FURFURAL

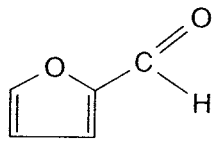
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 98-01-1
Chem. Abstr. Name: 2-Furancarboxaldehyde
IUPAC Systematic Name: 2-Furaldehyde
Synonyms: Artificial ant oil; 2-formylfuran; fural; furaldehyde; 2-furanaldehyde; 2-furancarbaldehyde; furancarbonal; 2-furancarbonal; 2-furfural; furfuraldehyde; 2-furfuraldehyde; furfurol; furfurole; furfurylaldehyde; furole; α-furole; 2-furylaldehyde; 2-furylcarboxaldehyde; pyromucic aldehyde

1.1.2 Structural and molecular formulae and relative molecular mass



$C_5H_4O_2$ Relative molecular mass: 96.09

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Clear, colourless oily liquid with a benzaldehyde-like odour (Budavari, 1989; United States National Toxicology Program, 1990)

(*b*) *Boiling-point*: 161.7 °C (Lide, 1993)

(*c*) *Melting-point*: –38.7 °C (Lide, 1993)

(*d*) *Density*: 1.1594 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [113]; grating [35]), ultraviolet [42], nuclear magnetic resonance (proton [10203]; C-13 [1618]) and mass [200] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Moderately soluble in water (83 g/L at 20 °C); soluble in acetone, benzene, chloroform, diethyl ether and ethanol (Verschueren, 1983; Lide, 1993)

(*g*) *Volatility*: Vapour pressure, 1 mm Hg [0.13 kPa] at 20 °C; relative vapour density (air = 1), 3.31 (Verschueren, 1983)

(*h*) *Stability*: Turns yellow to brown on exposure to air and light (Budavari, 1989)

(*i*) *Reactivity*: Vapour forms inflammable mixture with air; reacts with oxidizing materials, strong alkalis and strong acids (Sittig, 1985; Sax & Lewis, 1989; United States National Institute for Occupational Safety and Health, 1994a)

(*j*) *Octanol/water partition coefficient (P)*: log (P), 0.41 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 3.93 \times ppm$[1]

1.1.4 Technical products and impurities

Furfural is available commercially at a purity > 98% (Aldrich Chemical Co., 1994; Lancaster Synthesis Ltd, 1994; TCI America, 1994).

1.1.5 Analysis

Selected methods for the analysis of furfural in various matrices are presented in Table 1.

Table 1. Methods for the analysis of furfural

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on sorbent coated with 2-(hydroxymethyl)piperidine on XAD-2; desorb with toluene; analyse for oxazolidine derivative	GC/FID	5 µg/sample	Eller (1994)
		GC/FID & GC/MS	2 µg/sample	Eller (1994)
	Adsorb on petroleum-based charcoal; desorb with carbon disulfide containing 1% dimethylformamide; remove water with magnesium sulfate	GC/FID	29.9 µg/sample (166 µg/m^3)	US Occupational Safety and Health Administration (1990)
	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	About 25 ppb [98 µg/m^3]	Feldstein *et al.* (1989)
Urine	Treat urine with sodium hydroxide, acidify, extract with ethyl acetate; esterify (furoic acid) with diazomethane	GC/FID	NR	Šedivec & Flek (1978)
Distilled liquors	Steam distil; measure at 277 nm; compare with standard curve	UV	NR	Helrich (1990)

GC/FID, gas chromatography/flame ionization detection; MS, mass spectrometry; UV, ultraviolet spectrophotometry; NR, not reported

A method for identifying carbonyl compounds, including furfural, in environmental samples involves derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydro-

[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

chloride, followed by gas chromatography (GC)–mass spectrometry (Le Lacheur *et al.*, 1993). A similar method was used for the quantitative analysis of carbonyl compounds in cognac at a level of parts per billion (10^{-9}) (Vidal *et al.*, 1993).

Traces of hydrophilic and volatile organic compounds, including furfural, can be determined in water after preconcentration with activated carbon. Organic substances adsorbed on the activated carbon are eluted with acetone and dichloromethane, and quantitative analysis is carried out by GC–mass spectrometry (Kadokami *et al.*, 1990). In a method for determining picomolar concentrations of carbonyl compounds, including furfural, in natural waters such as seawater, the samples were derivatized with 2,4-dinitrophenylhydrazine and analysed by liquid chromatography. The detection limit for aldehydes after direct injection of derivatized water samples was 0.5 nmol [48 ng] (Kieber & Mopper, 1990).

