Draft screening assessment

Furan Compounds Group

Chemical Abstracts Service Registry Numbers
77-09-8
98-00-0
109-99-9
110-00-9

Environment and Climate Change Canada
Health Canada

August 2018

Synopsis

Pursuant to section 68 or 74 of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health conducted a screening assessment of four of five substances referred to collectively under the Chemicals Management Plan as the Furan Compounds Group. These four substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns. One of the five substances was subsequently determined to be of low concern through other approaches, and proposed decisions for this substance are provided in separate reports.[1] Accordingly, this screening assessment addresses the four substances listed in the table below.

Substances in the Furan Compounds Group

CAS RN	Domestic Substances List (DSL) name	Common name
77-09-8[b]	1(3H)-Isobenzofuranone, 3,3-bis(4-hydroxyphenyl)-	Phenolphthalein
98-00-0	2-Furanmethanol	Furfuryl alcohol
109-99-9	Furan, tetrahydro-	Tetrahydrofuran
110-00-9[b]	Furan	Furan

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

[b] 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.

In 2011, no Canadian imports were reported for furan or phenolphthalein. Furfuryl alcohol and tetrahydrofuran were each reported to be imported into Canada in quantities ranging from 100 000 to 1 000 000 kg. These substances were not reported to be manufactured in Canada in 2011.

Food is expected to be the primary source of exposure to furan for Canadians. It can be formed in very low quantities from natural food constituents during heat treatment. Furan is released to air as a gas phase component of cigarette smoke, wood smoke and exhaust gas from diesel and gasoline engines. Furan is also used as a solvent for resins and as a reactant/intermediate in the production of agricultural chemicals and pharmaceuticals, but was not identified in products available to consumers.

[1] Proposed conclusions for the substance bearing the CAS RN 126-33-0 are provided in the “Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances” screening sssessment.

Phenolphthalein is primarily used as an acid/base indicator. It is also used in adhesives and sealants, including colour-change glue sticks.

Furfuryl alcohol is used as a solvent in cleaning and paint-removal, as an intermediate in the manufacture of resins and plastics, and as a viscosity reducer for epoxy resins. It may also be used as a food flavouring agent. Furfuryl alcohol is an ingredient in a wood stripper that is available to the general population in Canada.

Tetrahydrofuran is used mainly as a solvent in the production of resins and plastics, particularly polytetramethylene ether glycol (PTMEG), as well as in the manufacture of paints and coatings, paint and varnish removers, and adhesives, such as PVC cement.

The ecological risks of the substances in the Furan Compounds Group in this assessment 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, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. The ERC identified furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran 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 furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran. It is proposed to conclude that furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran 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.

Furan was assessed by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) in 2011 and, more recently, the National Center for Toxicology Research of the US Food and Drug Administration (US FDA) has further characterized the potential hazard of furan. The critical effect for characterization of risk to human health for furan is liver toxicity. Exposure of the general population of Canada to furan is expected to be primarily through the diet. The margins between estimates of exposure to furan in the diet and levels associated with liver effects from laboratory studies are considered adequate to address uncertainties in exposure and health effects data used to characterize risk.

The International Agency for Research on Cancer (IARC) classified phenolphthalein as Group 2B (“possibly carcinogenic to humans”), with “inadequate evidence” of

carcinogenicity in humans and “sufficient evidence” of carcinogenicity in laboratory animals based on tumours in a range of tissues, possibly related to a mutagenic process. The US National Toxicology Program (NTP) considers phenolphthalein “reasonably anticipated” to be a carcinogen. The critical non-cancer effects are changes to sperm parameters and decreased fertility in laboratory animals. Exposure of the general population to phenolphthalein through environmental media and food is not expected. Phenolphthalein was identified in a limited number of products (colour-change glue sticks) available to Canadians, including children. The margins between levels of exposure to phenolphthalein in glue sticks and estimates of cancer potency and non-cancer effect levels from laboratory studies are considered adequate to address uncertainties in exposure and health effects data used to characterize risk.

Furfuryl alcohol has been previously evaluated by the US Environmental Protection Agency (US EPA) Cancer Assessment Review Committee (CARC), and its use as a food flavouring agent has been evaluated by JECFA. The US EPA CARC report classified furfuryl alcohol as “likely to be carcinogenic to humans” on the basis of studies in laboratory animals. Critical non-cancer effects are liver toxicity in laboratory animals exposed orally. By the dermal route, critical effects are skin sensitization and adverse clinical signs and mortality. Critical effects following inhalation exposure are a decreased breathing rate, decreased body weight gain, and mortality.

Oral exposure to furfuryl alcohol may occur through consumption of food as well as from ingestion of dust. The majority of dietary exposure is expected to be from its presence as a naturally-occurring component of food. Margins of exposure for oral exposure to furfuryl alcohol from environmental media are considered adequate to account for uncertainties in exposure and health effects data used to characterize risk.

Inhalation and dermal exposure to furfuryl alcohol may occur during use of products available to consumers. The margins of exposure between the acute inhalation exposure to furfuryl alcohol during the use of wood stripper and the lowest acute inhalation effect level in laboratory studies are considered potentially inadequate to account for uncertainties in exposure and health effects data used to characterize risk.

Tetrahydrofuran has been assessed by the US EPA Integrated Risk Information System (IRIS). Under the US EPA’s 2005 guidelines for carcinogen risk assessment, tetrahydrofuran has “suggestive evidence of carcinogenic potential” based on studies in laboratory animals. Critical non-cancer endpoints for repeated inhalation exposure to tetrahydrofuran are central nervous system toxicity (narcosis), increased liver weight, and reduced pup survival in a developmental toxicity study. The critical effect for a single inhalation exposure to tetrahydrofuran was effects on the central nervous system (diminished response to stimulus).

Exposure of Canadians to tetrahydrofuran occurs primarily through inhalation of indoor air. The margins of exposure between the measured indoor air concentrations in Canada with the cancer and non-cancer critical effect levels are considered adequate to account for uncertainties in exposure and health effects data used to characterize risk.

The margin of exposure between the acute inhalation exposure to tetrahydrofuran during the use of PVC cement and the critical acute inhalation effect level results in a margin of exposure that is considered potentially inadequate to account for uncertainties in exposure and health effects data used to characterize risk.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that furan and phenolphthalein do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in quantities or concentrations 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 furfuryl alcohol and tetrahydrofuran meet the criteria under paragraph 64(c) of CEPA as they are entering the environment in quantities or concentrations or under conditions that constitute or may constitute a danger in Canada to human life or health.

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

Therefore, it is proposed to conclude that furfuryl alcohol and tetrahydrofuran meet one or more of the criteria set out in section 64 of CEPA.

It is proposed that furfuryl alcohol and tetrahydrofuran do not meet the persistence or bioaccumulation criteria as set out in the Persistence and Bioaccumulation Regulations of CEPA.

1. Table of Contents

Synopsis ..... **i**
1. Introduction **1**
2. Identity of Substances **3**
3. Physical and Chemical Properties **4**
4. Sources and Uses **5**
5. Environmental Fate and Behaviour **9**
5.1 Environmental Persistence 9
5.2 Potential for Bioaccumulation 9
6. Potential to Cause Ecological Harm **9**
6.1 Characterization of Ecological Risk 9
7. Potential to Cause Harm to Human Health **12**
7.1 Furan 12
7.1.1 Exposure assessment 12
7.1.2 Health effects assessment 13
7.1.3 Characterization of risk to human health 15
7.1.4 Uncertainties in evaluation of risk to human health 16
7.2 Phenolphthalein 16
7.2.1 Exposure assessment 16
7.2.2 Health effects assessment 17
7.2.3 Characterization of risk to human health 18
7.2.4 Uncertainties in evaluation of risk to human health 20
7.3 Furfuryl Alcohol 20
7.3.1 Exposure assessment 20
7.3.2 Health effects assessment 23
7.3.3 Characterization of risk to human health 26
7.3.4 Uncertainties in the evaluation of risk to human health 29
7.4 Tetrahydrofuran 30
7.4.1 Exposure assessment 30
7.4.2 Health effects assessment 31
7.4.3 Characterization of risk to human health 35
7.4.4 Uncertainties in evaluation of risk to human health 36
8. Conclusion **37**
References **39**
Appendices **45**
Appendix A. Dietary exposure estimates 45
Appendix B. Estimated exposure to phenolphthalein 46
Appendix C. Estimated exposures to furfuryl alcohol 47
Appendix D. Estimated exposures to tetrahydrofuran 49

List of Tables

Table 2-1. Substance identities 3
Table 3-1. Physical and chemical property values (at standard temperature) for furan 4
Table 3-2. Physical and chemical property values (at standard temperature) for phenolphthalein 4
Table 3-3. Physical and chemical property values (at standard temperature) for furfuryl alcohol 4
Table 3-4. Physical and chemical property values (at standard temperature) for tetrahydrofuran 4
Table 4-1. Summary of information on Canadian imports of the Furan Compounds Group submitted pursuant to a survey under section 71 of CEPA[a] 5
Table 4-2. Summary of Canadian uses of the Furan Compounds Group (based on consumer and commercial DSL codes reported by the user, pursuant to a survey under section 71 of CEPA (Environment Canada 2013) 6
Table 4-3. Additional uses in Canada for each of the substances in the Furan Compounds Group 7
Table 6-1. Ecological Risk Classification results for the four substances in the Furan Compounds Group 11
Table 7-1. Margins of exposure (MOE) between usual dietary exposure to furan and a BMDL10 of 86 ug/kg bw/ per day. 16
Table 7-2. Relevant exposure and non-cancer critical health effect values for phenolphthalein, as well as margins of exposure, for determination of risk. 19
Table 7-3. Relevant exposure and hazard values for furfuryl alcohol, as well as margins of exposure, for determination of risk 28
Table 7-4. Relevant exposure and hazard values for tetrahydrofuran, as well as margins of exposure, for determination of risk 36

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 on four of the five substances referred to collectively under the Chemicals Management Plan as the Furan and Derivatives Group, to determine whether they present or may present a risk to the environment or to human health. These four substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

One other substance (CAS RN[2] 126-33-0, thiophene, tetrahydro-, 1,1-dioxide) was considered in the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016a) and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Document (Health Canada 2016a) and was identified as being of low concern to both human health and the environment. As such, it is not further addressed in this report. A proposed conclusion for this substance is provided in the Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Draft Screening Assessment (ECCC, HC 2017). The four substances addressed in this draft screening assessment report will hereinafter be referred to as the Furan Compounds Group.

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

Although the four substances included here were grouped together on a structural basis, given the significant differences in use patterns and health effects, they are considered individually in this assessment.

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

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure, including additional information submitted by stakeholders. Data relevant to the health assessment were identified up to May 2016. Empirical data from key studies as well as some results from models were used to reach proposed conclusions.

All of the individual substances in the Furan Compounds Group currently being evaluated have previously been reviewed internationally. Furan has been evaluated by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA 2011). Phenolphthalein has been assessed through the IARC Monographs Programme, and an IARC monograph is available (IARC 2000). Furfuryl alcohol has been evaluated as a flavouring agent by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and there is a recent review by the JECFA available (WHO 2012). Tetrahydrofuran has been assessed by the US EPA and there is a recent toxicological review in support of the summary information on the Integrated Risk Information System (IRIS) (US EPA 2011). These assessments undergo rigorous review and endorsement. Health Canada and Environment and Climate Change Canada consider these assessments reliable. These documents were used to inform the health effects characterization in this screening assessment. Literature searches were conducted from one year prior to the publication of each review.

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 ERC document was subject to an external peer review and a 60-day public comment period. The human health portions of this assessment have undergone peer review. Comments on the technical portions relevant to human health were received from Lynne Haber (Department of Environmental Health, College of Medicine, University of Cincinnati), Pam Williams (E-Risk Sciences), and Michael Dourson (Department of Environmental Health, College of Medicine, University of Cincinnati). While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

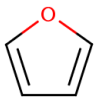
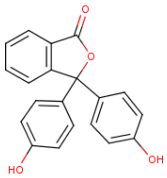
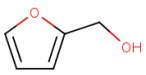
This screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA, by examining scientific

information and incorporating a weight–of-evidence approach and precaution.[3]The draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

2. Identity of substances

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

Table 2-1. Substance identities

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
110-00-9	Furan	 C_4H_4O	68.07
77-09-8	1(3H)-Isobenzofuranone, 3,3-bis(4-hydroxyphenyl)- (Phenolphthalein)	 $C_{20}H_{14}O_4$	318.33
98-00-0	2-Furanmethanol (Furfuryl alcohol)	 $C_5H_6O_2$	98.10
109-99-9	Furan, tetrahydro- (Tetrahydrofuran)	 C_4H_8O	72.11

[3]A determination of whether one or more of the criteria of section 64 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 used by 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.

