FURAN
CAS No. 110-00-9
First Listed in the *Eighth Report on Carcinogens*

CARCINOGENICITY

Furan is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals (IARC 1995).

When administered by gavage, furan induced an increase in the incidence of hepatic cholangiocarcinoma, hepatocellular adenoma, hepatocellular carcinoma, and mononuclear cell leukemia in male and female F344/N rats treated for up to 2 years (NTP 1993). Gavage administration of furan to male F344 rats for 9, 12, or 13 months resulted in high incidences of cholangiocarcinoma by 16 months after cessation of treatment (Maronpot *et al*. 1991, Elmore and Sirica 1993). When administered by gavage, furan induced a dose-dependent increase in the incidence of hepatocellular adenoma and carcinoma and benign pheochromocytoma in male and female $B6C3F_1$ mice treated up to 2 years (NTP 1993).

No adequate human studies of the relationship between exposure to furan and human cancer have been reported.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

In bacteria, furan induced gene mutations in *Salmonella typhimurium* strain TA100 (Lee *et al.* 1994) and in *E. coli* containing bacteriophage T7 (Ronto *et al.* 1992), but not in *S. typhimurium* strains TA98 (Lee *et al.* 1994), TA1535, or TA1537 (Mortelmans *et al.* 1986). In *Drosophila melanogaster*, it did not induce gene mutations (Foureman *et al.* 1994). In mammalian *in vitro* systems, it induced gene mutations in mouse lymphoma cells (McGregor *et al.* 1988), DNA damage in Chinese hamster ovary (CHO) cells (NTP 1993), and chromosomal damage in CHO cells with an exogenous metabolic activation system (NTP 1993, IARC 1995), but it did not induce DNA damage in mouse or rat hepatocytes (Wilson *et al.* 1992, NTP 1993). In mammalian *in vivo* systems, furan induced chromosomal aberrations in bone marrow of $B6C3F_1$ mice (NTP 1993), but did not induce DNA damage in bone marrow or hepatocytes of $B6C3F_1$ mice (Wilson *et al*. 1992, NTP 1993) or hepatocytes of F344/CrIBr rats (Wilson *et al.* 1992).

A current hypothesis for the mechanism of furan-induced carcinogenesis is metabolic activation of furan by cytochrome P450 to a reactive and cytotoxic intermediate that stimulates cell replication, increasing the likelihood of tumor induction (Chen *et al.* 1995, Kedderis *et al.* 1993). The postulated reactive metabolite is *cis*-2-butene-1,4-dial, which was recently characterized as a furan metabolite by Chen *et al.* (1995). This reactive metabolite probably explains furan's binding reactivity with proteins both *in vitro* (uninduced and induced F344 male

rat liver microsomes) and *in vivo* (F344 male rat liver protein) in biological systems (Burka *et al.* 1991, Parmar and Burka 1993). Furan metabolites may react with DNA, but Burka *et al.* (1991) did not detect any radiotracer in DNA from livers of rats treated with [^{14}C]furan.

No data were available that would suggest that the mechanisms thought to account for tumor induction by furan in experimental animals would not also operate in humans.

PROPERTIES

Furan, which is classified as a cyclic, dienic ether, is a clear, colorless, flammable liquid with an ethereal odor. It is sensitive to heat and light and may turn brown upon standing. Furan reacts with oxidizers, acids, peroxides, and oxygen and, if uninhibited, forms explosive peroxides on exposure to air. It is stable to alkalis, but forms resins on evaporation or in contact with mineral acids. It is insoluble in water, but is soluble in alcohol, ether, and most common organic solvents including acetone, benzene, toluene, petroleum, ether, and chloroform. When heated to decomposition it emits toxic fumes of carbon monoxide and carbon dioxide (IARC 1995, HSDB 2001, NTP 2001).

USE

Furan is used primarily as an intermediate in the synthesis and production of tetrahydrofuran, pyrrole, and thiophene. Hydrogenation of furan over a nickel catalyst produces high yields of tetrahydrofuran and is a source of commercial tetrahydrofuran (NTP 1993, IARC 1995). Furan is also used in the formation of lacquers, as a solvent for resins, and in the production of agricultural chemicals (insecticides), stabilizers, and pharmaceuticals (IARC 1995, HSDB 2001).

PRODUCTION

One company in the United States produces furan. Commercial production of furan involves decarbonylation of furfural over a palladium/charcoal catalyst. The minimal purity of the commercial product is 99% (IARC 1995). Approximately 9.7 million lb of furan resins were imported in 1986 (HSDB 2001). Chem Sources (2001) identified 18 U.S. suppliers.

EXPOSURE

The primary route of potential human exposure to furan is inhalation. Since the industrial processes in which furan is used are conducted in closed systems and its volatility requires that furan be handled in closed containers, occupational exposure is limited (NTP l993). However, furan may be released in the effluent from oil refining, coal mining, and coal gasification (HSDB 2001). It has been detected in cigarette smoke, wood smoke, and automobile exhausts, and it occurs naturally in pine rosin and sorb trees (IARC 1995, HSDB 2001).

The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 244 workers were potentially exposed to furan in the workplace (NIOSH 1976). The National Occupational Exposure Survey (1981-1983) indicated that 35 workers, including 7 women, were potentially exposed to furan (NIOSH 1984, HSDB 2001). The pattern of commercial use suggests that minimal exposure to the general public would be expected through

contact with products contaminated with furan (NTP 1993).

Furan has been detected in surface water, industrial effluents, ambient air, foods, human milk samples, and in the breath of both smokers and nonsmokers; however, in most cases, the frequency of detection and concentrations were low. Furan was detected in the indoor air of homes in the Chicago and Washington D.C. metropolitan areas (Jarke *et al.* 1981); in 1 of 63 industrial effluents at a concentration of <10 µg/L; at 7 µg/L in aqueous condensate samples from low-temperature gasification of rosebud coal; and in one of 12 milk samples obtained from women in four different urban areas (IARC 1995, HSDB 2001).

In one study in Texas, furan was detected in the exhaled breath of two out of three male smokers and four out of five male nonsmokers (Conkle *et al.* 1975, HSDB 2001). Smokers exhaled between 0.25 to 98 µg/h of furan and nonsmokers exhaled between 0.33 and 28 µg/h. In another study in Chicago, 15 of 387 samples collected from 54 male and female nonsmokers had detectable levels of furan in their breath. The mean concentration in breath samples was 0.55 ng/L (HSDB 2001).

REGULATIONS

EPA regulates furan under the Resource Conservation and Recovery Act (RCRA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Superfund Amendments and Reauthorization Act (SARA), and the Toxic Substances Control Act (TSCA). EPA has established rules for regulating hazardous spills and for reporting such spills or releases. EPA has also set general threshold amounts and established requirements for handling and disposal of furan wastes. Furan is regulated as a hazardous constituent of waste under RCRA and is subject to reporting and record-keeping requirements under RCRA and SARA. EPA has set a reportable quantity (RQ) of 100 lb (45.4 kg) under CERCLA.

The Department of Transportation (DOT) has its own regulations for the transportation of furan in tank cars and tank trucks.

OSHA regulates furan under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 90.

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