MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 17, 2017

TO: File for Furfuryl Alcohol (CAS No. 98-00-0)

FROM: Michael Depa, Toxics Unit, Air Quality Division

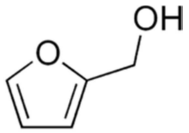
SUBJECT: Screening Level Derivation

The initial risk screening level (IRSL) for furfuryl alcohol is 0.09 µg/m³ (annual average). The secondary risk screening level (SRSL) is 0.9 µg/m³ (annual average). The initial threshold screening level (ITSL) for furfuryl alcohol is 5 µg/m³ (annual average).

Previously (5/15/2002) an IRSL of 0.03 µg/m³ and an ITSL of 1 µg/m³ (24-hr average) were derived according to U.S. Environmental Protection Agency (EPA) Reference Concentration (RfC) Methodology (EPA, 1994) using a regional gas dose ratio of 0.31. Newer guidance by EPA (2012) recommends that for chemicals with adverse effects in the extrathoracic region of the respiratory tract, the dose in animals is equal to that in humans. Specifically, for chemicals with critical effects in the nasal tract, the dosimetric adjustment factor (DAF) is equal to 1. Additionally, Air Pollution Control Rules changes on December 22, 2016, specifically, Rule 232(2)(b), now specify that annual averaging time is applied to ITSLs derived from RfCs, whereas previously it was 24-hr. An updated literature search is not performed at this time.

In 2002, the following references or databases were searched to identify data to determine the screening levels: EPA's Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967 – April 8, 2002), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. Review of these sources found that EPA has not established a reference concentration (RfC) or reference dose (RfD) for furfuryl alcohol. The ACGIH and NIOSH have established occupational exposure limits (OELs) for furfuryl alcohol at 40 mg/m³ (10 ppm)(verified 1/17/2017 from OSHA, 2017). Additionally, a ceiling TLV of 60 mg/m³ was established by the ACGIH (OSHA, 2017). Note that ACGIH has a Notice of Intended Changes for the TLV for furfuryl alcohol (ACGIH, 2017). Furfuryl alcohol has a vapor pressure of 0.4 mmHg at 20°C and a boiling point of 170°C. The molecular weight of furfuryl alcohol is 98.10g. The molecular structure is shown in Figure 1.

Figure 1. Molecular Structure of Furfuryl Alcohol



Animal Studies

In an inhalation study 80 male 3-month old Wistar rats were exposed to 0, 1, 2, or 4 µmol/liter furfuryl alcohol (0, 25, 50, or 100 ppm, respectively) for 4 to 16 weeks, 6 hours/day, 5 days/week (Savolainen and Pfaffle, 1983). The exposure concentrations can also be expressed in the more conventional mg/m³ as 0, 100, 200, or 400 mg/m³, respectively. Body weights of the 200 and 400 mg/m³ exposure groups differed significantly ($P<0.001$) from control rats after 16 weeks of exposure. Urinary furoic acid excretion was in a linear relationship to the exposure at the same time. Analysis for cerebellar creatine kinase showed increased activity in all groups throughout the experiment while succinate dehydrogenase activity decreased in a dose dependent manner at later time points. Glial cell fractions isolated from cerebral hemispheres showed decreased succinate dehydrogenase activity while 2',3'-cyclic nucleotide 3'-phosphohydrolase activity increased at 4 µmol/liter (400 mg/m³) for 16 weeks. This change was accompanied by decreased basic protein content of isolated myelin fractions. The authors stated that the results indicate that furfuryl alcohol may have significant mitochondrial effects in the brain which lead to glial cell degeneration and initiation of demyelination.

The National Toxicology Program (NTP) performed acute and subchronic inhalation studies in male and female rats and mice, the results of which are reported in *Toxicology and Carcinogenisis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)* (NTP, 1999).

