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Additional Risk Characterization Document in Support of the Draft Screening Assessment for Furan Compounds Group:

Furfuryl alcohol and tetrahydrofuran outdoor air exposure and human health risk characterization

Health Canada

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Canada

Synopsis

A draft of the screening assessment report for the Furan Compounds Group was published on September 1, 2018. This current document contains additional information to support that screening assessment of 2-furanmethanol (CAS RN[1] 98-00-0) and furan, tetrahydro (CAS RN 109-99-9), hereinafter referred to as furfuryl alcohol and tetrahydrofuran, respectively, two of the four substances in the Furan Compounds Group. Data identified or generated since the publication of the draft screening assessment report are included herein.

The scope of this additional risk characterization document is limited to assessing potential human health concerns from releases of furfuryl alcohol and tetrahydrofuran into air from facilities in Canada. Since the publication of the draft screening assessment report, a more thorough investigation of the updated National Pollutant Release Inventory (NPRI) data on furfuryl alcohol and tetrahydrofuran has been conducted. The data and analysis herein provide the opportunity for public comment on the new information prior to it being considered in the finalization of the screening assessment of furan compounds, and if appropriate, the corresponding risk management approach document.

In 2011, furfuryl alcohol and tetrahydrofuran were not reported to be manufactured in Canada but were reported to be imported into Canada in quantities ranging from 100 000 kg to 1 000 000 kg for furfuryl alcohol and 384 594 kg for tetrahydrofuran. Both substances can be released into air because of industrial activities. Data from the NPRI indicated that approximately 0.024 tonnes to 590 tonnes of furfuryl alcohol and 0.0002 tonnes to 96 tonnes of tetrahydrofuran were released into air in Canada in 2019. For furfuryl alcohol, this was from various sectors including foundries and non-metallic mineral product manufacturing, and for tetrahydrofuran, this was from sectors including textile and fabric finishing and fabric coating, and petroleum manufacturing.

Furfuryl alcohol is classified as “likely to be carcinogenic to humans” by the US Environmental Protection Agency (US EPA) Cancer Assessment Review Committee (CARC). Since the publication of the draft screening assessment, the International Agency for Research on Cancer (IARC) classified furfuryl alcohol as Group 2B (“possibly carcinogenic to humans”) and the European Chemicals Agency considers furfuryl alcohol as “suspected of causing cancer” (Carc. 2B). Risk estimates were derived for potential exposures to furfuryl alcohol from outdoor air for residents living near facilities releasing the substance. Estimated acute and chronic exposure to furfuryl alcohol in ambient air near releasing facilities were compared to the cancer and non-

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cancer critical effect levels (acute and chronic). The margins for certain facilities (that is, foundries, non-metallic product manufacturing) were considered inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

The US EPA Integrated Risk Information System (IRIS) has assessed tetrahydrofuran as having “suggestive evidence of carcinogenic potential”. Since the publication of the draft screening assessment, IARC classified tetrahydrofuran as Group 2B (“possibly carcinogenic to humans”). Risk estimates were derived for potential exposures to tetrahydrofuran from outdoor air for residents living near facilities releasing the substance. Estimated acute and chronic exposure to tetrahydrofuran in ambient air near releasing facilities were compared to the cancer and non-cancer critical effect levels (acute and chronic). The margin between the inhalation critical effect levels for cancer and chronic inhalation exposure to tetrahydrofuran for Canadians living near certain facilities (that is, fabric coating facility) are considered inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

On the basis of information presented in this risk characterization document, the release of furfuryl alcohol and tetrahydrofuran into air by certain facilities may be harmful to human health.

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List of Tables and Figures

1. Introduction

Pursuant to section 74 of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health conducted a screening assessment of 2-furanmethanol (CAS RN[2] 98-00-0) and furan, tetrahydro- (CAS RN 109-99-9), hereinafter referred to as furfuryl alcohol and tetrahydrofuran, respectively as part of the screening assessment of the Furan Compounds Group. A draft of the screening assessment report for the Furan Compounds Group was published September 1, 2018 (ECCC, HC 2018), and proposed that furfuryl alcohol and tetrahydrofuran met one or more of the criteria set out in section 64 of CEPA.

This additional risk characterization document contains additional information to support the screening assessment of furan compounds. This includes data identified or generated since the publication of the draft screening assessment report (September 2018). Relevant data were identified up to November 2019. Targeted literature searches were conducted up to October 2021.

The scope of this document is limited to assessing potential chronic and acute human health concerns for Canadians living near facilities releasing furfuryl alcohol and tetrahydrofuran into air. Since the publication of the draft screening assessment report, releases into air reported by certain facilities to the National Pollutant Release Inventory (NPRI) more than doubled since 2015 and 2016. As such, a thorough investigation of the NPRI data on furfuryl alcohol and tetrahydrofuran was conducted, including use of satellite images (Google Maps) which identified several facilities located close to residences. Therefore, additional exposure scenarios for individuals living near facilities reporting release of furfuryl alcohol and tetrahydrofuran were assessed and results show additional potential human health concerns.

The data and analysis herein provide the opportunity for public comment on the new information prior to it being considered in the finalization of the screening assessment of the Furan Compounds Group, and if appropriate, the corresponding risk management approach document.

2. Sources and uses

Furfuryl alcohol can be formed from naturally occurring components of food (Burdock 2010; Health Canada 2016b). Furfuryl alcohol 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

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al. 1995, as cited in HSDB 1983- c). Tetrahydrofuran does not occur naturally in the environment.

2.1 Information submitted in response to a CEPA section 71 survey

Furfuryl alcohol and tetrahydrofuran were included in a survey issued pursuant to CEPA section 71 (Canada 2012) and were reportedly not manufactured in Canada in 2011 while total import quantities ranged between 100 000 kg to 1 000 000 kg for furfuryl alcohol and 384 594 kg for tetrahydrofuran for that same year (Canada 2012). Furfuryl alcohol was reported to be used in the automotive, aircraft and transportation sector, in building or construction material, in metal materials as well as in paint and coatings (Canada 2012). Tetrahydrofuran was reported to be used in adhesives and sealants, automotive, aircraft and transportation sector, building or construction material, paints and coatings as well as plastic and rubber material (Canada 2012).

Additional uses of furfuryl alcohol and tetrahydrofuran including presence in products available to consumers are described in section 4 of the draft screening assessment report (ECCC, HC 2018).

3. Releases to the environment

3.1 National Pollutant Release Inventory (NPRI)

Furfuryl alcohol and tetrahydrofuran release data from the NPRI[3] were noted in the draft screening assessment report. Quantities released into air from 2015 to 2019 are presented in Table 3-1 below. The substances were not reported to be released to other environmental compartments such as water under the NPRI.

Table 3-1. Quantities of furfuryl alcohol and tetrahydrofuran released annually into air from 2015 to 2019

Reporting year[a]	Quantity of furfuryl alcohol (tonnes)[b]	Quantity of tetrahydrofuran (tonnes)[b]
2015	241	21
2016	206	19
2017	544	13
2018	613	121
2019	641	96

[a] Data used for this table is current as of March 11, 2021. Facilities may periodically update their information reported to the NPRI. As such, repeated analysis with data extracted at a different time may produce different results. There is

[3] For details see:
About the National Pollutant Release Inventory, available online: https://www.canada.ca/en/environment-climate-change/services/national-pollutant-release-inventory/about-national-pollutant-release-inventory.html#wb-cont; and Substance list by threshold, available online: https://www.canada.ca/en/environment-climate-change/services/national-pollutant-release-inventory/substances-list/threshold.html

a degree of complexity surrounding NPRI data interpretation, such as meeting reporting thresholds and the use of various acceptable methods and data sources.
[b] Sum of releases from facilities meeting NPRI reporting threshold requirements. Values are rounded to the nearest tonne.

The sectors responsible for the release of furfuryl alcohol into air for the reporting years in
Table 3-1 included foundries, iron and steel mills, coating, engraving, cold and heat treating and allied activities, and other non-metallic mineral product manufacturing (NPRI 2021). The sectors responsible for the release of tetrahydrofuran into air presented in Table 3-1 included textile and fabric finishing and fabric coating, plastic product manufacturing, oil and gas extraction, petroleum manufacturing, paint, coating and adhesive manufacturing, and other chemical product manufacturing.

