MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Furan (CAS# 110-00-9)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 30, 2017

SUBJECT: Furan (CAS# 110-00-9) ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for furan is 4 µg/m^3 based on an annual averaging time. The ITSL was originally established on 11/2/1994 and was set at 4 µg/m^3 based on a 24-hour averaging time. The ITSL is based on an EPA RfD of 1 x 10^{-3} mg/kg/day based on an NTP (1993) subchronic gavage study in rats and mice. The critical effect was hepatic lesions in male and female rats and female mice. When the screening level was derived in 1994 the averaging time was set at 24 hours. As the basis of the screening level is based on a 13-week gavage study, the averaging time may appropriately be set at annual. Therefore, the averaging time is being changed from 24 hours to annual.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

EPA. 1987. Integrated Risk Information System. Furan; CASRN 110-00-9. Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=56

NTP. 1982. Subchronic toxicity report on furan in B6C3F1 mice. National Toxicology Program. Prepared by Southern Research Institute under Contract No. 1-CP-95641-01 for NTP Bethesda, MD.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

NOVEMBER 2, 1994

TO: File for Furan (CAS# 110-00-9)

FROM: Michael Depa, Toxics Unit

SUBJECT: Screening Level Determination

The initial risk screening level (IRSL) for furan is 0.0002 $\mu g/m^3$ based on annual averaging time. The ITSL for furan is 4 $\mu g/m^3$ based on a 24 hour averaging time.

The following references or databases were searched to identify data to determine the screening level: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967-July 23, 1994), National Library of Medicine, Health Effects Assessment Summary Tables, and NTP Status Report. Occupational exposure limits were not available for furan. The EPA has not established an RfC for furan. There was no data meeting the minimum criteria for establishing an RfC. The EPA established an RfD of 1×10^{-3} mg/kg/day based on a subchronic oral study performed in mice. The National Toxicology Program (NTP, 1993) completed a two year gavage study which showed clear evidence of carcinogenic activity in both male and female F344/N rats based on increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and on increased incidences of mononuclear cell leukemia. This study also showed clear evidence of carcinogenic activity in male and female B6C3F1 mice based on increased incidences of hepatocellular neoplasms of the liver and benign pheochromocytoma of the adrenal gland. Tables 1 - 4 show the adjusted cancer incidence rates of tumors detected in male and female rats and mice. The number of animals per dose group was adjusted by subtracting the number of rats or mice that died before the first tumor was detected.

Table 1. Adjusted Incidence* of Cholangiocarcinoma and Hepatocellular Neoplasms in Male and Female F344/N Rats

	Male Rats		Female Rats	
Dose Level	Incidence of Cholangio-carcinoma	Incidence of Hepatocellular Neoplasms	Incidence of Cholangio-carcinoma	Incidence of Hepatocellular Neoplasms
Vehicle Control	0/50	1/50	0/50	0/50
2 mg/kg	43/43	5/24	49/50	2/34
4 mg/kg	48/48	22/41	50/50	4/34
8 mg/kg	49/49	35/44	48/50	8/31

* Adjusted Incidence = Crude Incidence - # of animals that died before the first case of tumor was identified.

Table 2. Adjusted Incidence*of Monocellular Leukemia in Male and Female F344/N Rats

Dose Level	Male Rats	Female Rats
Vehicle Control	8/40	8/47
2 mg/kg	11/45	9/43
4 mg/kg	17/45	17/44
8 mg/kg	25/49	21/49

* Adjusted Incidence = Crude Incidence - # of animals that died before the first case of tumor was identified.

Table 3. Adjusted Incidence* of Hepatocellular Adenoma or Carcinoma and Benign Pheochromocytoma in B6C3F1 Mice

	Male Mice		Female Mice	
Dose Level	Incidence of Hepatocellualr Adenoma or Carcinoma	Incidence of Benign Pheochromo-cytoma	Incidence of Hepatocellualr Adenoma or Carcinoma	Incidence of Benign Pheochromo-cytoma
Vehicle Control	26/49	1/37	7/41	2/39
8 mg/kg	44/44	6/33	34/49	1/12
15 mg/kg	50/50	10/50	48/50	6/30

* Adjusted Incidence = Crude Incidence - # of animals that died before the first case of tumor was identified.

