</sup> )	W (mg)	k (h <sup>-1</sup> )
68.7	0.1	0.779	<b>8.82</b>
0.237	0.1	0.779	<b>0.03</b>

Step 3: Calculate the concentration in a standard room using equation 1

EF <sub>0</sub> (mg/m <sup>2</sup> /h)	A (m <sup>2</sup> )	V (m <sup>3</sup> )	N (h <sup>-1</sup> )	k (h <sup>-1</sup> )	t (h)	Concentration (mg/m <sup>3</sup> )
68.7	0.1	17.4	0.5	8.82	1	<b>0.0288</b>
0.237	0.1	17.4	0.5	8.82	1	<b>0.0001</b>

For 5.8 mg diacetyl/m<sup>3</sup>

Time (min)	Conc (mg/m <sup>3</sup> )
0	0
10	0.0328
20	0.0377
30	0.0364
40	0.0339
50	0.0313
60	0.0288
120	0.0175
180	0.0106
240	0.0064
300	0.0039
360	0.0024
Avg after 6 hrs	0.02

For 0.02 mg/diacetyl/m<sup>3</sup>

Time (min)	Conc (mg/m <sup>3</sup> )
0	0
10	0.00011
20	0.00013
30	0.00013
40	0.00012
50	0.00011
60	0.00010
120	0.00006
180	0.00004
240	0.00002
300	0.00001
360	0.00001
Avg after 6 hrs	0.00007

## Appendix D. Parameters for extrapolation

Substance	Study Parameters	Original dose	Converted dose	Formula
MIBK	2-year; 6h/day; 5 day/week	1843 mg/m <sup>3</sup>	101 mg/kg-bw/d	$1843 \times 0.31^a \times (6h/24h)^b \times (5d/7d)^c$
MIAK	69 exposure spanning 96 calendar days; 6h/day;	934 mg/m <sup>3</sup>	52 mg/kg-bw/d	$934 \times 0.31^a \times (6h/24h)^b \times (69d/96d)^d$
2.3-PD	RA from diacetyl 90- day study	90 mg/kg-bw/d	105 mg/kg-bw/d	$90 \times (100.12 / 86.09)^e$
2.3-PD	14-week; 6h/day; 5 day/week	51 mg/m <sup>3</sup>	12 mg/kg-bw/d	$51 \times 1.33^f \times (6h/24h)^b \times (5d/7d)^c$
2.3-PD	14-week; 6h/day; 5 day/week	102 mg/m <sup>3</sup>	24 mg/kg-bw/d	$102 \times 1.33^f \times (6h/24h)^b \times (5d/7d)^c$
2.4-PD	6h/day;GD6- 15	827 mg/m <sup>3</sup>	64 mg/kg-bw/d	$827 \times 0.31^a \times (6h/24h)^b$
2.4-PD	6h/day;5day/ week; 14- week	417 mg/m <sup>3</sup>	23 mg/kg-bw/d	$417 \times 0.31^a \times (6h/24h)^b \times (5d/7d)^c$
MO	6-week; 8h/day; 5 day/week	200 mg/m <sup>3</sup>	15 mg/kg-bw/d	$200 \times 0.31^a \times (8h/24h)^b \times (5d/7d)^c$

<sup>a</sup> Considering a standard rat body weight of 0.35 kg and volume of inhalation of 0.11 m<sup>3</sup>/day, resulting into a constant of 0.31 (from Health Canada 1994)

<sup>b</sup> exposure duration in a day

<sup>c</sup> duration of the study

<sup>d</sup> number of exposition

<sup>e</sup> molecular weight (substance/Read-across)

<sup>f</sup> Considering a standard mice body weight of 0.03 kg and volume of inhalation of 0.04 m<sup>3</sup>/day, resulting into a constant of 1.33 (from Health Canada 1994)