In an inhalation bioassay performed by the National Toxicology Program (NTP), groups of 50 male and female F344/N rats and 50 male and female B6C3F1 mice were exposed to 0, 2, 8, or 32 ppm (0, 8, 32 or 128 mg/m³) furfuryl alcohol vapor for up to 2 years (NTP, 1999). Complete clinical and histological examination was performed on each animal. RESULTS - RATS: All male rats exposed to 32 ppm furfuryl alcohol died by week 99. Survival of all other exposed groups of male and female rats was similar to that of the control groups. Mean body weights of the 32 ppm male rats were less than those of the controls beginning week 19; mean body weights of 2 and 8 ppm male groups and all exposed female groups were similar to those of the control groups. There were no exposure-related clinical findings. All groups of exposed male and female rats had significantly increased incidences of non-neoplastic changes in the nose (e.g., squamous metaplasia, olfactory epithelium atrophy, respiratory epithelium hyperplasia). The authors stated that, "In general, the severity increased with increasing exposure concentration, but the overall architecture of the nasal turbinates was not distorted and the mucosal lining remained intact." Nephropathy was present in all rats in this study. The authors stated that, "Nephropathy is a common spontaneous renal disease of the F344/N rats characterized by renal tubule epithelial necrosis and regeneration, interstitial fibrosis, inflammation, and renal tubule dysfunction." The incidence of nasal respiratory epithelium adenoma, carcinoma and squamous cell carcinoma (combined) was statistically increased ($P<0.05$) compared to control at the 32 ppm dose level (see Table 1).

RESULTS - MICE: Survival of exposed males and female mice was similar to that of the chamber control groups. Mean body weight of exposed males were similar to those of the chamber control group throughout the study. Mean body weights of female mice exposed to 2, 8, or 32 ppm were less than those of the chamber control group beginning weeks 59, 59, or 39, respectively. Female mice exposed to 32 ppm developed corneal opacities. All groups of exposed male and female rats and mice had significantly increased incidences of non-neoplastic changes in the nose similar to those observed in rats. Male mice exposed to 32 ppm had statistically increased numbers of renal tubule neoplasms. The incidence of renal tubule degeneration in the 32 ppm male mice was statistically increased ($P<0.01$) compared to control mice. The incidence of renal tubule adenoma and carcinoma (combined) was statistically increased ($P<0.05$) compared to control at the 32 ppm dose level. CONCLUSIONS: Exposure of male and female rats and male mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and increased severities of nephropathy. Exposure of female mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and corneal degeneration. There was no evidence of a response in the lung during the 13-week or 2-year studies, suggesting that the majority of furfuryl alcohol vapors were removed by the upper respiratory tract, specifically the nose.

Under the condition of this study, there was some evidence of carcinogenic activity of furfuryl alcohol in male F344/N rats based on increased incidences of combined nasal neoplasms (adenoma, carcinoma or squamous cell carcinoma). There was equivocal evidence of carcinogenic activity of furfuryl alcohol in female F344/N rats based on marginally increased incidences of neoplasms of the nose and renal tubule neoplasms. The incidences of neoplasms in the female F344/N rats were not statistically increased compared to control rats. There was some evidence of carcinogenic activity of furfuryl alcohol in male B6C3F1 mice based on increased incidences of renal tubule neoplasms. There was no evidence of carcinogenic activity of furfuryl alcohol in female B6C3F1 mice exposed to 2, 8 or 32 ppm. The incidence of neoplasms that were statistically increased compared to control animals are shown in Table 1.

Table 1. Adjusted Incidence of Selected Neoplasms (taken from NTP, 1999)**

Tumor	Control (0 mg/m³)	2 ppm (8 mg/m³)	8 ppm (32 mg/m³)	32 ppm (128 mg/m³)
MALE RAT: Raw incidence of combined nasal adenomas, carcinomas, and squamous cell carcinomas	0/50	1/50	1/50	4/50*
MALE RAT: Adjusted** incidence of combined nasal adenomas, carcinomas, and squamous cell carcinomas	0/50	1/34	1/34	4/33*
MALE MOUSE: Raw incidence of combined renal tubule adenoma or carcinoma	0/50	0/49	0/49	5/50*
MALE MOUSE: Adjusted** incidence of combined renal tubule adenoma or carcinoma	0/50	0/45	0/45	5/45*

* significant at $p<0.01$

**In order to determine “adjusted incidences” it was assumed that animals that died before the first occurrence of the specific neoplasm were not exposed long enough to develop cancer; therefore, they were not included in the denominator of the final incidence calculation.