3. Physical and chemical properties

A summary of physical and chemical properties of the substances in the Furan Compounds Group are presented in Table 3-1, Table 3-2, Table 3-3, and Table 3-4. Additional physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Physical and chemical properties (at standard temperature) for furan

Property	Value	Reference(s)
Physical state	liquid	Haynes 2017
Melting point (°C)	-85.6	Haynes 2017
Vapour pressure (Pa)	8.0×10^4	Haynes 2017
Water solubility (mg/L)	1×10^4	Haynes 2017
log K_{ow} (dimensionless)	1.34	Haynes 2017

Table 3-2. Physical and chemical properties (at standard temperature) for phenolphthalein

Property	Value	Reference(s)
Physical state	solid	Haynes 2017
Melting point (°C)	262	Haynes 2017
Vapour pressure (Pa)	8.99×10^{-11}	US EPA 2003, cited in HSDB 1983- b
Water solubility (mg/L)	3.36	ECHA c2007-2016a
log K_{ow} (dimensionless)	0.9	ECHA c2007-2016a

Table 3-3. Physical and chemical properties (at standard temperature) for furfuryl alcohol

Property	Value	Reference(s)
Physical state	liquid	Haynes 2017
Melting point (°C)	-14.5	Haynes 2017
Vapour pressure (Pa)	97	Haynes 2017
Water solubility (mg/L)	1×10^6; miscible	ECHA c2007-2016b; McKillip and Sherman 1978
log K_{ow} (dimensionless)	0.15	ECHA c2007-2016b

Table 3-4. Physical and chemical properties (at standard temperature) for tetrahydrofuran

Property	Value	Reference(s)
Physical state	liquid	Haynes 2017
Melting point (°C)	-108.4	Haynes 2017
Vapour pressure (Pa)	1.7×10^4	ECHA c2007-2016c
Water solubility (mg/L)	1×10^6; miscible	ECHA c2007-2016c
log K_{ow} (dimensionless)	0.46	Haynes 2017

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

4. Sources and uses

Furan and furfuryl alcohol can be formed from naturally occurring components of food (Burdock 2010; Health Canada 2016b). Furan in foods can form through multiple pathways involving different naturally present starting compounds that undergo thermal degradation or chemical rearrangement during food processing. It has been detected at low levels in various foods, including coffee, canned foods, juices and sauces (Health Canada 2016b). Furan is released to air as a gas phase component of cigarette smoke, wood smoke and exhaust gas from diesel and gasoline engines (Kleindienst et al. 1986, as cited in HSDB 1983-a; Hampton et al. 1982, as cited in HSDB 1983-a). Furfuryl alcohol is naturally occurring in a wide range of foods, including coffee, roasted nuts and grains, alcoholic beverages, fruits, vegetables, meats, and dairy products (Burdock 2010; HSDB 1983-c). It can be formed from the acid hydrolysis or heating of polysaccharides that contain pentose and hexose fragments (Adams et al. 1997). Furfuryl alcohol has also been found in smoke from burning wood (McKenzie et al. 1995, as cited in HSDB 1983-c).

Phenolphthalein and tetrahydrofuran do not occur naturally in the environment.

All of the substances in the Furan Compounds Group have been included in surveys issued pursuant to section 71 of CEPA (Canada 2012). None of these substances were reported to be manufactured in Canada in 2011. Table 4-1 presents a summary of the total import quantities for the Furan Compounds Group in 2011.

Table 4-1. Summary of information on Canadian imports of the Furan Compounds Group submitted pursuant to a survey under section 71 of CEPA[a]

Common name	Total imports (kg)	Reporting year
Furan	NR	2011
Phenolphthalein	NR	2011
Furfuryl alcohol	100 000–1 000 000	2011
Tetrahydrofuran	384 594	2011

Abbreviations: NR, No report of import above the reporting threshold

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

Data from the National Pollutant Release Inventory (NPRI) indicate that approximately 200 to 300 tonnes of furfuryl alcohol were released to air in 2013, 2014 and 2015, that approximately 200 tonnes of tetrahydrofuran were released to air in 2013, and that approximately 20 tonnes of tetrahydrofuran were released to air in 2014 and 2015 (NPRI 2016).

Table 4-2 presents a summary of Canadian uses for phenolphthalein, furfuryl alcohol, and tetrahydrofuran based on information received pursuant to survey under section 71 of CEPA (Environment Canada 2013). Other uses were reported but are not indicated herein as they were identified by the submitter as constituting confidential business information. No uses were reported for furan. Information submitted for the 2011 calendar year showed that in Canada furan was manufactured or imported solely as a contaminant or by-product (Environment Canada 2013).

Table 4-2. Summary of Canadian uses of the Furan Compounds Group (based on consumer and commercial DSL codes reported by the user, pursuant to a survey under section 71 of CEPA (Environment Canada 2013)

Uses	Phenolphthalein	Furfuryl alcohol	Tetrahydrofuran
Adhesives and sealants	Y	N	Y
Automotive, aircraft and transportation	N	Y	Y
Building or construction material	N	Y	Y
Metal materials	N	Y	N
Paints and coatings	N	Y	Y
Other	N	N	Y
Plastics and rubber material	N	N	Y

Furan is used elsewhere as a solvent for resins and as a reactant/intermediate in the production of agricultural chemicals and pharmaceuticals (NTP 2014; ECHA c2007-2015).

Globally, phenolphthalein is used as an acid/base indicator, as a laboratory reagent, and as an intermediate in the manufacture of other chemicals and products (ECHA c2007-2016a; ChemIDplus 1993- ; HSDB 1983- b). Phenolphthalein is used in glue sticks that are available to the general population in Canada (MSDS 2015). In addition, limited information suggests the possibility that phenolphthalein may be present in other colour-change glue products and certain colour-change children's toys sold in Canada.

Furfuryl alcohol is used as a solvent in cleaning and paint-removal, as an intermediate in the manufacture of resins and plastics, and as a viscosity reducer for epoxy resins; (HSDB 1983- c; ECHA c2007-2016b). Furfuryl alcohol is used in a wood stripper that is available to the general population in Canada (MSDS 2016).

Tetrahydrofuran is used mainly as a solvent in the production of resins and plastics, particularly polytetramethylene ether glycol (PTMEG), as well as in the manufacture of paints and coatings, paint and varnish removers, and adhesives such as PVC cement. There are some reports of use in furniture polish and cleaners, laundry starch preparations and stain removers, but no evidence of consumer applications of these uses was identified in Canada (HSDB 1983- d; OECD 2000; ECHA c2007-2016c). Tetrahydrofuran is used in products available to the general population in Canada (PVC cement) (MSDS 2014; MSDS 2013).

Additional Canadian uses of the substances in the Furan Compounds Group are listed in Table 4-3.

Table 4-3. Additional uses in Canada for each of the substances in the Furan Compounds Group

Use	Furan	Phenolphthalein	Furfuryl alcohol	Tetrahydrofuran
Food additive[a]	N	N	N	N
Food packaging materials[b]	Y (component of adhesives for use in some non-food contact applications)	N	N	Y (residual in resins, which are intended to be used as a film, coating or molded articles)
Internal Drug Product Database as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products in Canada	N	Y (all products cancelled post-market)	N	N
Natural Health Products Ingredients Database[d]	N	N	Y	N
Licensed Natural Health Products Database as being present as medicinal or non-medicinal ingredient in natural health	N	N	N	N

Use	Furan	Phenolphthalein	Furfuryl alcohol	Tetrahydrofuran
products in Canada[e]				
List of Prohibited and Restricted Cosmetic Ingredients[f]	N	Y	N	N
Notified to be present in cosmetics, based on notifications submitted under the Cosmetic Regulations to Health Canada[g]	N	N	N	Y (may be in nail adhesives)
Formulant in pest control products registered in Canada[h]	N	N	Y (no list assigned)	Y (list 3)

[a] personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced
[b] personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced
[c] DPD [modified 2015]
[d] NHPID [modified 2017]
[e] LNHPD [modified 2016]
[f] Health Canada [modified 2015]
[g] personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced
[h] Health Canada 2010; personal communications, emails from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced

Historically, phenolphthalein was used as a medical drug (laxative). In Canada, the authority to sell and distribute phenolphthalein drug products was revoked in 1997 (DPD [modified 2015]).

Furfuryl alcohol may be used as a food flavouring. The Food Chemicals Codex (FCC) indicates that furfuryl alcohol has the function of a flavouring agent (FCC USP 2016), and it is listed in Fenaroli's Handbook of Flavor Ingredients (Burdock 2010). The European Union permits furfuryl alcohol to be used as a flavouring agent in food (EU Food Flavourings Database [modified 2016]). No definitive information is available concerning the potential use of furfuryl alcohol as a food flavouring in Canada (personal communication, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated December 2016; unreferenced). Furfuryl alcohol is listed in the Natural Health Products Ingredients Database with a non-medicinal role for oral use as flavour enhancer in natural health products (NHPs).

However, it is not listed in the Licensed Natural Health Products Database as being present in currently licensed NHPs in Canada (LNHPD [modified 2016]; NHPID [modified 2017]).

Tetrahydrofuran may be present as a residual in resins used in food packaging materials. Tetrahydrofuran has also been identified as a component in cleaners for possible use in food processing establishments (personal communication, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated December 2016; unreferenced).

5. Environmental fate and behaviour

5.1 Environmental persistence

According to models used in ERC (ECCC 2016b), furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran are expected to degrade and not be persistent in water, air, sediment or soil .

5.2 Potential for bioaccumulation

Given their low K_{ow} and low bioconcentration factors (ECCC 2016b), furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran 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 Furan Compounds 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, with weighted considerations of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., LC_{50}) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and from responses to

surveys under section 71 of CEPA, or they were generated using selected Quantitative Structure-Activity Relationship (QSAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

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

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

ERC uses a weighted approach to minimize the potential for both over and under classification of hazard, exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016a. The following describes two of the more substantial areas of uncertainty. Error 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 value 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 according to 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 four substances in the Furan Compounds Group and the hazard, exposure and risk classification results are presented in ECCC (2016c).

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

Table 6-1. Ecological risk classification results for the four substances in the Furan Compounds Group

Common name	ERC hazard classification	ERC exposure classification	ERC risk classification
Furan	low	low	low
Phenolphthalein	low	low	low
Furfuryl alcohol	low	low	low
Tetrahydrofuran	low	low	low

On the basis of low hazard and low exposure classifications according to ERC, furan, furfuryl alcohol, and terahydrofuran 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.

On the basis of low hazard and low exposure potential according to ERC, phenolphthalein was classified as having a low potential for ecological risk. However, structural alerts from the OECD toolbox identified phenolphthalein as having endocrine disrupting properties. The potential effects and how they may manifest in the environment were not further investigated due to the low exposure of this substance. On the basis of current use patterns, it is unlikely that this substance results in concerns for the environment in Canada.

7. Potential to cause harm to human health

7.1 Furan

7.1.1 Exposure assessment

Environmental media and food

Exposure of the general population to furan from air (Won and Lusztyk 2011; Crews 2009), water, soil and/or dust is not expected to be significant.

Furan has been detected in a variety of foods, notably those in cans or jars, where it can be formed in very low quantities (µg/kg or parts per billion range) from natural food constituents during heat treatment.

Dietary exposure estimates to furan for the general Canadian population were derived by Health Canada's Food Directorate. Estimates of dietary exposure to furan can include certain alkylated derivatives that may also be present, including 2-methylfuran and 3-methylfuran. However, the estimates from this assessment are limited to furan. Detailed dietary exposures to furan for various age-sex groups are provided in Table A-1 of Appendix A. Canadian occurrence data were obtained from targeted surveys conducted by Health Canada (Becalski et al. 2016, 2010, 2005) as well as targeted surveys conducted by the Canadian Food Inspection Agency (CFIA) between 2013 and 2016. In total, results from over 550 food samples, including canned or jarred foods such as baby foods, fruits, vegetables, meats, pasta and soups, as well as brewed coffee, sauces, potato chips, breakfast cereals and alcoholic beverages, were available. Canadian data for furan in infant formula were very limited. Therefore, data from the United States Food and Drug Administration (US FDA 2008) were used as a surrogate, as the types and brands of infant formula available in the United States are similar to those available in Canada.

Food consumption data from the Canadian Community Health Survey (CCHS) Cycle 2.2 (Statistics Canada 2004) were used to estimate usual dietary exposures, which were calculated using a probabilistic approach. Usual exposures reflect the usual amount of furan exposure in the population and better represent average and higher percentile long-term dietary intakes. The furan concentration in a given food was randomly multiplied by the relevant food consumption rate reported by each individual respondent of the CCHS. Furan exposure from all food and beverage commodities was summed to give an estimate of total dietary exposure for each individual, as well as a distribution of total dietary exposure to furan for the population. Mean and 90th percentile exposures range from 0.08 to 0.25 µg/kg bw/day and from 0.14 to 0.52 µg/kg bw/day, respectively. From early childhood to late teens, exposure to furan decreases with age and shows a tendency to increase in adults. Coffee is the main contributor to furan exposure in adult age groups, and the increase in furan exposure in adults is

mainly attributed to increased coffee consumption. For children, jarred and canned foods, canned fruit juices and sauces were identified as the largest contributors to dietary furan exposure.

Products available to consumers

No information was identified that would indicate the presence of furan in products available to consumers. Therefore, exposure to furan from this source is not expected.

7.1.2 Health effects assessment

The health effects of furan have been extensively summarized in JECFA (WHO 2011), in which the liver was identified as the primary site of toxicity and hepatocellular neoplasms in female B6C3F_1 mice were selected as the critical effect for hazard characterization. Using benchmark dose modelling software, JECFA (WHO 2011) calculated a benchmark dose of a 10% response above background ($BMDL_{10}$) of 960 µg/kg bw/day and a genotoxic or 'non-threshold' mode of action was conservatively assumed. However, at the time of the JECFA assessment, significant uncertainty regarding furan's hazard characterization and mode of action was identified. Specifically, although the evidence in mice indicated a threshold mode of action for cancer at lower doses (Moser et al. 2009), adequate dose response data for cholangiocarcinomas in F344 rats, a more sensitive species, were not available, and it was uncertain whether furan might act via a DNA-reactive genotoxic metabolite or via repeated cytotoxicity and regenerative proliferation. At the time of the assessment, the JECFA Committee noted that there were "ongoing studies in rats to extend the dose-response data and address mechanistic aspects."

Subsequent to the JECFA (WHO 2011) assessment, significant work has been completed to further characterize the potential hazard of furan, including a chronic toxicity study in rats conducted by the US FDA's National Center for Toxicology Research (NCTR) and a number of studies that elucidate furan's carcinogenic mode of action.

A brief overview of mechanistic and toxicological information considered critical to the hazard characterization for dietary exposure to furan is provided herein.

