FURAN

1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 110-00-9
Chem. Abstr. Name: Furan
IUPAC Systematic Name: Furan
Synonyms: Divinylene oxide; 1,4-epoxy-1,3-butadiene; furfuran; furfurane; oxacyclopentadiene

1.1.2 Structural and molecular formulae and relative molecular mass

C_4H_4O Relative molecular mass: 68.08

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Clear colourless liquid with strong ether-like odour (McKillip *et al.*, 1989; United States National Toxicology Program, 1993)

(*b*) *Boiling-point*: 31.4 °C (Lide, 1993)

(*c*) *Melting-point*: –85.6 °C (Lide, 1993)

(*d*) *Density*: 0.9514 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [3664]; grating [33 024]), ultraviolet [28 593], nuclear magnetic resonance (proton [16 937], C-13 [570]) and mass [51] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Insoluble in water; soluble in acetone, benzene, diethyl ether and ethanol (Spectrum Chemical Mfg Corp., 1992; Lide, 1993)

(*g*) *Volatility*: Relative vapour density (air = 1), 2.3 (Spectrum Chemical Mfg Corp., 1992)

(*h*) *Stability*: Stable to alkalis; forms resin on evaporation and when in contact with mineral acids (Budavari, 1989); forms unstable peroxides on exposure to air; vapour-air mixtures are explosive above the flash-point (–35 °C closed cup) (Spectrum Chemical Mfg Corp., 1992)

(*i*) *Reactivity*: Lower inflammable/explosive limit in air, 2.3%; dangerous fire hazard and moderate explosive hazard when exposed to heat or flame (Spectrum Chemical Mfg Corp., 1992)

(*j*) *Octanol:water partition coefficient (P)*: log P, 1.34 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 2.78 \times ppm$[1]

1.1.4 Technical products and impurities

Furan is available commercially with the following typical specifications (wt%): minimal purity, 99.0; methylfuran, 0.2 max; tetrahydrofuran, 0.05 max; furfural (see monograph, this volume), 0.05 max; water, 0.2 max; peroxide, 0.015 max; butylated hydroxytoluene (see IARC, 1987), 0.025–0.040 max (McKillip *et al.*, 1989). Trade names for furan include Axole, Oxole, Tetrol, Tetrole and U124.

1.1.5 Analysis

A method for the identification and determination of biogenic and anthropogenic volatile organic compounds, including furan, in ambient air is based on the combined use of carbon absorption traps and high-resolution gas chromatography–mass spectrometry (Ciccioli *et al.*, 1993). Furan can be detected in water by direct aqueous injection on a glass column packed with Tenax GC and analysis by gas chromatography with flame ionization detection. The detection limit is about 1.0 µg/ml (Knuth & Hogland, 1984).

1.2 Production and use

1.2.1 Production

Furan is produced commercially by the decarbonylation of furfural over a palladium/-charcoal catalyst (McKillip *et al.*, 1989). It is produced by one company each in Belgium, the Russian Federation and the United States of America (Chemical Information Services, Inc., 1994).

1.2.2 Use

Furan is an intermediate in the manufacture of tetrahydrofuran, pyrrole and thiophene and in the formation of lacquers and solvent for resins. It is also used in the production of pharmaceuticals, agricultural chemicals and stabilizers (McKillip & Sherman, 1980; McKillip *et al.*, 1989).

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

1.3 Occurrence

1.3.1 Natural occurrence

Furan occurs in oils obtained by the distillation of pine wood containing rosin (Budavari, 1989). It has also been identified in volatile emissions from sorb trees (Isodorov *et al.*, 1985).

1.3.2 Occupational exposure

No data were available to the Working Group.

1.3.3 Air

Furan is released into the air as a gas-phase component of cigarette smoke, wood smoke and exhaust gas from diesel and gasoline engines. It has been detected in the expired air of both smokers, at 0–98 μg/h, and nonsmokers, at 0–28 μg/h (Howard *et al.*, 1990). Residential burning of brown-coal briquets also led to emission of furfural, at an emission factor of 1.70 mg/kg. The estimated total amount of furfural emitted in the city of Leipzig was 550 kg/year (Engewald *et al.*, 1993). In a study of nuisance odours in Flanders, a concentration of 170 μg/m^3 furan was detected in the emission from a deep-frier (Moortgat *et al.*, 1992).