4. Furfuryl alcohol

4.1 Exposure assessment

There were no significant changes from exposure to furfuryl alcohol in drinking water, dust, soil and food, as well as exposure from use of wood strippers, as described in section 7.3.1 of the draft screening assessment report (ECCC, HC 2018). Since the publication of the draft screening assessment report, air releases reported by certain facilities to the NPRI had increased significantly (that is, more than doubled from 2016 to 2017,

Table **3-1**). As such, a thorough investigation of the NPRI data on furfuryl alcohol, including use of satellite images of facilities, was conducted. Several of the facilities are located close to residences; therefore, additional exposure scenarios for those living near facilities reporting release of furfuryl alcohol to air have been derived.

The NPRI reported that furfuryl alcohol is released into air in Canada by several different types of facilities including non-metallic mineral product manufacturing facilities, foundries, coating, engraving, as well as cold and heat-treating and allied activities (NPRI 2021). In the absence of measured concentrations in ambient air, the US EPA exposure model SCREEN3 (SCREEN3 1996) was used to estimate ambient air concentrations of furfuryl alcohol near releasing facilities in Canada using the 2019 NPRI data (NPRI 2021). Maximum 1-hour air concentrations at various distances from the source facilities (representing distance to residential areas, refer to Appendix A for details) were estimated assuming a receptor height of 1.74 m (Curry et al. 1993) (Table 4-1). For exposure events happening over the span of a year, it can be expected that the direction of the prevalent winds will be more variable and uncorrelated to the wind direction for a single event. Therefore, the maximum amortized exposure concentration for one year can be determined by multiplying the maximum 1-hour exposure by a

scaling factor of 0.2 (US EPA 1992). Results of the modelled air concentrations are presented in

Table **4-1**, and model inputs and assumptions can be found in Appendix A (Table A-1).

Table 4-1. Estimated concentration of furfuryl alcohol from on-site releases to air using 2019 NPRI data

Sectors	Exposure parameter	Concentration of furfuryl alcohol (mg/m^3)[a]
Foundries	1-hour maximum concentration 24-hour maximum concentration[b] Annual concentration[c]	0.03 – 3.474 0.012 – 1.390 0.006 – 0.695
Non-metallic mineral product manufacturing	1-hour maximum concentration 24-hour maximum concentration[b] Annual concentration[c]	0.064 0.026 0.013
Coating, engraving, cold and heat treating, and allied activities	1-hour maximum concentration 24-hour maximum concentration[b] Annual concentration[c]	1.43E-04 5.74E-05 2.87E-05

[a] These values describe the range of estimated furfuryl alcohol concentrations from similar facilities reporting to release the substance. Details on model parameters for each facility can be found in Appendix A.
[b] With an assumption of a continuous release occurring over a 24-hour period and considering the changing wind direction over this period, a maximum concentration during a 24-hour exposure period is estimated by multiplying a factor of 0.4, with the maximum 1-hour exposure (US EPA 1992).
[c] For exposures occurring over a year, it can be expected that with changing wind directions, the substance air concentrations within an area release source may not vary to the same extent as those of point release sources. The meteorological conditions giving rise to a maximum 1-hour exposure can persist for a longer duration; thus, the maximum concentration for one year is determined by multiplying the maximum 1-hour concentration by a factor of 0.2 (US EPA 1992).

4.2 Health effects assessment

Hazard characterization for furfuryl alcohol is described in section 7.3.2 of the draft screening assessment report (ECCC, HC 2018). There were no significant changes in the effects of concern identified. The inclusion of releases from industrial facilities in this report required further consideration of the inhalation route of exposure for chronic exposure scenarios, as only the oral route was presented in the draft screening assessment for this duration. Both chronic cancer and non-cancer effects for the inhalation route were evaluated in this report.

As presented in the draft screening assessment report (ECCC, HC 2018), a critical effect of chronic exposure to furfuryl alcohol is carcinogenicity. Since publication of the draft screening assessment report, reports by the International Agency for Research on Cancer (IARC) (IARC 2019) and the European Chemicals Agency (ECHA) (ECHA 2018) were available. ECHA (2018) considers furfuryl alcohol as “suspected of causing cancer” (Carc. 2B). IARC (2019) classified furfuryl alcohol to be possibly carcinogenic to humans (Group 2B). These reports (ECHA 2018, IARC 2019) as well as the US EPA

Cancer Assessment Document (2014) summarized the health effects literature, and were used to inform the health effects characterization for furfuryl alcohol.

Acute toxicity

The draft screening assessment (ECCC, HC 2018), outlined an acute inhalation study in rats exposed for 4-hours (cited in ECHA 2007-2016b). An effect level of 510 mg/m^3 was determined from that study based on the occurrence of decreased breathing rate in the last hour of exposure. Decreased breathing rate was reported throughout exposure at 820 mg/m^3, with labored breathing in the last hour of exposure. 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/m^3. Additional studies report similar effects on breathing and body weight at concentrations from 842 mg/m^3, as well as mortalities at concentrations of 953 mg/m^3 and above (ECCC, HC 2018).

Repeated-dose toxicity

The National Toxicology Program (NTP) carcinogenicity study on furfuryl alcohol (NTP 1999) included 16-day, 14-week, and 2-year inhalation exposures for mice and rats. In the 16-day inhalation study, mice and rats were exposed to 0, 16, 31, 63, 125 or 250 ppm furfuryl alcohol (equivalent to 0, 64, 124, 252, 500 or 1000 mg/m^3) for 6 hours/day, 5 days/week (NTP 1999). None of the rats exposed to 250 ppm (1000 mg/m^3) survived to the end of the study, and one died at 125 ppm (500 mg/m^3) on day 5. Rats of both sexes exhibited necrosis, regeneration, and squamous metaplasia of the respiratory epithelium; and/or necrosis and degeneration of the olfactory epithelium at 64 mg/m^3 furfuryl alcohol and above, with acute and/or suppurative inflammation significantly increasing at higher concentrations. Other effects observed in the 16-day study in rats were clinical signs including dyspnea, hypo-activity, nasal and ocular discharge at 63 ppm (252 mg/m^3) and above, and decreased body weight gain at 31 ppm (124 mg/m^3) or 125 ppm (500 mg/m^3) and above in males or females, respectively. Mice also had decreased survival at high concentrations, as all animals at 250 ppm (1000 mg/m^3) and one female at 125 ppm (500 mg/m^3) died on study day 2 and 14, respectively. Nasal lesions in mice of both sexes at 16 ppm (64 mg/m^3) included squamous metaplasia in the respiratory epithelium and degeneration of the olfactory epithelium. Necrosis of the respiratory and olfactory epithelium, as well as acute and/or suppurative inflammation were reported at 124 mg/m^3 and above. In mice, decreased body weight and body weight gains were observed at 63 and 125 ppm (252 and 500 mg/m^3).

In a subchronic study, rats and mice were exposed to concentrations of furfuryl alcohol (0, 2, 4, 8, 16 or 32 ppm, equivalent to 0, 8, 16, 32, 64 or 128 mg/m^3) by inhalation for 6 hours/day, 5 days/week for 14 weeks (NTP 1999). In rats, females in the high concentration group (32 ppm or 128 mg/m^3) had decreased body weights compared to

controls. The study authors considered changes in hematology and clinical chemistry effects as not toxicologically relevant. At the low concentration (2 ppm or 8 mg/m^3), male and female rats had a significant incidence of squamous metaplasia of the transitional epithelium of the nose compared to control. Starting at 4 ppm (16 mg/m^3) and with increasing concentration of furfuryl alcohol, the incidence of degeneration, hyperplasia and surface exudate in the olfactory epithelium were generally observed to increase in male and female rats. Significant incidence of goblet cell hyperplasia and squamous metaplasia in the respiratory epithelium were reported at 8 ppm and above. Compared to controls, significant incidences of cellular infiltrate in the lamina propria were reported at 16 ppm and above in both sexes of rats. In mice, males in the high concentration group were observed to have decreased relative heart weights. Similar to rats, nasal lesions were observed in mice - male or female mice showed increased incidence of hyaline droplets in the respiratory epithelium, or metaplasia and degeneration of the olfactory epithelium at 2 ppm (8 mg/m^3), although with minimal severity. At higher concentrations of furfuryl alcohol, incidence and severity of these lesions increased. Increased incidences of chronic inflammation of the olfactory epithelium and squamous metaplasia in the transitional epithelium were also reported in both sexes of mice starting at 4 ppm and 8 ppm, respectively (NTP 1999).