Mice

Moser et al. (2009) demonstrated that furan does not initiate cancer in the livers of female B6C3F1 mice in the absence of significant prolonged cytotoxicity (for a comprehensive evaluation of the full study, refer to JECFA 2011). To further elucidate the carcinogenic mode of action of furan in mice, Terrell et al. (2014) exposed female B6C3F1 Big Blue® transgenic mice to a carcinogenic dose of furan by gavage (i.e., 15 mg/kg bw/day; the top dose in the NTP 2-year cancer study in mice) for 5 days per week for 6 weeks or once weekly for 3 weeks. Big Blue® transgenic mice are bred to have multiple copies of recoverable target genes integrated into their genome; this

allows gene mutations to be specifically measured in target tissues. Terrell et al. (2014) reported that furan did not significantly increase the percentage of mutation frequencies under either treatment condition. Histopathological analysis revealed multifocal, hepatocellular necrosis admixed with reactive leukocytes and pigment-laden Kupffer cells, enhanced oval-cell hyperplasia, and increased hepatocyte mitoses, some of which were atypical. On the basis of these findings, Terrell et al. (2014) proposed that an indirect mechanism of genotoxicity is responsible for the hepatocellular tumours in mice (i.e., chronic cytotoxicity followed by inflammation and secondary cell proliferation).

Additionally, Jackson et al. (2014) conducted a toxicogenomic analysis on the livers of B6C3F1 female mice that had been exposed to 0, 1, 2, 4 or 8 mg furan/kg bw/day by oral gavage for 3 weeks (n = 10 per dose). The analysis was focussed on female mice because females have a lower spontaneous hepatocellular tumour rate than males. The results from Jackson et al. (2014), which indicated enrichment for pathways responsible for cytotoxicity and the involvement of genes known to be required for liver regeneration, support the hypothesis that furan's primary mode of action in mice is cytotoxicity, followed by cellular proliferations and regeneration. Jackson et al. (2014) also suggested that at higher doses an indirect genotoxic mechanism may be at work via reactive oxygen species generation.

Rats

Similar to the Moser et al. (2009) cancer study in female mice, NCTR (2016) demonstrated that furan does not initiate cancer in the livers of male F344 rats in the absence of significant, prolonged cytotoxicity. A review of the NCTR (2016) study was published by Von Tungeln et al. (2016). In the NCTR (2016) study, the most sensitive effect observed in treatment animals appears to be cholangiofibrosis, which is characterized by dilated to cystic bile ducts, often irregular, filled with mucinous and cellular debris, surrounded by dense collagenous connective tissue, with a prominent inflammatory cell infiltrate. The NOAEL for this study is considered to be 0.044 mg/kg bw/day. The LOAEL of 0.092 mg/kg bw/day is based on a single incidence of 'minimal' cholangiofibrosis being observed following 2 years of exposure. Although no evidence of cholangiocarcinomas were evident, at the top dose (2 mg/kg bw/day) hepatocholangiocarcinomas were observed in 2/50 treatment animals.

To further investigate the carcinogenic mode of action of furan, McDaniel et al. (2012) exposed male Big Blue® transgenic rats to furan at doses of 2, 8, 16 or 30 mg/kg bw/day via gavage for 8 weeks (5 days/week). Systemic genotoxicity was evaluated using the peripheral blood micronucleus assay, the Hprt lymphocyte gene mutation assay, and the Pig-a lymphocyte and peripheral red blood cell (RBC) gene mutation assays. In addition, liver ceII mutant frequency in the Big Blue® transgene and liver DNA damage were measured using the in vivo Comet assay. The responses in the micronucleus assay and all the gene mutation assays were uniformly negative. However, positive responses in the Comet assay were observed in the two high-dose groups (i.e., 16 and 30 mg/kg bw/day).

Dong et al. (2016) demonstrated that furan-induced liver toxicity in male F344 rats exposed to 0.03, 0.12, 0.5 or 2 mg/kg bw/day over 90 days was associated with changes in the expression of genes associated with oxidative stress, inflammation, apoptosis, and cell proliferation. According to Dong et al. (2016), the vast majority of gene expression changes were observed in the highest-dose group, where the majority of the changes were unique and indicated a clear transition in the nature of the transcriptional response. For example, at 0.03 mg/kg bw/day dose, gene expression was not significantly different from control for the vast majority of the genes measured; at 0.12 and 0.5 mg/kg bw/day doses, genes predominantly associated with oxidative stress and inflammation were affected; and at 2 mg/kg bw/day, some genes associated with a DNA damage response were affected.

Mechanistic aspects

In the case of furan, the relative role of threshold and non-threshold modes of action likely varies with dose, species, and environmental conditions. Available evidence supports that at high doses (≥ 2 mg/kg bw/day), the combination of threshold and non-threshold mechanisms may lead to the proliferation of stable genetic alterations. The weight of evidence, however, for carcinogenesis at lower doses (< 2 mg/kg bw/day), strongly suggests that the predominant mode of furan carcinogenesis is via a threshold mode of action and is consistent with secondary genotoxicity associated with cytotoxicity, oxidative stress, and inflammation. Therefore, a biological threshold is believed to exist, and a level of human exposure without significant risk can be established based on the available data.

7.1.3 Characterization of risk to human health

The critical effect for characterization of risk to human health for furan is liver cell (e.g., hepatocyte and cholangiocyte) cytotoxicity. An average lower 95% confidence interval for the $BMDL_{10}$ for furan was computed using the methodology in Wheeler and Bailer (2008) and the online EFSA benchmark dose response modelling tool, the EFSA ShinyProxy. The average $BMDL_{10}$ of 86 µg/kg bw/day is based on the incidence of cholangiofibrosis in male F344 rats observed in NCTR (2016), adjusting for the 5 days/week dosing regimen.

Exposure of the general population of Canada to furan is expected to be primarily through the diet. During childhood and adolescence, the majority of dietary exposure is likely to be from jarred and canned foods, while most of the exposure during adulthood is expected to be from coffee consumption. Average usual dietary exposures considering all age groups range from 0.08 to 0.25 µg/kg bw/day, and high-end usual exposure estimates range from 0.14 to 0.52 µg/kg bw/day.

A comparison of the lowest estimated $BMDL_{10}$ (86 µg/kg bw/day) with the estimated average dietary exposures to furan in food yield margins of exposure (MOEs) of between 355 and 1057, depending on the age group (Table 7-1). The MOEs based on high-end exposures range from 171 to 572. The MOEs were calculated for age groups

9 years and above by averaging the usual exposure estimates after adjusting for the number of male and female survey respondents in each age group. These MOEs are considered to be adequate to address the uncertainties in the health effects and exposure databases.

Table 7-1. Margins of exposure (MOE) between usual dietary exposure to furan and a BMDL10 of 86 ug/kg bw/ per day.

Age group (years)*	Margin of exposure	
	Mean	90th percentile
1 to 3	397	251
4 to 8	612	357
9 to 13	975	560
14 to 18	1057	572
19 to 30	541	247
31 to 50	355	171
51 to 70	361	180
≥ 71	408	198

*Males and females are both included in each age group

7.1.4 Uncertainties in evaluation of risk to human health

Furan levels can be reduced in certain foods through volatilization when the foods are heated and stirred. Jarred and canned foods were not heated and stirred prior to measuring furan concentrations, while brewed coffee samples were transferred to an air-tight container and cooled, thus preventing any volatilization of furan. As a result, dietary exposures to furan in this assessment may be overestimated.

7.2 Phenolphthalein

7.2.1 Exposure assessment

Environmental media and food

No environmental monitoring data relevant to current exposures in Canada have been identified for phenolphthalein. No food uses of this substance have been identified. Exposure of the general population of Canada to phenolphthalein from environmental media and food is not expected considering the physical-chemical properties (low water solubility, very low vapour pressure, and low log K_{ow}), volumes, and uses of this substance.

Products available to consumers

Phenolphthalein is used in certain glue sticks (purple glue sticks, at 0.2%) that may result in consumer exposure (MSDS 2015). Exposures were estimated using ConsExpo Web (ConsExpo 2016) or algorithms from the model (RIVM 2007, 2002). Estimates of exposure range from 0.001 mg/kg bw/day for adults to 0.004 mg/kg bw/day for toddlers. A dermal load of 80 mg was assumed on the basis of the do-it-yourself product factsheet from RIVM (2007). This scenario was for universal glue in a tube, used by adults. A frequency of use of 3 times per week was assumed on the basis of information on use of children's products (Health Canada 2011) and considering additional information on craft supplies and do-it-yourself products (RIVM 2007; ECETOC 2004). Exposure to phenolphthalein during use of glue sticks is expected to be primarily via the dermal route, but it was considered that some of the exposure may be through the oral route for toddlers and children, resulting from object-to-mouth or hand-to-mouth behaviours. It was assumed that complete absorption occurs by both the oral and dermal routes. Direct oral exposure of younger children due to incidental ingestion is also possible (Health Canada 2011; personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced). However, such exposure was not quantified. The volatility of phenolphthalein is very low, which leads to a negligible estimate of exposure from inhalation during product use (per-event air concentration of $2x10^{-10}mg/m^3$) (see Appendix B for parameters used in exposure estimates).

7.2.2 Health effects assessment

The health effects of phenolphthalein are summarized in IARC (2000) and the US NTP Report on Carcinogens (2014). IARC considers phenolphthalein to be in Group 2B ("possibly carcinogenic to humans"), with "inadequate evidence" of carcinogenicity in humans and "sufficient evidence" of carcinogenicity in experimental animals. The NTP considers phenolphthalein to be "reasonably anticipated to be a human carcinogen." A literature search was conducted from the year prior to the publication of the IARC document (i.e., January 1999 to July 2016).

Limited human carcinogenicity data are available. In the few case-control studies available at the time of the IARC report, there was no consistent association between the occurrence of colon cancer or adenomatous colorectal polyps and use of phenolphthalein-containing laxatives. Other cancer sites were not considered, and the available studies were of limited statistical power (IARC 2000). More recent studies were described in the NTP Report on Carcinogens; in two case-control studies, no significant association was found between epithelial ovarian cancer and the use of phenolphthalein as a laxative (NTP 2014).

In mice exposed via the diet, phenolphthalein induced histiocytic sarcomas and lymphomas in males and females and benign ovarian tumours in females. In female mice missing one allele of the p53 gene, the incidences of thymic lymphomas were increased. In rats, renal tumours (adenoma and carcinoma) were induced in males, and

benign pheochromocytomas (adrenal tumours) were induced in both males and females (IARC 2000; NTP 2014). More recently, dietary administration of phenolphthalein to human c-Ha-ras transgenic mice was shown to promote tumour development following a single injection of N-ethyl-N-nitrosourea (NTP 2014).

Using EPA's Benchmark Dose Software (BMDS, v. 2.5) (BMDS 2017), tumour incidence data in rats and mice from the NTP cancer bioassay (NTP 1996) was modeled. The benchmark dose (BMD_{10}; a 10% increase in tumour incidence relative to controls), and the $BMDL_{10}$ (the lower one-sided 95% confidence limit on the BMD_{10}) were calculated, and the best fit model was selected for each endpoint on the basis of the US EPA BMDS guidance document (US EPA 2012a). The lowest BMD_{10} and corresponding $BMDL_{10}$ for rats are 344 and 243 mg/kg bw/day, respectively, based on kidney tubule combined adenomas and carcinomas in males. The lowest BMD_{10} and corresponding $BMDL_{10}$ for mice are 81 and 48 mg/kg bw/day, respectively, based on malignant lymphoma (all types) in females (highest dose excluded due to mortality).

Phenolphthalein caused gene mutations and chromosomal aberrations, but not sister chromatid exchanges in mammalian cells in vitro, with and without metabolic activation. It also induced morphological transformation in mammalian cells in vitro. Mutagenicity (Ames) tests in bacteria were negative. In vivo, micronuclei were formed in mouse erythrocytes after repeated (but not single) exposure by gavage or diet (IARC 2000; NTP 2014).

The thymic lymphomas induced by phenolphthalein in heterozygous p53-deficient female mice showed loss of the normal p53 allele, suggesting a mutagenic process in tumour induction and/or progression (IARC 2000; NTP 2014).

In a continuous breeding protocol, female mice given phenolphthalein in the feed at 1000 mg/kg bw/day and above had dose-dependent decreases in the number of litters and the number of pups per litter, while males had a significantly reduced testes weight and epididymal sperm count at 1000 mg/kg bw/day and above, as well as seminiferous tubular degeneration. The effects on fertility and sperm parameters were not observed in mice in the 150 mg/kg bw/day group (NTP 1996, as cited in IARC 2000; Chapin et al. 1997b, as cited in IARC 2000).

No dermal toxicity data were available for phenolphthalein.

7.2.3 Characterization of risk to human health

The critical effect for characterization of risk to human health for phenolphthalein is carcinogenicity, as determined principally on the basis of the assessments of the International Agency for Research on Cancer (IARC 2000) and the US NTP (2014). The lowest estimated $BMDL_{10}$ for phenolphthalein, based on malignant lymphoma (all types) in female mice, is 48 mg/kg bw/day. The critical non-cancer effects are changes to sperm parameters and decreased fertility based on a feeding study in mice.

Exposure of the general population to phenolphthalein through environmental media and food is not expected. Phenolphthalein was identified at low concentrations (0.2%) in a limited number of products available to Canadians (colour-change glue sticks). Exposure is expected to be primarily via the dermal route, but it was considered that for toddlers and children, some of the exposure may be through the oral route, resulting from object-to-mouth or hand-to-mouth behaviours. A comparison of the lowest cancer and non-cancer effect levels with estimated exposures for use of phenolphthalein-containing glue sticks gives MOEs as shown in Table 7-2. In the absence of dermal toxicity data, read-across to the oral route was conducted. The MOEs for exposure to phenolphthalein in products available to consumers, namely colour-change glue sticks, are considered adequate to account for uncertainties in the exposure and health effects databases. Direct oral exposure of younger children due to incidental ingestion is also possible (Health Canada 2011; personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced).

While exposure of the general population to phenolphthalein is not of concern at current levels, this substance is considered to have a health effect of concern based on its potential carcinogenicity. Therefore, there may be a concern for human health if exposures were to increase.

Table 7-2. Relevant exposure and non-cancer critical health effect values for phenolphthalein, as well as margins of exposure, for determination of risk.

