

FURFURAL
CAS # 98-01-1
ORAL RISK ASSESSMENT DOCUMENT

**NSF International
Ann Arbor, MI
January 2004**

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EXECUTIVE SUMMARY

Furfural – Oral Risk Assessment CAS# 98-01-1			
PARAMETER	LEVEL	UNITS	DERIVED
BMDL₁₀ (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 BMDL₁₀ 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 <i>Salmonella</i> reverse mutation response in TA104, a weak response in the mouse lymphoma assay, and a convincingly positive <i>in vitro</i> chromosomal aberration response. Smaller responses were seen with metabolic activation, and were not seen in the <i>in vivo</i> 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, <i>inadequate information to assess the carcinogenic potential</i> 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 LED₁₀ or BMDL₁₀ 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.

This accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question to drinking water.

Finally, a short-term-exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED₁₀ of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to the TAC or below under static conditions or to the SPAC or below under flowing conditions within 90 days based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a; U.S. EPA, 1999b; U.S. EPA, 2003). If there is sufficient evidence to use a non-linear model, the LED₁₀ or BMDL₁₀, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED₁₀ or BMDL to zero, is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10⁻⁶ to 10⁻⁴ is considered by the U.S. EPA to be safe and protective of public health (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2003e) and 61 (2003e), the TAC is set at the 10⁻⁵ risk level, and the SPAC is set at the 10⁻⁶ risk level. Use of a higher risk level is not ruled out, but would generally require documentation of a benefit to balance the additional risk.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2003e) and 61 (2003e). Application of these values to other exposure scenarios should be done with care, and with a full understanding of the derivation of the values and of the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation, and require the use of additional uncertainty factors to protect public health.

The general guidelines for this risk assessment include those from the National Research Council (1983) and from The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a, 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999b), draft final Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2003), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), A Review of the Reference Dose and Reference Concentration Process (U.S. EPA, 2002a), and Health Effects Testing Guidelines (U.S. EPA 1996c; U.S. EPA, 2002b).

The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemID Plus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Developmental and Reproductive Toxicology (DART/ETIC)
- TOXLINE
- Toxicology Literature from Special Sources (TOXLIT)
- CANCERLIT
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Furfural has common synonyms of 2-furaldehyde, 2-formylfuran, 2-furaldehyde, 2-furancarboxaldehyde, 2-furfuraldehyde, 2-furyl-methanal, 2-furylaldehyde, and 2-furylcarboxaldehyde and is represented by the following chemical structure:

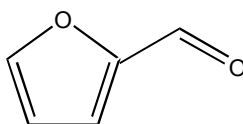


Table 1. The physical and chemical properties of furfural

Property	Data	Reference
Empirical Formula	C ₅ H ₄ O ₂	HSDB, 2002
CAS#	98-01-1	HSDB, 2002
Molecular Weight	96.09	IARC, 1995
Physical State and Color	Clear, colorless liquid	IARC, 1995
Density	1.1563 at 25 °C	Budavari, 1996
Melting Point	-38.7 °C	Lide, 1993
Boiling Point	161.7 °C	Lide, 1993
Vapor Pressure	1 mm Hg at 20 °C	Verschueren, 1983
Water Solubility	83 g/L at 20 °C	Verschueren, 1983
n-Octanol/Water Partition Coefficient (log K _{ow})	0.41 (experimental)	Hansch et al., 1995

2.1 Organoleptic Properties

Furfural is described as having an almond-like odor resembling that of benzaldehyde (NIOSH, 1994; Budavari, 1996). Likewise, furfural has been reported to have a distinct caramel taste (Furia, 1980). Odor and taste thresholds in water have not been reported in the literature.

3.0 PRODUCTION AND USE

3.1 Production

Furfural is produced from annually renewable agricultural sources containing pentosans such as corncobs, cottonseed, wood and wood products. Pentosans are hydrolyzed to pentoses when the raw materials are heated in a digester with a strong inorganic acid. The pentoses then undergo cyclodehydration to form furfural, which is recovered from the digester by steam distillation (Grayson, 1985).

Furfural is a high production volume chemical listed by the United States and the European Union, indicating that the compound is produced and/or imported at more than one million pounds per year in both locations (U.S. EPA, 2002c; OECD, 2000).