The NTP (1999) summarized the metabolism and excretion of furfuryl alcohol,

> "...[T]he major biotransformation pathway for furfuryl alcohol in rodents and humans is oxidation to furfural, which is further oxidized to furoic acid. Furoic acid is then conjugated with glycine to form furoylglycine and eliminated in urine. Furfuryl alcohol is also converted to furanacrylic acid and conjugated with glycine to form furanacryloglycine, which is also eliminated in urine. The data in Appendix I indicate that elevated concentrations of these two major metabolites were present in the urine of rats at the end of the 2-year studies. Although the liver is the primary site of these biotransformations, the kidney also contains the necessary enzymes. Therefore, the increased severity of nephropathy in rats may be associated with the renal metabolism and/or urinary elimination of furfuryl alcohol and its metabolites."

Concerning the mechanism of toxicity of furfuryl alcohol the authors stated,

> "The results of the present studies demonstrate that furfuryl alcohol is an obvious nasal irritant in both rats and mice. However, it is unknown if the primary irritant is the parent alcohol or a metabolite. At vapor concentrations similar to those used in the present study, simple aliphatic alcohols such as methanol and ethanol are essentially nontoxic to the nose (Andrews et al., 1987; Poon et al., 1994). By contrast, their respective aldehydes, formaldehyde and acetaldehyde, are nasal toxicant and nasal carcinogens (Swenberg et al., 1980; Appelman et al., 1982; Woutersen et al., 1984; Monticello et al., 1996). Furfural, an aldehyde, is the major metabolite of furfuryl alcohol. In the only inhalation study of furfural in which the nose was examined histologically, Syrian golden hamsters were exposed to 0, 20, 115 or 552 ppm furfural, 6 hours/day, 5 days per week for 13 weeks (Feron et al., 1979). In this study, the nose was the only target organ; 20 ppm was the no-observable-effect level, while 115 and 552 ppm caused atrophy and hyperplasia of the olfactory epithelium, but were without effect on the respiratory epithelium. These results indicate that furfural is considerably less toxic to the nose than furfuryl alcohol."

Genetic Toxicity

The NTP (1997) report also summarized mutagenicity studies. Furfuryl alcohol was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation (Mortelmans et al., 1986). It did induce sister chromatid exchanges in cultured Chinese hamster ovary cells (NTP, 1999); however, no induction of sister chromatid exchanges was noted following treatment with furfuryl alcohol in the presence of S9. Furfuryl alcohol did not induce chromosomal aberrations in cultured Chinese hamster ovary cells treated with furfuryl alcohol in the absence of S9, but in the presence of S9, the first trial showed a clear dose-related increase in aberrations, with significant elevation seen at 500 and 1,000 µg/mL. Results of the second trial were negative, and the assay overall was determined to be equivocal by NTP. *In Vivo*, no induction of sister chromatid exchanges, chromosomal aberrations, or micronuclei was noted in bone marrow cells of male B6C3F1 mice after administration of furfuryl alcohol by interperitoneal injection. In the chromosomal aberrations test, results of the initial 36-hour trial were positive (P=0.003); however, results of two additional 36-hour trial were

negative and the assay was concluded to be negative overall. The NTP (1999) concluded that with the exception of the positive response observed in the sister chromatid exchange test in cultured Chinese hamster ovary cells *in vitro*, no indication of genetic activity was seen with furfuryl alcohol.

Assessment of Carcinogenicity

The available literature on furfuryl alcohol was evaluated in order to determine the weight of evidence for potential human carcinogenicity. With the exception of the positive response in the sister chromatid exchange test in cultured Chinese hamster ovary cells *in vitro*, no indication of genetic activity was seen with furfuryl alcohol. No epidemiological studies were found that examined the carcinogenicity of furfuryl alcohol exposure in humans. Nonetheless, based on the significantly increased incidence of nasal tumors observed in male rats exposed to 32 ppm furfuryl alcohol and the significantly increased incidence of kidney tumors observed in male mice exposed to 32 ppm furfuryl alcohol, it was determined that furfuryl alcohol meets the definition of a carcinogen pursuant to Rule 103(c)(iii).

Dosimetric Adjustment

The dose equivalency between animals and humans was evaluated pursuant to Rule 231(2)(c). From the study performed by NTP (1999), it was established that furfuryl alcohol was in the gaseous phase at the lower exposure concentrations. Because there was no specific information on the furfuryl alcohol target-tissue dose, EPA (2012) guidance was used to calculate a dosimetric adjustment factor (DAF). EPA (2012) recommends that for chemicals with adverse effects in the extrathoracic (e.g., nasal) region of the respiratory tract, the DAF is equal to 1.