Exposure scenario	Systemic exposure	Critical effect level	Critical health effect endpoint	MOE
Glue stick	0.001 mg/kg bw/day for adults to 0.004 mg/kg bw/day for toddlers	$BMDL_{10}$ of 48 mg/kg bw/day	Malignant lymphoma (all types) in female mice. (NTP 1996)	10 700 – 49 900
Glue stick	0.001 mg/kg bw/day for adults	NOAEL of 150 mg/kg bw/day	Decreased fertility (decreases in the number of litters and the number of pups per litter), and in males significantly reduced testes weight and epididymal sperm count, seminiferous tubular degeneration (NTP 1996; Chapin et al. 1997b, as cited in IARC 2000)	158 000

7.2.4 Uncertainties in evaluation of risk to human health

Limited information is available on the use frequency and amount of glue that ends up on the skin for various age groups. In its Do-It-Yourself Fact Sheet, RIVM (2007) includes a scenario for adult dermal exposure to glue in a tube. However, the dermal load for adults may underestimate children's exposure. Limited information is available on oral exposure to glue by toddlers and children, but some data are available to indicate that hand-to-mouth and object-to-mouth behaviours occur. The behaviours associated with this exposure are more likely to occur for the younger ages (i.e., toddlers) and likely decrease with age. Although not quantified here, the potential for additional exposure to phenolphthalein via direct incidental ingestion by young children is recognized. In addition, there is the possibility for phenolphthalein to be present in other colour-change glue products and certain colour-change children's toys sold in Canada.

The health effects of phenolphthalein are well characterized by the oral route only; route-to-route extrapolation for dermal exposure was used for risk characterization. Although the mode of action for induction of all tumour types observed in experimental animals has not been determined, the identification of p-53 mutations in the thymic lymphomas induced by phenolphthalein in female mice suggests a mutagenic process.

7.3 Furfuryl alcohol

7.3.1 Exposure assessment

Environmental media and food

No quantitative data on concentrations of furfuryl alcohol in indoor or ambient air were identified. However, it was qualitatively detected in 1 of 44 air samples taken from a chamber simulating indoor conditions containing wood-based furniture with different coatings (Salthammer 1997, as cited in HSDB 1983-c).

No data were identified for concentrations of furfuryl alcohol in drinking water. Given the sources of furfuryl alcohol and its reported uses, exposure of Canadians from drinking water is not expected. In addition, modelling using ChemCAN (ChemCAN 2003) indicates that exposure from air and drinking water is expected to be negligible.

No Canadian data were identified on the levels of furfuryl alcohol that may be present in foods. However, furfuryl alcohol occurs naturally in a range of foods, including coffee, roasted nuts and grains, alcoholic beverages, fruits, vegetables, meats, and dairy products (Burdock 2010; HSDB 1983-c), and can be formed from the acid hydrolysis or heating of polysaccharides which contain pentose and hexose fragments (Adams et al. 1997). It is also identified as a food flavouring agent. Furfuryl alcohol has been detected

in breast milk in earlier studies (Erickson et al. 1980, as cited in HSDB 1983-c; Pellizzari et al. 1982 as cited in HSDB 1983-c). However, no quantitative data are available.

The predominant source of dietary exposure to furfuryl alcohol is expected to result from its natural occurrence in foods. In the absence of quantitative data specific to furfuryl alcohol, total intake of furfural and precursors, which include furfuryl alcohol, have been estimated at approximately 300 µg/kg bw/day (Stofberg and Grundschober 1978; Adams et al. 1997; EC 2008). Therefore, while data are insufficient to quantify dietary exposure estimates for furfuryl alcohol because of the lack of data on naturally occurring levels, total intakes are not expected to exceed this amount.

JECFA evaluated a flavouring group of furfuryl derivatives, including furfuryl alcohol (WHO 2001). As part of that evaluation, it estimated the per capita intake of furfuryl alcohol from its use as a food flavouring agent to be 0.4 µg/kg bw/day for the US population. This intake estimate, which used a maximized survey-derived daily intake (MSDI) approach, was derived by assuming that the reported annual production amount of furfuryl alcohol in the United States was consumed by just 10% of the US population ("eaters only") and that only 80% of the annual production amount was reported in the poundage surveys (International Organization of the Flavor Industry 1995, as cited in WHO 2001; Lucas et al. 1999 as cited in WHO 2001).

A similar approach was also used by the Flavor and Extract Manufacturers Association (FEMA) in its safety assessment of furfuryl alcohol (Smith et al. 2001). In the FEMA assessment, dietary intakes of furfuryl alcohol as a flavouring agent were also estimated using a per capita daily intake (PCI) approach. The PCI method assumes an even distribution of the annual production volume among the entire population. Therefore, the PCI value is multiplied by 10 to assume a more conservative estimate for exposure by the eaters of the flavouring substance. Exposure to furfuryl alcohol using FEMA's PCI X 10 method was estimated to be 3.42 µg/kg bw/day (Smith et al. 2001) and was considered by FEMA to provide reasonably conservative estimates for assessing exposure to flavouring substances.

In addition to the above per capita approaches to estimating exposure, furfuryl alcohol exposure from possible use as a flavouring agent has also been estimated using a theoretical added maximum daily intake (TAMDI) approach (Smith et al. 2001), which assumes that all foods in a food category contain the maximum concentration of substance and that the food category is consumed daily. Exposure to furfuryl alcohol was also estimated using a possible average daily intake (PADI) approach (Munroe and Danielewska-Nikiel 2006). This approach assumes that the flavouring is added at the average use levels to all foods within a category of foods in which the flavouring was anticipated to be used by industry at the time it was evaluated. The TAMDI and PADI approaches are similar and are expected to generate worst-case estimates of intake that would be considered overly conservative with respect to long-term exposure scenarios.

Considering the estimated potential exposure to furfuryl alcohol from its possible use as a food flavouring ingredient, the majority of dietary exposure is still expected to result from its presence as a natural component of food. Insufficient data were identified on naturally occurring levels of furfuryl alcohol in food. Therefore, no quantitative estimate of dietary exposure specific to furfuryl alcohol from natural sources was conducted for this assessment.

Although no data on levels of furfuryl alcohol in dust or soil in Canada were identified, furfuryl alcohol was quantified in dust in a study of homes in Sweden (Nilsson et al. 2005) and was detected but not quantified in dust in a study from Norway. Nilsson et al. (2005) reported that furfuryl alcohol was detected in 340 of 389 samples of settled dust taken from children's bedrooms, at concentrations of 0.4 to 500 µg/g. On the basis of the mean concentration of furfuryl alcohol in dust detected in Sweden (60 µg/g), intake is estimated to range from 0.002 µg/kg bw/day for adults to 0.3 µg/kg bw/day for infants 0 to 0.5 years of age (see Appendix C). In the absence of Canadian data, the dust data from Sweden were considered representative of potential exposure in Canada.

Products available to consumers

Furfuryl alcohol is used in products that may result in consumer exposure. Dermal and inhalation exposures to furfuryl alcohol from use of wood strippers were estimated using ConsExpo Web (ConsExpo 2016) and the US EPA's Consumer Exposure Model (CEM) version 1.4 (US EPA 2016) (see Appendix C).

Although no studies on dermal absorption of furfuryl alcohol were identified, significant percutaneous absorption of the related substance furfural occurred in humans exposed to either vapour (8 hours at 30 mg/m^3) or liquid (hand immersed for 15 minutes), as based on measured urine metabolites (Flek and Sedevic 1978, as cited in NTP 1999). In this study, an 8-hour exposure to furfural vapour (while breathing clean air through a tube) resulted in percutaneous absorption of about one quarter of the dose that was retained by the lungs (pulmonary retention was determined to be approximately 78%). Percutaneous absorption following a 15-minute immersion in liquid furfural was shown to be the same as for an inhalation exposure of 8 hours at 10 mg/m^3 (i.e., approximately 20%) (Flek and Sedevic 1978, as cited in NTP 1999). Furfuryl alcohol is expected to be similarly absorbed following dermal exposure (NTP 1999; WHO 2001).

Furfuryl alcohol was identified in wood stripper at concentrations of up to 13% (MSDS 2016). An estimate of dermal exposure was generated, assuming that the product was used full strength and at the highest identified concentration (13%). Complete dermal absorption was assumed. However, considering data available on the related substance furfural, absorption of furfuryl alcohol is likely to be lower than 100%. Dermal exposure to furfuryl alcohol during use of wood stripper was estimated to be 0.92 mg/kg bw. The label for the product identified is intended for outdoor use only. Taking those directions into consideration, inhalation exposure was estimated to account for the possibility of use in a garage setting. Using the ConsExpo scenario for paint stripper in a garage gave a mean event concentration of 1 100 mg/m^3, while using the CEM, peak

concentrations using similar assumptions were estimated to range from 39 to 182 mg/m^3 (see Appendix C for model parameters).

7.3.2 Health effects assessment

Furfuryl alcohol has been previously evaluated by the US EPA Cancer Assessment Review Committee (2014) and the JECFA (WHO 2001, 2012). Those reviews were used to inform this assessment. Since furfuryl alcohol follows the same metabolic pathway as the related substance furfural, toxicological data on furfural were also used to inform the assessment of furfuryl alcohol. Furfural (CAS 98-01-1) was previously assessed under the Challenge phase of the CMP (Environment Canada, Health Canada 2011).A literature search was conducted from the year prior to the publication of the WHO document (i.e., January 2000 to July 2016).

Carcinogenicity and genotoxicity

Carcinogenicity is a critical endpoint for furfuryl alcohol. A 2-year inhalation study in mice and rats was available (NTP 1999, and reviewed in US EPA 2014) in which whole-body exposures to vapour were 0, 2, 8 or 32 ppm (0, 8, 32 or 128 mg/m^3, equivalent to 0, 2.5, 10 or 40 mg/kg bw/day for rats and 0, 10.6, 42.6 or 170 mg/kg bw/day for mice (Health Canada 1994), for 6 hours per day, 5 days per week. In male rats, there was some evidence of carcinogenicity based on an increased incidence of nasal tumours: a non-statistically significant increase in adenomas at the low and mid-concentrations, and a statistically significant increase in carcinomas at the high concentration compared to controls. Evidence of carcinogenicity was equivocal in female rats: nasal and renal adenomas were marginally increased in mid- and high-concentration groups compared to controls (not significant and not concentration-related). In male mice, there was an increased incidence of kidney tumours: a statistically significant increase in combined adenomas and carcinomas at the high concentration compared to controls. There was no evidence of carcinogenic activity in female mice (US EPA 2014). On the basis of the results of the NTP studies, the EPA classified furfuryl alcohol as “likely to be carcinogenic to humans.” Using the BMDS 2.5 software (BMDS 2017), tumour incidence data in rats and mice from the NTP cancer bioassay (NTP 1999) was modelled. The BMD_{10} and the $BMDL_{10}$ were calculated, and the best fit model was selected for each endpoint on the basis of the US EPA BMDS guidance document. The BMD_{10} and corresponding $BMDL_{10}$ for rats are 51 and 25 mg/kg bw/day, respectively, based on nasal tumours (adenoma and carcinoma) in males. The BMD_{10} and corresponding $BMDL_{10}$ for mice are 172 and 131 mg/kg bw/day, respectively, based on kidney combined adenoma and carcinoma in males.

A 20-week skin carcinogenicity study in female transgenic mice (hemizygous Tg-AC, zetaglobin promoted v-Ha-ras) was available (Spalding et al. 2000). Furfuryl alcohol was applied dermally, 5 days per week at 0, 0.25, 0.75 or 1.5 mg per animal (corresponding to 8, 25, or 50 mg/kg bw per application). No skin tumours were reported, and clinical observations and necropsy found no signs of systemic toxicity.

With respect to in vitro genotoxicity, furfuryl alcohol was not mutagenic in bacteria in standard strains with and without liver metabolic activation (S9) (Mortelmans et al. 1986, as cited in EPA 2014). However, it induced mutations in Ames tests in bacterial strains expressing human or rodent sulfotransferases (SULT) (Monien et al. 2011, as cited in EPA 2014; Glatt et al. 2012, as cited in WHO 2012). More recently, in a Comet assay in SULT-expressing cells in vitro, furfuryl alcohol did not induce DNA damage (Huffman et al. 2016). Furfuryl alcohol did not cause chromosomal aberrations (CA) in Chinese hamster ovary (CHO) cells with and without metabolic activation (S9) (Stitch et al. 1981, as cited in EPA 2014). However, it induced sister chromatid exchange (SCE) in CHO cells without S9, but not with S9 (Stitch et al. 1981, as cited in EPA 2014). In cultured human lymphocytes, furfuryl alcohol was negative for SCE- induction without metabolic activation (Gomez-Arroyo and Souza 1985, as cited in EPA 2014). In a more recent study for SCE in cultured human lymphocytes without metabolic activation (Sujatha 2008b, as cited in WHO 2012), a positive result was reported only for the middle concentration at 24 hours, but for all concentrations at 48 hours. At 72 hours, negative results were obtained for all concentrations. However, no positive control was used in this study.

In vivo, furfuryl alcohol did not cause CA, micronuclei (MN) or SCE in bone marrow of male mice exposed by intraperitoneal injection (NTP 1999, as cited in EPA 2014), nor were SCEs observed in lymphocytes from occupationally exposed humans (Gomez-Arroyo and Souza 1985, as cited in EPA 2014). In one study, it was reported that furfuryl alcohol induced SCE in bone marrow of female mice exposed by gavage (Sujatha 2007, as cited in WHO 2012), but no positive controls were included. Monien et al. (2011, as cited in EPA 2012b) identified DNA adducts in the liver, lungs and kidneys of mice receiving approximately 390 mg/kg bw/day of furfuryl alcohol in their drinking water for 28 days. It should be noted that this dose is equivalent to more than double the highest tested concentration in the inhalation carcinogenicity study by the NTP.

