United States
Environmental Protection
Agency

FINAL DRAFT
ECAO-CIN-G020
November, 1987

Research and Development

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR FURAN

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval, for example, one that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. A carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided instead. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer-based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

Furan is a colorless, low-boiling and highly flammable liquid at room temperature, with a strong ethereal odor (McKillip and Sherman, 1980). Unless stabilized, it will react slowly with air to form an unstable, explosion-prone peroxide (Dunlop, 1966). It is miscible with most common organic solvents (McKillip and Sherman, 1980) and the solubility in water is 10 g/ℓ at 25°C (Dunlop, 1966). Furan is produced commercially by decarbonylation of furfural (McKillip and Sherman, 1980). QO Chemicals, Inc., Memphis, TN, is the only domestic manufacturer of this compound (SRI, 1986; USITC, 1986). Production volume data could not be located in the available literature as cited in Appendix A. Furan is used as an intermediate in the production of other industrial chemicals, especially pyrrole, tetrahydrofuran and thiophene; for use as pharmaceuticals, herbicides and various polymers (Hawley, 1981; McKillip and Sherman, 1980).

If released to the atmosphere, furan is expected to exist almost entirely in the vapor phase. Reaction with photochemically generated hydroxyl radicals is predicted to be the primary removal mechanism during daylight (half-life, 2-6 hours) and reaction with nitrate radicals is predicted to be the primary removal mechanism (half-life, ~1/2 hour) during nighttime. Removal from the atmosphere by reaction with ozone or physical processes is expected to be relatively insignificant. If furan is released to water, volatilization is expected to be an important, if not the dominant, removal mechanism. The volatilization half-life of furan in a typical river 1 m deep, flowing 1 m/sec, with a wind speed of 3 m/sec was estimated to be 2.5 hours (see Section 2.2.4.). Chemical hydrolysis, bioaccumulation in aquatic organisms and physical adsorption to suspended solid or sediments are not expected to be important fate processes. If

released to moist soil, furan may be susceptible to rapid volatilization. In the absence of significant biotic or abiotic processes, residual furan in moist soils is susceptible to significant leaching to groundwater. If released to dry soil, furan may volatilize rapidly.

The most probable route of human exposure to furan is by inhalation. Infants may be exposed to this compound by ingestion of mother's milk, since furan had been detected in 1 of 12 samples of mother's milk (Pellizzari et al., 1982). Furan has also been identified as a volatile component of roasted filberts (Kinlin et al., 1972). Furan has been identified as a gas-phase component of cigarette smoke (Sakuma et al., 1975), wood smoke (Kleindienst et al., 1986), exhaust gas from deisel and gasoline engines (Hampton et al., 1982) and volatile emissions from sorb trees (Isidorov et al., 1985). Furan was detected in the expired air of two out of three male smokers and four out of five male nonsmokers from Brooks Air Force Base, TX. The rate of furan expiration ranged between 0.25-98 for smokers and 0.33-28 µg/hr for nonsmokers (Conkle et al., 1975). This compound has also been detected in the expired air from male and female nonsmokers from Chicago, IL (Krotoszynski et al., 1979). This compound has been qualitatively identified in the Niagara River and two creeks in the Niagara River watershed (Elder et al., 1981; Great Lakes Water Quality Board, 1983).

Little information was available concerning toxicity of furan to aquatic biota. Veith et al. (1983) reported a 96-hour LC_{50} of 61 mg/ℓ for fathead minnows. Call et al. (1985) calculated an MATC of 10.0 mg/ℓ based on a NOEC of 8.27 mg/ℓ and a LOEC of 12.2 mg/ℓ from a 31-33 day continuous flow bioassays with early life stages of fathead minnows.

Information regarding the pharmacokinetics of furan was limited. The available data indicate that furan is absorbed extensively by the inhalation route (Egle and Gochberg, 1979) and was distributed to the lungs, kidney and

liver following intraperitoneal injection (Gammal et al., 1984; Wiley et al., 1984). Metabolic activation may be required for furan induced toxicity (Masuda et al., 1984).

