MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

April 2, 1993

TO: File for Furfural (CAS #98-01-1)

FROM: Mary Lee Hultin, Toxics Unit

SUBJECT: Screening level for Furfural

The following sources were searched for toxicity data:

RTECS
EPA IRIS
DNR EPB and NUTSHELL
NIOSH and ACGIH TLV documentation
CAS Online
NTP Management Status Report
EPA HEAST

The ACGIH TLV of 2 ppm (7.9 mg/m3) appears to be based primarily on irritant effects. The TLV documentation cites an odor threshold for furfural of 0.078 ppm. The Russian single concentration daily maximum for occupational exposure is 0.05 mg/m3. This may be based upon work published by Ubaydullayev (1) which reported conditioned electrocortical reflex changes at 0.084 mg/m3, but none at 0.05 mg/m3 in humans and a NOAEL of 0.052 mg/m3 vapor from a 60 day exposure to rats.

The EPA HEAST provides an "alternate methods" RfC of 5 x 10E-2 mg/m3 based on a 13 week study of inhalation in hamsters, effects seen included nasal cavity degeneration. The hamster data is not available in English. The EPA IRIS database lists an RfD of 3 x 10E-3 based on hepatocellular vacuolization using gavage data from a subchronic rat bioassay. The assay used constituted the preliminary data for a 2 yr. NTP carcinogenicity bioassay. The IRIS determination was made prior to the publication of the NTP chronic bioassay. According to EPA, there are no current plans for updating the IRIS data on furfural in the near future.

The NTP bioassay, Toxicology and Carcinogenesis Studies of Furfural in F344/N Rats and B6C3F1 Mice (2) was published in March, 1990. The NTP determinations for carcinogenicity included: Sufficient evidence in male F344/N rats and female mice; clear evidence in female mice via gavage. Mice exhibited increased hepatocellular adenomas and carcinomas. Male rats exhibited rare cholangiocarcinomas and bile duct dysplasia with fibrosis.

Mutagenicity data indicates that furfural was negative in most Salmonella assays and positive in cultured Chinese hamster ovary cells, causing chromatid breaks and exchanges (3). The NTP bioassay also reports citations of positive results from mouse lymphoma and sister chromatid exchange assays. Reynolds, et al. (4) examined the pattern of oncogene activation in spontaneous and chemically induced mouse liver tumors. Furfural appeared to cause an increased incidence in mouse liver tumors at least partly due to induction of novel weakly activating point mutations in ras genes. The novel nature of the mutations (as opposed to those found in spontaneously occurring tumors) indicates a possible direct genotoxic effect of furfural. Furfural is used in the production of furan, which was recently determined to also exhibit clear evidence of carcinogenic activity in male and female F344/N rats based on cholangiocarcinomas and hepatocellular neoplasms in rats and B6C3F1 mice by NTP.

Based on the NTP bioassay and supportive mutagenicity data, an Initial Risk Screening Level is developed based on carcinogenic effects using the methodology from Rule 231. The highest q_1^* value was produced by the data from hepatocellular carcinomas and adenomas in male mice. Doses were adjusted to a study average dose, accounting for administration for only 5 of 7 days per week. Numbers of animals per group were adjusted to include only those mice surviving until the time of the first tumor appearance. A printout of the Global82 model input and output is attached.

MLE dose on 1×10^{-6} risk = 1.367858310
95% Upper confidence level = 6.852516×10^{-3}

$q_1^*(\text{animal}) = (6.852516 \times 10^{-3})/(1.367858310) = 5.0097 \times 10^{-3}$ $(\text{mg/kg/d})^{-1}$

$q_1^*(\text{human}) = 5.0097 \times 10^{-3} \times (70 \text{ kg}/0.048 \text{ kg})^{1/3} = 5.68 \times 10^{-2}$ $(\text{mg/kg/d})^{-1}$

q_1^* $(\text{ug/m}^3) = 5.68 \times 10^{-2}$ $(\text{mg/kg/d})^{-1} \times (20 \text{ m}^3/70 \text{ kg}) \times (1 \text{ mg}/1000 \text{ ug}) \times 1 = 1.62 \times 10^{-5}$

IRSL = $(1 \times 10^{-6}/1.62 \times 10^{-5}) = 6.16 \times 10^{-2}$ $\text{ug/m}^3 = 6 \times 10^{-2}$ ug/m^3
SRSL = $(1 \times 10^{-5}/1.62 \times 10^{-5}) = 6.16 \times 10^{-1}$ $\text{ug/m}^3 = 6 \times 10^{-1}$ ug/m^3

References

(1) Ubaydullayev, R., 1970, "Biological Effect of Low Concentrations of Furfurol Under Experimental Conditions", Journal of Hygiene, Epidemiology, Microbiology and Imunology (sic), v. 14, p. 240-251

(2) U.S. Department of Health and Human Services, 1990, National Toxicology Program, Technical Report Series No. 382, Toxicology and Carcinogenesis Studies of Furfural in F344/N Rats and B6C3F1 Mice (Gavage Studies).

(3) Stich, H., et al., 1981, "Clastogenicity of Furans found in Food", Cancer Letters, v. 13, p. 89-95.

(4) Reynolds, et al., 1987, "Activated Oncogenes in B6C3F1 Mouse Liver Tumors: Implications for Risk Assessment", Science, v. 237, p. 1309-1316.