Derivation of Inhalation Unit Risk

The Inhalation Unit Risk (IUR) was derived according to EPA (2005a, 2005b) guidance. The Global 82 computer model was used to quantitate the excess risk of cancer from inhalation exposure to furfuryl alcohol. The incidence of nasal tumors in male rats and the incidence of kidney tumors in male mice were used to develop the IUR. The adjusted incidence of tumors and the duration adjusted[1] exposure concentrations were used in the Global 82 input file (see appendix). The duration adjusted exposure concentration was calculated by multiplying the exposure concentration by 6hr/24hr and 5days/7days to account for the hours exposed per day and days exposed per week, respectively.

To derive the unit risk the upper 95% confidence limit on risk at the 1 in 1,000,000 risk level is divided by the maximum likelihood estimate (MLE) dose at the same level of risk which determines the IUR. The IUR for male rat nasal tumors was calculated as follows:

$$\text{IUR(rat)} = (\text{95\% upper confidence limit})/\text{MLE}$$
$$\text{IUR(rat)} = (1.936852 \times 10^{-6})/(1.676434 \times 10^{-4}\ \text{mg/m}^3)$$
$$\text{IUR(rat)} = 1.155 \times 10^{-2}\ (\text{mg/m}^3)^{-1}$$

A mouse IUR of $4.429 \times 10^{-3}\ (\text{mg/m}^3)^{-1}$ for male mouse kidney tumors was also calculated using a DAF of 1 (blood:gas, animal to human ratio of 1). However, its potency is lower

[1] The exposure concentration is “duration adjusted” to reflect lifetime continuous exposure.

that the rat IUR calculated above. Therefore, pursuant to Rule 231(3)(b) it was not used to derive the IRSL.

An IRSL was developed from the IUR(rat) nasal tumors according to Rule 231(1) as follows:

$IRSL(rat) = (1 \times 10^{-6})/(\text{unit risk})$
$IRSL(rat) = (1 \times 10^{-6})/[1.155 \times 10^{-2} (mg/m^3)^{-1}]$
$IRSL(rat) = 8.658 \times 10^{-5}$ mg/m³ x 1000µg/mg
$IRSL(rat) = 8.658 \times 10^{-2}$ µg/m³

Finally, to calculate the human IRSL the rat IRSL is multiplied by the DAF.

IRSL(human) = IRSL(rat) x DAF
$IRSL(human) = (8.658 \times 10^{-2}$ µg/m³) x 1
$IRSL(human) = 8.658 \times 10^{-2}$ µg/m³
IRSL (human) = 0.09 µg/m³ (rounding to 1 significant figure)

Derivation of the Initial Threshold Screening Level (ITSL)

A reference concentration (RfC) can be developed from the NTP (1999) chronic inhalation study. The incidence of nasal olfactory epithelium atrophy was significantly increased in all animals (male and female rats and mice) and at all doses compared to controls; therefore, the lowest dose of 2 ppm or 8 mg/m³ was determined to be a lowest-observed-adverse-effect-level (LOAEL). To calculate the RfC the LOAEL was duration adjusted to obtain the $LOAEL_{ADJ}$ of 1.43 mg/m³ by multiplying the LOAEL by 6/24 and 5/7. The $LOAEL_{ADJ}$ was then converted to the human equivalent concentration ($LOAEL_{HEC}$) by multiplying the $LOAEL_{ADJ}$ by the DAF. Since the critical non-cancer effects were all in the extrathoracic region of the respiratory tract, the DAF is equal to 1.

$LOAEL_{HEC} = LOAEL_{ADJ}$ x DAF
$LOAEL_{HEC} = 1.43$ mg/m³ x 1

An RfC is calculated using uncertainty factors according to EPA (1994, 2012) as follows:

$RfC = LOAEL_{HEC}/(UF1 \times UF2 \times UF3)$

Where, a total UF equals 300, and
UF1 is 10 for extrapolation of a LOAEL to a no-observed-adverse-effect-level (NOAEL)
UF2 is 10 for protection of sensitive individuals
UF3 is 3 for extrapolation of animal data to that of humans

RfC = (1.43 mg/m³)/(10 x 10 x 3) x 1000 µg/mg
RfC = 4.76 µg/m³
RfC = 5 µg/m³, rounded to 1 significant figure

Pursuant to Rule 232(1)(a) the ITSL is equal to the RfC. Pursuant to Rule 232(2)(b) the averaging time associated with the ITSL is annual.