Dose-related toxic hepatitis was reported in both sexes of F-344 rats and B6C3F1 mice when furan was administered by gavage for 13 weeks (SRI, 1982a,b). The liver lesions were considered minimal in low-dose rats and did not occur in the two lowest dose groups of male and female mice. High-dose male and female rats and high-dose male mice had reduced body weight gains. Dose-related increase in liver weight was reported in all treated rats except low-dose females and in male and female mice at the two highest dose levels.

Pertinent data regarding the carcinogenicity, teratogenicity or other reproductive effects of furan could not be located in the available literature as cited in Appendix A. Furan was reported to be nonmutagenic when tested in the presence and absence of S-9 in assays with Salmonella typhimurium and Euglena gracilis (Mortelmans et al., 1986; Ebringe et al., 1979). Furan was clastogenic to Chinese hamster ovary cells when cultured in the presence of S-9 (Stich et al., 1981).

A subchronic RfD for oral exposure of 1 mg/day was based on the NOAEL of 2 mg/kg for mice in the 13-week gavage study (SRI, 1982b). Application of an additional uncertainty factor yielded an RfD of 0.1 mg/day for chronic oral exposure. An RQ of 100 for furan was based on the occurrence of severe liver lesions in male mice in the same study (SRI, 1982b).

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LOEC	Lowest-observed-effect concentration
MATC	Maximum acceptable toxicant concentration
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
ppb	Parts per billion
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Furan is also known as furfuran, oxole, divinylene oxide and tetrole (Windholz, 1983). The structure, molecular weight, empirical formula and CAS Registry number for this compound are as follows:

Molecular weight: 68.08

Empirical formula: C_4H_4O

CAS Registry number: 110-00-9

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Furan is a flammable, colorless liquid at room temperature with a strong, ethereal odor (McKillip and Sherman, 1980). Although it will turn brown while standing in air, the addition of a small amount of water will retard color change (Hawley, 1981). Unless stabilized, furan will react slowly with air to form an unstable, explosion-prone peroxide (Dunlop, 1966). Butylated hydroxytoluene (BHT) is added to inhibit this reaction (Verschueren, 1983). Furan is miscible with most common organic solvents including ethyl acetate, methanol, ethanol, acetone, toluene, petroleum ether and chloroform (McKillip and Sherman, 1980; Dunlop, 1966). Pertinent physical properties are as follows:

Melting point, °C:	-85.6	Riddick et al., 1986
Boiling point, °C:	31.4	Riddick et al., 1986
Vapor pressure at 25°C:	600 mm Hg	Boublik et al., 1984
Water solubility at 25°C:	1.01×10^4 mg/ℓ	Valvani et al., 1981
Log K_{OW}:	1.34	Hansch and Leo, 1985
Specific gravity, 20/4°C:	0.9378	Riddick et al., 1986
Refractive index, n_D^{20}:	1.4214	Riddick et al., 1986

Flashpoint, °C:	-36 (closed cup)	Riddick et al., 1986

Furan undergoes substitution and addition reactions under controlled conditions (McKillip and Sherman, 1980). Furan is hydrolyzed by aqueous acids, and this reaction is accompanied by resinification (U.S. EPA, 1986b).

1.3. PRODUCTION DATA

Furan is produced commercially by decarbonylation of furfural (McKillip and Sherman, 1980). QO Chemicals, Inc., Memphis, TN, is the only domestic manufacturer of this compound (SRI, 1986; USITC, 1986). Production volume data could not be located in the available literature as cited in Appendix A.

1.4. USE DATA

Furan is used as an intermediate in the production of other industrial chemicals, especially pyrrole, tetrahydrofuran and thiophene (Hawley, 1981; McKillip and Sherman, 1980). It is also used as an intermediate in the production of pharmaceuticals, herbicides, stabilizers and various polymers (McKillip and Sherman, 1980).

