FURFURAL

CAS # 98-01-1

ORAL RISK ASSESSMENT DOCUMENT

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EXECUTIVE SUMMARY

Furfural – Oral Risk Assessment CAS# 98-01-1			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (95% confidence limit at 10% response level)	3.3	mg/kg-day	From a chronic rat study
Oral RfD (oral reference dose)	0.03	mg/kg-day	From the $BMDL_{10}$ with a 100x total uncertainty factor
TAC (total allowable concentration)	0.2	mg/L	For a 70 kg adult drinking 2 L/day, with a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.02	mg/L	From the TAC, assuming 10 potential sources of furfural in drinking water
STEL (short term exposure level)	3	mg/L	From a subchronic rat study, for a 10 kg child drinking 1 L/day

KEY STUDY	National Toxicology Program. 1990. Toxicology and carcinogenesis studies of furfural (CAS No. 98-01-1) in F344/N rats and B6C3F1 mice (gavage studies).
CRITICAL EFFECT	Centrilobular hepatocellular necrosis in male rats at the $BMDL_{10}$. Remaining critical responses confined to high-dose rats and mice.
UNCERTAINTY FACTORS	Furfural was evaluated by the benchmark dose approach, with a total uncertainty factor of 100x, considered adequately protective and including the following areas of uncertainty: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for study duration, since a chronic study was used • 1x for extrapolation from a LOAEL to a NOAEL, since a $BMDL_{10}$ was used • 3x for database deficiencies
TOXICITY SUMMARY	No treatment-related lesions were observed following short-term oral exposure in rats or mice at doses up to those dose levels responsible for significantly reducing survival. Significant increases in absolute and relative liver and kidney weights were identified following subchronic oral high-dose exposure in the rat, and centrilobular coagulative necrosis developed after subchronic oral high-dose exposure in the mouse. Limited evidence for high-dose hepatic carcinogenicity in the rat (cholangiocarcinoma) and mouse (hepatocellular adenoma/carcinoma) was reported following chronic oral exposure. Non-neoplastic lesions observed in the chronic oral bioassays were limited to centrilobular hepatocellular necrosis in rats and chronic hepatic inflammation in mice. There was no indication of developmental toxicity when furfural was evaluated in the rat. There is a weak *Salmonella* reverse mutation response in TA104, a weak response in the mouse lymphoma assay, and a convincingly positive *in vitro* chromosomal aberration response. Smaller responses were seen with metabolic activation, and were not seen in the *in vivo* chromosomal aberration assay, suggesting the intrinsic genetic toxicity is not expressed. The U.S. EPA includes furfural in the IRIS on-line database. Although the oral RfD indicates that the last revision was in 1996, revisions since the 1987 verification date were editorial or administrative, and the 1990 NTP study was not included in the U.S. EPA evaluation.
CONCLUSIONS	Based on the 1990 NTP study, it is proposed that a threshold exists below which no significant adverse responses to furfural are observed following chronic oral exposure. As carcinogenic lesions have been observed at doses above this threshold in chronic oral bioassays in two species, furfural exhibits suggestive evidence of carcinogenicity at high doses in rodents. There is, however, *inadequate information to assess the carcinogenic potential* of furfural in humans. Uncertainties in the data set have been addressed through use of appropriate factors for interspecies and intraspecies extrapolation and database deficiencies. Based on the available data, the drinking water action levels established in this document are protective of public health.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **furfural** in drinking water, as an extractant from one or more drinking water system components tested under NSF/ANSI 61 (2003e), or as a contaminant in a drinking water treatment chemical under NSF/ANSI 60 (2003e). This chemical has also been evaluated as a drinking water treatment chemical for direct addition to water under NSF/ANSI 60 (2003e). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993; U.S. EPA, 2002a), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data, or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED_{10} or $BMDL_{10}$ from benchmark dose programs) can be used (U.S. EPA, 2001). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988; U.S. EPA, 1993; U.S. EPA, 1999a).

NSF uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70\ \text{kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70\ \text{kg}}{2\text{L/day}} \times 0.2\ \text{(RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the estimated total number of sources of the substance in the drinking water treatment and distribution system. In the absence of source data, a default multiple source factor of 10 is used.