STATE OF MICHIGAN
Rick Snyder, Governor

DEPARTMENT OF ENVIRONMENTAL QUALITY
AIR QUALITY DIVISION
Constitution Hall ● 525 West Allegan Street ● P.O. Box 30260 ●
Lansing, Michigan 48909-7760
www.michigan.gov/air

September 11, 2017

Response to Public Comments for Furfuryl Alcohol (CAS No. 98-00-0)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the Initial Risk Screening Level (IRSL), Secondary Risk Screening Level (SRSL), and Initial Threshold Screening Level (ITSL) for furfuryl alcohol. As a result of that review, the AQD is retaining the current IRSL, SRSL, and ITSL. Therefore, the IRSL is 0.09 µg/m³ and the SRSL is 0.9 µg/m³. Both these screening levels have annual averaging time. The ITSL is 5 µg/m³ with annual averaging time.

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14, 2017. The AQD must respond to these comments within 180 days; the latest date for response is October 11, 2017.

[1] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994.PA 451, as amended (NREPA).

Comments and Responses:

Comment: DEQ should update its literature review to determine whether new data is available to provide the best available basis for a revised IRSL and ITSL values.

Response:
An updated literature review was performed which included a search of the following databases: SciFinder, Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), International Agency for Research on Cancer (IARC), EPA Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), and U.S. National Library of Medicine (NLM) Toxline. Regarding the carcinogen risk assessment and derivation of the IRSL, the relevant new information obtained from the updated literature review is discussed. The updated literature review confirmed that the ITSL previously derived (Depa, 2017) from a chronic inhalation study in rats and mice is based on the most appropriate key study and effects (NTP, 1999). The AQD does not have a short-term ITSL for furfuryl alcohol at this time. Pursuant to Rule 232(1)(c), an ITSL can be derived from an occupational exposure limit, such as the ACGIH TLV. The AQD is in the process of obtaining the ACGIH TLV Documentation for furfuryl alcohol and will evaluate the basis of the new 2017 TLV of 0.2 ppm (time weighted average).

Comment: None of the major Federal agencies that classify materials as carcinogens, including the National Toxicology Program, the International Agency for Research on Carcinogens, OSHA, ACGIH or NIOSH have classified furfuryl alcohol as a suspect human carcinogen considering the animal data. The classification of furfuryl alcohol as a carcinogen by DEQ based on animal studies may be inappropriate and introduces a significantly higher level of conservatism into the screening level derivation process.

Response:
Recently, IARC identified furfuryl alcohol as, “Possibly Carcinogenic to Humans” and “Group 2B” (Gross et al., 2017) (IARC, 2017). Furfuryl alcohol meets the definition of a carcinogen based on Michigan’s Air Pollution Control Rule 103(c)[2]. The European Chemical Agency classifies furfuryl alcohol as “suspected of causing cancer (inhalation)” (ECHA, 2017).

Comment: The exposures from food seem to dwarf the potential exposure from industrial sources. The screening level derivation process should consider that furfuryl alcohol is present in common food items at significant levels such as pineapple juice (8 mg/l), coffee (typical furfuryl alcohol concentrations exceed 100 mg/kg), and many other

[2] Ibid., carcinogen definition from Rule 103(c)(iii): “Group C -- Any substance for which there is limited evidence of carcinogenicity in animals in the absence of human data and which causes a significant increased incidence of benign or malignant tumors in a single, well-conducted animal bioassay.”

common food items (e.g., butter, potato chips, wine, etc.). Using TAC spreadsheet methodology, an allowable emission rate of 36 lbs./month results in very low offsite air concentrations. These low allowable emissions rates (sic) are based on unreasonably high uncertainly (sic) multipliers used in the IRSL derivation process, including the combined effects of a 95% confidence level, and 1-in-a-million risk factor. There is no evidence of carcinogenic effects of furfuryl alcohol at such low concentrations.

Response: AQD recognizes that furfuryl alcohol occurs in many common foods. However, the food pathway of furfuryl alcohol exposure is via the oral route. It is conceivable that inhalation exposure to furfuryl alcohol causes nasal cancer in animals and possibly to humans by a mechanism not observed via the oral route of exposure because of the different chemical and physiological environments of the respiratory and digestive tracts. Furthermore, the wide-spread human exposure to furfuryl alcohol from food and the absence of documented carcinogenic effects is not necessarily confirmation that it does not cause cancer in humans via the oral pathway. For example, ethanol consumption in the form of alcoholic beverages is a known human carcinogen (IARC, 2017), yet the carcinogenic effects of alcohol were not widely acknowledged by the scientific community until relatively recently (PubMed, 2017).

When evaluating carcinogenic risks from chemical exposures, including furfuryl alcohol, the AQD follows EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). There is limited data on a carcinogenic mode of action[3] for furfuryl alcohol. However, furfuryl alcohol was found to be mutagenic in Salmonella typhimurium TA100 engineered for expression of human sulfotransferase (SULT) 1A1, suggesting that furfuryl alcohol may be a human mutagen (Monien et al., 2011). Transgenic mice expressing human sulfotransferases 1A1 and 1A2 showed DNA adducts after a single oral dose of 250 mg/kg furfuryl alcohol (Høie et al., 2015). In the absence of sufficiently, scientifically justifiable mode of action information, the U.S. Environmental Protection Agency (EPA, 2005) generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity.