1.5. SUMMARY

Furan is a colorless, flammable liquid at room temperature, with a strong ethereal odor (McKillip and Sherman, 1980). Unless stabilized with BHT, it will react slowly with air to form an unstable, explosion-prone peroxide (Dunlop, 1966). It is miscible with most common organic solvents and is slightly soluble in water (McKillip and Sherman, 1980). Furan is produced commercially by decarbonylation of furfural (McKillip and Sherman, 1980). QO Chemicals, Inc., Memphis, TN, is the only domestic manufacturer of this compound (SRI, 1986; USITC, 1986). Production volume data could not be located in the available literature as cited in Appendix A. Furan is used as an intermediate in the production of other industrial chemicals;

especially pyrrole, tetrahydrofuran and thiophene; for use as pharmaceuticals, herbicides and various polymers (Hawley, 1981; McKillip and Sherman, 1980).

2. ENVIRONMENTAL FATE AND TRANSPORT

Pertinent data regarding the environmental fate and transport of furan are limited. When possible, information concerning fate and transport of this compound were derived from physical property data or molecular structure.

2.1. AIR

Because of its relatively high vapor pressure of 600 mm Hg at 25°C (Boublik et al., 1984), furan is expected to exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al., 1981).

2.1.1. Reaction with Hydroxyl Radicals. The half-life for the reaction of furan with photochemically generated hydroxyl radicals at 22°C has been calculated to be 6.0 and 2.3 hours, using experimentally derived rate constants of 4.0×10^{-11} and 1.05×10^{-10} cm^3/molecule-sec (Atkinson, 1985; Lee and Tang, 1982), respectively, and an average atmospheric hydroxyl radical concentration of 8.0×10^5 molecules/cm^3 (U.S. EPA, 1987)

2.1.2. Reaction with Ozone. The half-life for furan reaction with ozone in the atmosphere was estimated to be 3.3 days, using an experimentally derived reaction rate constant of 2.4×10^{-18} cm^3/molecule-sec at room temperature (Atkinson et al., 1985) and average ambient ozone concentration of 1×10^{-12} molecules/cm^3 (U.S. EPA, 1987).

2.1.3. Reaction with Nitrate Radicals. The half-life for the nighttime reaction of furan with nitrate radicals (nitrate radicals are unstable to sunlight) in the atmosphere was calculated to be 34 minutes, using an experimentally determined reaction rate constant of 1.4×10^{-12} cm^3/molecule-sec at room temperature and an average ambient nitrate radical concentration of 2.4×10^8 molecules/cm^3 during nighttime hours (Atkinson et

al., 1985). By analogy to alkenes and dialkenes, nitrate radical reaction with furan is expected to proceed initially by addition of the NO_3 radical to the olefinic double bonds, followed by rapid addition of O_2 to yield a peroxy radical. Reaction of the peroxy radical with NO_2 can then yield the thermally unstable peroxynitrates. Although the ultimate fate of the peroxy radical is not known, it is likely that ring cleavage would eventually occur, resulting in such species as CHOCH=CHOCHO (Atkinson et al., 1985).

2.1.4. Physical Removal Processes. Reaction of furan with hydroxyl radicals or nitrate radicals is expected to limit the importance of wet deposition as an atmospheric removal process. Furthermore, most furan removed by wet deposition is likely to reenter the atmosphere by volatilization (Section 2.2.4.).

2.2. WATER

2.2.1. Hydrolysis. Based on the molecular structure, furan is expected to be resistant to chemical hydrolysis under environmental conditions (Lyman et al., 1982).

2.2.2. Bioaccumulation. BCFs of 3.4-6.1 were estimated using a log K_{ow} of 1.34 (Hansch and Leo, 1985), a water solubility(S) of 1.01×10^4 mg/ℓ at 25°C (Valvani et al., 1981) and the following linear regression equations (Lyman et al., 1982):

$$\log BCF = 0.76 \log K_{ow} - 0.23 \qquad (2\text{-}1)$$

$$\log BCF = 2.791 - 0.564 \log S \qquad (2\text{-}2)$$

These BCFs suggest that bioaccumulation in aquatic organisms is not a significant environmental fate process for furan.

2.2.3. Adsorption. Estimated K_{oc} values of 27-128 (Section 2.3.1.) suggest that physical adsorption of furan to sediments and suspended solids in water would not be significant.