Several methods have been described for the determination of furfural in processed citrus juices (orange, grapefruit, apple), including high-performance liquid chromatography (HPLC) of the 2,4-dinitrophenylhydrazine derivative; solid–liquid extraction of the juice before reversed-phase separation, followed by HPLC, with detection at 280 nm; micellar electrokinetic capillary chromatography after direct sample injection, with sodium dodecyl sulfate as the anionic surfactant; and colorimetry (Dinsmore & Nagy, 1974; Marcy & Rouseff, 1984; Lee *et al.*, 1986; Beeman, 1987; Li *et al.*, 1988; Blanco Gomis *et al.*, 1991; Corradini & Corradini, 1992; Lo Coco *et al.*, 1994).

Furfural was determined in commercial, aged brandies and in aqueous alcohol solutions of caramels by direct injection of the samples and HPLC (Villalón Mir *et al.*, 1992). A complexometric method has also been used to determine furfural in cognacs and cognac brandies (Maltabar & Girenko, 1969; Girenko *et al.*, 1970).

Dissolved gases and furan-related compounds, including furfural, were determined in transformer insulating oils by static headspace capillary GC with porous-layer open tubular columns. The detection limit for furfural was 0.5 ppm [mg/L] (Leblanc *et al.*, 1993). A reversed-phase liquid chromatographic method was developed for determining furfural in lubricating oils. After a simple extraction step to remove interfering hydrocarbons, residual furfural was determined with an ultraviolet detector (DiSanzo *et al.*, 1988).

The furan components, including furfural, in the aqueous condensate from wood smoke were extracted with dichloromethane, and the extract was analysed by GC–mass spectrometry (Edye & Richards, 1991).

A fluorimetric method has been described for the determination of aromatic aldehydes, including furfural, based on their reaction in dilute acid with 4,5-dimethoxy-1,2-diaminobenzene, to give a compound that fluoresces in alkaline solution (Nakamura *et al.*, 1982). A similar method is based on the reaction of furfural in dilute sulfuric acid with 2,2′-dithiobis(1-aminonaphthalene) in the presence of tri-*n*-butyl phosphine, sodium sulfite and sodium phosphite (Ohkura *et al.*, 1978).

Biological monitoring is best done by determining the total concentration of furoic acid in urine taken after an entire work shift and expressed in milligrams per unit of time (Šedivec & Flek, 1978; Dutch Expert Committee on Occupational Standards, 1992).

1.2 Production and use

1.2.1 Production

Furfural has been produced since 1832 from renewable agricultural sources, such as non-food residues of food crops and wood wastes (Hitchcock, & Duffey, 1948). The pentosan polysaccharides of these vegetable materials (xylan and arabinan) are almost as widely distributed in nature as is cellulose and are the major precursors of furfural. All pentosan-containing substances are potentially usable, but only a relatively few (corn cobs, oat hulls and bagasse), which are available in large tonnages within a limited radius of furfural production facilities, are commercially significant. Furfural is produced commercially in batch or continuous digesters, in which the pentosans are hydrolysed with strong inorganic acids to pentoses and the pentoses are subsequently cyclodehydrated to furfural (McKillip & Sherman, 1980). Furfural is also produced by continuous hydrolysis of bark at 190 °C and 12 atmospheres [1012 kPa], with acetic acid as a catalyst (Dutch Expert Committee on Occupational Standards, 1992).

Worldwide consumption of furfural was estimated to have been 91 thousand tonnes in 1965, 136 thousand tonnes in 1973 and 159 thousand tonnes in 1978 (McKillip & Sherman, 1980). It is produced by 31 companies in 15 countries (Chemical Information Services, Inc., 1994), with eight producers in China and six in the Russian Federation. In the United States of America, 45–57 thousand tonnes were used annually between 1965 and 1989 (Mannsville Chemical Products Corp., 1984).

1.2.2 Use

Large quantities of furfural are used in solvent extraction in the petroleum refining industry. It is also used as a solvent (for nitrated cotton, cellulose acetate and gums), to accelerate vulcanization, as an ingredient of phenolic resins (Durite), as an intermediate in the synthesis of furan derivatives, as a weed killer, as a fungicide and as a flavouring agent (McKillip & Sherman, 1980; Budavari, 1989). In the Netherlands, furfural is used as a component of a diesel fuel colourant at 50 g/L (Dutch Expert Committee on Occupational Standards, 1992).

1.3 Occurrence

1.3.1 Natural occurrence

Furfural is a volatile component of a wide range of fruits and vegetables (Dutch Expert Committee on Occupational Standards, 1992).