1.3.4 Water

Furan was identified qualitatively in the Niagara River, United States, and in one creek in the Niagara River watershed (Elder *et al.*, 1981; Howard *et al.*, 1990).

It was detected in one of 63 industrial effluents at a concentration of < 10 μg/L (Perry *et al.*, 1979). It was also detected in aqueous condensate samples from low-heat gasification of rosebud coal, at a concentration of 7 ± 4 ppb [μg/L]. It was not detected (detection limit, 0.1 ppb) in groundwater or coal water before coal gasification *in situ*, in water samples obtained during coal gasification *in situ*, in retort water from shale processing *in situ* or in boiler blowdown water from oil-shale processing *in situ* (Pellizzari *et al.*, 1979).

1.4 Regulations and guidelines

The occupational exposure limit for furan in the Russian Federation is 0.5 mg/m^3, with a notation of skin irritancy (ILO, 1991).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 mice, eight weeks of age, were administered 0, 8 or 15 mg/kg bw furan (purity, > 99%) by gavage in corn oil on five days per week for 104 weeks. The numbers of surviving animals at the end of the study were reduced: 33/50 male controls, 17/50 at the low dose and 16/50 at the high dose ($p = 0.009$); and 29/50 female controls, 25/50 at the low dose and 2/50 at the high dose ($p < 0.001$). The incidence of hepatocellular adenomas was increased, with 20/50 among male controls, 33/50 at the low dose ($p = 0.001$, logistic regression analysis) and 42/50 at the high dose ($p < 0.001$); and 5/50 among female controls, 31/50 at the low dose and 48/50 at the high dose groups ($p < 0.001$)). The incidence of hepatocellular carcinoma was also increased, occurring in 7/50 male controls, 32/50 at the low dose and 34/50 at the high dose ($p < 0.001$); and in 2/50 female controls, 7/50 at the low dose ($p = 0.08$) and 27/50 at the high dose ($p < 0.001$)). All treated groups had high incidences of biliary hyperplasia, cholangiofibrosis, hepatocellular necrosis and focal hyperplasia (United States National Toxicology Program, 1993).

Rat: Groups of 70 male and 70 female Fischer 344/N rats, seven to eight weeks of age, were administered 0, 2, 4 or 8 mg/kg bw furan (purity, > 99%) dissolved in corn oil by gavage on five days a week for 102 weeks. Interim evaluations were made on 10 rats from each group at 9 and 15 months. The numbers of animals still alive at the end of the study were 33/50 male controls, 28/50 at the low dose, 26/50 at the middle dose and 16/50 at the high dose ($p < 0.001$); and 34/50 female controls, 32/50 at the low dose, 28/50 at the middle dose and 19/50 at the high dose ($p = 0.006$). The incidence of hepatocellular adenomas was increased, and many rats had multiple adenomas; adenomas were found in 1/50 male controls, 4/50 at the low dose, 18/50 at the middle dose ($p < 0.001$, logistic regression analysis) and 27/50 at the high dose ($p < 0.001$); and in none of 50 female controls, 2/50 at the low dose, 4/50 at the middle dose ($p = 0.048$) and 7/50 at the high dose ($p = 0.002$). Hepatocellular carcinomas occurred only in males: 0/50 controls, 1/50 at the low dose, 6/50 at the middle dose ($p = 0.009$) and 18/50 at the high dose ($p < 0.001$). Cholangiocarcinomas were found in none of the control animals and in 43/50 males at the low dose, 48/50 at the middle dose and 49/50 at the high dose; and in 49/50 females at the low dose, 50/50 at the middle dose and 49/50 at the high dose ($p < 0.001$ for any group and either sex in comparison with controls). Biliary hyperplasia, cholangiofibrosis, hepatocellular necrosis and hyperplasia occurred in treated rats of each sex. The incidence of mononuclear-cell leukaemia increased with dose, occurring in 8/50 male controls, 11/50 at the low dose, 17/50 at the middle dose ($p = 0.016$, life-table test) and 25/50 at the high dose ($p < 0.001$); and in 8/50 female controls, 9/50 at the low dose, 17/50 at the middle dose ($p = 0.022$) and 21/50 at the high dose ($p < 0.001$). Cholangiocarcinomas, but no other tumours of the liver, were observed at 9 and 15 months, the incidence increasing with dose up to 100% at the high dose. In a 'stop-exposure' experiment, 50 males received 30 mg/kg bw furan for 13 weeks, and 10 rats were killed and examined at 13 weeks and at 9 and 15 months; all animals were observed for two years. In addition to the lesions seen previously, cholangiocarcinomas were seen in all treated rats that survived for at least nine months, and 6/40 had hepatocellular carcinomas (United States National Toxicology Program, 1993).