2.2.4. **Volatilization.** Henry's Law constant for furan was estimated to be 5.3×10^{-3} atm-m³/mol at 25°C using a vapor pressure of 600 mm Hg at 25°C (Boublik et al., 1984) and a water solubility of 1.01×10^4 mg/ℓ at 25°C (Valvani et al., 1981). Based on this value of Henry's Law constant the half-life for furan volatilizing from a typical river 1 m deep, flowing 1 m/sec, with a wind speed of 3 m/sec was estimated to be 2.5 hours, using the method of Lyman et al. (1982). Therefore, volatilization is expected to be the primary transport process for furan in water.

2.2.5. **Biodegradation.** Pertinent data regarding the biodegradation of furan in water could not be located in the available literature as cited in Appendix A.

2.3. SOIL

2.3.1. **Leaching.** K_{oc} values of 27-128 were estimated for furan, using a log K_{ow} value of 1.34 (Hansch and Leo, 1985), a water solubility of 1.01×10^4 mg/ℓ at 25°C and the following linear regression equations (Lyman et al., 1982):

$$\log K_{oc} = -0.55 \log S + 3.64 \qquad (2\text{-}3)$$

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \qquad (2\text{-}4)$$

These K_{oc} values suggest that furan would be highly mobile in soil and susceptible to significant leaching in the absence of significant biotic or abiotic degradation processes (Swann et al., 1983).

2.3.2. **Volatilization.** The relatively high vapor pressure of furan (600 mm Hg at 25°C) (Boublik et al., 1984) suggests that this compound would volatilize fairly rapidly from dry soil surfaces. It appears that volatilization of furan from moist soil surfaces would also be rapid since the compound does not have a tendency to adsorb to soil and it was predicted to volatilize rapidly from water (see Sections 2.2.4. and 2.3.1.).

2.4. SUMMARY

If released to the atmosphere, furan is expected to exist almost entirely in the vapor phase. Reaction with photochemically generated hydroxyl radicals is predicted to be the primary removal mechanism during daylight (half-life, 2-6 hours) and reaction with nitrate radicals is predicted to be the primary removal mechanism (half-life, ~1/2 hour) during nighttime. Removal from the atmosphere by reaction with ozone or physical processes is expected to be relatively insignificant. If furan is released to water, volatilization is expected to be an important, if not the dominant, removal mechanism. The volatilization half-life of furan in a typical river 1 m deep, flowing 1 m/sec, with a wind speed of 3 m/sec was estimated to be 2.5 hours (see Section 2.2.4.). Chemical hydrolysis, bioaccumulation in aquatic organisms and physical adsorption to suspended solid or sediments are not expected to be important fate processes. If released to moist soil, furan may be susceptible to rapid volatilization. In the absence of significant biotic or abiotic processes, residual furan in moist soils is susceptible to significant leaching to groundwater. If released to dry soil, furan may volatilize rapidly.

3. EXPOSURE

The National Occupational Hazard Survey (NOHS), prepared by NIOSH during 1972-1974, estimates that 6804 workers may be exposed to furan in occupational settings, annually (NIOSH, 1984).

3.1. WATER

Limited data are available on the detection of furan in water samples. This compound has been qualitatively identified in Gill Creek and Bloody Run Creek, part of the Niagara River watershed (Elder et al., 1981), and in the Niagara River (Great Lakes Water Quality Board, 1983). This compound was detected in aqueous condensate samples from low-Btu gasification of Rosebud coal at a concentration of 7±4 ppb; however, it was not detected (detection limit 0.1 ppb) in groundwater or coal steam water before in situ coal gasification, product water samples obtained during in situ coal gasification, Omega 9 retort water from in situ oil shale processing or boiler blowdown water from in situ oil shale processing (Pellizzari et al., 1979).

3.2. FOOD

Furan can be found in a great variety of food products and beverages, especially in heated food products, contributing to the flavor of these foods (Stich et al., 1981). Furan has been qualitatively identified in 1 of 12 samples of mothers' milk obtained from women from four different urban areas (Pellizzari et al., 1982). This compound was also identified as a volatile component of roasted filberts (Kinlin et al., 1972).