1.3.2 Occupational exposure

In the National Occupational Exposure Survey conducted between 1981 and 1983 it was estimated that 135 914 workers were potentially exposed to furfural in 6447 plants in the United States (United States National Institute for Occupational Safety and Health, 1994b). The estimate is based on a survey of companies and did not involve measurements of actual exposures. In the Harvard job–exposure matrix (Hoar *et al.*, 1980), potential exposure to furfural

was linked to work in several industries, including construction, metal, food, tobacco, textiles, chemicals, drugs, paints, rubber, plastics, paints and leather, and to several jobs in agriculture, medicine, science, art and even to work as a homemaker or chambermaid.

Furfural production is either semicontinuous or batch, and few workers are involved in either case (Mutchler & Proskie, 1982). The main steps in the production of furfural are: unloading and storage of raw materials; mixing and feeding raw materials to a reactor; digestion, reaction, steam distillation and emptying the reactor; finishing by condensation, stripping, separation and distillation and storage and loading. Exposure to furfural may occur at the end of the reaction stage in the batch operation, and furfural vapours can escape into the workroom when the reactors are emptied of residue. Intermittent exposure to furfural can occur if the seals of the reaction vessel lose their integrity, especially in the packing glands and the mechanical shaft seals of rotating, pressurized equipment.

The warm, damp residue from the reactor passes through a hopper and, depending on the workplace configuration, vapour and gases may be carried by convection into the workplace. The part of the process in which the furfural produced during the reaction phase is recovered, enriched and refined is totally enclosed and includes several condensate-level tanks, decanters, stripping columns and final distillation. Exposure to furfural during this stage of the production process is unlikely. Storage and shipping of furfural takes place in a pump house, drum-filling stations and railcar or truck-loading facilities. In all of these operations, exposure to furfural is incidental and usually occurs only if there is a significant spill, leak or equipment malfunction. The pump station and drum-filling operations may have local exhaust ventilation. Transfers during storage and shipping usually take place out-of-doors or in semi-enclosed spaces where there is also natural ventilation (Mutchler & Proskie, 1982).

In two reports in which worker response was related to measured air concentrations, a time-weighted threshold limit value of 5 ppm [19.7 mg/m^3] was determined on the basis of 'comfort'. A study in a grinding-wheel plant showed a widespread incidence of eye and respiratory tract irritation, which was attributed to furfural vapours, found at concentrations of 5–16 ppm [19.7–62.9 mg/m^3] (American Conference of Governmental Industrial Hygienists, 1983). A study in a refinery yielded an 8–10-h time-weighted average exposure of 1.9 mg/m^3 (range, 1.2–2.6 mg/m^3) over six samples (Herwin & Froneberg, 1982). Four samples from selected work areas in a plant where furfural was produced by wood hydrolysis contained 4–16 mg/m^3 (Troshina *et al.*, 1986).

In a plant for the manufacture of arc carbon electrodes and dry-cell electrodes in India, furfural was used as a solvent for a phenol–formaldehyde resin, and the resulting mass was used as a binder with petroleum coke. The concentrations of furfural in air were 11–70 mg/m^3 (Ghose, 1991).

The exposure of California wildland firefighters was assessed during three consecutive fire seasons (1986–89). The mean time-weighted average personal exposure to furfural was 0.13 mg/m^3 (25 observations) and ranged from undetectable to 0.23 mg/m^3. Furfural was found in 83% of the samples taken (Materna *et al.*, 1992).

Environmental monitoring was conducted at 17 locations in Italy in the section of a chemical plant in which furfural was extracted from wood. At four locations, the threshold limit value of 8 mg/m^3 was exceeded. Twelve employees were investigated for the presence of furoic acid (expressed in mg/g creatinine) in urine, while 18 'blue collar' workers at a paper mill were

used as matched controls. Urine was collected during the same 8-h period on two occasions: one at work and the other at home. The mean concentration of furoic acid in the urine of the blue-collar workers was significantly higher (27.1 ± 16.6 mg/g creatinine) than that in urine taken at home from workers exposed to furfural (21.4 ± 15.6 mg/g creatinine) ($p < 0.01$) but significantly lower than that in urine of furfural-exposed workers taken at work (34.5 ± 13.3 mg/g creatinine) ($p < 0.0001$) (Di Pede *et al.*, 1991).

1.3.3 Air

Furfural was measured at a concentration of 0.19 μg/m^3 at the foot of Mount Everest in Nepal (Ciccioli et al., 1993). It was identified as one of the main components of smoke condensates of pine and cottonwood (Edye & Richards, 1991). It was also a major constituent of glowing fires of conifer logs (Mallory & Van Meter, 1976). Residential burning of brown-coal briquets led to emission of furfural, at an emission factor of 1.63 mg/kg. The estimated total amount of furfural emitted in the city of Leipzig was 530 kg/year (Engewald *et al.*, 1993).

