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Proposed Occupational Exposure Limits for Furans

May 2019

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U.S. DEPARTMENT OF ENERGY

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Executive Summary

This report documents the re-evaluation of Hanford Tank Farm occupational exposure limits ($_{HTF}$OEL) for furan and 13 associated substituted furans identified as Chemicals of Potential Concern. Furan causes liver toxicity and cancer in laboratory animals. Recent toxicity studies in animal models have established a non-genotoxic mechanism of action and new data to support re-evaluation of the furan $_{HTF}$OEL. As such, Pacific Northwest National Laboratory (PNNL) proposes to adjust the $_{HTF}$OEL for furan from 1 ppb to 1.9 ppb. This proposed change is based on a no-observed-adverse-effect level in Fischer-344 rats (the most sensitive species tested) exposed to subchronic oral administration of furan as a point of departure modified by species extrapolation of dose and route, inter- and intra-species uncertainty factors, and adjustments for life-time versus occupational exposure periods. Because of limited data and similar hypothesized mechanisms of toxicity, PNNL recommends continuing to use the furan $_{HTF}$OEL as a surrogate for substituted furans until further data for substituted furans become available. Further toxicity investigations or new OELs proposed by authoritative organizations (e.g., National Institute of Occupational Safety and Health, Occupational Safety and Health Administration, and the American Conference of Government Industrial Hygienists) would warrant re-evaluation of the $_{HTF}$OEL for furan and substituted furans.

Acronyms and Abbreviations

AEGL	Acute Exposure Guideline Levels
BDA	cis-2-butene-1,4-dial
BMD	benchmark dose
COPC	Chemicals of Potential Concern
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
HTF	Hanford Tank Farm
$_{HTF}$OEL	Hanford Tank Farm Occupational Exposure Limit
NOAEL	No-Observed-Adverse-Effect Level
NTP	National Toxicology Program
OEL	Occupational Exposure Limit
PAC	Protective Action Criteria
PNNL	Pacific Northwest National Laboratory
UF	uncertainty factor

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1.0 Introduction

The Industrial Hygiene Chemical Vapor Technical Basis (Meacham et al. 2006) is the current basis for identifying and managing Chemicals of Potential Concern (COPC) at the Hanford Tank Farm (HTF). By documenting occupational exposure limits (OEL) for HTF COPCs, that report provides guidance for safe HTF operations. The term $_{HTF}$OELs, originally defined by Poet and Timchalk (2006) and Meacham et al. (2006), is used to refer to OELs established specifically for use in HTF operations.

In 2016, Pacific Northwest National Laboratory (PNNL) reviewed $_{HTF}$OELs to determine if new toxicity data existed or if new OELs had been proposed by authoritative organizations (e.g., the National Institute of Occupational Safety and Health, the Occupational Safety and Health Administration, and the American Conference of Government Industrial Hygienists) that would warrant revisions of OELs proposed in the 2016 update.[1] The review found sufficient new information that warranted $_{HTF}$OEL updates for multiple chemicals. This report documents the re-evaluation of $_{HTF}$OELs for furan and associated substituted furans.

[1] Smith JN, C Timchalk, and TJ Weber. 2016. *State of Knowledge Assessment: COPC/Exposure Limits*. PNNL-25790, Pacific Northwest National Laboratory, Richland, Washington. (unpublished)

2.0 Furan Background

Furan is a highly volatile, highly lipophilic, organic chemical used for chemical synthesis. It is found and formed (via heating) in food and tobacco products and also formed via high-energy irradiation of organic compounds. Various derivatives of furan (i.e., substituted furans) can be generated by heating food and also are found in flavoring agents (Gill et al. 2010, Gill et al. 2014). Furan and 13 substituted furans have been identified as high-priority COPCs (Table 1).

Table 1. High-Priority COPC Furans

Compound	Chemical Abstract Service Registry Number	Current OEL (ppb)
Furan	110-00-9	1
2-Heptylfuran	3777-71-7	1
2-Octylfuran	4179-38-8	1
2-Pentylfuran	3777-69-3	1
2-Methylfuran	534-22-5	1
2-Propylfuran	4229-91-8	1
2-Ethyl-5-methlyfuran	1703-52-2	1
2-(2-Methyl-6-oxoheptyl)furan	51591-87-0	1
2-(3-Oxo-3-phenylprop-1-enyl)furan	717-21-5	1
2,3-Dihydrofuran	1191-99-7	1
2,5-Dihydrofuran	1708-29-8	1
2,5-Dimethylfuran	625-86-5	1
3-(1,1-Dimethylethyl)-2,3- dihydrofuran	34314-82-4	1
4-(1-Methpropyl)-2,3- dihydrofuran	34379-54-9	1