3.3. INHALATION

Furan has been identified as a gas-phase component of cigarette smoke (Sakuma et al., 1975), wood smoke (Kleindienst et al., 1986), exhaust gas from diesel and gasoline engines (Hampton et al., 1982) and volatile emissions from sorb trees (Isidorov et al., 1985). Furan was detected in

the expired air of two out of three male smokers and four out of five male nonsmokers from Brooks Air Force Base, TX. The rate of expiration ranged from 0.25-98 μg/hour for smokers and 0.33-28 μg/hour for nonsmokers (Conkle et al., 1975). This compound, also identified in the expired air of male and female nonsmokers from Chicago, IL, was found in 15 of 387 expired air samples (mean concentration 0.547 ng/ℓ) taken from 54 subjects (Krotoszynski et al., 1979). Since furan is a volatile compound, it is likely that workers involved in the use or handling of this compound would be exposed by inhalation.

3.4. DERMAL

Pertinent data regarding exposure to furan by dermal contact could not be located in the available literature as cited in Appendix A.

3.5. SUMMARY

The most probable route of human exposure to furan is by inhalation. Infants may be exposed to this compound by ingestion of mother's milk, since it was detected in 1 of 12 samples of mother's milk (Pellizzari et al., 1982). Furan has been identified as a volatile component of roasted filberts (Kinlin et al., 1972), and as a gas-phase component of cigarette smoke (Sakuma et al., 1975), wood smoke (Kleindienst et al., 1986), exhaust gas from deisel and gasoline engines (Hampton et al., 1982) and volatile emissions from sorb trees (Isidorov et al., 1985). Furan was detected in the expired air of two out of three male smokers and four out of five male nonsmokers from Brooks Air Force Base, TX. The rate of furan expiration ranged between 0.25-98 for smokers and 0.33-28 μg/hour for nonsmokers (Conkle et al., 1975). This compound has also been detected in the expired air from male and female nonsmokers from Chicago, IL (Krotoszynski et al., 1979). This compound has been qualitatively identified in the Niagara River

and two creeks in the Niagara River watershed (Elder et al., 1981; Great Lakes Water Quality Board, 1983).

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

The aquatic toxicity data base for furan is limited. Veith et al. (1983) reported a 96-hour LC_{50} of 61 mg/ℓ for fathead minnows, Pimephales promelas, in a continuous flow bioassay.

4.2. CHRONIC EFFECTS

The only information concerning chronic toxicity of furan was provided by Call et al. (1985) who conducted continuous flow bioassays with early life stages of fathead minnows exposed to contaminants for 31-33 days. In this study, the NOEC was 8.27 mg/ℓ. The LOEC was 12.2 mg/ℓ, which resulted in significant reductions in growth in terms of length and weight. Based on these results, the authors estimated an MATC, which was the geometric mean of NOEC and LOEC, of 10.0 mg/ℓ.

4.3. PLANT EFFECTS

Pertinent data regarding effects of furan on aquatic plants could not be located in the available literature as cited in Appendix A.

4.4. SUMMARY

Little information was available concerning toxicity of furan to aquatic biota. Veith et al. (1983) reported a 96-hour LC_{50} of 61 mg/ℓ for fathead minnows. Call et al. (1985) calculated an MATC of 10.0 mg/ℓ based on a NOEC of 8.27 mg/ℓ and a LOEC of 12.2 mg/ℓ from a 31-33 day fathead minnow early life stage test.

5. PHARMACOKINETICS

Pertinent information regarding the pharmacokinetics of furan was limited.

5.1. ABSORPTION

Egle and Gochberg (1979) investigated absorption of furan vapor by the respiratory tracts of mongrel dogs weighing 9-23 kg. Total respiratory tract, lower tract and upper tract (proximal to the tracheal bifurcation) retention was measured in dogs anesthetized with pentobarbital and allowed to breath spontaneously from a respirometer, or artificially ventilated in the case of upper tract determinations. Percent retention was estimated as the difference between the amount of material inspired and expired or recovered at the end of the trachea. Total tract retention was estimated at 90.8-95.3% for inspired concentrations of 0.4-0.6 µg/mℓ (400-600 mg/m³). Lower tract retention ranged from 87.3-93.2%, which is inversely related to ventilation rate. Upper tract retention ranged from 85.4-89.9%, and apparently identical values were obtained from one-way (furan-containing air moving in one direction) and two-way (air movement in both directions) experiments. Retention varied inversely with ventilation rate, which ranged from 6-18 cycles/minute.