The US EPA (2014) concluded that furfuryl alcohol does not present a mutagenic concern. This conclusion was based primarily on the battery of in vitro and in vivo tests from the NTP. The in vitro and in vivo SCE studies by Sujatha (2007, 2008b, as cited in WHO 2012) were not included in the review by the US EPA (2014), but the bacterial and mouse data from Monien et al. (2011) were discussed. The US EPA conclusion was that these latter data “do not provide reliable evidence of an in vivo genotoxic response” for the following reasons: no historical control data were available on the bacterial strains, there was no independent confirmation of the results, no primary data were available (only mean values were presented), the detection of DNA adducts in liver, lung and kidney of both male and female mice does not correspond to the single site of tumour formation (kidney) in male mice only, and the doses used in the in vivo study were higher than the maximum tolerated dose and the tumorigenic dose (US EPA 2014). However, the JECFA (WHO 2012) concluded that these new in vitro and in vivo studies raise concerns regarding the potential genotoxicity of furfuryl alcohol.

Repeated-dose toxicity

The NTP carcinogenicity study on furfuryl alcohol (NTP 1999) included 16-day, 14-week, and 2-year inhalation exposures for mice and rats. Furfuryl alcohol was shown to be a nasal irritant, causing concentration- and time-related increases in incidence and severity of inflammatory, degenerative and proliferative lesions of the nasal epithelium in both mice and rats of both sexes. No NOAECs were determined, and LOAECs were the lowest tested concentrations of 16 ppm (64 mg/m^3) for the 16-day study and 2 ppm (8 mg/m^3) for the 14-week and 2 year studies. Other effects observed in the 16-day study in rat were clinical signs including dyspnea, hypoactivity, nasal and ocular discharge at 63 ppm (252 mg/m^3) and above, and decreased body weights at 125 ppm (500 mg/m^3) and above. In mice, decreased body weights were observed at 63 and 125 ppm (252 and 500 mg/m^3). In the 14-week study, decreased body weights were observed in female rats at the high concentration, and decreased heart weights were observed in male mice at the high concentration (32 ppm or 128 mg/m^3) (NTP 1999). In the 2-year study, nephropathy was present in all animals, and the severity increased with exposure concentration. The incidence of renal tubule degeneration was statistically significant in high concentration male mice compared to controls. Corneal degeneration was significantly increased in female mice at the high concentration (32 ppm or 128 mg/m^3).

Limited oral data are available for furfuryl alcohol. In one study in mice, gavage doses of 0, 0.5, 1 or 2 mg per day (equivalent to 0, 17, 33 or 67 mg/kg bw/day based on a body weight of 30 g (Health Canada 1994)) were given to 4 animals per group for 5, 10, 20, 30, 60 or 90 days (Sujatha 2008a, as cited in WHO 2012). Only liver and kidney were examined. Hepatotoxicity was observed in mid- and high-dose animals at 60 and 90 days (pycnosis, vacuolation and focal necrosis). Also at the mid and high dose, liver and kidney enzymes were increased at some time points. On the basis of the information provided in the study, the NOEL and LOEL are considered to be 17 and 33 mg/kg bw/day, respectively. The WHO (2012) concluded that this study was not suitable for risk assessment because of limited endpoints, uncertainty of doses on a body-weight basis, and limited reporting.

In the 20-week skin carcinogenicity study in transgenic mice described above (Spalding et al. 2000), there was no evidence of local or systemic toxicity at up to the highest tested dose of 50 mg/kg bw per application. Endpoints evaluated were body weight, examination of the application site, and necroscopy, including histopathology of major organs and tissues for high dose and control animals.

In a combined irritancy/ sensitization assay in mouse, furfuryl alcohol was found to be a dermal irritant following 4 days of exposure to 25 uL per day of a 75% solution (approximately 625 mg/kg bw), but not a 50% solution (approximately 417 mg/kg bw/day). A dose responsive increase in proliferation in the local lymph node assay was observed and was statistically significant starting at the 50% exposure group (Franko et al. 2012).

Since furfuryl alcohol follows the same detoxification pathway as furfural, dermal data on furfural were also considered to inform the assessment of furfuryl alcohol. In a 28-

day dermal study in rats, adverse clinical signs (hypothermia, hypoactivity, hind limb immobility) were observed in males, and increased mortality occurred in males and females at 500 mg/kg bw/day of furfural. The high dose in this study began at 1000 mg/kg bw/day, but owing to high mortality in both sexes, the dose was reduced to 750 mg/kg bw/day on day 11. However, the mortality rate remained high, and the high dose portion of the study did not continue past day 19. A NOAEL of 250 mg/kg bw/day was established (US EPA 2010, as cited in Environment Canada, Health Canada 2011).

Acute toxicity

In single-exposure inhalation studies, estimated LC_{50} values for furfuryl alcohol ranged from 340 to >2 800 mg/m^3 in rat, mouse, dog, monkey, and rabbit (NIOSH 1979; Terrill et al. 1989, as cited in ECHA 2007-2016b). Exposure durations ranged from 1 to 8 hours. Rat appears to be the most sensitive species with respect to inhalation-induced mortality. In an unpublished report from 2005 (cited in ECHA 2007-2016b), no deaths were observed at 510 or 820 mg/m^3 in rats exposed to furfuryl alcohol vapour for 4 hours (nose only), whereas at 2 070 mg/m^3, 4 of 5 males and 4 of 5 females died during the exposure. At 510 mg/m^3, a slight decrease in breathing rate was noted in the last hour of exposure, and at 820 mg/m^3, decreased breathing rate was observed throughout exposure and was accompanied by laboured breathing by the end of the exposure period. The day after the exposure, signs of irritation were observed (sniffing and nasal encrustations). Body weight gain was decreased in animals exposed to 510 or 820 mg/m^3 in the first week following exposure, but not in the second week. Macroscopic changes were observed in the lungs and respiratory tract of animals exposed to 2 070 mg/m^3, but not those exposed to 510 or 820 mg/mg^3. In two other reports of acute toxicity testing, effects at the lowest tested concentrations (842 and 953 mg/m^3) included laboured or irregular breathing and weight loss, which in some cases was not recovered in 14 days. Mortalities were observed in these studies at concentrations of 953 mg/m^3 and above, with calculated LC_{50} values of 1 170 and 1 350 mg/m^3.

7.3.3 Characterization of risk to human health

Environmental media and food

A critical effect of furfuryl alcohol is carcinogenicity. Nasal tumours that developed in male and female rats following inhalation exposure are thought to be a site-specific effect, arising from chronic irritation, and therefore thus were not considered a relevant endpoint for risk characterization of exposure by the oral route. However, the kidney tumours observed in male mice were considered to be evidence of systemic toxicity and therefore relevant for route-to-route extrapolation. The lowest estimated $BMDL_{10}$ for male mice is 131 mg/kg bw/day, based on combined adenoma and carcinoma in kidney. The mode of action of furfuryl alcohol-induced tumour formation in the mouse kidney has not been fully elucidated. However, the majority of in vitro and in vivo genotoxicity studies on furfuryl alcohol gave negative results.

With respect to non-cancer effects, the NOEL and LOEL in the only available oral study on furfuryl alcohol were 17 mg/kg bw/day and 33 mg/kg bw/day, respectively, based on liver toxicity and enzyme changes in mice following 60 to 90 days of gavage dosing. Although this study was limited in terms of endpoints and reporting, it was selected as it is specific to furfuryl alcohol, and effects were observed at a lower dose than in any of the available oral studies on furfural.

The predominant source of exposure to furfuryl alcohol for the general population is through the diet. On the basis of the available data, it is expected that the majority of the dietary exposure to furfuryl alcohol results from its natural occurrence in foods. The derivation of margins of exposure for this source was not considered to be meaningful. The estimated intake from the use of furfuryl alcohol as a possible flavouring agent in foods is less than intakes that have been estimated from natural occurrence for furfural and derivatives, including furfuryl alcohol. Furthermore, these estimates of dietary exposure from possible food flavouring uses are below the upper bound of the group acceptable daily intake of 0 to 0.5 mg/kg bw/day established for a group of related substances including furfuryl alcohol by JECFA (WHO 2001). More recently, the EFSA (2011) critically reviewed the JECFA's approach and agreed with the Committee's conclusion of "no safety concern with the estimated levels of intake as flavouring substances" based on the JECFA's dietary exposure estimates for substances in this flavouring grouping.

Exposure to furfuryl alcohol from other environmental media (i.e., dust) is expected to be lower than background levels in food. MOEs for both cancer and non-cancer effects (Table 7-3) were considered adequate to account for uncertainties in the exposure and health effects databases.

Products available to consumers

In a single 4-hour exposure study in rats, at the lowest test concentration of 510 mg/m^3, a slight decrease in breathing rate was observed during the last hour of exposure, and in the first but not the second week following exposure, body weight gain was decreased (ECHA 2007-2016b). Two additional studies showed similar effects, as well as mortalities at 953 mg/m^3 and above. Estimated inhalation exposure from product use was compared to the critical inhalation effect levels to derive MOEs for determination of risk (see **Error! Reference source not found.**3). These MOEs are considered potentially inadequate to account for uncertainties in the exposure and health effects databases.

With respect to dermal toxicity, the only short-term study available on furfuryl alcohol was a 4-day irritation/sensitization assay in mice. A dose-responsive increase in proliferation in the local lymph node assay was statistically significant at 417 mg/kg bw/day and above. As a more comprehensive short-term dermal toxicity study on furfuryl alcohol was not available, data on furfural were used to support the risk characterization. A dermal NOAEL for furfural of 250 mg/kg bw/day was derived in rats on the basis of adverse clinical signs and mortality at 500 mg/kg bw/day for 28 days.

Estimated dermal exposure from product use was compared to the critical dermal effect levels to derive MOEs for determination of risk (see Table 7-3). Although the MOEs for dermal exposure are higher than those for inhalation exposure, the severity of effects (mortality) observed at the LOAEL in the 28-day dermal study on furfural was taken into consideration.

Table 7-3. Relevant exposure and hazard values for furfuryl alcohol, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure	Critical effect level	Critical health effect endpoint	MOE
Chronic oral exposure from dust	0.002 µg/kg bw/day for adults to 0.3 µg/kg bw/day for infants 0 to 0.5 years of age	$BMDL_{10}$ = 130.9 mg/kg bw/day based on chronic inhalation study in mouse (furfuryl alcohol)	Kidney adenomas and carcinomas in male mouse (NTP 1999)	>430 000
Chronic oral exposure from dust	0.002 µg/kg bw/day for adults to 0.3 µg/kg bw/day for infants 0 to 0.5 years of age	NOEL = 17 mg/kg bw/day based on a 60- to 90-day gavage study in mouse (furfuryl alcohol)	Hepatotoxicity and enzyme changes at 33 mg/kg bw/day (Sujatha 2008a, as cited in WHO 2012)	>50 000
Acute inhalation exposure from wood stripper	39 to 1 100 mg/m^3 per event	LOEC/ NOAEC = 510 mg/m^3 based on 4-hour inhalation study in rat (furfuryl alcohol)	Slight decrease in breathing rate, laboured breathing, transient decreased body weight gain at 820 mg/m^3. Mortality at 953 mg/m^3 (ECHA 2007-2016b)	0.5–13
Acute dermal exposure from wood stripper	0.92 mg/kg bw per event	LOEL = 417 mg/kg bw/day based on 4 day dermal study in mouse (furfuryl alcohol)	Statistically significant increase in proliferation in local lymph node assay (Franko et al. 2012)	450
Acute dermal exposure from wood stripper	0.92 mg/kg bw per event	NOAEL = 250 mg/kg bw/day based on 28 day dermal	Adverse clinical signs and mortality at 500 mg/kg bw/day	270

		study in rat (furfural)	(Environment Canada, Health Canada 2011)	

7.3.4 Uncertainties in the evaluation of risk to human health

There is uncertainty in the lack of data on exposure to furfuryl alcohol from environmental media, particularly air and drinking water. However, considering the reported uses of furfuryl alcohol, exposure of Canadians from these sources is not expected. A quantitative estimate of exposure to furfuryl alcohol from its natural sources in food was not conducted, but the available data indicate that potential exposure from possible use of furfuryl alcohol as a flavouring agent is reasonably expected to be a very minor contributor to total dietary exposure. No Canadian data were identified on levels of furfuryl alcohol in dust. It is uncertain whether the use of dust data from European studies to estimate exposure to Canadians is appropriate. However, the contribution of dust to total oral exposure is expected to be small, considering that most of the dietary intake is expected to be from natural sources.

There is uncertainty in the estimates of exposure to furfuryl alcohol in products available to consumers, with respect to the concentration of furfuryl alcohol and the prevalence in Canada of products containing the highest concentrations. For wood strippers, the exposure estimate assumed the highest concentration identified and no dilution of product. In the absence of quantitative dermal absorption data on furfuryl alcohol, complete absorption was assumed. However, considering the data available on furfural, absorption is likely to be lower than 100% (a study on furfural showed percutaneous absorption to be about 20%), although there may also be some exposure via inhalation. In addition, the product is intended for outdoor use, but the possibility of use indoors, such as in a garage, where inhalation exposure could be significant, is conceivable. Two different models (ConsExpo and CEM) were used to estimate inhalation exposure from products to increase confidence in the estimates.

Route-to-route extrapolation was used for cancer MOEs for oral exposure, as only inhalation data were available. This was considered appropriate as the kidney tumours in male mice are evidence of systemic toxicity. However, there is uncertainty regarding the absorption rates and modes of action of toxicity by different routes.

Only one oral study on furfuryl alcohol was available, and despite its limitations, the NOEL from this study was used for risk characterization. Only one short-term dermal study was available on furfuryl alcohol and, as limited endpoints were assessed in that study, read-across to a short-term dermal toxicity study on furfural was used.

7.4 Tetrahydrofuran

7.4.1 Exposure assessment

Environmental media and food

Tetrahydrofuran was surveyed in a comprehensive indoor air study conducted in 18 cities and towns across Canada (2009 to 2011). It was detected in 60% of the 3 857 residences at a geometric mean of 0.05 µg/m^3 (arithmetic mean of 0.34 µg/m^3). The 95th and 99th percentiles were 1.26 and 6.12 µg/m^3, respectively (Zhu et al. 2013). In a smaller study of 50 homes in Quebec City from the winter of 2009, tetrahydrofuran was detected above the limit of detection in 21 samples (42%), at levels ranging from 0.05 to 7.38 µg/m^3. The geometric mean was 0.15 µg/m^3 (Won and Lusztyk 2011).