Furan causes liver toxicity and cancer in laboratory animals. Its toxicity and carcinogenicity is hypothesized to involve enzymatic bioactivation by CYP2E1, forming cis-2-butene-1,4-dial (BDA) (Gates et al. 2012, Gates et al. 2014, Webster et al. 2013). BDA is hypothesized to cause cytotoxicity and oxidative stress in the liver at sufficiently high exposures (e.g. ≥1.0 mg/kg/day for 3 weeks in mice). Both cytotoxicity and oxidative stress are key biological events in the development of cancer following chronic exposures (Moser et al. 2008, Webster et al. 2013). The absence of toxicity would be expected to be protective for developing cancer. In support of this hypothesis, cytotoxicity was observed at doses ≥1.0 mg/kg/day, while cancer was observed at doses ≥4.0 mg/kg/day in mice exposed to furan for 3 weeks or 2 years (Moser et al. 2008). Older alternative hypotheses suggest BDA may be mutagenic (Lu et al. 2009). Furan is classified as possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer. Respiratory irritation and anesthesia effects have also been observed after furan inhalation exposure (Pohanish 2008).

Current $_{HTF}$OELs for furan and substituted furans are 1 ppb (Table 1) (Meacham et al. 2006). Authoritative bodies have not recommended chronic OELs for furan or substituted furans, and the existing $_{HTF}$OEL was derived using data from a chronic bioassay conducted by the National Toxicology Program (NTP) (Maronpot et al. 1991, NTP 1993). In the NTP study, furan orally administered to rats (2 to 8 mg/kg/day) and mice (8 to 15 mg/kg/day) produced a high incidence of hepatic billiary tract hyperplasia, cholangiofibrosis, cholangiocarcinomas, and hepatocellular neoplasms (Maronpot et al. 1991, NTP 1993). Rats were more sensitive than mice and demonstrated nearly 100% tumor incidence in all treatments (NTP 1993). A linear extrapolation of billiary tract hyperplasia of female rats was used to determine a point of departure of 5.71×10^{-4} mg/kg/day based on a 0.01% response (1×10^{-4} risk). The point of departure derived from this oral route of administration study was converted to an inhalation $_{HTF}$OEL based on an occupational inhalation rate (10 m^3/day) and body weight of females commonly used to derive OELs (65 kg).

The 2016 report prepared by PNNL[2] recommended that $_{HTF}$OELs for furan and substituted furans be re-evaluated based on new information. We first considered Acute Exposure Guideline Levels (AEGL) and Protective Action Criteria (PAC) for furan (Table 2) established by the U.S. Environmental Protection Agency (EPA) and the U.S. Department of Energy (DOE), respectively. Because of insufficient data, the EPA did not recommended AEGL-1 values for furan. The DOE adopted 1 hour AEGL-2 and AEGL-3 values as the PAC (Revision 29) for furan (Table 2). Because EPA did not recommend AEGL-1 values for furan, the DOE selected 0.62 ppm for the PAC-1. PAC-1 is airborne concentration in which the general population (including susceptible individuals) if exposed for 1 hour could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL and PAC values are acute exposure levels derived from a short-term, acute inhalation study (Terrill et al. 1989). As such, PNNL concluded that AEGLs and PACs are not appropriate for use as chronic occupational exposure guidelines and were not considered further.

Table 2. AEGL Values for Furan

	AEGL Values (ppm)				
Classification	10 Minutes	30 Minutes	1 Hour	4 Hours	8 Hours
AEGL-1[a]	NR[d]	NR[d]	NR[d]	NR[d]	NR[d]
AEGL-2[b]	12	8.5	6.8	1.7	0.85
AEGL-3[c]	35	24	19	4.8	2.4

[a] AEGL-1 is the airborne concentration in which the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects.
[b] AEGL-2 is the airborne concentration in which the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
[c] AEGL-3 is the airborne concentration in which the general population, including susceptible individuals, could experience life-threatening health effects or death.
[d] No recommendation for AEGL-1 was made due to insufficient data.