5.2. DISTRIBUTION

Furan was distributed to the lungs, kidney and liver of mice following intraperitoneal injection. Gammal et al. (1984) and Wiley et al. (1984) administered a 4.1 mmol/kg (~279 mg/kg) dose of furan in sesame oil by intraperitoneal injection to young adult male ICR mice, and measured the concentration of furan in the lung, liver and kidney at 1, 2 and 5 hours after treatment. Peak levels in the lung and liver of ~200 nmols/g of

tissue (~14 μg/g tissue) were observed at the 1-hour sampling. In the kidney, a concentration of ~110 nmol/g (~7.5 μg/g) at 1 hour increased to ~500 nmol/g (~34 μg/g) by 2 hours after treatment. Terminal concentrations (5 hours) in liver and kidney had declined to ~50 nmol/g (~3.4 μg/g) and in lung, to ~100 nmol/g (~7 μg/g).

5.3. METABOLISM

Studies specifically designed to identify metabolites of furan could not be located in the available literature as cited in Appendix A. Masuda et al. (1984), however, reported that furan-induced nephrotoxicity in mice was increased when mice were pretreated with carbon tetrachloride, a toxicant that selectively destroys the metabolic function of the liver. The investigators concluded that more unmetabolized furan was available for transformation to nephrotoxic compound(s) by the kidney. Administration of diethyldithiocarbamate or carbon disulfide, known inhibitors of the microsomal enzyme system of the liver and kidney, reduced the nephrotoxicity of furan in untreated or carbon tetrachloride treated mice. The investigators hypothesized that diethyldithiocarbamate and carbon disulfide acted directly on the kidney to suppress the metabolic activation of furan to nephrotoxic compound(s).

5.4. EXCRETION

Pertinent data regarding the excretion of furan could not be located in the available literature as cited in Appendix A.

5.5. SUMMARY

Information regarding the pharmacokinetics of furan was limited. The available data indicate that furan is absorbed extensively by the inhalation route (Egle and Gochberg, 1979) and was distributed to the lungs,

kidney and liver following intraperitoneal injection (Gammal et al., 1984; Wiley et al., 1984). Metabolic activation may be required for furan induced toxicity (Masuda et al., 1984).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures. Pertinent data regarding the subchronic and chronic toxicity of furan as a result of inhalation exposure could not be located in the available literature as cited in Appendix A.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- SRI (1982a,b) conducted subchronic gavage studies on furan and used F-344 rats and B6C3F1 mice for 13 weeks at doses ranging from 0-60 mg/kg furan in corn oil, 5 days/week. Groups of 10 male and 10 female rats and 10 female mice received doses of 60, 30, 15, 8, 4 and 0 mg/kg. Groups of 10 male mice received doses of 30, 15, 8, 4, 2 and 0 mg/kg. Gross necropsy was performed on all animals and data regarding mortality, body weight, organ weights, and clinical and histopathological signs of toxicity were evaluated. Complete histopathology was performed on all rats at the 60 and 30 mg/kg levels, all control rats and mice, female mice at the 60 mg/kg level and male mice at the 30 mg/kg level. Clinical signs of toxicity were mostly confined to male and female rats and female mice in the high-dose (60 mg/kg) group. Mortality occurred in 9/10 male and 4/10 female rats at the high-dose level. High-dose male and female rats and high-dose (30 mg/kg) male mice had treatment-related reduced rates of body weight gain. In rats, a dose-related increase in liver size was reported in all treated groups of males and in all but the low-dose group of females. Histopathological examination revealed a dose-related increased severity in liver lesions in the rats, with mild to minimal lesions observed at 4 mg/kg, the lowest level tested. Liver alterations associated with administration of furan included cytomegaly, degeneration, necrosis and nodular hyperplasia of the hepatocytes, cholangiofibrosis, hyperplasia of the bile duct epithelium and a pigment deposition in Kupffer cells. Additional lesions

found only in high-dose animals that were considered treatment related were atrophy of the thymus and gonads, renal tubular dilatation and degeneration and necrosis of the renal tubular epithelium.