Conclusions

Furfuryl alcohol is a potent irritant in the nasal cavity (e.g. squamous metaplasia, olfactory epithelium atrophy, respiratory epithelium hyperplasia). The initial risk screening level (IRSL) for furfuryl alcohol is 0.09 µg/m³ (annual average). The secondary risk screening level (SRSL) is 0.9 µg/m³ (annual average). The initial threshold screening level (ITSL) for furfuryl alcohol is 5 µg/m³ (annual average).

References

ACGIH. 1996. Documentation of threshold limit values and biological exposure indicies. Furfuryl Alcohol. American Conference of Governmental Industrial Hygienists. ACGIH Publications, Cincinnati, OH, 45240. page 696.

ACGIH. 2017. 2017 American Conference of Governmental Industrial Hygienists (ACGIH®) 1330 Kemper Meadow Drive | Cincinnati, Ohio 45240 | Tel: 513-742-2020 http://www.acgih.org/tlv-bei-guidelines/documentation-publications-and-data/notice-of-intended-changes/notice-of-intended-changes-list

Andrews LS, Clary JJ, Terrill JB, Bolte HF. 1987. Subchronic inhalation toxicity of methanol. Journal of Toxicology and Environmental Health. 20: 117-124.

Appelman LM, Woutersen RA, Feron VJ. 1982. Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology. 23: 293-307.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. United States Environmental Protection Agency. Office of Research and Development, Washington DC, 20460. EPA/600/8-90/066F.

EPA. 2005a. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. U.S. Environmental Protection Agency. Washington DC. March 2005. EPA/630/P-03/001B.

EPA. 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. Risk Assessment Forum. U.S. Environmental Protection Agency. Washington DC. March 2005. EPA/630/R-03/003F

Feron VJ, Kruysee A, Dreff-van der Meulen H. 1979. Repeated exposure to furfural vapor; 13-week study in Syrian golden hamsters. Zbl. Bakt. Hyg. 168: 442-451.

Monticello TM, Swenberg JA, Gros EA, Leininger JR, Kimbell JS, Seilkop S, Starr TB, Gibson JE, Morhan KT. 1996. Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. Cancer Research. 56: 1012-1022.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. 1986. Solmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ. Mutagen. 8 (Supplement 7), 1-119.

NTP. 1999. Toxicology and carcinogenesis studies of furfuryl alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (inhalation studies). National Toxicology Program (NTP) Technical Report 482. National Institute of Health Publication No. 99-3972. U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

OSHA. 2017. OSHA Annotated Table Z-1(a). Occupational Safety and Health Administration. United States Department of Labor. <accessed 1-17-2017> https://www.osha.gov/dsg/annotated-pels/tablez-1.html

Poon R, Chu I, Bjarnason S, Potvin M Vincent R, Miller R, Valli V. 1994. Inhalation toxicity study of methanol, toluene, and methanol/toluene mixtures in rats: Effects of 28-day exposure. Toxicology and Industrial Health. 10: 231-245.

Savolainen H, Pfaffli P. 1983. Neurotoxicity of furfuryl alcohol vapor in prolonged inhalation exposure. Environmental Research. 31: 420-427.

Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL. 1980. Induction of squamous cell carcinomas if the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Research. 40: 3398-3402.

Woutersen RA, Appelman LM, Feron JV, Van der Heijden CA. 1984. Inhalation toxicity of acetaldehyde in rats. II Carcinogenicity study: Interim results after 15 months. Toxicology. 31: 123-133.

Appendix Input Files for GLOBAL82.exe

Input file for male rat nasal tumors:

```
male rat nose cancers
4,3,0,2,3,0,0
50,34,34,33
0,1.429,5.714,22.857
0,1,1,4
.01 2,.1d-4 2,.1d-5 2
```

Input file for male mice kidney tumors:

```
male mice kidney cancer
4,3,0,2,3,0,0
50,45,45,45
0,1.429,5.714,22.857
0,0,0,5
.01 2,.1d-4 2,.1d-5 2
```