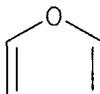


ABSTRACT



FURAN

CAS No. 110-00-9

C₄H₄O Molecular Weight: 68.08

Synonyms: Divinylene oxide, tetrole, furfuran, oxole, 1,4-epoxy-1,3-butadiene, axole, oxacyclopentadiene

Furan serves as an intermediate in the synthesis and preparation of numerous linear polymers used to prepare temperature-resistant structural laminates and to prepare copolymers used in machine dish-washing products as alternatives to phosphorus- and nitrogen-containing detergents. Toxicology and carcinogenesis studies were conducted by administering furan (purity > 99%) in corn oil by gavage to groups of F344/N rats and B6C3F₁ mice of each sex for 16 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Drosophila melanogaster*, mouse bone marrow cells, mouse L5178Y lymphoma cells, and Chinese hamster ovary cells.

16-Day Studies

Groups of five male rats received doses of 0, 5, 10, 20, 40, or 80 mg of furan per kg of body weight and groups of five female rats and five mice of each sex received doses of 0, 10, 20, 40, 80, and 160 mg/kg in corn oil by gavage. All male and female mice and female rats that received 160 mg/kg, all male and female rats and all male and four female mice that received 80 mg/kg, and three male mice that received 40 mg/kg died by day 8. Final mean body weights of male rats that received 20 mg/kg and of male and female rats that received 40 mg/kg were significantly lower than controls. Final mean body weights of male mice that received 10 or 20 mg/kg were significantly greater than controls. Mottled and enlarged livers were observed at necropsy in male rats that received 20, 40, or 80 mg/kg and in females that received 40, 80, or 160 mg/kg. No lesions were

observed at necropsy that were considered related to furan administration in mice.

13-Week Studies

Groups of 10 rats of each sex and groups of 10 female mice received doses of 0, 4, 8, 15, 30, or 60 mg of furan per kg of body weight, and groups of 10 male mice received doses of 0, 2, 4, 8, 15, or 30 mg/kg in corn oil by gavage. Nine male and four female rats that received 60 mg/kg died before the end of the studies. There were no chemical-related deaths in mice. Final mean body weights of male rats that received 15 or 30 mg/kg and female rats that received 60 mg/kg were significantly lower than controls. Final mean body weights of male mice that received 60 mg/kg were significantly lower than controls. Relative and absolute liver weights in both sexes of rats and mice were increased in groups that received furan, as were relative and absolute kidney weights in female rats that received furan. Thymus weights were decreased in all groups of rats that received furan.

Toxic lesions of the liver (bile duct hyperplasia, cholangiofibrosis, cytomegaly and degeneration of hepatocytes, and nodular hyperplasia of hepatocytes) were associated with furan administration in all dose groups of rats; the severity of the lesions increased with dose. Kidney lesions (tubule dilatation and necrosis of tubule epithelium) were present in rats that received 30 or 60 mg/kg. Thymic atrophy and testicular or ovarian atrophy were also observed in rats exposed to 60 mg/kg furan. Toxic liver lesions (cytomegaly, degeneration, and necrosis of hepato-

cytes) were also present in all groups of furan-exposed mice. Bile duct hyperplasia and cholangiofibrosis were observed in groups of mice receiving 30 or 60 mg/kg.

Doses selected for the 2-year studies of rats and mice were based on the hepatotoxicity associated with exposure to furan.

2-Year Studies

Groups of 70 rats of each sex were administered 2, 4, or 8 mg furan per kg body weight in corn oil by gavage 5 days per week for 2 years. After 9 and 15 months of chemical exposure, 10 rats per group were evaluated for the presence of treatment-associated lesions. Groups of 50 mice of each sex received doses of 8 or 15 mg/kg furan 5 days per week for 2 years.

Body Weight and Survival. Mean body weights of male rats that received 8 mg/kg furan were lower than controls from approximately week 73 to the end of the study. Survival of male and female rats that received 8 mg/kg was lower than controls from approximately week 85 to the end of the studies as a result of moribund condition associated with liver and biliary tract neoplasms and mononuclear cell leukemia.

Mean body weights of male and female mice that received 15 mg/kg furan were lower than controls during the studies. Survival of low- and high-dose male and high-dose female mice was lower than controls from approximately week 80 to the end of the studies as a result of moribund condition associated with liver neoplasms.