3.2 Use

Furfural is used in the synthesis of furan, furfuryl alcohol, tetrahydrofuran, and their derivatives (Grayson, 1985). In addition, furfural can be used as a solvent for separating saturated from unsaturated compounds in petroleum lubricating oil, gas oil, and diesel fuel; as a resin solvent and wetting agent; and as a solvent in various other industrial processes (Parmeggiani, 1983). Furfural has also been used as an effective insecticide, fungicide, and germicide (Budavari, 1996).

4.0 ANALYTICAL METHODS

4.1 Analysis in Water and Biological Matrices

Quantitative analysis of furfural in liquids is most frequently carried out by gas chromatography coupled with flame ionization detection (HSDB, 2002; IARC, 1995). However, high performance liquid chromatography has been employed to determine furfural in beverages, such as orange juice. Furfural has been detected by NSF International in water using gas chromatography with mass spectrometric detection and high-performance liquid chromatography. Typical limits of detection range from 2-30 µg/sample.

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

5.1 Sources of Human Exposure

Occupational exposure to furfural may occur by inhalation or dermal contact during its production or use (ACGIH, 1991). A survey performed by NIOSH in the early 1980s estimated that as many as 134,000 individuals could be occupationally exposed to furfural in the United States each year.

(NIOSH, 1983). However, the nature of the enclosed production process limits greatly the potential for occupational exposure to furfural (IARC, 1995). The general population may be exposed to furfural by inhalation of smoke from wood fires or by inhalation or dermal contact during the use of commercial products that contain this aldehyde. The most common sources of exposure to the general population are from furfural-containing foodstuffs and contaminated drinking water.

As furfural is formed during the thermal decomposition of carbohydrates, furfural has been identified in numerous processed food and beverage products including cocoa, coffee, tea, beer, wine, milk products, fruits, vegetables, and bread. The typical levels of furfural in foods and beverages range from 0.8 ppm (gelatins) to 45 ppm (chewing gum). Furfural is listed by the U.S. Food and Drug Administration (U.S. FDA, 2002) as an indirect food additive under 21 CFR 175.105, for use only as a component in adhesives where there is a functional barrier between the adhesive and the food. FEMA (The Flavor and Extract Manufacturers' Association) reviewed the available scientific data on furfural and has classified the compound generally recognized as safe (GRAS) for use as a flavor ingredient (Adams et al., 1997). The estimated daily intake of furfural naturally occurring in food is 0.3 mg/kg-day and an additional 8 µg/kg (16 µg/day) is added as a flavor ingredient (Adams et al., 1997; WHO, 2000a; WHO, 2000b).

Furfural has been detected in laboratory extractions at NSF as a component in coatings (NSF/ANSI 61, Section 5), as well as a contaminant from an adsorption process media (NSF/ANSI 61, Section 7). Detected concentrations have ranged from 15 µg/L when analyzed with an authentic standard by high performance liquid chromatography to approximately 200 µg/L when detected by gas chromatography/mass spectrometry.

5.2 Sources of Environmental Exposure

Furfural is a naturally occurring compound that is also produced commercially. The aldehyde has been detected as a component in the essential oils of several species of plants, including lavender, lemongrass, calamus, eucalyptus, and tobacco (HSDB, 2002). Furfural has been detected at a concentration of 2 µg/L in one of 204 surface water samples collected near heavily industrialized sites in the United States (HSDB, 2002).

The natural sources and commercial applications of furfural suggest that it may be released to the environment during its production or use in other commercial products. If released to soil in sufficient quantities, furfural is expected to be highly mobile, with significant potential for leaching into ground water (HSDB, 2002). While furfural is not likely to volatilize from contaminated soil, the compound may volatilize from water. The aldehyde is expected to undergo rapid aerobic and anaerobic microbial degradation in soil and water. Furfural is not expected to adsorb to sediment or organic matter and is not likely to bioaccumulate in aquatic organisms (HSDB, 2002).