Aldehydes were measured both indoors and outdoors for six days at six houses in suburban New Jersey (United States) during the summer of 1992 under controlled conditions of ventilation and gas combustion. The mean concentration of furfural was 0.27 ppb [1.06 μg/m^3] in 36 samples taken indoors and 0.17 ppb [0.67 μg/m^3] in 36 samples taken outdoors. The presence of furfural indoors may be due to emissions during cooking (Zhang *et al.*, 1994).

Furfural was detected in two of five houses that had been damaged by fire and refurbished, at concentrations of 0.02 and 0.23 ppb [0.08 and 0.90 μg/m^3] (Tsuchiya, 1992).

1.3.4 Water

Information on actual concentrations in water is very limited. Low levels of furfural (up to 30 mg/L) were reported in wastewater from a furfural production plant; however, derivatives of furfural occurred at concentrations up to 300 mg/L (Dodolina *et al.*, 1977).

1.3.5 Food

Furfural has been identified in 150 foods, including fruits, vegetables, beverages, bread and bread products. The highest reported concentrations were found in wheat bread (0.8–14 ppm) [mg/kg], cognac (0.6–33 ppm), rum (22 ppm), malt whisky (10–37 ppm), port wine (2–34 ppm) and coffee (55–255 ppm). The concentrations of furfural in juices were 0.01–4.93 ppm. Furfural is formed during the reaction of amino acids with sugars at 100 °C for 4 h (Dutch Expert Committee on Occupational Standards, 1992). The occurrence of furfural in stored citrus products is recognized as an indication of deterioration; the concentrations in grapefruit juice samples stored at ambient temperature for over one year were 2.1–9.0 ppm (Lee *et al.*, 1986).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for furfural in a number of countries are given in Table 2.

Table 2. Occupational exposure limits and guidelines for furfural

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1991	8	TWA; skin notation
Belgium	1991	7.9	TWA; skin notation
Denmark	1991	20	TWA; skin notation
Finland	1993	20	TWA; skin notation
		40	STEL
France	1991	8	STEL
Germany	1993	20	TWA; skin notation
Japan	1991	9.8	TWA; skin notation
Netherlands	1994	8	TWA
Poland	1991	10	TWA
Russian Federation	1991	10	STEL; skin notation
Sweden	1991	20	TWA; skin notation
		40	STEL
Switzerland	1991	8	TWA; skin notation
United Kingdom	1993	8	TWA; skin notation
		40	STEL; skin notation
USA			
ACGIH	1994	7.9	TWA; skin notation
OSHA	1994	20	TWA; skin notation

From ILO (1991); Dutch Expert Committee on Occupational Standards (1992); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); United Kingdom Health and Safety Executive (1993); Arbeidsinspectie (1994); United States Occupational Safety and Health Administration (1994)
TWA, time-weighted average; STEL, short-term exposure limit

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F1 mice, aged nine weeks, were administered 0, 50, 100 or 175 mg/kg bw furfural (purity, 99%) dissolved in corn oil by gavage on five days a week for 103 weeks. Survival at the end of the study was 35/50 male controls, 28/50 at the low dose, 24/50 at the middle dose and 27/50 at the high dose; and 33/50 female controls, 28/50 at the low dose, 29/50 at the middle dose and 32/50 at the high dose. There was a dose-related increase in the incidence of chronic inflammation of the liver. In males, the incidences of hepatocellular adenomas were 9/50 controls, 13/50 at the low dose, 11/49 at the middle dose and 19/50 at the high dose ($p = 0.008$, logistic regression analysis); the incidences of hepatocellular carcinoma were 7/50 controls, 12/50 at the low dose, 6/49 at the middle dose and 21/50 at the high dose ($p = 0.001$). Female mice also had a higher incidence of hepatocellular adenomas, with 1/50 in controls, 3/50 at the low dose, 5/50 at the middle dose and 8/50 at the high dose ($p = 0.017$); the incidences of hepatocellular carcinoma (4/50, 0/50, 2/50, 4/50) were not increased. The combined incidences of hepatocellular adenomas and carcinomas were: 16/50 male controls, 22/50 at the low dose, 17/49 at the middle dose and 32/50 at the high dose ($p < 0.001$); and 5/50 female controls, 3/50 at the low dose, 7/50 at the middle dose and 12/50 at the high dose ($p = 0.051$). There was a marginal increase in the incidence of forestomach papillomas in females at the high dose: 6/50 in comparison with 1/50 in controls ($p = 0.058$) (United States National Toxicology Program, 1990).