Comment: The methods employed in the screening level development process do not take into effect (sic) the environmental fate and transport of furfuryl alcohol. According to the peer-reviewed data provided on the National Libraries of Medicine's Hazardous Substances Data Bank, "Vapor-phase furfuryl alcohol will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 3.7 hours. Furfuryl alcohol absorbs light at wavelengths >290 nm and therefore may be susceptible to direct photolysis by sunlight." Since atmospheric transport is the sole transport route for furfuryl alcohol emissions to the receptor population that is accounted for in the IRSL and ITSL's (sic), the decrease in concentration that may occur during transport may have a significant effect on the receptor concentrations, and the IRSL and ITSL values are thus overly

[3] "Mode of action" is defined as a sequence of key events and processes, starting with the interaction of the agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation (U.S. EPA, 2005).

conservative. The risk assessment process should consider degradation when it is a potentially significant factor.

Response: The commenter is correct that when AQD derives screening levels for toxic air contaminants, including furfuryl alcohol, we do not typically consider atmospheric degradation. AQD's health protective screening levels apply to ambient air, which begins at the secured property line for a facility applying for a Permit to Install. The information provided by the commenter and by the Hazardous Substances Data Bank does not support the supposition that atmospheric degradation of furfuryl alcohol occurs to a significant extent over such small distances and transport times. The "3.7 hours" stated by the commenter for a half-life of furfuryl alcohol in the atmosphere is greater than a reasonable time estimate that furfuryl alcohol would take to travel from the emission source to the property line.

Summary and Conclusions:

Considering IARC's 2B "possibly carcinogenic to humans" designation, and the statistically significant increased rate of tumors in a well-designed animal study, the AQD finds that the evidence that furfuryl alcohol may cause cancer in humans is reasonable. The IRSL and SRSL for furfuryl alcohol are 0.09 and 0.9 µg/m^3 (annual averaging time) are retained. Based on an updated literature review, the long-term ITSL for furfuryl alcohol of 5 µg/m^3 (annual avg. time) for non-carcinogenic effects was re-evaluated and found to be appropriate.

The primary AQD reviewer for these comments was Mike Depa, AQD Toxics Unit toxicologist. The secondary (peer) reviewer was Robert Sills, AQD Toxics Unit Supervisor.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2017. Online databases. 4770 Buford Hwy NE, Atlanta, GA 30341. [accessed Sept-5-2017]
https://www.atsdr.cdc.gov/mrls/index.asp
https://www.atsdr.cdc.gov/toxprofiles/index.asp

Depa M. 2017. Memorandum to the File for Furfuryl Alcohol (CAS No. 98-00-0). Subject: Screening Level Derivation. Toxics Unit of the Air Quality Division. Michigan Department of Environmental Quality. Dated January 17, 2017.
http://www.deq.state.mi.us/aps/downloads/ATSL/98-00-0/98-00-0_annual_ITSL_IRSL.pdf

European Chemical Agency (ECHA). 2017. Summary of Classification and Labelling for Furfuryl Alcohol. Harmonised classification - Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation). https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/71434

Gross Y, Loomis D, Guyton KZ, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. 2017. Some chemicals that cause tumours of the urinary tract in rodents. Lancet Oncol. 2017 Aug;18(8):1003-1004. doi: 10.1016/S1470-2045(17)30505-3. Epub 2017 Jun 27.

Høie AH, Monien BH, Sakhi AK, Glatt H, Hjertholm H, Husøy T. 2015. Formation of DNA adducts in wild-type and transgenic mice expressing human sulfotransferases 1A1 and 1A2 after oral exposure to furfuryl alcohol. Mutagenesis. 2015 Sep;30(5):643-9. doi: 10.1093/mutage/gev023.

International Agency for Research on Cancer (IARC). World Health Organization (WHO). Online search. http://monographs.iarc.fr/ENG/Classification/index.php [accessed Sept-05-2017]

IARC. 2017. List of classifications, Volumes 1–119. http://monographs.iarc.fr/ENG/Classification/ClassificationsCASOrder.pdf http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf

Monien BH, Herrmann K, Florian S, Glatt H. 2011. Metabolic activation of furfuryl alcohol: formation of 2-methylfuranyl DNA adducts in Salmonella typhimurium strains expressing human sulfotransferase 1A1 and in FVB/N mice. Carcinogenesis. 2011 Oct;32(10):1533-9. doi: 10.1093/carcin/bgr126.

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

PubMed. 2017. "alcohol cancer risk" search terms. Sort by: publication date. https://www.ncbi.nlm.nih.gov/pubmed [accessed Sept-8-2017)

Registry of Toxic Effects of Chemical Substances (RTECS). Online database. Canadian Centre for Occupational Health and Safety (CCOHS). http://ccinfoweb.ccohs.ca/rtecs/search.html [accessed Sept-05-2017]

SciFinder. 2017. Chemical Abstracts Service: Columbus, OH, 2017. Copyright © 2017 American Chemical Society. RN 98-00-0. [accessed Sept-05-2017]

U.S. Environmental Protection Agency (EPA) 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. EPA/630/P-03/001B. https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

U.S. EPA. Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV) 2017. Online database. https://hhpprtv.ornl.gov/quickview/pprtv.php

[accessed Sept-05-2017]

U.S. EPA. Integrated Risk Information System (IRIS). 2017. Online database. https://www.epa.gov/iris
[accessed Sept-05-2017]

U.S. National Library of Medicine (NLM) 8600 Rockville Pike, Bethesda, MD 20894 National Institutes of Health (NIH), Health & Human Services (HHS). TOXLINE A TOXNET database (online database). https://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
[accessed Sept-05-2017]