A 2-year inhalation study in mice and rats (NTP 1999) investigated whole-body exposures to furfuryl alcohol vapour of 0, 2, 8 or 32 ppm (0, 8, 32 or 128 mg/m^3) for 6 hours per day, 5 days per week. Nasal lesions were present in rats and mice at all treatment concentrations. At the low concentration (8 mg/m^3), significant incidences of hyperplasia in the lateral wall; metaplasia, hyaline degeneration and atrophy in olfactory epithelium; and hyperplasia, hyaline degeneration in respiratory epithelium of the nose of rats were reported. Increased incidence was seen at higher concentrations. Additional nasal lesions in the lateral wall (squamous metaplasia), olfactory epithelium (hyperplasia, fibrosis, hyaline degeneration) and respiratory epithelium (squamous metaplasia, hyaline degeneration) were reported in the mid- and high concentration (32 or 128 mg/m^3) groups in rats. In addition, suppurative inflammation and hyperplasia of the Bowman's glands were also observed in male and female rats at the mid- and/or high concentration. In mice, hyperplasia and metaplasia of the Bowman's gland, squamous metaplasia in the lateral wall of the nose, metaplasia and atrophy in the olfactory epithelium and hyaline degeneration in the respiratory epithelium were observed at 8 mg/m^3 in male or female mice. Supperative inflammation was noted to start at 8 mg/m^3 in female mice, or 32 mg/m^3 in males. At 32 mg/m^3 and above, significant incidence of squamous metaplasia in the respiratory epithelium was seen in males, squamous metaplasia in Bowman's gland in females while hyaline degeneration of the olfactory epithelium was reported in male and female mice. Regeneration of the respiratory epithelium was also observed at 32 mg/m^3 and above. In addition, nephropathy was present in all treated rats and mice, and the severity increased with exposure concentration. An extended evaluation (step sections) of the kidney identified rental tubule hyperplasia in rats in the high concentration group (128 mg/m^3). 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) (NTP 1999).

From the non-cancer effects reported in the NTP (1999) studies described above, 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 respiratory and olfactory epithelium in both mice and rats of both sexes. No NOAECs were determined, and LOAECs based on nasal respiratory and/or olfactory epithelial lesions were at 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. From the 2-year study of furfuryl alcohol inhalation exposure, the NTP (1999) also noted that the overall architecture of the nasal turbinates was not distorted and the mucosal lining remained intact. Additionally, because the concentration of metabolites was proportional to dose throughout the range of doses used, the metabolic capacity did not appear to be exceeded (NTP 1999). Together, this suggests that effects observed are not associated with tissue destruction caused by corrosion or due to overwhelming the metabolic capacity of the target tissue.

For risk characterization of scenarios involving chronic inhalation, inflammatory, degenerative and proliferative lesions of the respiratory, transitional and olfactory tissue in the nose of rats and mice from the 14-week study (NTP 1999) were also considered a critical endpoint. Given that this effect was observed across all doses, the lowest exposure dose (8 mg/m^3) from the 14-week NTP (1999) study in rats and mice was selected for risk characterization and adjusted to reflect continuous exposure (1.4 mg/m^3).

Carcinogenicity and genotoxicity

As discussed in the draft screening assessment (ECCC, HC 2018), a 2-year inhalation study in mice and rats (NTP 1999) investigated whole-body exposures to furfuryl alcohol vapour of 0, 2, 8 or 32 ppm (0, 8, 32 or 128 mg/m^3, 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, as one adenoma of the nasal lateral wall was observed at the low-concentration, one adenoma of the respiratory epithelium was seen at the mid-concentration, and four respiratory epithelial carcinoma or squamous cell carcinoma (1 carcinoma, 3 squamous cell carcinoma) were seen at the high-concentration level. At the high-concentration level, these incidences were statistically significant 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 renal tubule adenomas and carcinomas at the high concentration compared to controls (combined standard and extended evaluation). In addition, although not significant compared to study controls, the combined incidence of renal tubule adenoma (2 animals) and carcinoma (2 animals) at the high-concentration (128 mg/m^3) using

standard kidney histopathology evaluation was higher than historical control, and had a positive trend. There was no evidence of carcinogenic activity in female mice.

Using the Benchmark Dose Modelling Software (BMDS 2.5) (BMDS 2017), tumour incidence data in rats and mice from the NTP cancer bioassay (NTP 1999) were modelled for this risk characterization document (Appendix, Table B-1) and the best fit model was selected for each endpoint on the basis of the US EPA BMDS guidance document (US EPA 2012a). BMDS modelling was conducted in the draft screening assessment to address oral routes of exposure; however, modifications were made to the modelling in this report to address inhalation exposures. For nasal tumors (combined adenoma and carcinoma) in male rats, the BMC_{10} and corresponding $BMCL_{10}$ are 165 mg/m^3 and 79 mg/m^3 (respectively) (Appendix B, Figure B-1). The BMC_{10} and corresponding $BMCL_{10}$ for combined adenoma and carcinoma of the kidney in male mice are 129 mg/m^3 and 98 mg/m^3 (respectively) (Appendix B, Figure B-2). The $BMCL_{10}$ values have been adjusted to be representative of continuous exposure, resulting in $BMCL_{10}$ values of 14 mg/m^3 for nasal tumours in male rats and 18 mg/m^3 for kidney tumours in male mice.

Reviews of the genotoxicity of furfuryl alcohol have been conflicting. As discussed in the draft screening assessment report (ECCC, HC 2018), 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 (US EPA 2014). Similarly, ECHA (2018) concluded that furfuryl alcohol has no significant genotoxic activity. However, IARC (2019a) concluded that there was moderate evidence of genotoxicity, based on DNA adduct formation in lung tissue of exposed humans (Monien et al 2015 in IARC 2019a), as well as positive in vitro results for sister chromatid exchange (SCE) (without metabolic activation) in mammalian cells, and mutation in cell lines where human or rodent sulfotransferase were expressed (IARC 2019a). Negative in vitro results were reported for SCE in human cells, chromosomal aberrations in mammalian cells and mutagenicity in the Ames assay (IARC 2019a). In in vivo assays, chromosomal aberration, micronucleus formation and SCE findings were negative in mice (IARC 2019a). IARC (2019a) also considers that there is strong evidence that furfuryl alcohol is metabolically activated to an electrophile. There is support for the hypothesis that neoplastic effects may originate from the bioactivation of furfuryl alcohol to a reactive intermediate by sulfotransferases which are not expressed in conventional cell lines used for in vitro genotoxicity testing (Glatt et al. 2012).

While chronic irritation of the nasal tissue is likely a significant factor in the formation of nasal tumours, there is concern regarding whether and to what extent genotoxicity impacts this effect. For kidney tumours, exposure to furfuryl alcohol clearly exacerbated age-related nephropathy in male rats. However, renal tubule neoplasms were also observed in female rats and male mice, which are considered uncommon (NTP 1999). Similar to the observed nasal tumours, the potential for genotoxicity to impact kidney tumours is unknown.

Reviews of the carcinogenicity of furfuryl alcohol have been somewhat conflicting regarding the relevance of the observed tumours. On the basis of the NTP (1999) studies, the US EPA (2014) concluded that the nasal and kidney tumours observed in male rats and male mice (respectively) warranted classification as “likely to be carcinogenic to humans”. IARC (2019a) considered that there is “sufficient evidence in experimental animals for the carcinogenicity of furfuryl alcohol”. ECHA (2018) concluded that the tumours are induced by a non-genotoxic mechanism and that, although limited evidence of carcinogenicity was seen (as an increase in the incidence of tumours at toxic dose levels and associated with tissue damage), a classification of “[s]uspected of causing cancer” is considered appropriate based on the available data. Based on the available information, carcinogenicity is considered to represent a critical health effect for risk characterization from chronic exposure to furfuryl alcohol in this report.