In the only recent Canadian study identified (HAMN 2015), tetrahydrofuran was detected in ambient air in 1 of 30 samples taken in Hamilton, Ontario, from January to December 2015, at a level of 1.24 µg/m^3.

One Canadian drinking water study was identified in which tetrahydrofuran was analyzed, but it was not detected above the method limit of detection of 0.46 µg/L (Ville de Montreal 2009). No other reports of analysis for tetrahydrofuran in drinking water in Canada were identified. Tetrahydrofuran was measured in drinking water in a few US states (Komsta et al. 1988, as cited in HSDB 1983-d; NDWD 2011). In addition, data from the US Geological Survey are available on tetrahydrofuran in ground water and surface water in a large number of samples from across the country (Carter et al. 2007). In the vast majority of the samples in these studies, tetrahydrofuran was not detected. In addition, given its very high vapour pressure, the exposure of the general population of Canada to tetrahydrofuran from water is expected to be much lower than exposure from air.

Tetrahydrofuran is not directly or intentionally added to food packaging materials. Rather, it has been identified as an impurity that may be formed during the manufacture of some resins used in food packaging materials with direct food contact, including films, coatings or molded articles. Potential dietary exposure from tetrahydrofuran as an impurity in some food packaging materials is expected to be negligible. Tetrahydrofuran has also been identified as a component in cleaners for possible use in food processing establishments. However, for such use, there would be no direct contact with food (personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated 2016; unreferenced).

Tetrahydrofuran has been identified as a volatile component of some foods, including coffee, cooked meat, honey, and blackberries (HSDB 1983-d; VCF 1992-2016). Tetrahydrofuran was also detected in breastmilk in 1 of 12 samples (Pellizzari et al. 1982, as cited in HSDB 1983-d), but no quantitative data are available. Overall, given the physical and chemical properties (very high vapour pressure, low log K_{ow}) and uses

of tetrahydrofuran, exposure of the general population of Canada to tetrahydrofuran from food and breastmilk is expected to be much lower than exposure from air.

Products available to consumers

Tetrahydrofuran is used in products available to consumers (PVC cement) that may result in consumer exposure (MSDS 2014; MSDS 2013). Inhalation exposure to tetrahydrofuran from use of PVC cement was estimated using ConsExpo Web (ConsExpo 2016) and the US EPA's Consumer Exposure Model (CEM) version 1.4 (US EPA 2016) (see Appendix D for model parameters). Tetrahydrofuran was identified in many products from multiple brands of PVC cement at concentrations up to 80%, and an estimate of inhalation exposure was therefore generated using 80% as the weight fraction in the product. Using the ConsExpo scenario for glue gave a mean event concentration of 150 mg/m^3. Using the CEM, peak concentrations using similar assumptions were estimated to range from 57 to 359 mg/m^3 (see Appendix D for model parameters). While it is recognized that some dermal exposure may also occur, inhalation is expected to be the primary exposure route for these products. In addition, some products require the use of a primer before the PVC cement is applied. These products may also contain tetrahydrofuran, thereby increasing the potential exposure.

7.4.2 Health effects assessment

US EPA 2012b summarized the health effects literature and characterized the hazard related to tetrahydrofuran. It was used to inform the hazard section of this assessment, including selection of effect levels for critical endpoints (e.g., NOAEL/Cs and/or LOAEL/Cs). The IRIS review included a carcinogenicity assessment as well as non-cancer assessments for oral and inhalation exposure.

A literature search was conducted from the year prior to the IRIS document (i.e., January 2012 to July 2016). No health effects studies, which could impact the risk characterization (i.e., result in different critical endpoints or lower points of departure/target margins of exposure than those stated in US EPA 2012b), were identified.

Carcinogenicity and genotoxicity

Carcinogenicity is a critical endpoint for tetrahydrofuran. The US EPA (2012) considered that there is "suggestive evidence of carcinogenic potential" based on a 2-year inhalation study in which there was a marginally increased incidence of renal tubule adenomas and carcinomas in male rats (statistically significant exposure-response trend) and an increased incidence of hepatocellular adenomas and carcinomas in female mice (statistically significant trend and increased incidence at the highest tested concentration) (NTP 1998, as cited in US EPA 2012b). The NTP (1998) concluded that there was "some evidence" of carcinogenicity in male rats and "clear evidence" of carcinogenicity in female mice. Concentrations tested were 0, 200, 600, and 1800 ppm

(0, 590, 1 770, and 5 310 mg/m^3), and animals were exposed for 6 hours per day, 5 days per week for 105 weeks. The US EPA considered the kidney tumours in male rats and the liver tumours in female mice to be relevant to humans, although the modes of action of tumour induction have not been established (US EPA 2012b). The US EPA (2012) discussed the possibility of involvement of $\alpha_{2\mu}$ -globulin and chronic nephropathy in the male rat kidney tumours, and the potential role of a proliferative response in female mouse liver tumours, but concluded that the available evidence does not support these pathways.

In in vitro genotoxicity assays, tetrahydrofuran was negative for induction of mutations in bacteria, micronuclei in Syrian hamster embryo (SHE) cells, and sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells, although there was a slight increase in chromosomal aberrations (CA) in CHO cells with metabolic activation (not considered positive by the study authors). Tetrahydrofuran was also negative in transformation assays in several cell types. In vivo, tetrahydrofuran was negative for sex-linked recessive lethal mutations in drosophila, for CA and SCE in mouse bone marrow, and for unscheduled DNA synthesis (UDS) in mouse hepatocytes. An equivocal result was obtained in an assay for micronuclei in mouse peripheral blood erythrocytes following 13 weeks of inhalation exposure to tetrahydrofuran.However, the only statistically significant increase was observed at the middle concentration in males; the effect was not concentration-dependent and was not observed in females. The US EPA concluded that tetrahydrofuran is not likely genotoxic. It based its conclusion on the conclusively negative results in in vitro and in vivo assays, with only a few equivocal results reported (US EPA 2012b).

Given the lack of data on the mode of action of tumour formation and on the shape of the dose-response curve at low doses, the US EPA conducted a linear low-dose extrapolation for the tetrahydrofuran-induced tumours in rats and mice. Incidence data for female mice and male rats were fitted to the multistage model of the EPA's BMDS version 2.0 (US EPA 2008, as cited in US EPA 2012b). The human equivalent concentrations (HEC) associated with a 10% increase in tumour incidence relative to controls (BMC_{10}) and its 95% confidence limits ($BMCL_{10}$) were derived. For the hepatocellular adenoma or carcinoma data in female mice, the BMC_{10} and $BMCL_{10}$ are 52 and 35 mg/m^3 respectively. For the renal tubule adenoma or carcinoma data in male rats, the BMC_{10} and $BMCL_{10}$ are 260 and 127 mg/m^3, respectively.

Repeated-dose toxicity

The critical non-cancer effects for repeated-dose toxicity following inhalation exposure to tetrahydrofuran are central nervous system (CNS) toxicity (narcosis) and effects on the liver (weight increase and cytomegaly) (US EPA 2012b). In the 2-year inhalation bioassay described in the carcinogenicity section (NTP 1998, as cited in US EPA 2012b), narcosis was observed for up to 1 hour following exposure in male mice at the high concentration (5 310 mg/m^3), and a slight increase in liver necrosis was observed at the high concentration (5 310 mg/m^3) in female mice. However, given the comprehensive reporting and better characterization of low-exposure effects, the

subchronic portion of the NTP study was selected as the critical study for the derivation of the non-cancer inhalation reference concentration (RfC) by the US EPA (2012).

In the subchronic portion of the NTP study (NTP 1998, as cited in US EPA 2012b), rats and mice were exposed by inhalation for 6 hours per day, 5 days per week for 90 days at 0, 195, 590, 1 770, 5 310, or 14 750 mg/m^3. Narcosis was observed in rats at 14 750 mg/m^3, and in mice at 5 310 mg/m^3 and above. A LOAEC of 5310 and a NOAEC of 1 770 mg/m^3 were derived for CNS effects in mice; however, no dose-response modelling was conducted due to a lack of incidence data. The NOAEC for CNS effects was converted to a Human Equivalent Concentration (HEC) of 316 mg/m^3 (US EPA 2012b).

In the subchronic study (NTP 1998, as cited in US EPA 2012b), absolute and relative liver weights were significantly increased in a concentration-dependent manner at 1 770 mg/m^3 and above in male mice, and the incidence of centrilobular cytomegaly was significantly increased at 14 750 mg/m^3. The toxicological significance of the liver weight changes was considered uncertain at 1 770 mg/m^3 and below given a weight increase of less than 10% and because there were no other signs of toxicity. However at 5 310 mg/m^3, liver weight was increased by more than 10%, and some histopathology was observed (non-statistical increase in centrilobular cytomegaly) and increased with increasing concentration. Therefore, a LOAEC of 5 310 mg/m^3 and a NOAEC of 1 770 mg/m^3 were derived for liver effects in mice (US EPA 2012b).

Data sets for absolute liver weight and centrilobular cytomegaly in male mice were modelled using the EPA's BMDS version 2.0 (US EPA 2008, as cited in US EPA 2012b). The exposure concentrations representing a 10% increase in absolute liver weight relative to controls and a 10% extra risk of centrilobular cytomegaly (BMC_{10}), and their 95% confidence limits ($BMCL_{10}$) were derived. For absolute liver weight in male mice, the BMC_{10} and $BMCL_{10}$ are 783 and 246 mg/m^3, respectively (shown as HECs). For centrilobular cytomegaly in male mice, the BMC_{10} and $BMCL_{10}$ are 805 and 256 mg/m^3, respectively. More details on the BMD modelling are found in the US EPA's Toxicological Review of Tetrahydrofuran (2012b).

CNS effects have been reported in numerous other studies in laboratory animals at similar exposure concentrations to those of the NTP study, including a neurotoxicity study in rats, developmental toxicity studies in mice and rats, and acute and short-term toxicity studies in dogs, mice, and rats (US EPA 2012b). Similarly, liver effects (fatty liver degeneration, increased serum liver enzymes, bilirubin and cholesterol in the absence of liver histopathology) have been observed in other inhalation studies in rodents at similar exposure concentrations to those of the NTP study. In addition, CNS effects (headaches, dizziness, diminished sense of smell, tiredness) and increased liver enzymes were observed in occupationally exposed humans in several case reports, including several cases of pipe fitters and plumbers exposed to PVC pipe glue. However, in these studies, exposures were often to multiple chemicals, and the concentrations of tetrahydrofuran in the products and in the air are unknown (US EPA 2012b).

Reproductive and developmental toxicity

The developmental toxicity of tetrahydrofuran by inhalation exposure has been studied in mice and rats. In mice, a LOAEC of 5 310 mg/m^3 and a NOAEC of 1 770 mg/m^3 were identified on the basis of maternal toxicity (narcosis and decreased uterine weight) and fetal toxicity (reduced pup survival) (Mast et al. 1992, as cited in US EPA 2012b). In rats, maternal body weight and pup body weight were reduced at 14 750 mg/m^3 but not at 5 310 mg/m^3 (Mast et al. 1992, as cited in US EPA 2012b). In another rat study, the maternal NOAEC, based on CNS effects (diminished response to stimulus) at the LOAEC of 2 950 mg/m^3, was 1 475 mg/m^3. Fetal body weight and sternal ossifications were decreased at 14 750 mg/m^3 but not 7 375 mg/m^3 (Dupont 1980, as cited in US EPA 2012b).

According to the US EPA (2012), the critical effect for repeated-dose toxicity by the oral route was delayed pup body weight gain in F1 and F2 rats of a two-generation reproductive study in rats dosed via drinking water. These changes were observed in the absence of maternal toxicity. Using benchmark dose modelling, the critical effect level was a $BMDL_{1SD}$ of 928 mg/kg bw/day (the lower confidence limit of a one standard deviation change from controls in F1 males on days 7 to 14).

Acute toxicity

Following single inhalation exposure to tetrahydrofuran, the primary effects are similar to the CNS effects observed in repeated-dose studies. In studies in dogs, mice, and rats, symptoms of toxicity included sedation, decreased responses to stimuli, and altered respiration. The lowest LOAEC identified for CNS effects in a single exposure study was 7 375 mg/m^3 in a neurotoxicity study conducted in rats (Dupont Haskell Laboratory 1996a, as cited in US EPA 2012b; Malley et al. 2001, as cited in US EPA 2012b). Diminished response to stimulus was observed after 2 or more hours of exposure at 7 375 mg/m^3. At the higher concentration of 14 750 mg/m^3, additional signs of sedation and altered parameters in the functional battery were observed (abnormal gait, righting reflex). The effects were not observed the day following the 6-hour exposure. A NOAEC of 1 475 mg/m^3 was identified (US EPA 2012b). In other studies, similar effects were observed at higher concentrations.

Respiratory tract irritation and toxicity were also observed in rats and rabbits in some single exposure studies. A LOAEC of 2 950 mg/m^3 was identified in rabbits following a single 4-hour exposure, based on morphological changes to nasal epithelial cells (Ohashi et al. 1983, as cited in US EPA 2012b) (NOAEC = 738 mg/m^3). However, in a follow-up study using the same protocol, the effects on the tracheal morphology were mild compared to those in the nasal epithelium in the previous study, and a LOAEC of 35 400 mg/m^3 was identified (Ikeoka et al. 1988, as cited in US EPA 2012b) (NOAEC = 17 770 mg/m^3).

7.4.3 Characterization of risk to human health

Environmental media

A critical effect of tetrahydrofuran is carcinogenicity. Following chronic inhalation exposure, male rats had increased incidences of kidney tumours and female mice had increased incidences of liver tumours. In vitro and in vivo genotoxicity data on tetrahydrofuran are primarily negative, with equivocal results reported only in a few studies. Therefore, although the modes of action of tetrahydrofuranan-induced tumour development have not been fully elucidated, it has been proposed that tumours likely arise through non-genotoxic pathways (US EPA 2012b). The exposure concentrations representing the 95% confidence limits on a 10% increase in tumour incidence relative to controls ($BMCL_{10}$) were 35 and 127 mg/m^3 for hepatocellular adenoma or carcinoma in female mice, and renal tubule adenoma or carcinoma in male rats, respectively (concentrations adjusted for continuous exposure for humans).