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Furfural consists of a heteroaromatic furan ring with a reactive aldehyde functional group at the second position. In general, low molecular weight aldehydes like furfural undergo rapid

oxidation or condensation reactions associated with the aldehyde function, either in digestive fluids prior to absorption or in body fluids prior to entering the cell (Adams et al., 1997). If any aldehyde remains available to enter the cell, it would be subject to rapid oxidation and conjugation of the resulting carboxylic acid. Low molecular weight aldehydes have demonstrated the ability to form imine adducts with soluble proteins, protein components of cell membranes, and the amino groups of lower molecular weight amines, amino acids, proteins, and nucleic acids (Schauenstein et al., 1977; Adams et al., 1997).

Furfural is efficiently and rapidly absorbed and eliminated in humans and laboratory animals. Qualitatively, it appears that the pattern of metabolites is similar between species (Figure 1). Adams et al. (1997) reviewed the current understanding of the metabolic profile for furfural based on the work of Nomeir et al. (1992), Parkash and Caldwell (1994) and Flek and Sedevic (1978). Furfural is thought to be metabolized primarily by oxidation to furoic acid that, as the CoA thioester, is subsequently conjugated with glycine and either excreted or condensed with acetyl CoA to form 2-furanacryloyl CoA (Figure 1). 2-Furanacryloyl CoA is then believed to conjugate with glycine and is excreted primarily in the urine. In rats and mice, furoic acid is known to decarboxylate to yield carbon dioxide, presumably by oxidation of the furan ring. However, there is no evidence to suggest that oxidation of the furan ring occurs in humans as in rodents. The absorption, tissue distribution, extent of metabolism, relative amounts of metabolites, and rates of excretion in rodents were linear over the 0.1-200 mg/kg dose range examined to date (Nomeir et al., 1992; Parkash and Caldwell, 1994; Adams et al., 1997).

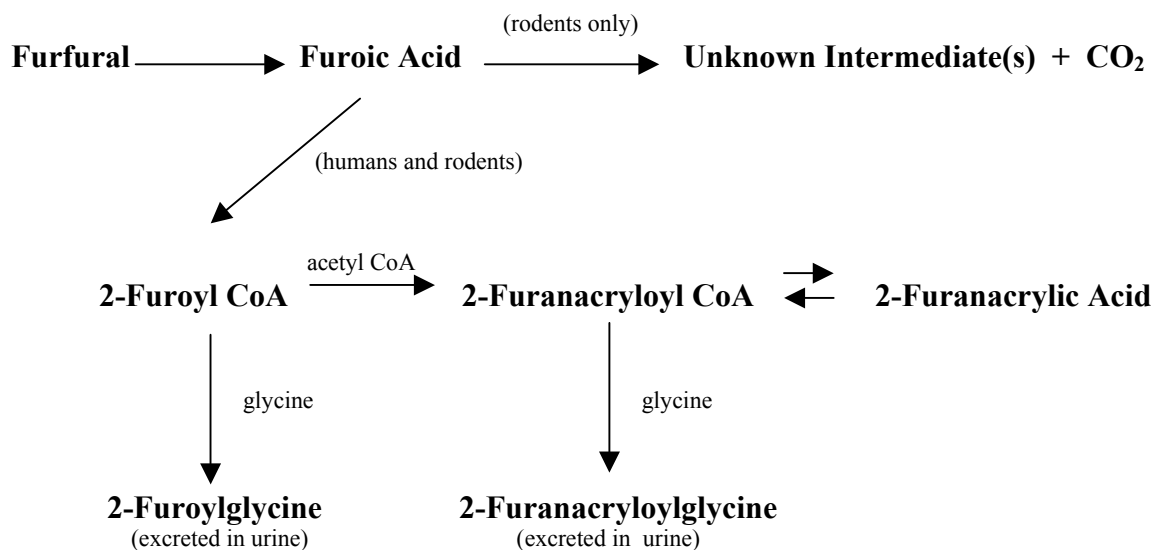


Figure 1. Metabolism of furfural (based on Adams et al., 1997)

6.1 Humans

Six human volunteers inhaled 30 mg/m³ (8.6 mg/kg-day) furfural for a single eight-hour exposure (Flek and Sedevic, 1978). Furfural was efficiently and rapidly absorbed through the lungs and skin of these individuals. The mean pulmonary retention was 77.9% and the biological half-life was approximately two hours. While 96.9% of absorbed furfural was

oxidized to 2-furoic acid and excreted as the glycine conjugate, only 0.5-5% was excreted as furanacrylic acid and less than 1% was exhaled unchanged. There was no evidence of decarboxylation observed at levels of exposure (~ 2 mg/kg) similar to those known to produce CO₂ in female mice (0.1 mg/kg) and in rats (12.5 mg/kg).