4.3 Characterization of human health risk

As indicated in the draft screening assessment report, additional sources of exposure to furfuryl alcohol include through the diet, primarily from its natural occurrence in foods, from household dust and from use of certain wood strippers containing furfuryl alcohol. Section 7.3.3 of the draft screening assessment report addressed the risk characterization of furfuryl alcohol through its possible presence in the diet both from its natural occurrence in food, and its possible use as a food flavouring agent as well as from use of certain wood strippers. Potential exposures to furfuryl alcohol from dust are considered insignificant in comparison to exposures from air and have therefore not been included in the risk characterization for furfuryl alcohol.

A critical effect of furfuryl alcohol is carcinogenicity from chronic exposure. In a 2-year study where rodents were exposed to furfuryl alcohol by inhalation, the most sensitive tumorigenic effects observed were nasal tumours in rats, and are considered protective of the observed kidney tumours in mice. There are mixed results for available genotoxicity studies, which has resulted in conflicting interpretation among agencies. A full mode of action for furfuryl alcohol tumour development has not been established, and the role of genotoxicity in nasal and kidney tumour formation is unknown. As a conservative approach, the adjusted $BMCL_{10}$ of 14 mg/m^3 for nasal tumours was selected as the critical cancer-based effect value. Table 4-2 provides all relevant chronic exposure and cancer effect values for furfuryl alcohol, as well as the margins of exposure (MOEs) for determination of cancer risk.

Table 4-2. Exposure and cancer effect values, as well as margins of exposure for residents near facilities releasing furfuryl alcohol

Exposure scenario	Exposure (mg/m^3)	Critical effect level	Critical health effect endpoint	MOE
Chronic inhalation exposure from air for residents near foundries releasing furfuryl alcohol	0.006 to 0.695 (annual concentration)	$BMCL_{10}$ = 14 mg/m^3 (adjusted for continuous exposure)[a]	Nasal tumours (combined adenoma and carcinomas) in male rats (NTP 1999)	20 – 2333
Chronic inhalation exposure from air for residents near non-metallic mineral product manufacturing facilities releasing furfuryl alcohol	0.013 (annual concentration)	$BMCL_{10}$ = 14 mg/m^3 (adjusted for continuous exposure)[a]	Nasal tumours (combined adenoma and carcinomas) in male rats (NTP 1999)	1077
Chronic inhalation exposure from air for residents near coating, engraving, cold and heat treating, and allied activities facilities releasing furfuryl alcohol	2.87E-05 (annual concentration)	$BMCL_{10}$ = 14 mg/m^3 (adjusted for continuous exposure)[a]	Nasal tumours (combined adenoma and carcinomas) in male rats (NTP 1999)	488 145

[a] Adjusted $BMCL_{10}$ = 79 mg/m^3 × (6 hours/24 hours)(5 days/7 days) = 14 mg/m^3; adjusted for continuous exposure as animals were exposed for 6 hours/day, 5 days/week in the toxicological study.

Non-cancer effects were also considered for chronic exposure to furfuryl alcohol from certain facilities. The critical chronic non-cancer effect is considered to be development of inflammatory, degenerative and proliferative lesions of the respiratory, transitional and olfactory tissue in the nose of rats and mice at 8 mg/m^3, which results in an effect value of 1.4 mg/m^3 after adjusting for continuous exposure.

Canadians may also be exposed to higher concentrations of furfuryl alcohol emitted from facilities for short periods. These emissions may have effects on Canadians

residing nearby. For acute scenarios, the critical inhalation effect level of 510 mg/m^3 was selected based on decreased breathing rate and decreased body weight gain reported in rats (representing a sensitive indicator for more severe respiratory depression and death occurring at higher acute exposure concentrations).

Table 4-3 presents the acute and chronic exposure estimates, non-cancer effect values and resulting margins of exposure for determination of non-cancer risk for furfuryl alcohol.

Table 4-3. Exposure estimates, non-cancer effect values, and margins of exposure for residents near certain facilities releasing furfuryl alcohol

Industry type	Exposure scenario	Exposure (mg/m^3)	Critical effect level	Critical health effect endpoint	MOE
Foundries	Chronic exposure	0.006 to 0.695 (annual concentration)	LOAEC = 1.4 mg/m^3 (adjusted for continuous exposure)[a]	Nasal tissue lesions from 14-week study in male and female rats and mice (NTP 1999)	2 to 233
Non-metallic mineral product manufacturing	Chronic exposure	0.013 (annual concentration)	LOAEC = 1.4 mg/m^3 (adjusted for continuous exposure)[a]	Nasal tissue lesions from 14-week study in male and female rats and mice (NTP 1999)	108
Coating, engraving, cold and heat treating, and allied activities	Chronic exposure	2.87E-05 (annual concentration)	LOAEC = 1.4 mg/m^3 (adjusted for continuous exposure)[a]	Nasal tissue lesions from 14-week study in male and female rats and mice (NTP 1999)	48 815
Foundries	Acute exposure	0.03 to 3.474 (1-hour maximum concentration)	510 mg/m^3	Decreased breathing rate and decreased body weight gain reported in rats.	147 to 17 000
Non-metallic mineral product manufacturing	Acute exposure	0.064 (1-hour maximum concentration)	510 mg/m^3	Decreased breathing rate and decreased body weight	7969

				gain reported in rats.	
Coating, engraving, cold and heat treating, and allied activities	Acute exposure	1.43E-04 (1-hour maximum concentration)	510 mg/m^3	Decreased breathing rate and decreased body weight gain reported in rats.	> 3 million

[a] Adjusted $BMCL_{10}$ = 8 mg/m^3 × (6 hours/24 hours)(5 days/7 days) = 1.4 mg/m^3; adjusted for continuous exposure as animals were exposed for 6 hours/day, 5 days/week in the toxicological study.

The margins between the critical cancer and non-cancer (acute and chronic) inhalation effect levels and inhalation exposures to furfuryl alcohol for Canadians living near certain facilities from various sectors (that is, foundries, non-metallic product manufacturing) releasing this substance to air are considered inadequate to account for uncertainties in the health effects and exposure data used to characterize risk. Therefore, the release of furfuryl alcohol into air by certain facilities may be harmful to human health.

4.4 Uncertainties in evaluation of risk to human health

For furfuryl alcohol, the lack of ambient air monitoring data near facilities releasing furfuryl alcohol in Canada, as well as monitoring data for general population exposure are uncertainties.

Further information on the cancer mode of action on the formation of tumours in the nasal cavity and kidney is an uncertainty. Additional information the role of sulfotransferases on genotoxicity would also be of interest.

5. Tetrahydrofuran

5.1 Exposure assessment

There were no significant changes from exposure to tetrahydrofuran for the general population of Canada in ambient and indoor air, drinking water, food and from use of PVC cement and PVC cement primers as described in section 7.4.1 of the draft screening assessment report (ECCC, HC 2018). Since the publication of the draft screening assessment report, releases into air reported by certain facilities to the NPRI had increased significantly (that is, almost 10 times higher in 2018 compared to 2017, Table 3-1). As such, a thorough investigation of the NPRI data on tetrahydrofuran, including use of satellite images of facilities (Google Maps), was conducted. Several of the facilities are located close to residences; therefore, additional exposure scenarios

for those living near facilities reporting release of tetrahydrofuran into air have been derived.

According to information reported to the NPRI for 2019, fourteen facilities released tetrahydrofuran into air in Canada (NPRI 2021). The highest releases were by facilities from sectors such as fabric coating, and petrochemical manufacturing (NPRI 2021).