Heat-induced food contaminants have attracted considerable scientific and public attention leading to several recent subchronic studies conducted with furan in mice and rats. Health Canada in particular has been interested in the risk of furan-induced toxicity because of its extensive presence in food. Subchronic (90 day) oral gavage studies at doses (0.03 to 8 mg/kg/day, 5 days/week) lower than those in previous NTP chronic bioassays have been completed with furan (Gill et al. 2010, Gill et al. 2011). Biological pathway analysis of gene expression and other toxicogenomic data from these studies have been published, and novel pathway-based benchmark dose analyses (BMD) have been conducted using toxicogenomic data (Webster et al. 2013, Dong et al. 2016, Kuo et al. 2015). While toxicogenomic pathway BMD analysis has been advocated as a potential point of departure for future human risk assessments, practical application of such techniques is still in its infancy (Kuo et al. 2015). Regardless, available histological and other toxicity data from recent subchronic mouse and rat studies conducted using lower furan doses than those used in the NTP study (Maronpot et al. 1991, NTP 1993) offer sufficient evidence to refine the $_{HTF}$OEL for furan based on protection against non-cancer, precursor effects.

[2] Smith JN, C Timchalk, and TJ Weber. 2016. *State of Knowledge Assessment: COPC/Exposure Limits*. PNNL-25790, Pacific Northwest National Laboratory, Richland, Washington. (unpublished)

3.0 Approach and Results for Furan

PNNL proposes refinement of the $_{HTF}$OEL for furan using data from recent subchronic oral gavage studies in mice and rats. The recent subchronic oral toxicity study of furan in B6C3F1 mice (Gill et al. 2011) reported a no-observed-adverse-effect level (NOAEL) for liver toxicity of 0.12 mg/kg/day based on clinical biochemical and histological changes (Gill et al. 2011). BMD analysis identified hepatocyte apoptosis of the caudate lobe as the most sensitive apical endpoint using the lower 95% confidence interval of the BMD (BMD level = 0.11 mg/kg/day), and other cytotoxicity apical endpoints had BMD levels ranging from 0.28 to 1.35 mg/kg/d (Webster et al. 2013). BMD levels derived from biological pathways associated with cancer were 0.92 and 1.57 mg/kg/d (Webster et al. 2013). In agreement with previous studies (Maronpot et al. 1991, NTP 1993), a subchronic oral toxicity study of furan in Fischer-344 rats, suggested that rats were more sensitive than B6C3F1 mice (Gill et al. 2010). In rats, Gill et al. (2010) reported a NOAEL of 0.03 mg/kg/day, and mild histological lesions were observed at higher doses (>0.12 mg/kg/day). Pathway analysis of toxicogenomic data from the Fischer-344 rat study (Gill et al. 2010) identified median BMD levels ranging from 0.08 to 1.43 mg/kg/day (Dong et al. 2016). Considering these new data, we propose to use the lowest of the reported BMD levels or NOAEL (0.03 mg/kg/day) from the most sensitive animal model as a point of departure for refining the $_{HTF}$OEL.

The selected furan point of departure was used to derive the new $_{HTF}$OEL using standard methodology for species extrapolation of doses, inter- and intra-species uncertainty factors (UF), and adjustments for life-time versus occupational exposure periods (Rennen et al. 2004, Dankovic et al. 2015, Kuempel et al. 2015). Because metabolism is a key step in furan toxicity, the point of departure from rat data was extrapolated to a human equivalent dose using standard allometric scaling based on body weight (body weight$^{0.75}$) (Dankovic et al. 2015, Kuempel et al. 2015). Study-specific body weights were not published in the rat subchronic oral toxicity study (Gill et al. 2010). Based on the age of rats at termination in that study (~20 weeks; Gill et al. 2010), mean reference body weight for male and female Fischer-344 rats is 303 g (Brown et al. 1997). As such, 300 g and 65 kg body weight for rats and humans, repectively, were assumed to derive a human equivalent point of departure of 0.008 mg/kg/d (Equation 1). Because solubility of furan in water is poor, it is probably classified as a Category 3 gas and no further dosimetric adjustment is needed to account for regional gas deposition (Kuempel et al. 2015). The $_{HTF}$OEL was calculated by applying the human body weight (65 kg), an inhalation rate used for occupational exposures (10 m^3/d), and a composite UF. The composite UF was defined as the product of an inter-species UF (3×) applied for toxicodynamic factors and an intra-species UF (3×) applied by EPA for deriving AEGLs (Dankovic et al. 2015). Because the dose was extrapolated from rats to humans using allometric scaling, no additional UF was added for toxicokinetic factors. The composite UF (10×) is less than the composite UF (150×) used by EPA for furan AEGL derivation. EPA's composite 150× UF intended for the general public was derived from using a 10× inter-species UF (EPA did not conduct species extrapolation), 3× intra-species UF, and 5× modifying factor for a limited data set, where the highest nonlethal acute dose was used as a point of departure (Committee on Acute Exposure Guideline Levels 2010). The supporting data used for the $_{HTF}$OEL proposed here are much more extensive and robust than data used by EPA to establish an AEGL. As such, the additional modifying factor is probably not appropriate (Dankovic et al. 2015), and we did not include it in the $_{HTF}$OEL proposed here. Using these assumptions, we propose a $_{HTF}$OEL of 0.0052 mg/m^3 or 1.9 ppb for furan (Equations 2 and 3).