In mice, treatment-related increases in liver weight were reported in males at a dose of $\geq$15 mg/kg and in females at doses of $\geq$30 mg/kg. The histopathological examination revealed a dose-related toxic hepatitis at $\geq$15 mg/kg in females and at $\geq$8 mg/kg in males. Liver lesions were not found in male mice receiving doses of $\leq$4 mg/kg and in female mice receiving doses of $\leq$8 mg/kg. In addition to the hepatic alterations reported above in rats, other liver changes reported in mice were focal fibrosis, focal cytological alteration, focal necrosis and focal supportive inflammation.

6.1.2.1. CHRONIC -- Results of an ongoing 2-year NTP-sponsored carcinogenic gavage bioassay in rats and mice are currently not available (NTP, 1987). This study may provide information concerning the chronic toxicity of furan.

6.1.3. Other Relevant Information. In an abstract from a Russian Study, values of 4.2, 2.8 and 1.8 mg/ℓ were reported for LC_{64}, LC_{50} and LC_{16}, respectively, in albino rats (Stasenkova and Kochetkova, 1968). The length of exposure was not reported. Sax (1984) reported an inhalation LC_{50} of 120 mg/m^3 in mice for a 1-hour exposure and an intraperitoneal LD_{50} of 5200 µg/kg for rats. Egle and Gochberg (1979) reported intraperitoneal LD_{50} values of 5.2 mg/kg for rats and 7.0 mg/kg for mice.

6.2. CARCINOGENICITY

6.2.1. Inhalation and Oral. Pertinent data regarding the carcinogenicity of furan by oral or inhalation exposure routes could not be located in the available literature as cited in Appendix A. According to a recent Management Status Report (NTP, 1987), NTP is currently evaluating histopathological data from a chronic gavage study with rats and mice.

6.2.2. Other Relevant Information. Other relevant information regarding the carcinogenicity of furan could not be located in the available literature as cited in Appendix A.

6.3. MUTAGENICITY

Mortelmans et al. (1986) reported negative results in strains TA100, 1535, 1537 and 98 of Salmonella typhimurium when tested by plate incorporation at doses of furan ranging from 33.3-3333.3 µg/plate, both in the presence and absence of S-9, which was purified from livers of rats and hamsters following Aroclor 1254 pretreatment and contained metabolic activation system. Ebringe et al. (1979) also reported that furan was not mutagenic when tested in assays with Salmonella typhimurium and Euglena gracilis. When furan was added to Chinese hamster ovary cell cultures, Stich et al. (1981) reported a concentration-related increase in the incidence of chromatid breaks and exchanges in diploid metaphase cell only in the presence of metabolic activation. Concentrations tested ranged from ~25-225 mM.

6.4. TERATOGENICITY

Pertinent data regarding the teratogenicity of furan could not be located in the available literature as cited in Appendix A.

6.5. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of furan could not be located in the available literature as cited in Appendix A.

6.6. SUMMARY

Dose-related toxic hepatitis was reported in both sexes of F-344 rats and B6C3F1 mice when furan was administered by gavage for 13 weeks (SRI, 1982a,b). The liver lesions were considered minimal in low-dose rats and did not occur in the two lowest dose groups of male and female mice.

High-dose male and female rats and high-dose male mice had reduced body weight gains. Dose-related increase in liver weight was reported in all treated rats except low-dose females and in male and female mice at the two highest dose levels.

Pertinent data regarding the carcinogenicity, teratogenicity or other reproductive effects of furan could not be located in the available literature as cited in Appendix A. Furan was reported to be nonmutagenic when tested in the presence and absence of S-9 in assays with Salmonella typhimurium and Euglena gracilis (Mortelmans et al., 1986; Ebringe et al., 1979). Furan was clastogenic to Chinese hamster ovary cells when cultured in the presence of S-9 (Stich et al., 1981).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in Appendix A. U.S. EPA (1986c) has verified a chronic oral RfD of 0.1 mg/day for furan, based on a NOAEL of 2 mg/kg from a mouse subchronic oral gavage study (SRI, 1982b).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the effects of furan could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

Histopathological examination regarding the carcinogenicity of furan is currently in progress for the 2-year NTP gavage study using rats and mice (NTP, 1987); therefore, lack of data precludes quantitative assessment. However, sufficient data are available for derivation of an RfD for oral exposure.