3.1.2 Rat

Groups of 50 male and 50 female Fischer 344 rats, seven to eight weeks of age, were administered 0, 30 or 60 mg/kg bw furfural (purity, 99%) dissolved in corn oil by gavage on five days per week for 103 weeks. Survival at the end of the study was: 31/50 male controls, 28/50 at the low dose and 24/50 at the high dose; and 28/50 female controls, 32/50 at the low dose and 18/50 at the high dose (not significant). A dose-related increase in the frequency of centrilobular necrosis of the liver was seen in males: 3/50 controls, 9/50 at the low dose and 12/50 at the high dose. Two of 50 males given the high dose had bile-duct dysplasia, and two had rarely occurring cholangiocarcinomas. No such lesions were found in the other groups of males or among female rats. There were no other treatment-related lesions in the liver or other organs. The historical incidence of cholangiocarcinoma in control rats at the testing laboratory was 1/449 (United States National Toxicology Program, 1990).

In a study of enzyme-altered foci in the liver, six groups of six male Wistar rats, five weeks of age, were administered furfural [purity unspecified] in the diet at a concentration of 20 ml/kg of diet for 15–30 days and then at 30 ml/kg of diet for up to 150 days. The exposure of the six groups ceased on days 15, 30, 60, 90, 120 and 150, respectively. Six groups of four male controls were available. The rats were sacrificed 15 days after the end of exposure. Fibrosis was seen in the liver after 30 days of treatment and progressed with the length of exposure, resulting in pseudolobule formation after 150 days of treatment. Foci positive for glutathione *S*-transferase

placental form were seen in 4/6 rats after 30 days of treatment and in 6/6 after 150 days. No such foci were seen in the controls. No cancers or neoplastic nodules occurred in any of the groups (Shimizu *et al.*, 1989).

3.2 Skin application

Mouse: Groups of 20 female CD-1 mice, seven weeks of age, received topical applications of 50 μmol [4.8 mg] furfural ('special grade') dissolved in 0.1 ml dimethyl sulfoxide on the back twice a week for five weeks. One week after the last treatment, the mice were treated twice a week with 2.5 μg of the promoter 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in 0.1 ml acetone for 47 weeks. One control group was treated with furfural and acetone, a second with dimethyl sulfoxide (vehicle control) and TPA, a third with dimethyl sulfoxide and acetone and a fourth with a total dose of 100 μg 7,12-dimethylbenz[*a*]anthracene (DMBA) and TPA (positive control). Five of 19 mice given furfural and TPA developed seven skin papillomas and one squamous-cell cancer, whereas only one of 20 mice given DMSO and TPA had a papilloma [$p = 0.08$, Fisher's exact test]. None of the other negative controls developed tumours, but all 20 mice in the positive control group developed skin tumours (Miyakawa *et al.*, 1991).

3.3 Administration with known carcinogens

Hamster: The co-carcinogenic effect of furfural and the known carcinogens benzo[*a*]pyrene and *N*-nitrosodiethylamine on the respiratory tract of hamsters was studied in two experiments. In one study, long-term exposure to furfural vapour and repeated intratracheal instillations of benzo[*a*]pyrene or *N*-nitrosodiethylamine did not significantly affect the tumour incidence in hamster respiratory tissues (Feron & Kruysse, 1978). In the other study, repeated, simultaneous intratracheal instillations of furfural and benzo[*a*]pyrene solutions had a slight co-carcinogenic effect in the respiratory tract (Feron, 1972).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

Pulmonary uptake and exhalation and urinary excretion of furfural were studied in six healthy male volunteers, aged 30–55 years, exposed by inhalation in a laboratory measuring $5.4 \times 3.4 \times 3.5$ m [64 m^3], where the concentration of furfural in the atmosphere was kept constant by automatically controlled dispersion, within an accuracy of ± 5% at preselected levels of approximately 7–30 mg/m^3. [Data were presented for concentrations of 15, 20 and 31 mg/m^3.] The total duration of exposure was 8 h, interrupted by two 5-min breaks after the second and sixth hour and by one 20-min break in the middle of the experiment, to give an actual exposure of 7.5 h. Two to four individuals were exposed simultaneously and were seated throughout the

exposure. An average of 78% of the furfural was absorbed; the rate was not related to the level or duration of exposure. Only a small proportion of free furfural (< 1%) was excreted by the lungs [exhalation of carbon dioxide was not determined], and none was found in urine. The biological half-life of furfural was 2–2.5 h. Free furoic acid occurred in only negligible amounts in the urine, and a conjugated form of furoic acid [presumably furoylglycine] appeared to be the major urinary metabolite. The recovery of 'total furoic acid' (free furoic acid measured after alkaline hydrolysis of urine samples) indicated that the volunteers had also been exposed dermally. In experiments in which furfural was inhaled directly, through a mask, thus avoiding dermal absorption, 93–103% of a dose of 30 mg/m^3 was recovered as 'total furoic acid'. 'Total furanacrylic acid', measured as free furanacrylic acid after hydrolysis of urine samples, amounted to only 0.5–5% of the inhaled dose of furfural. When the volunteers were exposed dermally to furfural while breathing pure air, there was considerable but variable absorption. After volunteers submerged their hands up to the wrist in a vessel containing liquid furfural for 15 min, the total amount of 'total furoic acid' excreted indicated that about 27 mg furfural had been absorbed through the hand surface. Recalculation of this amount indicated that 1 cm^2 skin absorbed approximately 3 μg furfural per min (Flek & Šedivec, 1978).