6.2 Laboratory Animals

Nomeir et al. (1992) examined the absorption, distribution, metabolism and excretion of furfural in the rat following oral exposure. Three groups of four male Fischer 344 rats received single oral doses of 0.127, 1.15, or 12.5 mg/kg [¹⁴C]furfural in corn oil by gastric intubation. An additional group of three rats received a single oral dose of 12.5 mg/kg [¹⁴C]furfural and was used for the collection of radiolabeled ¹⁴CO₂ in the expired air. All study animals were housed individually in metabolism cages and food and water were available *ad libitum*. Urine and feces were collected from the first six groups of animals at 0-4, 4-8, 8-24, and 48-72 hours following oral administration of furfural. Likewise, radiolabeled ¹⁴CO₂ was recovered from the expired air from the second group of animals after being passed through a series of charcoal and potassium hydroxide traps at 0-4, 4-8, 8-18, 18-25, and 25-42 hours after administration of furfural. Seventy-two hours after administration, all of the treated rats were anesthetized for blood sample recovery and subsequently sacrificed. Liver, kidney, heart, lung, brain, adipose tissue, skeletal muscle, spleen and thymus were removed from each of the high-dose furfural animals. Removal and examination of tissues at the two lower doses was performed in an apparent dose- and compound-related manner that was not documented by the authors. Each cage was thoroughly washed with water at sacrifice for recovery of residual radioactivity. Duplicate samples of the charcoal, feces, and excised tissues were analyzed for total radioactivity by oxygen combustion and subsequent liquid scintillation counting. Duplicate samples of urine, plasma and cage wash were evaluated directly for total radioactivity using a liquid scintillation counter. The urine samples from each of the low- and high-dose rats were further evaluated using high performance liquid chromatography with two different procedures for comparison of authentic standard retention times and those of the metabolites eluting from the urine samples. The authors also employed high performance liquid chromatography with a diode array detector, which allowed for an analysis of absorbance versus wavelength to further elucidate the identity of the major and minor urinary metabolites.

In a second evaluation, Parkash and Caldwell (1994) investigated the metabolism and excretion of radiolabeled furfural following oral administration to rats and mice. Groups of five male and five female Fischer 344 rats received single oral gavage doses of 1, 10, or 60 mg/kg [¹⁴C]furfural. Similarly, groups of five male and five female CD1 mice were given 1, 20, or 200 mg/kg [¹⁴C]furfural. Urine and feces samples were collected from each group of rats and mice at 24, 48 and 72 hours and all of the study animal carcasses were retained for determination of radiolabeled furfural. The presence of radiolabeled furfural in expired air was assessed in samples collected from two high-dose male and two low-dose female mice. Urine samples collected from the high dose rats and mice were pooled for isolation and identification of radiolabeled urinary metabolites.

6.2.1 Absorption

Nomeir et al. (1992) concluded that furfural was readily absorbed from the gastrointestinal tract of rats under the reported test conditions. The absorption and subsequent excretion of furfural appeared to be unaffected by dose. While Parkash and Caldwell (1994) did not investigate the absorption of furfural, the absorption of the compound is implied by the metabolism and excretion results provided by this study.

6.2.2 Distribution

Recovered radiolabeled furfural in examined tissues ranged from 0.36 nmol/g in the brain to 3.41 nmol/g in the liver 72 hours after administration of 12.5 mg/kg to rats (Nomeir et al., 1992). The highest concentrations of radioactivity were recovered from the liver, kidney, thymus, adipose tissue, lung, spleen and heart of the treated rats. The total radioactivity recovered from the excreta (urine and feces), cage rinse, and tissues was approximately 90% for each of the three exposure doses (Nomeir et al., 1992). However, inclusion of the radioactivity recovered in the expired air following high-dose furfural exposure (12.5 mg/kg) resulted in a total dose recovery of approximately 97% in the treated rats. Parkash and Caldwell (1994) did not comment on the distribution patterns of furfural following exposure in rats or mice.