In a study to characterize the histopathogenesis of intrahepatic cholangiocarcinomas induced by furan, groups of 10–12 young adult male Fischer 344 rats, weighing 160–190 g, were treated with 30 mg/kg bw furan (purity, > 99%) in corn oil by gavage on five days a week for 6–13 weeks and observed up to 16 months. Lesions described as 'hepatic adenocarcinomas' occurred in the right caudate lobe of 4/9 rats treated for six weeks, 6/8 treated for nine weeks, 5/7 treated for 12 weeks and 9/10 treated for 13 weeks. Most of the tumours showed small-intestinal differentiation, as reflected by the presence of goblet, Paneth and serotonin-positive cells. Two hepatocellular carcinomas were also found in the animals treated for 13 weeks. Cells from the adenocarcinoma cells did not contain TGF-α, but hepatocellular carcinoma cells did (Elmore & Sirica, 1993).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

[2,5-^{14}]Furan (specific activity, 56 mCi/mmol; radiochemical purity, 99%) was administered by gavage to male Fischer 344 rats once a day for up to eight days at a dose of 8 mg/kg bw in corn oil. Furan was absorbed rapidly and extensively, and only about 14% of the administered dose was expired as unchanged furan, 11% within the first hour. After administration of a single dose, ^{14}C-carbon dioxide accounted for 26% of the radiolabel, 20% was found in urine and 22% was found in faeces within 24 h. Of the 19% of the administered radiolabel that remained in the tissues, 68% (13% of the dose) was found in the liver; smaller amounts were detected in the kidney and gastrointestinal tract. Only 20% of the radiolabelled material in the liver could be extracted with organic solvents, and the remaining radiolabel was assumed to be bound covalently to tissue macromolecules; none of the radiolabel was bound to liver DNA. Elimination of unbound radiolabelled material from the liver appeared to follow first-order kinetics, with a half-life of 1.8 days, whereas the kinetics of elimination from kidney and blood was more complex. The blood concentration of radiolabel remained at about 2–5 nmol equivalents of furan per gram for eight days after a single dose. The concentration of radiolabel increased with multiple doses, by about sixfold in blood and kidney and fourfold in the liver after eight doses, as compared with the levels seen after a single dose. The percentage of the administered radiolabel that was eliminated in the urine increased during multiple dosing from 20% after one day to 33% after four days. Furan appeared to be metabolized extensively, as high-performance liquid chromatography of the radiochromatogram of 24-h urine showed at least 10 peaks. The pattern of metabolites did not change appreciably after multiple doses. None of the urinary

metabolites was identified. Exhalation of radiolabel in carbon dioxide after administration of furan indicates opening of the furan ring (Burka *et al.*, 1991).

Male Fischer 344 rats were exposed to furan (purity, > 99%) by inhalation at 52, 107 or 208 ppm [145, 297 or 578 mg/m^3] for 4 h, at which time the concentrations of furan were determined in blood and liver. A physiologically based kinetic model was developed on the basis of the tissue partition coefficients for furan determined *in vitro* in a vial equilibration technique. The model adequately simulated the concentrations of furan after inhalation *in vivo* and revealed a single saturable process, with a maximal metabolic velocity (V_{max}) of 27 μmol[1.8 mg]/h per 250-g rat and a Michaelis-Menten constant (K_m) of 2 μmol[136 μg]/L. The biotransformation of furan by rat hepatocytes *in vitro* had a K_m of 0.4 μmol[27 μg]/L and a V_{max} of 0.02 μmol[1.4 μg]/h per 10^6 cells. The metabolism of this compound was increased by fivefold in hepatocytes isolated from rats treated with acetone, but not after phenobarbital treatment, and was inhibited by treatment of rats with aminobenzotriazole or after addition of ethanol and 1-phenylimidazole in vitro. The metabolism of furan *in vivo* was inhibited by pyrazole (Kedderis *et al.*, 1993).