4.1.2 Experimental systems

After [carbonyl-^{14}C]furfural (specific activity, 4.1 mCi/mmol; radiochemical purity, 95%) was administered by gavage to male Fischer 344 rats at single doses of 0.127, 1.15 or 12.5 mg/kg bw in corn oil, 86–89% of the dose was absorbed, and more than 60% was excreted after 12 h, reaching a plateau after 24 h. After 72 h, high concentrations of radiolabel were found in liver and kidney; brain had the lowest concentration. The concentrations in liver and kidney were approximately proportional to the dose. The major route of excretion was urine, which contained 83–88% of the dose; about 7% of a dose of 12.5 mg/kg bw was exhaled as ^{14}C-carbon dioxide, and 2–4% of the dose was detected in the faeces. Furoylglycine was the major urinary metabolite (73–80% of dose), and furanacrylic acid (3–8%) and furoic acid (1–6%) were minor metabolites. The extent and rate of excretion of furfural metabolites were unaffected by dose. Furoic acid is an oxidation product of furfural, which may be excreted unchanged or conjugated with glycine. Furanacrylic acid is presumably formed *via* condensation with acetyl coenzyme A (Nomeir *et al.*, 1992).

[Carbonyl-^{14}C]furfural (specific activity, 135.75 μCi/mg; radiochemical purity, 98.1%) was administered by gavage to male and female Fischer 344 rats at single doses of 1, 10 or 60 mg/kg bw and to male and female CD1 mice at single doses of 1, 20 or 200 mg/kg bw in trioctanoin. More than 90% of the dose was recovered in all animals after 72 h. The main route of elimination was the urine, and more than 60% of the dose was eliminated by this route within the first 24 h. Within 72 h, faecal elimination comprised 3–7% of the dose, and mice expired 5% of the radiolabel; the carcasses of both species contained < 1% of the dose by that time. Furoylglycine was the major urinary metabolite in both species: urine collected at 0–24 h contained 76–84% (rats) and 65–89% (mice) of this metabolite. Furanacryloylglycine was the second most abundant metabolite, constituting 15–24% of the radiolabel in 0–24-h urine of rats and 11–35% of that of mice. Only subtle differences in the metabolic profile were seen as a

function of dose, sex and species. The parent acids of the glycine conjugates were excreted at the higher doses (Parkash & Caldwell, 1994).

4.1.3 Comparison of humans and animals

Furfural is extensively absorbed and rapidly eliminated in humans after inhalation and in rats after oral administration. The pattern of metabolites appears to be qualitatively similar, involving oxidation of furfural to furanoic acid with subsequent conjugation, primarily with glycine. Because of limitations in the reporting of the study of humans (Flek & Šedivec, 1978), a closer, quantitative comparison of the toxicokinetic profiles of humans and rats is not possible.

4.2 Toxic effects

4.2.1 Humans

In a review, the main effect of furfural in humans was reported to be skin and mucous membrane irritation. Irritant dermatitis has in some cases led to eczema, and there have been reports of allergic skin sensitization and photosensitization (Mishra, 1992).

4.2.2 Experimental systems

In a short-term study, groups of six adult male albino rats [strain not specified] were exposed by inhalation to furfural [purity not specified] at 95 ppm [370 mg/mg^3] in a single exposure or at 38 ppm [150 mg/m^3] for 1 h daily on five days per week over 7, 15 or 30 days. Six rats served as controls. The single exposure resulted in moderate congestion and perivascuscular oedema in the lungs; these changes were more pronounced after repeated exposure. Alkaline phosphatase activity in the lung was substantially increased at all times, whereas lung glutamic pyruvic transaminase activity was increased after 15 and 30 days. Furfural was also reported to induce liver necrosis and to increase the activities of hepatic alkaline phosphatase, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase [details not given] (Mishra *et al.*, 1991).

In a short-term study, six adult male albino rats [strain not specified] were exposed to 40 ppm [155 mg/m^3] furfural (purity, 99%) for 1 h per day on five days per week for 7, 15 or 30 days. Six rats served as controls. Exposure to furfural increased the activities of acid and alkaline phosphatases and glutamic pyruvic transaminase, inhibited the activities of arginine and succinic dehydrogenases and increased the concentration of lactic acid in lung homogenates. [The Working Group noted that histopatological examination was not performed.] The exposure regimen was not lethal, whereas separate experiments determined an LC_{50} value of 189 ppm [735 mg/m^3] after a single exposure (Gupta *et al.*, 1991).