Limited ambient air data exists for tetrahydrofuran in Canada. Information available from the Hamilton Air Monitoring Network (HAMN) in Ontario indicates that tetrahydrofuran concentrations measured over various 24-hour periods between 2018 and 2020 in ambient air at 3 locations within the Hamilton Ontario industrial and residential sectors ranged between levels below the reliable detection limit (RDL, 1.18 µg/m^3) to a maximum of 38 µg/m^3. The average concentrations from these sites ranged from levels below the RDL to 8.38 µg/m^3 (HAMN c2009-2021). Tetrahydrofuran has also been monitored at a few stations in Sarnia, Ontario, an industrial area, as part of the Clean Air Sarnia and Area (CASA) initiative since 2019. Concentrations of tetrahydrofuran from two monitoring stations have consistently been below the detection limit of 0.59 µg/m^3 from 2019-2021 (CASA 2021). Measured ambient air concentrations were not identified for other areas with known facilities releasing tetrahydrofuran to air; therefore, the US EPA exposure model SCREEN3 (SCREEN3 1996) was used to estimate ambient air concentrations of tetrahydrofuran near the two highest releasing facilities in Canada using the 2019 NPRI data (NPRI 2021). Maximum 1-hour air concentrations at various distances from the source facilities (representing distance to residential areas, refer to Appendix A for details) were estimated assuming a receptor height of 1.74 m (Curry et al. 1993).

Table 5-1. Estimated concentration of tetrahydrofuran from sectors with highest on-site releases into air using 2019 NPRI data

Sectors	Exposure parameter	Concentration of tetrahydrofuran (mg/m^3)[a]
Fabric coating	1-hour maximum concentration	0.604
	24-hour maximum concentration[b]	0.242
	Annual concentration[c]	0.121
Petrochemical manufacturing	1-hour maximum concentration	0.070
	24-hour maximum concentration[b]	0.028
	Annual concentration[c]	0.014

[a] These values are exposure estimates of tetrahydrofuran concentrations from the top 2 facilities that reported releasing the substance to NPRI in 2019. Details on model parameters for each facility can be found in Appendix A.
[b] With an assumption of continuous release occurring over a 24-hour period and considering the changing wind direction over this period, a maximum concentration during a 24-hour exposure period is estimated by multiplying a factor of 0.4, with the maximum 1-hour exposure (US EPA 1992).
[c] For exposures occurring over a year, it can be expected that, with changing wind directions, the substance air concentrations within an area release source may not vary to the same extent as those of point release sources. The meteorological conditions giving rise to a maximum 1-hour exposure can persist for a longer duration; thus, the

maximum concentration for one year is determined by multiplying the maximum 1-hour concentration by a factor of 0.2 (US EPA 1992).

5.2 Health effects assessment

Hazard characterization for tetrahydrofuran is described in section 7.4.2 of the draft screening assessment report (ECCC, HC 2018). There were no significant changes in the effects of concern identified. The inclusion of releases from industrial facilities in this report required additional consideration of the inhalation route of exposure for chronic exposure scenarios. Both chronic cancer and non-cancer effects were evaluated in this report.

As presented in the draft screening assessment report (ECCC, HC 2018), a critical effect of chronic exposure to tetrahydrofuran is carcinogenicity. Since publication of the draft screening assessment report, a report from the IARC was available, which classified tetrahydrofuran as being “possibly carcinogenic to humans” (Group 2B) (IARC 2019b). This is aligned with other international jurisdictions, as tetrahydofuran is also classified as having “suggestive evidence of carcinogenic potential” by the US EPA (2012b), and “suspected of causing cancer” (Carc. 2B) by ECHA (2017). These reports (IARC 2019b, US EPA 2012b, ECHA 2017), as well as the report published by the National Industrial Chemicals Notification Assessment Scheme (NICNAS) (2016) summarized the health effects literature and were used to inform the health effects section of this document, including selection of effect levels for critical endpoints.

Acute toxicity

Adverse effects after acute exposure to tetrahydrofuran by inhalation was reviewed by the US EPA (2012b) and other jurisdictions such as ECHA (2017) and NICNAS (2016). Narcotic properties (as reversible dizziness, drowsiness and central nervous system (CNS) depression) are well documented in both animals and humans, although the mechanism of action for this effect is not known. 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. As mentioned above, these effects are considered reversible upon cessation of exposure. The lowest LOAEC identified for CNS effects was 7375 mg/m^3 in an acute neurotoxicity study conducted in rats Malley et al 2001, as cited in US EPA 2012b). Diminished response to stimulus was observed after 2 or more hours of a 6-hour exposure at 7375 mg/m^3. At the higher concentration of 14 750 mg/m^3, additional signs of sedation and altered parameters in the functional observation 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 (upper respiratory tract) (Ohashi et al. 1983, as cited in US EPA 2012a) (NOAEC of 738 mg/m^3). However, a follow-up study investigating the lower respiratory tract (tracheal mucosa) showed similar effects only at higher doses (a LOAEC of 35 400 mg/m^3 and a NOAEC of 17 770 mg/m^3 were identified) (Ikeoka et al. 1988, as cited in US EPA 2012b).

Repeated-dose toxicity

In the 2-year inhalation bioassay described in the carcinogenicity section below (NTP 1998, as cited in US EPA 2012b), narcosis was observed for up to 1 hour following exposure in male mice at the highest concentration (5 310 mg/m^3), in addition to significantly less survival (starting at 36 weeks). A slight increase in liver necrosis was observed at the highest concentration (5 310 mg/m^3) in female mice. Male rats also had decreased survival.

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 (including depressed activity and reduced coordination of movement) was observed in rats at 14 750 mg/m^3, and in mice at 5 310 mg/m^3 and above. These effects are considered reversible as they dissipate rapidly upon termination of exposure. A LOAEC of 5 310 and a NOAEC of 1 770 mg/m^3 were derived for CNS effects in mice. The authors of the NTP (1998) study also concluded that there was uncertainty as to whether the clinical findings of CNS toxicity (narcosis) were primary (that is, specific to tetrahydrofuran or its metabolites) or secondary (that is, nonspecific due to solvent interaction with cell membranes of the nervous system as seen with other solvents) and that further research is needed to better characterize tetrahydrofuran neurotoxicity.

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 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 ($BMC_{10/HEC}$), and their 95% confidence limits ($BMCL_{10}$) were derived. For absolute liver weight in male mice, the $BMC_{10/HEC}$ and $BMCL_{10/HEC}$ are 783 and 246 mg/m^3, respectively (shown as HECs). For centrilobular cytomegaly in male mice, the $BMC_{10/HEC}$ and $BMCL_{10/HEC}$ are 805 and 256 mg/m^3, respectively.

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 repeated dose (sub-acute to subchronic duration) 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. Female mice were exposed by inhalation to tetrahydrofuran at concentrations of 0, 1 770, 5 310 or 14 750 mg/m^3, 6 hours/day, 7 days/week on GDs 6-17. Mice exposed at 14 750 mg/m^3 demonstrated high toxicity, with > 25% mortality observed after 6 days of exposure. At concentrations of 5 310 mg/m^3 and greater, maternal narcosis was observed, and body weight and uterus weight of pregnant females were reduced. Also, at and above 5 310 mg/m^3 a significant decrease in the number of viable foetuses per litter was observed and the number of resorptions was increased. At the highest dose, a single litter with live-born pups remained. Based on these results, 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 terminal body weight and gravid uterine weight) and fetal toxicity (reduced fetal survival) (Mast et al. 1992, as cited in US EPA 2012b). In female rats exposed to the same concentrations as listed above on GDs 6-19, maternal body weight and pup body weight were reduced at 14 750 mg/m^3. Based on these effects, a LOAEC of 14 750 mg/m^3 and NOAEC of 5 310 mg/m^3 was identified (Mast et al. 1992, as cited in US EPA 2012b).