Incubation of [2,5-^{14}C]furan (specific activity, 56 mCi/mmol; radiochemical purity, > 99%) with liver microsomes from male Fischer 344 rats in the presence of NADPH resulted in covalent binding of radiolabel to microsomal protein. The rates of covalent binding to protein *in vitro* were increased by two- to threefold after treatment of rats with phenobarbital and by four- to fivefold after treatment with imidazole or pyrazole, but were reduced in the presence of microsomes from rats treated with β-naphthoflavone. Addition of semicarbazide, *N*-acetylcysteine or glutathione inhibited binding of ^{14}C-furan to microsomal protein. Twenty-four hours after a single oral administration of 8 or 25 mg/kg bw of furan, the liver microsomal P450 levels were reduced to 90 and 71% of those in controls, respectively, with concomitant decreases in the activities of aniline hydroxylase, 7-ethoxycoumarin-*O*-deethylase and 7-ethoxyresorufin-*O*-deethylase. The amount of radiolabel bound to microsomes was distributed almost equally between the haem and protein moieties of carbon monoxide-binding particles. The haem–furan adduct(s) was not identified (Parmar & Burka, 1993).

4.2 Toxic effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Groups of 10 male Swiss albino mice (GP strain) given furan [purity not given] at a single dose of 300 mg/kg bw in 0.9% sodium chloride intraperitoneally had centrilobular hepatic necrosis and coagulative necrosis of the proximal convoluted tubules of the outer renal cortex. Pretreatment of mice with the cytochrome P450 inhibitor piperonyl butoxide reduced the extent of liver necrosis and totally inhibited the renal necrosis (McMurtry & Mitchell, 1977).

The liver damage and hepatocyte proliferation induced by single and repeated oral doses of furan were studied in B6C3F1/CrIBR mice and Fischer 344/CrIBR rats. In the study of single doses, groups of five male mice and five male rats were administered corn oil or furan (same lot

as used in the two-year bioassay of the United States National Toxicology Program) in corn oil by gavage at doses of 30 or 50 mg/kg bw. Animals were killed at various times between 12 h and eight days; 2 h before being killed they were injected intraperitoneally with 2000 mCi/kg bw of [^{3}H-methyl]thymidine so that labelling indices could be determined. In the study of repeated doses, groups of six male mice and six male and female rats were administered the vehicle or doses of furan equivalent to the highest dose used in the bioassay (8 mg/kg bw for rats, 15 mg/kg bw for mice), by gavage, daily for five days per week for up to six weeks. Animals were killed after one, three or six weeks of treatment; six days before sacrifice, they received a subcutaneously implanted osmotic pump containing ^{3}H-thymidine. The effects observed after single doses were hepatocellular necrosis, marked increases in the activities of plasma aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase and a sharp increase in the labelling index (23.9 in mice and 17.8 in rats, in comparison with < 0.5 in controls). After six weeks of treatment, male and female rats, but not mice, had bile-duct hyperplasia and metaplasia, resembling intestinal cells, in areas of liver fibrosis. The hepatocyte labelling indices in male mice were 25.1 at week 1, 12.0 at week 3 and 3.2 at week 6, in comparison with control values of 0.41 at week 1 and 0.89 at week 6 (5–39-fold increase over combined control values). The hepatocyte labelling indices in male rats were 3.2 at week 1, 9.2 at week 3 and 6.5 at week 6, in comparison with control values of 0.08 at week 1 and 0.29 at week 6 (18–51-fold increase over combined control values). The hepatocyte labelling indices in female rats were 11.7 at week 1, 9.2 at week 3 and 14.4 at week 6, in comparison with control values of 0.77 at week 1 and 0.75 at week 6 (12–19-fold increase over combined control values) (Wilson *et al.*, 1992).

Groups of five male Fischer 344 rats were administered furan (purity, 99%) in corn oil by gavage at doses of 0, 15, 30, 45 or 60 mg/kg bw daily on five days per week for three weeks; liver lesions were assessed by histology and histo- and immunochemistry. Animals at the two highest doses showed rapid development of severe cholangiofibrosis in the caudate liver lobe. Histologically, the lesion was characterized by well-differentiated hyperplastic bile ductules and numerous metaplastic intestinal glands supported by fibrous tissue. At the highest dose, cholangiolar-like structures were also observed. Phenotypic analysis of the hyperplastic ductular structures and of the metaplastic intestinal glands in the cholangiofibrotic areas suggested a precursor relationship between the ductular cells and the metaplastic cells (Elmore & Sirica, 1991).