Neoplastic and Nonneoplastic Lesions. Cholangiocarcinoma of the liver occurred in all groups of dosed rats (males: control, 0/50; low dose, 43/50; mid dose, 48/50; high dose, 49/50; females: 0/50; 49/50; 50/50; 48/50) and was present in many rats of each sex at the 9- and 15-month interim evaluations (9-month: males - 0/10, 5/10, 7/10, 10/10; females - 0/10, 4/10, 9/10, 10/10; 15-month: males - 0/10, 7/10, 9/10, 6/10; females - 0/10, 9/10, 9/10, 7/10). Hepatocellular adenomas or carcinomas (combined) were significantly increased in male rats after 2 years of chemical administration (1/50, 5/50, 22/50, 35/50) and hepatocellular adenomas were significantly increased in female rats (0/50, 2/50, 4/50, 7/50); hepatocellular

neoplasms were not observed at the 9- or 15-month interim evaluations. Increased incidences of numerous nonneoplastic liver lesions were present in rats administered furan. These lesions included biliary tract fibrosis, hyperplasia, chronic inflammation, and proliferation and hepatocyte cytomegaly, cytoplasmic vacuolization, degeneration, nodular hyperplasia, and necrosis.

The incidence of mononuclear cell leukemia was increased in male and female rats that received 4 or 8 mg/kg furan (males: 8/50, 11/50, 17/50, 25/50; females: 8/50, 9/50, 17/50, 21/50); the incidence in the 8 mg/kg groups of each sex exceeded the historical control ranges for corn oil gavage studies.

The severity of nephropathy increased with dose and the incidence was significantly increased in all groups of dosed rats; this increased severity was accompanied by an associated increased incidence of parathyroid hyperplasia (renal secondary hyperparathyroidism).

The incidence of forestomach hyperplasia was increased in male and female rats (males: 1/50, 4/49, 7/50, 6/50; females: 0/50, 2/50, 5/50, 5/50) and the incidence of subacute inflammation of the forestomach was increased in female rats (0/50, 1/50, 5/50, 6/50). No forestomach neoplasms were observed in males; a squamous papilloma was present in one low-dose female.

The incidences of hepatocellular adenomas and carcinomas were significantly increased in mice receiving furan (males: adenoma - 20/50, 33/50, 42/50; carcinoma - 7/50, 32/50, 34/50; females: adenoma - 5/50, 31/50, 48/50; carcinoma - 2/50, 7/50, 27/50). The incidences of numerous nonneoplastic hepatocellular lesions were increased in dosed mice. These lesions included hepatocyte cytomegaly, degeneration, necrosis, multifocal hyperplasia, and cytoplasmic vacuolization and biliary tract dilatation, fibrosis, hyperplasia, and inflammation.

The incidences of benign pheochromocytoma and focal hyperplasia of the adrenal medulla were increased in low- and high-dose male and in high-dose female mice (benign pheochromocytoma: males - 1/49, 6/50, 10/50; females - 2/50, 1/50, 6/50).

The incidences of squamous papilloma, focal inflammation, and papillary hyperplasia of the forestomach were increased in male mice (squamous papilloma:

0/49, 1/50, 3/50; focal inflammation: 9/49, 13/50, 21/50; papillary hyperplasia: 7/49, 14/50, 22/50).

Stop-Exposure Study

A separate 2-year study was conducted in which 50 male rats were administered 30 mg/kg furan in corn oil by gavage 5 days per week for 13 weeks and then maintained for the remainder of the 2 years without additional furan administration. Groups of 10 animals were evaluated for the presence of treatment-related lesions at the end of the 13-week period of furan administration and at 9 and 15 months.

Neoplastic and Nonneoplastic Lesions. Cholangiocarcinoma of the liver occurred with an overall incidence of 100% (40/40) and hepatocellular carcinoma occurred with an overall incidence of 15% (6/40) in stop-exposure male rats that survived at least 9 months. Cholangiocarcinoma was observed in all 10 males at both the 9-month and 15-month interim evaluations. Hepatocellular carcinoma was first observed in 2 males at the 15-month interim evaluation.

Genetic Toxicology

Furan was negative for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in the presence and the absence of exogenous metabolic activation (S9). Furan was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* when administered either by feeding or

by injection. *In vitro* tests for genotoxicity in mammalian cells, however, were positive. Furan induced trifluorothymidine resistance in mouse L5178Y lymphoma cells in the absence of S9, and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, with and without S9. Furan administered to male B6C3F₁ mice by intraperitoneal injection induced chromosomal aberrations but not sister chromatid exchanges in bone marrow cells.