In another rat study, exposure concentrations for an initial range-finding study corresponded to 0, 590, 1 475, 7 375, or 14 750 mg/m^3 and 0, 2 950 or 14 750 mg/m^3 in a follow-up study for 6 hours/day on GDs 6–15. Sedation (as a reduced reaction to an acoustic stimulus) was observed at 7 375 mg/m^3 in the range-finding study and 2 950 mg/m^3 in the follow-up study. This effect was more pronounced at the highest dose and was also accompanied with lethargy and coordination problems (as reduced muscle

tone, and staggering gait). At 14 750 mg/m^3, dams were observed to have reduced body weight gain. The number of implants/dam and mean fetal body weight both were noted to be significantly decreased with increasing exposure (although no information is provided on the exposure concentration where significance was first observed). In addition, foetuses in the high-concentration group exhibited a significantly decreased incidence of sternal ossification. Based on decreased fetal weight and skeletal alterations, the LOAEC for developmental toxicity was identified as 14 750 mg/m^3 and the NOAEC as 7 375 mg/m^3. Based on clinical signs of sedation (diminished response to noise stimulus), the maternal LOAEL and NOAEL were 2 950 and 1 475 mg/m^3, respectively (Dupont 1980, as cited in US EPA 2012b).

Carcinogenicity and genotoxicity

Carcinogenicity is a critical endpoint for tetrahydrofuran. A 2-year NTP (1998) inhalation cancer bioassay reported an increased incidence of hepatocellular adenomas and carcinomas in female B6C3F1 mice (statistically significant trend; statistically significant at high concentration compared to control) and an increased incidence of renal tubule adenomas and carcinomas in male F344/N rats (statistically significant trend) following inhalation exposure to 0, 590, 1 770, and 5 310 mg/m^3 of tetrahydrofuran, 6 hours per day, 5 days per week for 105 weeks (NTP, 1998). The corresponding concentrations adjusted for continuous exposure are 0, 105, 316, and 948 mg/m^3. The NTP (1998) concluded that there was “some evidence” of carcinogenicity in male rats and “clear evidence” of carcinogenicity in female mice.

Given the nature of the observed tumours and the potential for mechanisms of carcinogenesis that are considered to be rodent-specific, several groups have reviewed the available mechanistic information in order to determine their biological relevance to humans. Specifically, some data suggest that the male rat kidney tumors are due to alpha-2u-globulin accumulation (Gamer et al. 2002) and chronic nephropathy (Bruner et al. 2010; Hard et al. 2013); while stimulation of liver cell proliferation has been postulated to be responsible for the female mouse liver tumours (Gamer et al. 2002; van Ravenzwaay et al. 2003; Choi et al. 2017). In its review, the US EPA (2012b) assessed the available mechanistic data and concluded that the modes of action leading to tumour induction were not well understood and the available evidence was considered insufficient to consider the observed liver and kidney tumours as being not biologically relevant to humans. This conclusion was also supported by NICNAS (2016), ECHA (2017) and IARC (2019b).

In the US EPA (2012b) assessment, incidence data for female mice and male rats per exposure concentration (adjusted for continuous exposure) were fitted to the cancer-multistage model of the EPA’s BMDS version 2.0 (US EPA 2008, as cited in US EPA 2012b). The human equivalent concentrations (HEC), assuming the ratio of animal to human air:blood partition coefficient is 1, 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 $BMC_{10/HEC}$ and $BMCL_{10/HEC}$ are 52 and 35 mg/m^3 respectively.

Results of several in vitro and in vivo genotoxicity assays of tetrahydrofuran are presented in section 7.4.2.1 of the draft screening assessment report. Since the draft screening assessment report, a study of oxidized metabolites of tetrahydrofuran resulting from natural oxidation and from the addition of rat liver microsomes have been shown to react in vitro with DNA, yielding DNA adducts (Hermida et al. 2006 as cited in IARC 2019b). The US EPA (2012b) concluded that tetrahydrofuran is not likely genotoxic. This conclusion is also supported by NICNAS (2016), ECHA (2017) and IARC (2019b).

5.3 Characterization of human health risk

As indicated in the draft screening assessment report, Canadians may also be exposed to tetrahydrofuran by inhalation of indoor air and during use of certain products available to consumers such as PVC cement primer and PVC cement. Section 7.4.3 of the draft screening assessment report addressed the risk characterization of tetrahydrofuran through chronic inhalation of indoor air and acute inhalation during use of PVC cement. Potential exposures through the diet – primarily as a volatile component of some foods and as an impurity in some food packaging materials – as well as from drinking water were considered insignificant in comparison to exposures from air and were therefore not included in the risk characterization for tetrahydrofuran in the draft screening assessment report.

Canadians may also be exposed to higher concentrations of tetrahydrofuran emitted to ambient air from industrial or manufacturing facilities. These emissions may have effects on Canadians residing nearby.

As indicated in the draft screening assessment report, a critical effect of tetrahydrofuran is carcinogenicity from chronic exposure. 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 tetrahydrofuran-induced tumour development have not been fully elucidated, it has been proposed that tumours likely arise through non-genotoxic pathways (US EPA 2012b). Conservatively using female mouse liver tumor data, a $BMCL_{10/HEC}$ of 35 mg/m^3 was selected as the critical cancer-based effect level. Table 5-2 provides relevant exposure and cancer hazard values for tetrahydrofuran based on the currently available exposure and toxicological information, as well as resulting MOEs for a determination of cancer risk.

Table 5-2. Exposure estimates, cancer effect values and margins of exposure for residents near certain facilities releasing tetrahydrofuran

Exposure scenario	Exposure (mg/m^3)	Critical effect level (mg/m^3)	Critical health effect endpoint	MOE
Chronic inhalation exposure from air for residents near fabric coating facilities releasing tetrahydrofuran	0.121 (annual concentration)	$BMCL_{10/HEC}$ = 35 (adjusted for continuous exposure)	Liver adenoma or carcinoma (female mice) in a 2-year inhalation study (NTP 1998, cited in US EPA 2012a)	289
Chronic inhalation exposure from air for residents near petrochemical manufacturing facilities releasing tetrahydrofuran	0.014 (annual concentration)	$BMCL_{10/HEC}$ = 35 (adjusted for continuous exposure)	Liver adenoma or carcinoma (female mice) in a 2-year inhalation study (NTP 1998, cited in US EPA 2012a)	2 500

The critical non-cancer endpoint associated with repeated inhalation exposure is considered to be increased liver weight and cytomegaly observed in mice after subchronic exposure (NTP 1998, as cited in US EPA 2012b). A corresponding BMCL10/HEC of 246 mg/m^3 was used to characterize the risk of repeated exposures.

The most sensitive effects observed after acute exposure are considered to be CNS depression manifesting as sedation/narcosis. It should be noted that for acute exposure scenarios, selection of narcosis/sedation as the critical endpoint is supported by the recent ECHA (2017) review of tetrahydrofuran. The acute inhalation NOAEC of 1475 mg/m^3 based on the CNS effects (behavioural sedation observed at 7375 mg/m^3) in rats exposed for 2 to 6 hours to tetrahydrofuran (Malley et al. 2001, as cited in US EPA 2012b) is used for risk characterization. Additionally, the NOAEC of 1770 mg/m3 based on maternal toxicity (narcosis/sedation, decreased body weight, decreased gravid uterine weight) and fetal toxicity (reduced fetal survival) at 5310 mg/m^3 in mice was also used to characterize risk to tetrahydrofuran from acute exposures. Although these effects were observed during a repeated dosing protocol, effects such as CNS depression and loss of pups may represent an acute effect.

Table 5-3 provides relevant exposure and non-cancer hazard values for tetrahydrofuran, as well as resulting MOEs for a determination of risk.

Table 5-3. Chronic and acute exposure estimates, non-cancer effect values, and margins of exposure for residents near certain facilities releasing tetrahydrofuran

Exposure scenario	Exposure (mg/m^3)	Critical effect level (mg/m^3)	Critical health effect endpoint	MOE
Chronic inhalation exposure from air for residents near fabric coating; or petrochemical manufacturing; facilities releasing tetrahydrofuran	0.028 to 0.242 (24-hour maximum concentration)	BMCL10/HEC = 246 (adjusted for continuous exposure)	Non-cancer effects: Liver weight increase in mice in a 13-week inhalation study (NTP 1998, cited in US EPA 2012a)	1016 - 8786
Acute inhalation exposure from air for residents near fabric coating; or petrochemical manufacturing; facilities releasing tetrahydrofuran	0.070 to 0.604 (1-hour maximum concentration)	NOAEC = 1 475 $NOAEC_{Maternal/Developmental}$ = 1 770	Acute CNS effects (as narcosis/sedation) in rats after 2-6 hours exposure (Malley et al. 2001, cited in US EPA 2012a) Maternal toxicity (narcosis/sedation decreased body weight, decreased gravid uterine weight) and fetal toxicity (reduced fetal survival) in mice (Mast et al. 1992, as cited in US EPA 2012a)	2 442 – 25 285

A comparison of the critical non-cancer inhalation effect levels (chronic and acute) and chronic and acute levels of exposure to tetrahydrofuran for Canadians living near certain facilities from specific sectors releasing this substance results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure data used to characterize risk. However, the margins between the critical cancer inhalation effect level and chronic inhalation exposure to tetrahydrofuran for

Canadians living near certain facilities from certain sectors (that is, fabric coating facility) releasing this substance into air are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk. Therefore, the release of tetrahydrofuran into air by certain facilities may be harmful to human health.