Groups of 10 male and 10 female Fischer 344/N rats were administered 0, 11, 22, 45, 90 or 180 mg/kg bw furfural (purity, 99%) in corn oil by gavage on five days per week for 13 weeks, and groups of 10 male and 10 female B6C3F1 mice were administered 0, 75, 150, 300, 600 or 1200 mg/kg bw on the same schedule. The incidence of cytoplasmic vacuolization in hepatocytes was increased in male rats. Severe, dose-dependent centrilobular coagulative necrosis of

hepatocytes, leading to death, was seen in mice at the high dose (United States National Toxicology Program, 1990).

In a 90–120-day study, furfural [purity not specified] was administered in the diet of four male Wistar/Slc rats at concentrations of 20 ml/kg [23 mg/kg] of diet for the first seven days, 30 ml/kg [35 mg/kg] for the next seven days and 40 ml/kg [46 mg/kg] from day 15 to day 90; from day 91 to day 120, rats were given repeated cycles of two days on basal diet and five days on 40 ml/kg [46 mg/kg] furfural [doses not calculated]. Four controls were available. Hepatic cirrhosis was seen in treated animals, and the fibrotic changes were more prominent in animals killed at 120 days than in those killed after 90 days. Massive liver necrosis was not observed after administration of a single dose of 50 mg/kg bw by gavage (Shimizu & Kanisawa, 1986).

Groups of 18 male and 18 female Syrian golden hamsters were exposed to distilled furfural at concentrations of 400 ppm [1550 mg/m^3] for 7 h per day on five days per week during the first nine weeks, 300 ppm [1280 mg/m^3] during weeks 10–20 and 250 ppm [970 mg/m^3] during weeks 21–52; 18 animals of each sex were exposed to air only. Severe damage of the olfactory epithelium of the nasal cavity was seen, with nearly complete atrophy of the sensory cells in the olfactory mucosa, large cyst-like, glandular structures in the lamina propria beneath the olfactory epithelium and karyo- and cytomegaly of Bowman's glands. There was neither evidence of recovery of the nasal changes after a period of six months nor any progression of the lesions. No changes in other parts of the respiratory tract or outside the airway system were seen that could be ascribed to treatment (Feron & Kruysse, 1978; Feron *et al.*, 1979).

Exposure of adult male albino rats [strain not specified] to 40 ppm [155 mg/m^3] furfural for 1 h daily, five days per week, for 7, 15 or 30 days led to increases in the activities of aminopyrine *N*-demethylase, aniline hydroxylase and glutathione *S*-transferase (1-chloro-2,4-dinitrobenzene as substrate) in the 9000 × *g* supernatant of lung, whereas benzo[*a*]pyrene hydroxylase activity was decreased (Gupta *et al.*, 1991).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 Humans

Six workers exposed to furfural and furfuryl alcohol in a furoic resin plant showed no significant difference in sister chromatid exchange frequency in peripheral blood lymphocytes in comparison with six control individuals (Gomez-Arroyo & Souza, 1985). [The Working Group noted the small number of individuals studied and the presence of both smokers and non-smokers; moreover, the furfural concentrations in the atmosphere of the plant were not reported.]

4.4.2 Experimental systems (see also Table 3 and Appendices 1 and 2)

Furfural reacts with DNA *in vitro*, primarily at AT base pairs, leading to destabilization of the secondary structure of DNA and to single-strand breaks.

Table 3. Genetic and related effects of furfural

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***, Destabilization of DNA secondary structure *in vitro*	+		1:2	Uddin (1993)
***, DNA strand breaks, calf thymus DNA *in vitro*	+		1:4	Uddin *et al.* (1991)
***, DNA strand breaks, calf thymus DNA *in vitro*	+		1:1	Hadi *et al.* (1989)
PRB, SOS repair, *Salmonella typhimurium umu*	–	–	1932	Nakamura *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2200	Zdzienicka *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2100	Loquet *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1280	US National Toxicology Program (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.00	Dillon *et al.* (1992) (Abstract)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	0.00	Dillon *et al.* (1992) (Abstract)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	–	0.00	Dillon *et al.* (1992) (Abstract)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1800	Loquet *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1280	US National Toxicology Program (1990)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1280	US National Toxicology Program (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	4400	Zdzienicka *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1800	Loquet *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1280	US National Toxicology Program (1990)
DMX, *Drosophila melanogaster,* sex-linked recessive lethal mutation	–		1000 feed	Woodruff *et al.* (1985)
DMX, *Drosophila melanogaster,* sex-linked recessive lethal mutation	+		100 inj	Woodruff *et al.* (1985)
DMH, *Drosophila melanogaster,* heritable translocation	–		100 inj	Woodruff *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	0	200	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	12	US National Toxicology Program (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	+	240	Stich *et al.* (1981)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	+	400	US National Toxicology Program (1990)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	0	1000	Nishi *et al.* (1989)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	7	Gomez-Arroyo & Souza (1985)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	–		200.0 ip × 1	US National Toxicology Program (1990)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		200.0 ip × 1	US National Toxicology Program (1990)