6.2.3 Metabolism

Examination of the high performance liquid chromatography chromatograms produced from the recovered urine samples identified furoylglycine as the major metabolite and furanacrylic acid and furoic acid as minor metabolites of furfural following exposure in rats (Nomeir et al., 1992). Of the dose ranges studied, the extent and rate at which the urinary metabolites of furfural were excreted appeared to be unaffected by dose (Nomeir et al., 1992). The mean percentage of furoylglycine recovered from the urine samples following administration of furfural ranged from approximately 27-80% over the evaluated time points (Nomeir et al., 1992). The percentage of furoic acid recovered ranged from 0.2-1.2% and the percentage of furanacrylic acid recovered ranged from 2-4% (Nomeir et al., 1992).

Using high performance liquid chromatography, radio-high performance liquid chromatography, gas chromatography/mass spectrometry and ³H-nuclear magnetic resonance, Parkash and Caldwell (1994) determined that furoylglycine and furanacryloylglycine were the major urinary metabolites of furfural following oral administration of the highest dose in rats and mice. Furoic acid and furanacrylic acid were identified in both species as minor metabolites. However, the authors did not report the percentages of any of the metabolites recovered in either species. The authors concluded that the increased excretion of the free acids at the high dose level examined suggested that glycine conjugation may be limited by the supply of endogenous glycine. They continued by suggesting that equilibrium is likely to exist between the two excreted acids, most likely at the level of their CoA thioesters. The equilibrium appears to favor furoic acid, as indicated by the greater excretion of furoylglycine as compared with furanacryloylglycine.

6.2.4 Excretion

Following oral administration of furfural in rats, approximately 83-88% of the administered dose was excreted in the urine (Nomeir et al., 1992). The majority of the dose was excreted within the first 24 hours following administration and there was not a dose-related trend in the excretion patterns of furfural. Graphically, the half-life for urinary excretion was approximately four hours. Likewise, the percent of the compounds excreted in the feces (2-4%) was unaffected by dose over the range studied (Nomeir et al., 1992). Of those rats receiving 12.5 mg/kg furfural, approximately 7% of the administered dose was exhaled as $^{14}\text{CO}_2$ in the expired air within the first 42 hours, with the majority of the exhaled dose recovered within the first 24 hours (Nomeir et al., 1992).

For the first 72 hours after administration, Parkash and Caldwell (1994) reported that essentially all of the administered dose was recovered in the urine of the rats and mice. After 72 hours, fecal elimination constituted 3-7% of the administered dose, expired carbon dioxide represented approximately 5% of the dose (in mice) and less than 1% of the administered dose was recovered in the carcasses.

6.2.5 Conclusions Regarding Comparative Kinetics and Metabolism

IARC (1995) concluded that the metabolite pattern was qualitatively similar in rats following oral administration and in humans following inhalation exposure. However, deficiencies in reporting in the human study precluded quantitative comparison of the toxicokinetic profiles.

7.0 EFFECTS ON HUMANS

There were no case reports or epidemiological evaluations of furfural located in the literature. Likewise, no specific cases of overexposure resulting in chronic toxicity or death were available for review.

Occupational overexposure to furfural is unlikely because the compound is manufactured by semicontinuous or batch processes and very few workers are involved in its production (IARC, 1995). Complaints of headache, fatigue, itching of the throat, lacrimation, loss of sense of taste, numbness of the tongue and tremor following occupational exposure usually resolve rapidly after removal from exposure to furfural (Apol and Lucas, 1975).

8.0 EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

Furfural is an acutely irritating substance in laboratory animals and humans at sufficiently high concentrations. With oral LD_{50} values ranging from 50 mg/kg (rat) to 950 mg/kg (dog), furfural has relatively high acute toxic potential. Significant treatment-related lesions identified in both short- and long-term oral evaluations of furfural were limited to the livers and bile ducts of high-dose animals. Although the evaluations have been limited, furfural has shown no evidence of developmental toxicity potential at doses high enough to induce maternal toxicity. The available data suggest that furfural has weak genotoxic potential.