Crude[1] cancer slope factors (q_1*) were calculated for all significantly elevated tumor incidences (Table 5). However, the Global82 program used to calculate the slope factor cannot use data which represents incidence rates of 100%. Therefore, it was necessary to subtract 1 from the numerator of those groups which showed 100% incidence. For example, in Table 3 at the 15 mg/kg dose level the incidence of hepatocellular adenoma or carcinoma is 50/50. This incidence was adjusted to 49/50 to meet the requirements of the Global82 program. Furthermore, in 2 instances the chi-

[1] The term "crude" was used to account for the unadjusted dose. Since the doses were given 5 out of 7 days, the doses must be adjusted by multiplying by the factor 5/7.

square goodness of fit was unacceptable(male and female cholangiocarcinoma), therefore, the highest dose group was omitted and the slope recalculated. This procedure is outlined in Rule 231(3)(b).

Output from the Global82 program includes (among other data) the upper 95% confidence limit and maximum liklihood estimate at a specified risk. The cancer slope factor (q_1*) is calculated from this data. An example of the q_1* calculation is presented using the incidence rate of female rat cholangiocarcinoma.

$$q_1^* = \frac{\text{Upper 95\% CL}}{\text{MLE (mg/kg)}} \times \sqrt[3]{\frac{W_H}{W_A}} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = \frac{1.367316 \times 10^{-5}}{6.7962456734 \times 10^{-6}} \times \sqrt[3]{\frac{70\ kg}{0.325\ kg}} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = 2.0119 \frac{kg}{mg} \times 5.99 \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = 3.45 \times 10^{-3}\ (\mu g/m^3)^{-1}$$

Where W_H = 70 kg, the default weight of a human,
W_A = the weight of the female F344/N rat, and
20 m^3 = the default inhalation rate per day of the average human

Table 5. Crude Cancer Slope Factors Determined from the NTP Furan Gavage Studies

Tumor Type	Species	Sex	Slope Factor $(\mu g/m^3)^{-1}$
Cholangiocarcinoma	rat	male	2.93×10^{-3}
Hepatocellualr Neoplasms	rat	male	3.28×10^{-4}
Monocellular Leukemia	rat	male	1.41×10^{-4}
Cholangiocarcinoma	rat	female	3.45×10^{-3}
Hepatocellular Neoplasms	rat	female	8.78×10^{-5}
Moncellular Leukemia	rat	female	1.39×10^{-4}
Hepatocellular Adenoma or Carcinoma	mice	male	1.36×10^{-3}
Benign Pheochromocytoma	mice	male	7.73×10^{-5}
Hepatocellular Adenoma or Carcinoma	mice	female	0.56×10^{-3}
Benign Pheochromocytoma	mice	female	7.13×10^{-5}

The highest crude q_1* was 3.45×10^{-3} $(\mu g/m^3)^{-1}$ (female rat cholangiocarcinoma). The doses given to the female rats were then adjusted to account for the five days per week dosing regimen. The doses 0 mg/kg, 1.43 mg/kg, and 2.86 mg/kg were used along

with the incidences described in Table 1 to calculate the q_1* using Global 82. A q_1* of 4.82×10^{-3} was derived and was subsequently used to calculate the IRSL as follows:

$$IRSL = \frac{1 \times 10^{-6}}{q_1 *}$$

$$IRSL = \frac{1 \times 10^{-6}}{4.82 \times 10^{-3} \ (\mu g / m^3)^{-1}}$$

$$IRSL = 2.07 \times 10^{-4} \ \mu g/m^3$$

$$IRSL = 2 \times 10^{-4} \ \mu g/m^3 \ \text{(based on annual averaging time)}$$

$$SRSL = 2 \times 10^{-3} \ \mu g/m^3 \ \text{(based on annual averaging time)}$$

The initial threshold screening level (ITSL) for furan was developed to account for the non-cancer health effects. The RfD was used to calculate the ITSL as shown below:

$$ITSL = RfD \times 70 \text{ kg}/20 \text{ m}^3$$

$$ITSL = 1 \times 10^{-3} \text{ mg/kg/day} \times 70 \text{ kg}/20 \text{ m}^3$$

$$ITSL = 0.0035 \text{ mg/m}^3$$

$$ITSL = 4 \ \mu g/m^3 \ \text{(based on a 24 hour averaging time)}$$

The ITSL for furan is 4 $\mu g/m^3$ based on a 24 hour averaging time. The IRSL for furan is 0.0002 $\mu g/m^3$ based on an annual averaging time. The SRSL for furan is 0.002 $\mu g/m^3$ based on an annual averaging time.

REFERENCES:

EPA, 1988. Recommendation for and documentation of biological values for use in risk assessment. PB 88-179874.

NTP. 1993. Toxicology and carcinogenesis studies of furan (CAS No. 110-009) in F344/N rats and B6C3F1 mice (Gavage Studies). National Toxicology Program. Technical Report Series No. 402. NIH Publication No. 93-2857. U. S. Department of Health and Human Services. Public Health Service. National Institutes of Health. January 1993.