5.4 Uncertainties in evaluation of risk to human health

For tetrahydrofuran, the lack of ambient air monitoring data near facilities releasing the substance in Canada is an uncertainty.

The US EPA considers the confidence in the hazard data to be moderate to high (US EPA 2012a). 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 and are well recognized by other international jurisdictions. The critical study (NTP 1998) considered relevant for chronic and repeated exposure scenarios was well conducted and well documented and included a comprehensive analysis. There is some uncertainty related to study quality, based on the low survival observed in male rodents. This low survival raises questions on the power of the resulting statistics due to the smaller number of animals, especially for male rats. For developmental effects observed after in utero exposure to tetrahydrofuran, there is uncertainty whether and to what extent maternal effects (narcosis/sedation and decreased body weight) may impact the observed developmental effect (fetal loss).

As the carcinogenicity modes of action and the shape of the dose-response curves for tumour incidence 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. An increased severity of effect with longer duration of exposure is not suggested for tetrahydrofuran. 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. This was taken into consideration in the determination of the adequacy of the margins of exposure.

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Appendix A. SCREEN3 input parameters and BMD modelling

SCREEN3

The SCREEN3 model (SCREEN3 1996) was used to estimate ambient air concentrations near facilities that report release of furfuryl alcohol and tetrahydrofuran to air. It was developed based on the Industrial Source Complex (ISC) model (for assessing pollutant concentrations from various sources in an industry complex). SCREEN3 is designed to estimate maximum concentrations of chemicals at chosen receptor heights and at various distances from a release source for a given continuous emission event. The maximum calculated exposure concentration is selected based on a built-in meteorological data matrix of different combinations of meteorological conditions, including wind speed, turbulence and humidity. The driver for air dispersion in the SCREEN3 model is wind. This model directly predicts concentrations resulting from point, area and volume source releases.

Furfuryl alcohol

Input parameters for the SCREEN3 model used to estimate ambient air concentrations of furfuryl alcohol for all reporting facilities in 2019 are outlined in Table A-1 below. Emission rates for the volume source, flare source and point source release types are calculated using the formula below and assumes continuous emission of the substance throughout the calendar year (NPRI 2021).

Emission rate (g/s): $\frac{Quantity\ of\ substance\ released\ to\ air\ from\ NPRI\ (g)}{31557600\ seconds\ (in\ one\ year)}$

Table A-1. SCREEN3 inputs provided according to source type

Inputs	Facility 1	Facility 2	Facility 3	Facility 4	Facility 5	Facility 6
Source type[a]	Flare	Point	Point	Point	Point	Point
Initial lateral dimension	NR	NR	NR	NR	NR	NR
Initial vertical dimension	NR	NR	NR	NR	NR	NR
Source release height (m)[b]	NR	NR	NR	NR	NR	NR

Inputs	Facility 1	Facility 2	Facility 3	Facility 4	Facility 5	Facility 6
Stack height (m)[c]	56.4	9.14	9	9	9	9
Stack inside diameter[a] (m)	NR	1	1	1	1	1
Emission rate (g/s)[d]	0.02	0.00076	0.41	0.59	18.70	0.16
Stack gas exit velocity[e] (m/s)	30.8	10.18	10.50	10.50	10.50	10.50
Stack gas exit/Ambient temperature (K)[e]	NR	293	293	293	293	293
Receptor height above ground (m)[f]	1.74	1.74	1.74	1.74	1.74	1.74
Distance from source facility to closest residential area for max. 1-hour conc. (m)[g]	900	50	50	50	50	700
Urban/ Rural option[a]	Urban	Urban	Urban	Urban	Urban	Rural

Abbreviations: NR: Not a required input for identified source type.
[a] Based on photo analysis of facility using Google Maps satellite and street view.
[b] 2.5 multiplied by height of building (assuming 4 m per storey) (AQCD 2021)
[c] US EPA 2004
[d] Estimated based on NPRI data for 2019 (NPRI 2021)
[e] SCREEN3 default; US EPA 1999
[f] A range of receptor heights was considered including the default value of 0.0 m (US EPA 1995); the value of 1.74 m was considered to be health protective and represents the breathing zone of an average Canadian adult (Curry et al. 1993).
[g] Estimated distance (using Google Maps satellite) used to determine maximum 1-hour air concentration from source facility to residential area.

Tetrahydrofuran

Input parameters for the SCREEN3 model used to estimate ambient air concentrations of tetrahydrofuran for the top two facilities that reported releasing diphenylamine in 2019 are outlined in Table A-2 below. The emission rate for point and volume sources are calculated using the formula below and assumes continuous emission of the substance throughout the calendar year (NPRI 2021).

$$\text{Emission rate (g/s)} = \frac{Quantity\ of\ substance\ released\ into\ air\ from\ NPRI\ (g)}{31557600\ seconds\ (in\ one\ year)}$$

Table A-2. SCREEN3 inputs provided according to source type

Inputs	Facility 1	Facility 2
Source type[a]	Point	Volume
Initial lateral dimension	NR	13.49
Initial vertical dimension	NR	24.71
Source release height (m)[b]	NR	20
Stack height (m)[c]	11.5	NR
Stack inside diameter (m)[a]	1	NR
Stack gas exit velocity[e] (m/s)	10.43	NR
Stack gas exit/Ambient temperature (K)[e]	293	NR
Emission rate (g/s)[d]	2.74	0.158
Receptor height above ground (m)[f]	1.74	1.74
Distance from source facility to closest residential area for max. 1-hour conc. (m)[g]	300	30
Urban/Rural option[a]	Urban	Urban

Abbreviations: NR: Not a required input for identified source type.
[a] Based on photo analysis of facility using Google Maps satellite and street view.
[b] 2.5 multiplied by height of building (assuming 4 m per storey) (AQCD 2021)
[c] US EPA 2004
[d] Estimated based on NPRI data for 2019 (NPRI 2021)
[e] SCREEN3 default; US EPA 1999

[f] 1.74 m is considered to be health protective and represents the breathing zone of an average Canadian adult (Curry et al. 1993).
[g] Estimated distance (using Google Maps satellite) used to determine maximum 1-hour air concentration from source facility to residential area.

Appendix B. Benchmark dose modelling for furfuryl alcohol

The US EPA Benchmark dose software (BMDS v 2.5) was used to model the benchmark dose (BMD) for furfuryl alcohol. The dose-response data used as input for the model is provided in Table B-1.