Groups of male Fischer 344 rats were administered furan (purity, 99%) at 45 mg/kg bw by gavage daily on five days per week for up to 32 days. Animals were killed on day 1, 3, 5, 7, 9, 12, 16 or 32. Severe hepatocellular necrosis was evident in the right and caudate lobes at the time of early sacrifices, and was followed by inflammatory cell infiltration, obvious bile-duct hyperplasia and then by development of metaplastic glands, ending with cholangiofibrosis by day 32 (Elmore & Sirica, 1992).

Synergism was demonstrated between bile-duct ligation in male Fischer 344 rats and administration of furan at 45 mg/kg bw per day, five times per week for five to six weeks beginning one week after bile duct ligation. In treated animals, 72.6 ± 16.3% of the liver was replaced by well-differentiated hyperplastic bile ductules, whereas in control rats, which were ligated and dosed with corn oil, 2.0 ± 4.2% of the liver was bile-duct tissue. Treatment with furan after a sham operation resulted in only 11.9 ± 3.1% bile-duct tissue. The combined

treatment also resulted in greatly increased activities of γ-glutamyl transpeptidase in liver homogenates (Sirica *et al.*, 1994a).

Furan administered by gavage to young adult male Fischer 344 rats at a dose of 60 mg/kg bw per day five times per week for 10–14 days was highly toxic and induced marked atrophy of the right liver lobe. The cholangiolar-like structures that developed in this region consisted of biliary epithelial cells and ductular hepatocytes in various stages of maturation. Immunohistochemical and other phenotypic features of the cells were considered to be consistent with the development of rare bile ductular-like cell types from hepatocytes; in contrast, less severe treatment with furan led to the development of small intestinal-like glands (Sirica *et al.*, 1994b).

Groups of 10 male and female Fischer 344/N rats and 10 female B6C3F1 mice received furan (purity, 99%) in corn oil at doses of 0, 4, 8, 15, 30 or 60 mg/kg bw by gavage on five days per week for 13 weeks. Groups of 10 male mice received doses of 0, 2, 4, 8, 15 or 30 mg/kg bw. In rats, dose-dependent bile-duct hyperplasia and cholangiofibrosis were observed, and animals at the high dose had renal tubular necrosis and dilatation and atrophy of the thymus, testes or ovaries. Mice had dose-dependent hepatic lesions, with cytomegaly, degeneration, necrosis and bile-duct hyperplasia (United States National Toxicology Program, 1993).

Repeated treatment of male Fischer 344 rats with furan by gavage at daily doses of 8 mg/kg bw in corn oil, five days per week, resulted in a sustained, approximately 35-fold increase in the percentage of hepatocytes in S-phase over that in controls at weeks 1, 3 and 6. Northern blot analysis of mRNA expression in the livers showed up to a doubling of Ha-*ras* expression, but no measurable expression of *fos*, at weeks 1, 3 and 6. At the end of week 6, but not earlier, an approximately 10-fold increase in the expression of *myc* was observed (Butterworth *et al.*, 1992, 1994).

Isolated hepatocytes from male Fischer 344 rats were incubated in suspension culture with 2–100 μmol[136–6808 μg]/L of furan (vacuum-distilled) for 4 h and then in a monolayer culture for an additional 25.5 h. Concentration-dependent cytolethality (5–70%) and modest glutathione depletion were observed. These concentrations were similar to the hepatotoxic tissue concentrations predicted by dosimetry modelling. Both glutathione depletion and cytolethality were prevented by addition of 1-phenylimidazole to the cultures and were enhanced by pretreatment of the rats with acetone (Carfagna *et al.*, 1993).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 Humans

No data were available to the Working Group

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

Furan was not mutagenic to *Salmonella typhimurium* after preincubation in the presence or absence of an exogenous metabolic activation system. It was reported in an abstract that furan was not mutagenic in a vapour-phase protocol.

Furan did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* when administered to adult flies by feeding or abdominal injection.

It was reported in an abstract that furan did not induce unscheduled DNA synthesis in rat or mouse hepatocytes after treatment *in vitro* or *in vivo*. It induced gene mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells in the absence of metabolic activation. Furan induced sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells both in the presence and absence of metabolic activation. In another study, a positive response for the induction of chromosomal aberrations was observed only at comparatively high doses in the presence of a liver activation system from Aroclor 1254-pretreated male Swiss rats.