8.1 Limited Exposure Effects

8.1.1 Irritation and Sensitization Studies

Furfural is much less irritating to the eyes, skin and mucous membranes than formaldehyde or acrolein (Brabec, 1993). However, irritant dermatitis and cases of skin sensitization have been reported (unknown concentrations; Parmeggiani 1983). There have not been any cases of food allergies associated with furfural ingestion reported in the literature.

Workers repeatedly exposed to furfural vapor complained of headaches, fatigue, itching of the throat, lacrimation, loss of sense of taste, and numbness of the tongue (unreported concentrations). However, symptoms typically resolve rapidly after cessation of exposure (Sittig, 1985). ACGIH (1991) reported that occupational exposure to 0.007 to 0.053 mg furfural per liter of air (7-53 mg/m³) was sufficient to cause headaches, itching of the throat and reddening of the eyes.

8.1.2 Ocular Exposure Studies

A 10% aqueous solution of furfural applied directly to the eyes of rabbits resulted in immediate pain, with delayed complete anesthesia of the cornea and conjunctiva and reddening and swelling of the lids and conjunctiva (Grant, 1986). Twenty-four hours after application, the treated eyes appeared normal. Ocular exposure to 100% furfural resulted in immediate swelling of the corneal epithelium, followed by loss of layers of the epithelium, small hemorrhages in the nictitating membrane and continued edema. The authors did not indicate whether the animals recovered from high-dose exposure.

8.2 Single-Exposure Studies

Based on the available oral acute toxicology data, furfural appears to be most toxic to the rat followed by the mouse and finally the dog. Oral LD₅₀ values range from 50 mg/kg to 149 mg/kg in the rat (Jenner et al., 1964; Deichmann and Gerarde, 1969; Fassett, 1963). In the mouse, oral LD₅₀ values range from 250 mg/kg to 500 mg/kg (Fassett, 1963; NTP, 1990). Oral LD₅₀ values in the dog range from 650 mg/kg to 950 mg/kg (Deichmann and Gerarde, 1969; Fassett, 1963).

Thirty-two male SPF Wistar/Slc rats received a single gastric intubation of 50 mg/kg furfural. Eight rats were sacrificed 6, 12, 24 or 48 hours following administration (Shimizu and Kanisawa, 1986). Four control animals were sacrificed prior to the treatment period. At sacrifice, the livers were removed, weighed, fixed, sectioned, stained and examined histologically. Terminal body weights were recorded for each animal. There was no evidence of gross lesions in either the control or treated livers. While the lobular architecture and arrangement of the cell plates were normal, the hepatic cells in the treated livers presented with sporadic eosinophilic degeneration with nuclear pyknosis and eosinophilic necrosis forming eosinophilic globules resembling Councilman bodies. A significant increase in the number of mitotic hepatocytes was also observed throughout the treated lobules. Both lesions were observed most frequently in the animals sacrificed six hours after administration, but decreased in frequency by 12 and 24 hours. There was no evidence of fibrosis in any of the experimental animals. The authors noted the rapid appearance of liver damage following acute exposure to furfural, suggesting rapid

metabolism of the compound. The apparent recovery from the observed liver changes by 48 hours suggested to the study authors that the observed morphological changes would not remain for more than a few days after a single oral exposure.

Three groups of seven Wistar rats received single intraperitoneal doses of 0, 20 or 50 mg/kg furfural in 0.1 mL propylene glycol (Jonek et al, 1975). Six hours after administration, the animals were sacrificed and multiple sections of liver were recovered for analysis of succinate dehydrogenase, ATPase, DNase II, and acid phosphatase. Exposure to furfural was associated with a decrease in succinic dehydrogenase and ATPase activities and with an increase in activity of acid phosphatase and DNase II. Furfural-induced alterations in enzyme activities lead to disruption of energy production and distribution and to an increase in intracellular catabolism.

8.3 Short-term Exposure Studies

8.3.1 Oral

8.3.1.1 Rats

Groups of five male and five female Fischer 344/N rats were administered 0, 30, 60, 90, 120, or 180 mg/kg-day microencapsulated furfural in the diet for 14 days (Jonker, 2000 in WHO, 2000a). Control animals received the maltodextrin and mixed sugar encapsulation material in the diet. All study animals were observed daily for clinical manifestations of exposure, and body weight and food consumption measurements were recorded weekly. Clinical chemistry and urinalyses were performed on all study animals (specific parameters not identified by WHO). Necropsy was performed at 14 days and all acquired tissues (not specified) were examined histopathologically.