$$0.008\ (mg/kg/d) = 0.03\ (mg/kg/d)\ \times \left(\frac{0.3\ kg}{0.3^{0.75} kg}\right) \times \left(\frac{65^{0.75} kg}{65\ kg}\right) \quad \text{Eq. 1}$$

$$0.0052\ (mg/m^3) = 0.008\ (mg/kg/d) \times 65\ kg/10\ (m^3/d)/10\ UF \quad \text{Eq. 2}$$

$$1.9\ ppb = 24.45\ (L/mol) \times 0.0052\ (mg/m^3)/68.07\ (g/mol) \times 1000\ (\mu g/mg) \times \left(\frac{g}{1\times10^6 \mu g}\right) \times \left(\frac{m^3}{1000\ L}\right) \quad \text{Eq. 3}$$

4.0 Substituted Furans

Substituted furans are often found in mixtures with furan, especially in foods. For example, 2-pentylfuran is known to be the primary flavor constituent in poppy seeds. Other 2-substituted furans also are commonly found in thermally treated foods (Becalski et al. 2010). 2-Methylfuran has been found to be 0.5 to 2× the level of furan in various foods measured in Canada (Becalski et al. 2010).

In general, limited toxicity data is available for substituted furans for which similar toxicity concerns exist compared to furan. Much like furan, 2-methylfuran and other substituted furans are metabolized to dialdehydes (Ravindranath et al. 1984, Ravindranath and Boyd 1985, Ravindranath et al. 1986), and it is hypothesized that many substituted furans have similar mechanisms of toxicity as furan (Gill et al. 2014). Recently, a 28-day oral toxicity study in Fischer 344 rats was completed with 2-methylfuran using doses ranging from 0.4 to 25 mg/kg/d (Gill et al. 2014). Histological changes in liver were observed in the lowest dose group, 0.4 mg/kg/d (Gill et al. 2014). This suggests 2-methylfuran and furan may have similar subchronic oral toxicity potencies, and a follow-up subchronic study has been proposed (Gill et al. 2014). Rats were exposed to high inhalation doses of 2-methylfuran (1270 to 9119 ppm) for 1 hour in |the same study that was used to define furan AEGL values (Terrill et al. 1989). A lower median lethal concentration was observed for 2-methylfuran compared to furan (1485 versus 3464 ppm), suggesting that 2-methylfuran may be more toxic in high-dose, acute exposures (Terrill et al. 1989). Eastman Chemical Company conducted an inhalation study in which rats were exposed to 125 to 1250 ppm 2,5-dihydrofuran for 6 hours/day for 5 days/week over 4 weeks (Bernard and David 1995). Minor loss of body weight was observed in the 125 ppm group, while rats receiving higher doses demonstrated exposure related changes in nasal passage histology (Bernard and David 1995). A NOAEL was not determined because of body weight effects, and 125 ppm was considered the NOAEL (Bernard and David 1995). Based on these limited data, substituted furans are expected to have similar toxicities as furan, and we propose to continue using the furan $_{HTF}$OEL as a surrogate until adequate data exist for further refinement.

5.0 Recommendations

PNNL proposes to adjust the $_{HTF}$OEL for furan from 1 ppb to 1.9 ppb based on data from several recent studies. Because of limited data and similar hypothesized mechanisms of toxicity, PNNL recommends continued use the furan $_{HTF}$OEL as a surrogate for substituted furans until further data for substituted furans become available. Further toxicity investiagations or new OELs proposed by authoritative organizations (e.g., the National Institute of Occupational Safety and Health, the Occupational Safety and Health Administration, and the American Conference of Government Industrial Hygienists) would warrant re-evaluation of $_{HTF}$OEL for furan and substituted furans.

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