No sister chromatid exchanges or chromosomal aberrations were induced in bone-marrow cells of B6C3F1 male mice injected intraperitoneally with furan at doses up to 350 mg/kg bw *in vivo*; however, chromosomal aberrations were induced at 250 mg/kg bw in an extended protocol involving a late harvest time.

Mutation of proto-oncogenes in tumours induced by furan

ras Proto-oncogene activation was studied in liver adenomas and carcinomas induced in B6C3F1 mice by furan. The frequency of activated H-*ras* and K-*ras* oncogenes was similar in hepatocellular tumours from 12/29 treated mice and in 15/27 vehicle controls, but the spectrum of activating mutations in the H-*ras* gene differed significantly: Although mutations occurred at codon 61 in tumours from both treated and untreated animals, mutations (G→T and G→C transversions) were observed at codon 117 only in animals treated with furan. The authors interpreted these findings as suggesting that the novel mutations in *ras* genes could have been due to a genotoxic effect of furan (Reynolds *et al.*, 1987).

5. Summary and Evaluation

5.1 Exposure data

Furan is produced commercially by decarbonylation of furfural. It is used mainly in the production of tetrahydrofuran, thiophene and pyrrole. It also occurs naturally in certain woods and during the combustion of coal and is found in engine exhausts, wood smoke and tobacco smoke.

5.2 Human carcinogenicity data

No data were available to the Working Group.

Table 1. Genetic and related effects of furan

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	3850	US National Toxicology Program (1993)
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	-	-	3850	US National Toxicology Program (1993)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	3850	US National Toxicology Program (1993)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	3850	US National Toxicology Program (1993)
DMX, *Drosophila melanogaster,* sex-linked recessive lethal mutation	-		10 000 feed	Foureman *et al.* (1994)
DMX, *Drosophila melanogaster,* sex-linked recessive lethal mutation	-		25 000 inj	Foureman *et al.* (1994)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	-		680	Wilson & Butterworth (1989) (Abstract); Wilson *et al.* (1990) (Abstract)
UIA, Unscheduled DNA synthesis, mouse primary hepatocytes *in vitro*	-		680	Wilson & Butterworth (1989) (Abstract); Wilson *et al.* (1990) (Abstract)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	0	1140	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	160	US National Toxicology Program (1993)

Table1 (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*	-	+	4800	Stich *et al.* (1981)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	+	100	US National Toxicology Program (1993)
UPR, Unscheduled DNA synthesis, rat primary hepatocytes *in vivo*	-		100 po × 1	Wilson & Butterworth (1989) (Abstract); Wilson *et al.* (1990) (Abstract)
UVM, Unscheduled DNA synthesis, mouse primary hepatocytes *in vivo*	-		200 po × 1	Wilson & Butterworth (1989) (Abstract); Wilson *et al.* (1990) (Abstract)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	-		350 ip × 1	US National Toxicology Program (1993)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+[c]		250 ip × 1	US National Toxicology Program (1993)

[a] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; -, 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; po, orally
[c] Extended harvest protocol (36-h harvest); negative result with standard protocol (17-h harvest)

5.3 Animal carcinogenicity data

Furan was tested for carcinogenicity by oral administration in one study in mice and in one study in rats. It produced hepatocellular adenomas and carcinomas in mice. In rats, it produced hepatocellular adenomas in animals of each sex and carcinomas in males; a high incidence of cholangiocarcinomas was seen in both males and females. The incidence of mononuclear-cell leukaemia was also increased in animals of each sex.

5.4 Other relevant data

Furan is rapidly and extensively absorbed by rats after oral administration; part of the absorbed dose becomes covalently bound to protein, mainly in the liver. No DNA binding could be demonstrated in the liver.

Repeated administration of furan to mice and rats leads to liver necrosis, liver-cell proliferation and bile-duct hyperplasia; in rats, prominent cholangiofibrosis develops.

Induction of chromosomal aberrations but not of sister chromatid exchange was observed in rodents treated *in vivo* in one study. Gene mutation, sister chromatid exchange (in single studies) and chromosomal aberrations were induced in rodent cells *in vitro*.

Furan was not mutagenic to insects or bacteria.

5.5 Evaluation[1]

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of furan.

Overall evaluation

Furan *is possibly carcinogenic to humans (Group 2B).*

6. References

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

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