No treatment-related effects on outward appearance, behavior, body weight or food consumption were noted by the study authors. Non-significant increases in cholesterol and phospholipid concentrations were observed in the high dose males (120 and 180 mg/kg-day). Non-significant decreases in blood urea nitrogen and creatinine were reported in treated females, but these changes were not related to dose. A significant decrease in alanine aminotransferase in the high dose females (180 mg/kg-day) was accompanied by significant increases in absolute (11%) and relative (15%) liver weights of these animals. Based on these observations, the authors identified the 120 mg/kg-day dose as a NOEL.

Groups of five rats of each sex were administered 0, 15, 30, 60, 120, or 240 mg/kg furfural in corn oil by gavage, 5 days per week for 16 days (adjusted 0, 11, 21, 43, 86, 171 mg/kg-day; NTP, 1990). All of the animals were observed two times per day and were weighed on days 0 and 7, as well as at the end of the study. Necropsy was performed on all of the study animals.

Eight of the ten 171 mg/kg rats died by the third day following administration. One additional female rat death was the result of administration error. The final mean body weights of the rats that received 86 mg/kg or less were similar to those of the vehicle controls. Labored breathing was reported in animals that received 171 mg/kg and animals that received 86 mg/kg were slightly inactive. However, no compound-related lesions were described in any of the study animals at necropsy.

While limited details were reported in the available English abstract, Bong et al. (1979) reported that 50% of the oral LD₅₀ (50-100 mg/kg) administered orally to rats caused a 40% increase in liver tyrosine aminotransferase activity and a nearly 50% decrease in kidney levels of the same enzyme. A 10% LD₅₀ dose caused no change in the liver enzyme after 14 days, but levels of the enzymes remained reduced in the kidney (26%).

8.3.1.2 Mice

Groups of five mice of each sex were administered 0, 25, 50, 100, 200, or 400 mg/kg furfural in corn oil by gavage, 5 days per week for 16 days (adjusted 0, 18, 36, 71, 143, 286 mg/kg; NTP, 1990). All of the animals were observed two times per day and were weighed on days 0 and 7, as well as at the termination of the study. Necropsy was performed on all study animals.

One high-dose male (286 mg/kg-day) died prior to the completion of the study. The deaths of one 18 mg/kg female and one 143 mg/kg female were considered by the authors to be administration errors. The final mean body weights were not affected by furfural treatment and no compound-related lesions were noted at necropsy.

8.3.2 Inhalation

Groups of six male albino rats were exposed (whole body) to a single exposure of 95 ppm (373 mg/m³) furfural or 38 ppm (149 mg/m³) furfural, one hour per day, five days per week, for up to 30 days (Mishra et al., 1991). Control animals were exposed to compressed air only. At the end of the exposure periods, the lungs and liver were removed from the study animals, fixed, sectioned, and stained for histopathological examination. Samples of treated lung were homogenized and assessed for cellular constituents and enzymatic activities.

Furfural-treated animals presented with discolored fur (yellowed), eye and nose irritation, lacrimation, perinasal and perioral wetness, and respiratory difficulty. Alkaline phosphatase activity was elevated in the lungs of all treated rats. Glutamic pyruvic transaminase activity was increased significantly 2-4 weeks after exposure. A similar decrease in glutamic oxaloacetic transaminase activity was observed in the lungs of furfural-exposed animals up to 4 weeks after exposure. Total sulphhydryl and non-protein sulphhydryl contents of the exposed lungs were significantly decreased, particularly in those animals exposed for the longest durations. All animals that died during the exposure periods (numbers not specified) and those sacrificed 15 and 30 days following exposure to furfural had enlarged and congested lungs. Similar treatment-related responses were not observed in the acutely exposed animals. There were no observations of treatment-related lesions in any of the exposed animals, regardless of exposure duration. The authors concluded that inhalation exposure to furfural was associated with biochemical tissue responses in the form of mucus membrane irritation.