Table B-1. Dose response data for tumours in NTP 2-year inhalation cancer study of furfuryl alcohol in male and female rats and mice (NTP 1999)

Sex and species	Tumour type	Dose (mg/kg bw/day)	Total number of animals	Number of animals affected	Historical control tumour type	Historical control incidence
Male rats	Nose adenoma, carcinoma or squamous cell carcinoma	0 2.48[a] 9.95 [a] 39.8 [a]	50 50 50 50	0 1 1 4	Nose adenoma, carcinoma or squamous cell carcinoma	1/897[c]
Male mice	Kidney adenoma or carcinoma (standard and extended evaluation)	0 10.6[b] 42.7 [b] 170.8 [b]	50 49 49 50	0 0 0 5	Kidney adenoma or carcinoma	4/1093[d]

[a] Inhalation concentrations converted to oral doses using a factor of 0.31 (Health Canada 1994), resulting in concentrations of: 0, 8, 32.1 or 128.4 mg/m^3, equivalent to 0, 2, 8 or 32 ppm furfuryl alcohol.
[b] Inhalation concentrations were converted to oral doses using a factor of 1.33 (Health Canada 1994), resulting in concentrations of 0, 8, 32.1 or 128.4 mg/m^3, equivalent to 0, 2, 8 or 32 ppm furfuryl alcohol.
[c] Overall historical control incidence for nasal neoplasms in chamber control male F344 rats = 1 adenoma in 897 total animals; overall range of historical control incidence for nasal adenoma is 0-2% (NTP 1999).
[d] Overall historical control incidence for renal tubule neoplasms in chamber control male B6C3F1 mice = 3 adenoma and 1 carcinoma in 1093 total animals; overall range of historical control incidence for renal tubule adenoma or carcinoma is 0-2% for each tumour type, and 0-4% for combined adenoma or carcinoma (NTP 1999).

The US EPA Benchmark dose software (BMDS) (v 2.5) (BMDS 2017) was used to predict the benchmark dose, BMD_{10} (10% extra risk of tumour incidence compared to control), and the lower bound of the BMD (BMDL) (the lower one-sided 95% confidence limit on the BMD_{10}). A benchmark response level (BMR) of an extra 10% was used based on the recommendations presented in the Benchmark Dose Technical Guidance (US EPA 2012) for quantal data. Based on the type of study (quantal/dichotomous data), several dichotomous models were used (US EPA 2012).

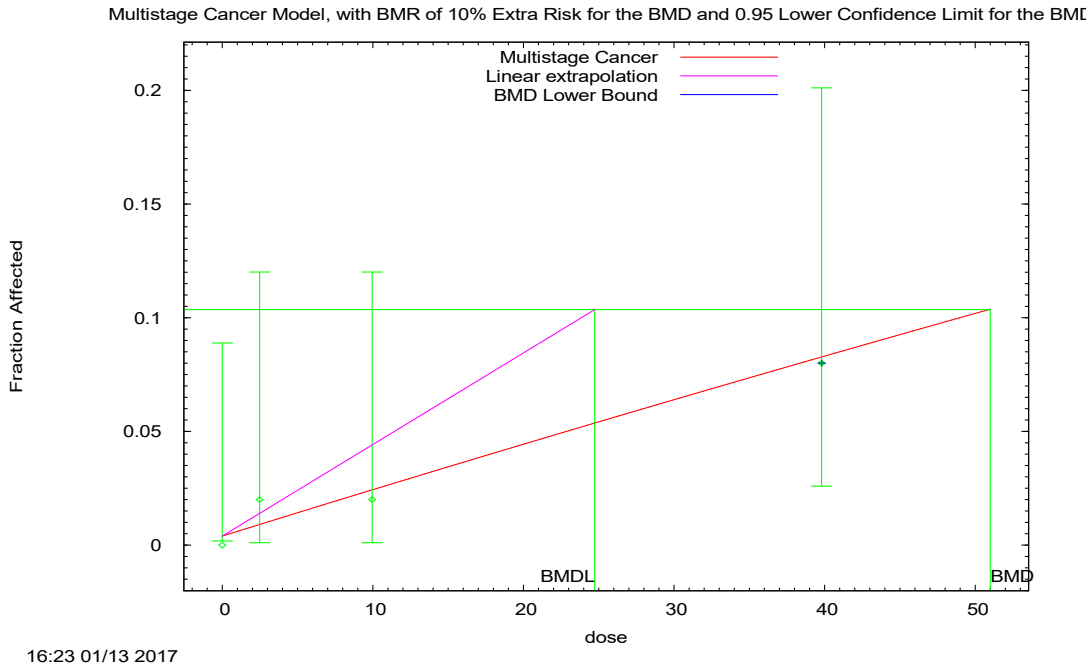

Figure B-1. BMD modelling (BMDS v. 2.5) (BMDS 2017) of incidence of nasal adenoma from a NTP (1999) inhalation cancer study of furfuryl alcohol in male rats

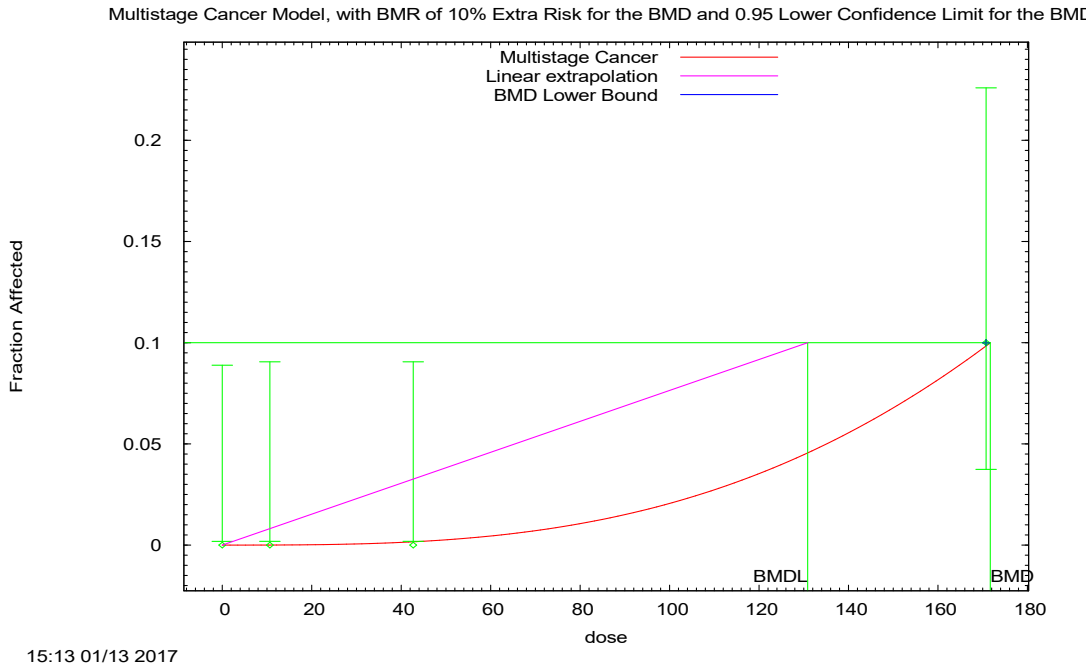

Figure B-2. BMD modelling (BMDS v. 2.5) (BMDS 2017) of incidence of kidney adenoma from a NTP (1999) inhalation cancer study of furfuryl alcohol in male mice

In the draft screening assessment report, only oral exposures (that is, diet and dust) were considered for furfuryl alcohol; however, given the identification and resulting exposures from the new inhalation scenario, the oral sources of exposure were considered insignificant in comparison to potential inhalation exposures. Therefore, long-term exposure via the inhalation route is considered for the risk characterization. The values derived from BMDS (v 2.5) (NTP 2017) in the draft screening assessment were converted back to air concentrations using a factor obtained from Health Canada (1994) either 0.31 or 1.33 for rats and mice, respectively.

Using BMDS (v 2.5) (US EPA), and a best-fit of the resulting curves, all multistage cancer models were selected for BMD and BMDL values as they derived the same result for the male rat data. For BMD and BMDL values in mice, the multistage cancer 3 model (BMDS v 2.5) was selected.

The BMD_{10} and $BMDL_{10}$ for increased incidence of nasal adenoma in rats and kidney adenoma in mice administered furfuryl alcohol were determined to be 51 and 25 mg/kg bw/day, and 172 and 131 mg/kg bw/day, respectively. After converting the doses, the resulting BMC_{10} and $BMCL_{10}$ were 165 and 80 mg/m^3 in male rats for nasal tumours (adenoma and carcinoma). The corresponding BMC_{10} and $BMCL_{10}$ were 129 and 98 mg/m^3 for combined kidney adenoma and carcinoma in male mice. These values were derived using studies in which animals were exposed for 5 days per week. The $BMCL_{10}$

for continuous exposure (7 days per week) would be 14 mg/m^3 and 18 mg/m^3 for male rats and mice, respectively.