[a] +, considered to be positive; –, considered to be negative; 0, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; *in vitro* tests, μg/ml; *in vivo* tests, mg/kg bw; 0.00, dose not reported; ip, intraperitoneally

***, Not included on the profile

Furfural did not induce *umu c'* gene expression, a function related to SOS DNA repair, in *Salmonella typhimurium* TA1535/pSK1002. It was reported to be mutagenic to *S. typhimurium* TA100 in the presence and absence of metabolic activation in one study, but this result was not confirmed in three subsequent studies, which gave equivocal or negative results. Furfural was also reported to be nonmutagenic in *S. typhimurium* strains G46, TA100, TA1535, C3076, TA1537, D3052, TA1538 and TA98 and in *Escherichia coli* strains WP2 and WP2 *uvr*A with a concentration gradient protocol (MacMahon *et al.*, 1979).

Injection, but not feeding, of furfural to adult flies *Drosophila melanogaster* induced sex-linked recessive lethal mutation. Furfural did not induce heritable reciprocal translocations in *D. melanogaster.*

Furfural induced gene mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells in the absence of metabolic activation. It induced sister chromatid exchange in Chinese hamster ovary cells and human lymphocytes and chromosomal aberrations in Chinese hamster ovary and V79 lung cells in the absence of metabolic activation.

The frequencies of sister chromatid exchange and chromosomal aberrations were not increased in the bone-marrow cells of B6C3F1 male mice injected intraperitoneally with single doses of furfural up to 200 mg/kg bw.

Mutation of proto-oncogenes in tumours induced by furfural

ras Proto-oncogene activation was studied in liver adenomas and carcinomas of B6C3F1 mice treated with furfural. The frequency of activated H-*ras* and K-*ras* oncogenes in hepatocellular tumours was no different in furfural-treated (10/16) and vehicle-treated (15/27) mice; however, the spectrum of activating mutations in the H-*ras* gene in tumours from the furfural-treated mice differed significantly from that in tumours of untreated animals. Mutations at codon 61 occurred in tumours from both furfural-treated and untreated animals, but mutations (G→T and G→C transversions) were observed at codons 13 and 117 only in furfural-treated animals. The authors interpreted their findings as suggesting that novel mutations in *ras* genes could have resulted from a genotoxic effect of furfural (Reynolds *et al.*, 1987).

5. Summary and Evaluation

5.1 Exposure data

Furfural is produced commercially by the acid hydrolysis of pentosan polysaccharides from non-food residues of food crops and wood wastes. It is used widely as a solvent in petroleum refining, in the production of phenolic resins and in a variety of other applications. Human exposure to furfural occurs during its production and use, as a result of its natural occurrence in many foods and from the combustion of coal and wood.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Furfural was tested for carcinogenicity by oral administration in one study in mice and one study in rats. In mice, it increased the incidence of hepatocellular adenomas and carcinomas in males and of hepatocellular adenomas and forestomach papillomas in females. Male rats had a low incidence of cholangiocarcinomas, which occur rarely. In a two-stage assay on mouse skin, furfural had weak initiating activity.

5.4 Other relevant data

Furfural is extensively absorbed and rapidly eliminated after inhalation by humans and rats. Furfural in air is also absorbed dermally by humans. Repeated exposure of hamsters to furfural by inhalation severely damages the olfactory epithelium. Repeated oral administration to rats causes liver necrosis and cirrhosis.

Neither chromosomal aberrations nor sister chromatid exchanges were observed in rodents treated with furfural *in vivo* in a single study.

Gene mutation (in a single study), sister chromatid exchange and chromosomal aberrations were induced in mammalian cells *in vitro*. Sex-linked recessive lethal mutations were induced in insects. Furfural induced weak or no mutagenicity in bacteria but damaged DNA *in vitro*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of furfural.

There is *limited evidence* in experimental animals for the carcinogenicity of furfural.

Overall evaluation

Furfural *is not classifiable as to its carcinogenicity to humans (Group 3).*

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[1] For definition of the italicized terms, see Preamble, pp. 22–26.

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