Critical non-cancer endpoints for repeated inhalation exposure to tetrahydrofuran are CNS toxicity (narcosis), increased liver weight and cytomegaly, and reduced pup survival in a developmental toxicity study. The NOAECs and $BMCL_{10}$ for these effects range from 246 to 316 mg/m^3 (concentrations adjusted for continuous exposure for humans).

As indicated in section 7.4.1, exposure of Canadians to tetrahydrofuran occurs primarily through inhalation of indoor air, and oral exposure to environmental media is expected to be much lower than exposure via the inhalation route. The majority of the health effects studies were conducted by inhalation exposure. Therefore, effect concentrations from animal studies (converted by the US EPA to human equivalent concentrations) were compared with Canadian indoor air concentration data to derive margins of exposure (MOEs) (**Error! Reference source not found.**4). These MOEs are considered adequate to account for uncertainties in the exposure and health effects databases.

Products available to consumers

Evidence of CNS toxicity was observed in single inhalation exposure studies in experimental animals. The critical effect level for a single exposure to tetrahydrofuran was a NOAEC of 1 475 mg/m^3, based on a diminished response to stimulus in rats at the next highest concentration of 7375 mg/m^3. This effect was observed in some animals at the first timepoint, 2 hours into the exposure, but was not observed the day following the 6 hour exposure. In longer term studies, more severe CNS effects (narcosis) were observed during and in some cases for some time following exposures to similar concentrations in mice and rats. Canadians may be exposed to tetrahydrofuran by inhalation during use of PVC pipe cement containing tetrahydrofuran at up to 80%. A comparison of the NOAEC for a single exposure with mean event air concentrations estimated for use of PVC pipe cement gives MOEs as shown in Table 7-4. The MOEs for exposure to tetrahydrofuran in products available to consumers,

namely PVC cement, are considered potentially inadequate to account for uncertainties in the exposure and health effects databases.

Table 7-4. Relevant exposure and hazard values for tetrahydrofuran, as well as margins of exposure, for determination of risk

Exposure scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Inhalation of indoor air	0.34 µg/m^3 (mean) (Zhu et al. 2013)	$BMCL_{10}$ = 35 mg/m^3	Hepatocellular adenoma or carcinoma (female mice) in a 2-year inhalation study (NTP 1998, cited in US EPA 2012b)	>100 000
Inhalation of indoor air	0.34 µg/m^3 (mean) (Zhu et al. 2013)	$BMCL_{10}$ = 246 mg/m^3	liver weight increase in mice in a 13-week inhalation study (NTP 1998, cited in US EPA 2012b)	>700 000
Acute inhalation exposure from PVC Cement	57 to 359 mg/m^3 per event	NOAEC = 1 475 mg/m^3 based on 6-hour inhalation study in rat	diminished response to stimulus (Dupont Haskell Laboratory 1996a and Malley et al. 2001, both cited in US EPA 2012b)	4–26

7.4.4 Uncertainties in evaluation of risk to human health

There is uncertainty in the lack of data on exposure to tetrahydrofuran from drinking water and food. However, given the data available and uses of tetrahydrofuran, exposure from these sources is expected to be much lower than exposure from indoor air. Although only one data point was identified for tetrahydrofuran in ambient air, the indoor air data are considered comprehensive and representative of Canadian exposure levels.

There is also uncertainty in the exposure estimate from PVC pipe cement, with respect to the modelled air concentration of tetrahydrofuran. However, many Canadian products were identified containing tetrahydrofuran at high concentrations (up to 80%), and

potential exposure may be increased by the use of both primer and cement containing tetrahydrofuran or from any dermal contact. Two different models (ConsExpo and CEM) were used to estimate inhalation exposure from products to increase confidence in the estimates.

The US EPA considers the confidence in the hazard database to be moderate to high (US EPA 2012b). Multiple studies were conducted in experimental animals by the relevant route of exposure (inhalation) over various durations and concentrations. Critical effects are supported by occupational data in humans. The critical study (NTP 1998) was well-conducted and well-documented and included a comprehensive analysis. Although the critical effect levels for non-cancer endpoints were derived from the subchronic rather than the chronic study, there is no evidence that increased duration of exposure increases the incidence or severity of effects. Results of developmental toxicity studies suggest that the fetus is not more sensitive than adults; In a two-generation oral study, the second generation did not appear to be more sensitive than the first generation. No two-generation reproductive toxicity studies by inhalation are available.

As the modes of action and the shape of the dose-response curves at low doses are unknown, the US EPA (2012b) used a default approach of linear low-dose extrapolation for quantification of cancer risk. However, tetrahydrofuran has a short biological half-life and pre-neoplastic lesions were not observed. The mode of action for generation of tumours in laboratory studies with tetrahydrofuran is considered by the EPA to be likely non-genotoxic with a threshold of exposure for tumour development. The EPA notes that the linear extrapolation therefore likely overestimates carcinogenic 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 furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran. It is proposed to conclude that furan, phenolphthalein, furfuryl alcohol, and tetrahydrofuran 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 furan and phenolphthalein do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in quantitiesor concentrations 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 furfuryl alcohol and tetrahydrofuran meet the criteria under paragraph 64(c) of CEPA as they are entering the environment in quantitiesor concentrations or under conditions that constitute or may constitute a danger in Canada to human life or health.

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

Therefore, it is proposed to conclude that furfuryl alcohol and tetrahydrofuran meet one or more of the criteria set out in section 64 of CEPA.

It is proposed that furfuryl alcohol and tetrahydrofuran do not meet the persistence or bioaccumulation criteria as set out in the Persistence and Bioaccumulation Regulations of CEPA.

References

Adams T, Doull J, Goodman J, Munro I, Newberne P, Portoghese P, Smith R, Wagner B, Weil C, Woods L, Ford R. 1997. The FEMA GRAS assessment of furfural used as a flavour ingredient. Food Chem Toxicol. 35(18):739-751.

Becalski A, Halldorson T, Hayward S, Roscoe V. 2016. Furan, 2-methylfuran and 3-methylfuran in coffee on the Canadian market. J Food Compos Anal. 47:113-119.

Becalski A, Hayward S, Krakalovich T, Pelletier L, Roscoe V, Vavasour E. 2010. Development of an analytical method and survey of foods for furan, 2-methylfuran and 3-methylfuran with estimated exposure. Food Addit Contam. Part A Chem Anal Control Expo Risk Assess. 27(6):764-775.

Becalski A, Forsyth D, Casey V, Lau B.P.-Y, Pepper K, Seaman S. 2005. Development and validation of a headspace method for determination of furan in food. Food Addit Contam. 22(6):535-540.

[BMDS] Benchmark Dose Software. 2017. Ver. 2.5. US Environmental Protection Agency.

Burdock GA. 2010. Fenaroli's handbook of flavor ingredients. 6th ed. Boca Raton (FL): CRC Press.

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

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

Carter JM, Delzer GC, Kingsbury JA, Hopple JA. 2007. Concentration data for anthropogenic organic compounds in ground water, surface water, and finished water of selected community water systems in the United States, 2002-05. Data Series 268. [Internet]. Reston (VA): US Geological Survey. [cited Nov 2016] (PDF).

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

ChemIDplus [database]. 1993- . Bethesda (MD): US National Library of Medicine. [updated 2016 Jul 20; accessed 2016 Sep 13].

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

Dong H, Gill S, Curran IH, Williams A, Kuo B, Wade MG, Yauk CL. 2016. Toxicogenomic assessment of liver responses following subchronic exposure to furan in Fischer F344 rats. Arch Toxicol. 90(6):1351-67.

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

[EC] European Commission. 2008. European Union risk assessment report: Furfural: CAS No.: 98-01-1. Luxembourg: Publications Office of the European Union. Report No: R050_0802_env_hh [accessed 2016 Nov 22].

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

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

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2017 Apr 20]. Categorization. Ottawa (ON): Government of Canada. [accessed 2016 Sep 8].

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2017. Draft Screening Assessment: Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances. Ottawa (ON): ECCC, HC. [accessed 2017 Sep].

[ECETOC] European Centre for Ecotoxicology and Toxicology of Chemicals. 2004. Targeted Risk Assessment: Technical Report No. 93. Brussels: ECETOC AISBL. 223 p.

[ECHA] European Chemicals Agency. c2007-2016a. Registered substances database; search results for CAS RN [77-09-8]. Helsinki (FI): ECHA. [updated 2016 Jan 14; accessed 2016 May].

[ECHA] European Chemicals Agency. c2007-2016b. Registered substances database; search results for CAS RN [98-00-0]. Helsinki (FI): ECHA. [updated 2016 Aug 19; accessed 2016 Nov].

[ECHA] European Chemicals Agency. c2007-2016c. Registered substances database; search results for CAS RN [109-99-9]. Helsinki (FI): ECHA. [updated 2016 Aug 30; accessed 2016 May].

[EFSA] European Food Safety Authority. 2011. Scientific Opinion on Flavouring Group Evaluation 66, Revision 1 (FGE.66 Rev1):Consideration of Furfuryl Alcohol and Related Flavouring Substances Evaluated by JECFA (55th meeting). EFSA Journal. 2011; 9(9):2314 [44 pp].

Environment Canada, Health Canada. 2011. Screening assessment for the Challenge: 2-Furancarboxaldehyde (Furfural): Chemical Abstracts Service Registry Number 98-01-1. Ottawa (ON): Environment Canada, Health Canada. [accessed 2016 Sep 13].

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

EU Food Flavourings Database [database]. [modified 2016]. Brussels (BE): European Commission Directorate-General for Health and Consumers. [accessed 2016].

[FCC USP] Food Chemicals Codex [database]. c2016. Rockville (MD): US Pharmacopeial Convention. [accessed June 2017].

Franko J, Jackson LG, Hubbs A, Kashon M, Meade BJ, Anderson SE. 2012. Evaluation of furfuryl alcohol sensitization potential following dermal and pulmonary exposure: enhancement of airway responsiveness. Toxicol Sci. 125(1):105-115.

[HAMN] Hamilton Air Monitoring Network. 2015. HAMN – VOC Report. Hamilton (ON). (PDF).

Haynes WM, editor. 2017. CRC Handbook of Chemistry and Physics. 97th ed. Boca Raton (FL): CRC Press/Taylor & Francis.

Health Canada. 1994. Human health risk assessment for priority substances. Ottawa (ON): Minister of Supply and Services Canada. Cat. No.: En40-215/41E. [accessed 2016 May 31].

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

Health Canada. 2011. Children's Product Usage Study: Management Summary. Prepared for Health Canada in September 2011. Unpublished report. Ottawa (ON): Health Canada.

Health Canada. [modified 2015 Dec 14]. Cosmetic ingredient hotlist: list of ingredients that are prohibited for use in cosmetic products. Ottawa (ON): Health Canada, Consumer Product Safety Directorate. [accessed 2016 Sep 8]. .

Health Canada. 2016a. Science Approach Document: Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances. [accessed 2017 Jun 1]. Gatineau (QC): ECCC. [accessed 2016 Oct 18].

Health Canada. 2016b. Furan. [modified 2016 Mar 8, accessed 2016 Oct 18].

[HSDB] Hazardous Substances Data Bank [database]. 1983- a. search results for CAS RN [110-00-9]. Bethesda (MD): National Library of Medicine (US). [updated 2004 Sep 10; accessed 2016 Oct 18].

[HSDB] Hazardous Substances Data Bank [database]. 1983- b. search results for CAS RN [77-09-8]. Bethesda (MD): National Library of Medicine (US). [updated 2004 Sep 10; accessed 2016 Oct 18].

[HSDB] Hazardous Substances Data Bank [database]. 1983- c. search results for CAS RN [98-00-0]. Bethesda (MD): National Library of Medicine (US). [updated 2006 Aug 30; accessed 2016 Oct 18].

[HSDB] Hazardous Substances Data Bank [database]. 1983- d. search results for CAS RN [109-99-9]. Bethesda (MD): National Library of Medicine (US). [updated 2011 Jun 16; accessed 2016 Oct 18].

Huffman MP, Høie AH, Svendsen C, Brunborg G, Murkovic M, Glatt H, Husøy T. 2016. An in vitro study on the genotoxic effect of substituted furans in cells transfected with human metabolizing enzymes: 2,5-dimethylfuran and furfuryl alcohol. Mutagenesis. 31:597-602.

[IARC] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2000. Phenolphthalein. IARC Monogr Eval Carcinog Risks Hum. 76:387-415.

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

Jackson AF, Williams A, Recio L, Waters MD, Lambert IB, Yauk CL. 2014. Case study on the utility of hepatic global gene expression profiling in the risk assessment of the carcinogen furan. Toxicol Appl Pharmacol. 274(1):63-77.

McDaniel LP, Ding W, Dobrovolsky VN, Shaddock JG Jr, Mittelstaedt RA, Doerge DR, Heflich RH. 2012. Genotoxicity of furan in Big Blue rats. Mutat Res. 742(1-2):72-8.

McKillip WJ, Sherman E. 1978. Furan derivatives. In: Mark HF, Grayson M, Eckroth D, editors. Kirk-Othmer encyclopedia of chemical technology. 3rd ed., vol. 11. New York (NY): Wiley. p. 499-527.

Moser GJ, Foley J, Burnett M, Goldsworthy TL, Maronpot R. 2009. Furan-induced dose-response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-induced liver tumorigenicity). Exp Toxicol Pathol. 61(2):101-11.

[MSDS] Material Safety Data Sheet. 2013. HB PVC 40 Grey Cement. Pickering (ON): Schwartz Advanced Chemistry Solutions. [accessed 2016 Nov 22] (PDF).

[MSDS] Material Safety Data Sheet. 2015. Permanent GlueStic Glue. Brea (CA): Avery. [accessed 2016 Nov 22].