Conclusions

Under the conditions of these 2-year gavage studies there was *clear evidence of carcinogenic activity** of furan in male and female F344/N rats based on increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and on increased incidences of mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of furan in male and female B6C3F₁ mice based on increased incidences of hepatocellular neoplasms of the liver and benign pheochromocytomas of the adrenal gland.

Nonneoplastic liver lesions associated with furan administration in rats and mice included biliary tract fibrosis, hyperplasia, inflammation, and proliferation, as well as hepatocellular cytomegaly, degeneration, hyperplasia, necrosis, and vacuolization. In rats, increased severity of nephropathy with an associated increased incidence of parathyroid hyperplasia was associated with exposure to furan.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of peer review comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and the Genetic Toxicology Studies of Furan

Male F344/N Rats	Female F344/N Rats	Male B6C3F ₁ Mice	Female B6C3F ₁ Mice
Doses			
0, 2, 4, or 8 mg/kg of furan in corn oil by gavage 5 days per week	0, 2, 4, or 8 mg/kg of furan in corn oil by gavage 5 days per week	0, 8, or 15 mg/kg of furan in corn oil by gavage 5 days per week	0, 8, or 15 mg/kg of furan in corn oil by gavage 5 days per week
Body weights			
High-dose less than control	Dosed similar to control	Dosed less than control	High-dose less than control
2-Year survival rates			
33/50; 28/50; 26/50; 16/50	34/50; 32/50; 28/50; 19/50	33/50; 17/50; 16/50	29/50; 25/50; 2/50
Nonneoplastic effects			
Kidney: nephropathy Liver: biliary tract - dilatation, chronic inflammation, fibrosis, and hyperplasia; hepatocyte - cytomegaly, degeneration, and necrosis Parathyroid: hyperplasia	Kidney: nephropathy Liver: biliary tract - chronic focal inflammation, cyst, focal fibrosis, focal hyperplasia, and metaplasia; hepatocyte - cytomegaly, cytoplasmic vacuolization, focal degeneration, focal hyperplasia, and focal necrosis Parathyroid: hyperplasia	Liver: biliary tract - chronic focal inflammation, cyst, focal fibrosis, focal hyperplasia, and metaplasia; hepatocyte - cytomegaly, cytoplasmic vacuolization, focal degeneration, focal hyperplasia, and focal necrosis	Liver: biliary tract - dilatation, chronic inflammation, fibrosis, and hyperplasia; hepatocyte - cytomegaly, degeneration, and necrosis
Neoplastic effects			
Liver: cholangiocarcinoma - 0/50; 43/50; 48/50; 49/50 hepatocellular adenoma or carcinoma - 1/50; 5/50; 22/50; 35/50 Mononuclear cell leukemia: 8/50; 11/50; 17/50; 25/50	Liver: cholangiocarcinoma - 0/50; 49/50; 50/50; 48/50 hepatocellular adenoma or carcinoma - 0/50; 2/50; 4/50; 8/50 Mononuclear cell leukemia: 8/50; 9/50; 17/50; 21/50	Liver: hepatocellular adenoma or carcinoma - 26/50; 44/50; 50/50 Adrenal gland: benign pheochromocytoma - 1/49; 6/50; 10/50	Liver: hepatocellular adenoma or carcinoma - 7/50; 34/50; 50/50 Adrenal gland: benign pheochromocytoma - 2/50; 1/50; 6/50
Level of evidence of carcinogenic activity			
Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology			
Gene Mutations			
<i>Salmonella typhimurium in vitro</i> : L5178Y/TK ⁺ mouse lymphoma <i>in vitro</i> :		Negative with and without S9 in strains TA98, TA100, TA1535, TA1537 Positive without S9	
Sister Chromatid Exchanges			
Chinese hamster ovary cells <i>in vitro</i> :		Positive with and without S9	
B6C3F ₁ mouse bone marrow cells <i>in vivo</i> :		Negative when administered by injection	
Chromosomal Aberrations			
Chinese hamster ovary cells <i>in vitro</i> :		Positive with and without S9	
B6C3F ₁ mouse bone marrow cells <i>in vivo</i> :		Positive when administered by injection	
Sex-linked Recessive Lethal Mutations			
<i>Drosophila melanogaster</i> :		Negative when administered in feed or by injection	