[MSDS] Material Safety Data Sheet. 2016. FLD 138 Pro Stain Stripper. Pittsburg (PA): PPG Industries Inc [accessed 2016 Dec 22].

Munroe IC, Danielewska-Nikiel B. 2006. Comparison of estimated daily intakes of flavouring substances with no-observed-effect levels. Food Chem Toxicol. 44:758-809.

National Centre for Toxicological Research (NCTR). 2016. Two-year carcinogenicity bioassay of furan in F344 Rats. Technical Report for NCTR Experiment No. E2168.08 (Test No. E2168.02).

[NDWD] National Drinking Water Database [database]. Washington DC: Environmental Working Group. [updated 2011; accessed 2016 Oct 5].

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2017 Oct 23]. Ottawa (ON): Health Canada. [accessed 2017 Nov 10].

Nilsson A, Lagesson V, Bornehag C, Sundell J, Tagesson C. 2005. Quantitative determination of volatile organic compounds in indoor dust using gas chromatography-UV spectrometry. Environ Int. 31:1141-1148.

[NIOSH] 1979. National Institute for Occupational Safety and Health. Criteria for a Recommended Standard: Occupational Exposure to Furfuryl Alcohol. DHHS (NIOSH) Publication Number 79-133.

[NPRI] National Pollutant Release Inventory. 2016. NPRI Datasets for 2013, 2014, 2015. Gatineau (QC): Environment and Climate Change Canada. [accessed 2017 Mar 7].

[NTP] National Toxicology Program (US). 2014. 13th Report on Carcinogens. Research Triangle Park (NC): US Department of Health and Human Services, National Toxicology Program. [accessed 2017 Mar 7].

[NTP] National Toxicology Program (US). 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS NO. 98-00-0) In F344/N Rats and B6C3F1 Mice (Inhalation Studies). Research Triangle Park (NC): US Department of Health and Human Services, National Toxicology Program. Report No.: TR482.

[NTP] National Toxicology Program (US). 1996. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Phenolphthalein (CAS NO. 77-09-8) in F344/N Rats and B6C3F1 Mice (Feed Studies). Research Triangle Park (NC): US Department of Health and Human Services, National Toxicology Program. Report No.: TR465.

[OECD] Organisation for Economic Co-operation and Development. 2000. SIDS initial assessment report: tetrahydrofuran: CAS No. 109-99-9. SIAM 10, March 15-17, 2000; United States. [accessed 2017 Mar 7].

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. 2007. Do-it-yourself products fact sheet: to assess the risks for the consumer. Bilthoven (NL): RIVM. Report No.: 320104007/2007. [accessed 2016 Nov 22] (PDF).

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. 2002. Children's Toys fact sheet: to assess the risks for the consumer. Bilthoven (NL): RIVM. Report No.: 612810012/2002. [accessed 2016 Nov 22] (PDF).

Smith RL, Doull J, Feron VJ, Goodman JI, Munro IC, Newberne PM, Portoghese PS, Waddell WJ, Wagner BM, Adams TB, McGowen MM. 2001. GRAS Flavoring Substances 20: The 20th publication by the Expert Panel of the Flavor and Extract Manufacturers Association on recent progress in the consideration of flavoring ingredients generally recognized as safe under the Food Additives Amendment. Food Technology. Vol 55, Issue 12. p. 34-55. (PDF).

Spalding JW, French JE, Stasiewicz S, Furedi-Machacek M, Conner F, Tice RR, Tennant RW. 2000. Responses of transgenic mouse lines p531/2 and TgzAC to agents tested in conventional carcinogenicity bioassays. Toxicol Sci. 53:213-223.

Statistics Canada. 2004. Canadian Community Health Survey – Nutrition (CCHS). Detailed information for 2004 (Cycle 2.2). Ottawa (ON): Statistics Canada.

Stofberg J, Grundschober F. 1978. Consumption ratio and food predominance of flavoring materials. Perfum Flavor. 12(4):27.

Sujatha PS. 2007. Genotoxic evaluation of furfuryl alcohol and 2-furyl methyl ketone by sister chromatid exchange (SCE) analysis. J Health Sci. 53(1):124-127.

Sujatha PS. 2008a. Monitoring cytotoxic potentials of furfuryl alcohol and 2-furyl methyl ketone in mice. Food Chem Toxicol. 46:286-292.

Sujatha PS. 2008b. Response of human lymphocytes in vitro to two dietary furans, furfuryl alcohol and 2-furyl methyl ketone. J Health Sci. 54(1):66-71.

Terrell AN, Huynh M, Grill AE, Kovi RC, O'Sullivan MG, Guttenplan JB, Ho YY, Peterson LA. 2014. Mutagenicity of furan in female Big Blue B6C3F1 mice. Mutat Res Genet Toxicol Environ Mutagen. 770:46-54.

[US EPA] US Environmental Protection Agency. 2011. IRIS Toxicological Review of Tetrahydrofuran (THF) (Interagency Science Discussion Draft). EPA/635/R-11/006D, [accessed 2017 Mar 7]. Washington (DC): US EPA.

[US EPA] US Environmental Protection Agency. 2012a. Benchmark Dose Guidance. (PDF).

[US EPA] US Environmental Protection Agency. 2012b. Toxicological review of tetrahydrofuran (CAS No. 109-99-9) in support of summary information on the Integrated Risk Information System (IRIS). Washington (DC): US EPA, National Center for Environmental Assessment.

[US EPA] US Environmental Protection Agency. 2014. Memorandum: Furfural and Furfuryl Alcohol: Report of the Cancer Assessment Review Committee. Washington DC: US EPA Office of Chemical Safety and Pollution Prevention. 43 p.

[US EPA] US Environmental Protection Agency. 2016. Consumer Exposure Model v1.4.

[US FDA] US Food and Drug Administration. 2008. Exploratory data on furan in food: individual food products. Data collected between 2004 and 2008.

[VCF] Volatile Compounds in Foods [database]. 1992-2016. Version 16.2. Zeist (NL): Triskelion. [updated continually; accessed 2016 Sep 13].

Ville de Montréal. 2009. Municipal drinking water produced by Atwater and Charles-J Des Baillets drinking water plants. Montreal (QC): Division de l'expertise technique, Service des infrastructures et de l'environnement.

Von Tungeln LS, Walker NJ, Olson GR, Mendoza MC, Felton RP, Thorn BT, Marques MM, Pogribny IP, Doerge DR, Beland FA. 2016. Low dose assessment of the carcinogenicity of furan in male F344/N Nctr rats in a 2-year gavage study. Food Chem Toxicol. 99:170-181.

Wheeler MW, Bailer AJ. 2008. Model averaging software for dichotomous dose response risk estimation. J Stat Softw. 26.5:1-15.

[WHO] World Health Organization. 2001. Evaluation of certain food additives: fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series. Geneva (CH): World Health Organization. 120 pages. Report No.: 901.

[WHO] World Health Organization. 2011. Safety evaluation of certain contaminants in food. WHO Food Additive Series: 63. Prepared by the seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives. Geneva (CH): World Health Organization. (PDF).

[WHO] World Health Organization. 2012. Evaluation of certain food additives: seventy-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series. Geneva (CH): World Health Organization. 194 pages. Report No.: 974.

Wilson R, Jones-Otazo H, Petrovic S, Mitchell I, Bonvalot Y, Williams D, Richardson GM. 2013. Revisiting dust and soil ingestion rates based on hand-to-mouth transfer. Hum Ecol Risk Assess 19(1):158-188.

Won D, Lusztyk E. 2011. Data gathering on chemicals released to indoor air of residences from building materials and furnishings. Final Report. Ottawa, (ON): NRC. 158 p. Report No.: B3332.2.

Zhu J, Wong SL, Cakmak S. 2013. Nationally representative levels of selected volatile organic compounds in Canadian residential indoor air: Population-based survey. Environ Sci Technol. 47:13276-13283.

Appendices

Appendix A. Dietary exposure estimates

Table A-1. Mean and 90th percentile furan dietary exposure estimates (with 95% confidence interval)

Age-sex groups (years)	Furan exposure (µg/kg bw/day)	
	Mean	90th percentile
1 to 3	0.22 (0.21, 0.22)	0.34 (0.33, 0.35)
4 to 8	0.14 (0.14, 0.14)	0.24 (0.23, 0.25)
9 to 13 – F	0.09 (0.09, 0.09)	0.16 (0.15, 0.17)
9 to 13 – M	0.09 (0.09, 0.09)	0.15 (0.14, 0.15)
14 to 18 – F	0.08 (0.08, 0.09)	0.16 (0.15, 0.17)
14 to 18 – M	0.08 (0.08, 0.08)	0.14 (0.13, 0.15)
19 to 30 – F	0.15 (0.14, 0.15)	0.33 (0.31, 0.34)
19 to 30 – M	0.17 (0.16, 0.18)	0.37 (0.35, 0.39)
31 to 50 – F	0.24 (0.24, 0.25)	0.52 (0.50, 0.55)
31 to 50 – M	0.24 (0.24, 0.25)	0.48 (0.46, 0.50)
51 to 70 – F	0.23 (0.23, 0.24)	0.46 (0.44, 0.47)
51 to 70 – M	0.25 (0.24, 0.25)	0.50 (0.48, 0.53)
≥ 71 – F	0.21 (0.20, 0.21)	0.43 (0.41, 0.45)
≥ 71 – M	0.22 (0.21, 0.23)	0.44 (0.42, 0.48)

Abbreviations: bw, body weight; F, female; M, male

Appendix B. Estimated exposure to phenolphthalein

Body weights and age groups are from Health Canada 1998. Scenario-specific assumptions are provided in Tables B-1 to B-2.

Table B-1. Dermal exposure parameter assumptions for phenolphthalein

Exposure scenario	Assumptions
Dermal exposure to glue stick	Scenario in ConsExpo Web: universal glue in a tube (RIVM 2007) Product amount (dermal load) = 0.08 g (RIVM 2007) Weight fraction = 0.2% (MSDS 2015) Frequency: 3 times per week (professional judgement, taking into consideration Health Canada 2011, RIVM 2007, ECETOC 2004)

Table B-2. Inhalation exposure parameter assumptions for phenolphthalein

Exposure scenario	Assumptions
Inhalation exposure to glue stick	Scenario in ConsExpo Web: universal glue in a tube (RIVM 2007) All ConsExpo default parameters were used Weight fraction = 0.2% (MSDS 2015)

Appendix C. Estimated exposures to furfuryl alcohol

Environmental media exposures were estimated on the basis of the following parameters: body weights (from Health Canada 1998), dust ingestion rates (from Wilson et al. 2013), and dust concentration (from Nilsson et al. 2005).

Table C-1. Estimates of daily intake (µg/kg bw/day) of furfuryl alcohol from dust

	0–0.5 years	0.5–4 years	5–11 years	12–19 years	20–59 years	≥60 years
Exposure to furfuryl alcohol from dust (µg/kg bw/day)	**3.0E-01**	**1.6E-01**	**6.0E-02**	**2.2E-03**	**2.1E-03**	**2.1E-03**

Product exposures were estimated on the basis of 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 from the model (RIVM 2007), as well as the US EPA's Consumer Exposure Model (CEM) version 1.4 (US EPA 2016). In the absence of dermal absorption data, dermal absorption was assumed to be complete. An inhalation rate of 16.2 m^3/day was assumed for adults (Health Canada 1998). Scenario-specific assumptions are provided in Table C-2.

Table C-2. Dermal and inhalation exposure parameter assumptions for furfuryl alcohol

Exposure scenario	Assumptions
Wood stripper (Dermal)	Model: ConsExpo Paint Remover scenario (RIVM 2007) Product amount (dermal load): 0.5 g/application (RIVM 2007) Concentration of Furfuryl Alcohol: up to 13% (MSDS 2016)
Wood stripper (inhalation)	Model: ConsExpo Paint Stripper scenario – garage (RIVM 2007) Product amount: 1000 g/use (RIVM 2007) Application duration: 60 min (RIVM 2007) Exposure duration: 60 min (RIVM 2007) Room volume: 34 m^3 (RIVM 2007) Ventilation rate: 1.5 per hour (RIVM 2007)

Exposure scenario	Assumptions
	Concentration of furfuryl alcohol: up to 13% (MSDS 2016)
Wood stripper (inhalation)	Model: CEM – garage (US EPA 2016) Product amount: 1000–2500 g/use (US EPA 2016) Application duration: 60–360 min (US EPA 2016) Room volume: 90 m^3 (US EPA 2016) Air exchange rate, zones 1 and 2: 0.45 per hour for both, or 1.5 for zone 1 and 0.6 for zone 2 (US EPA 2016) Interzone ventilation rate: 0 or 108.978 m^3/hr (US EPA 2016) Concentration of furfuryl alcohol: up to 13% (MSDS 2016)

Appendix D. Estimated exposures to tetrahydrofuran

Exposures were estimated on the basis of 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 from the model (RIVM 2007), as well as the US EPA's Consumer Exposure Model (CEM) version 1.4 (US EPA 2016). An inhalation rate of 16.2 m^3/day was assumed for adults (Health Canada 1998). Scenario-specific assumptions are provided in Table D-1.

Table D-1. Inhalation exposure parameter assumptions for tetrahydrofuran

Exposure scenario	Assumptions
PVC glue	Model: ConsExpo scenario for universal glue in a bottle (RIVM 2007) Concentration of tetrahydrofuran: 80%(MSDS 2014; MSDS 2013) Product amount used: 10 g/application (RIVM 2007) Application duration: 20 min (RIVM 2007) Exposure duration: 240 min (RIVM 2007) Room volume: 20m^3(RIVM 2007)
PVC glue	Model: CEM (US EPA 2016) Concentration of tetrahydrofuran: 80% (MSDS 2014; MSDS 2013) Product amount used: 10–30 g/application (US EPA 2016) Duration: 20–240 min (US EPA 2016) Room volume: 20 m^3 (US EPA 2016) Air exchange rate, zones 1 and 2: 0.45 or 0.6 per hour (US EPA 2016) Interzone ventilation rate: 0 or 108.978 m^3/hr (US EPA 2016)