8.1.1. Weight of Evidence. Since no data are currently available regarding the carcinogenicity of furan to humans or animals, it is classified as an EPA Group D compound (U.S. EPA, 1986d).

8.1.2. Quantitative Risk Estimates. Insufficient information precludes the derivation of quantitative risk estimates for the carcinogenicity of furan by either oral or inhalation exposure.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure. Pertinent data regarding the toxicity of furan by the inhalation route could not be located in the available literature as cited in Appendix A. RfDs for inhalation exposure cannot be derived.

8.2.2. Oral Exposures.

8.2.2.1. LESS THAN LIFETIME (SUBCHRONIC) -- An RfD for furan was previously derived and verified by U.S. EPA (1986c) from oral exposure data reported by SRI (1982a,b). The study was discussed in Section 6.1.2.1. and the following risk assessment was presented by U.S. EPA (1986c).

SRI (1982a,b) conducted a 13-week gavage study using groups of 10 male and female F-344 rats and 10 female B6C3F1 mice treated 5 days/week with doses of 0, 4, 8, 15, 30, and 60 mg/kg furan in corn oil. Male mice, however, were administered with doses of 0, 2, 4, 8, 15 and 30 mg/kg. Data regarding mortality, body weight, organ weights, and clinical and histopathological signs of toxicity were evaluated. High-dose male and

female rats and high-dose male mice had treatment-related reduced rates of body weight gain. Histopathological examination in rats revealed a dose-related increased severity in liver lesions, with lesions observed at the low-dose level considered minimal to mild. A dose-related increase in liver weight was also reported in all treated groups of males and all but the low-dose group of female rats. In mice, treatment-related increases in liver weight occurred in males at $\geq$15 mg/kg and in females at $\geq$30 mg/kg. Histopathological evaluation revealed dose-related toxic hepatitis in male mice at doses of $\geq$8 mg/kg and in female mice at doses of $\geq$15 mg/kg.

The SRI (1982a) data indicate that the rat study failed to define a threshold for toxic hepatitis, which was the critical effect in the target organ for the toxicity of furan. The mouse study (SRI, 1982b) identified a threshold for toxic hepatitis of 4 mg/kg, the highest dose in males at which lesions did not occur; mild lesions of toxic hepatitis occurred at 8 mg/kg in males. In females, lesions of toxic hepatitis were reported at 15 mg/kg but not 8 mg/kg. Since lesions of toxic hepatitis were present in rats at 4 mg/kg, the highest NOAEL identified for both species was 2 mg/kg in the male mice. Since the treatment was performed 5 days/week, the 2 mg/kg dose is transformed to an equivalent dose of 1.4 mg/kg/day. Applying an uncertainty factor of 100 to the mouse NOAEL of 1.4 mg/kg/day results in a subchronic oral RfD of 0.01 mg/kg/day, or 1 mg/day for a 70 kg human. The uncertainty factor of 100 was selected based on a factor of 10 to account for interspecies extrapolation and another factor of 10 to protect the unusually sensitive individuals of the population. The confidence in the RfD is considered medium since the critical study provided adequate toxicity endpoints in a well-designed multispecies oral study, but data were not

available regarding the carcinogenicity, developmental or reproductive toxicity of furan. Availability of the data from the NTP chronic gavage bioassay may change the RfD and the level of confidence (NTP, 1987).

8.2.2.2. CHRONIC EXPOSURES -- No pertinent data are available regarding the chronic oral exposure of furan to animals or humans; however, a chronic oral RfD can be derived from the subchronic RfD by applying an additional uncertainty factor of 10 for extrapolation from subchronic to chronic exposure. Applying an uncertainty factor of 1000 to the mouse NOAEL of 1.4 mg/kg/day results in a chronic oral RfD of 1 μg/kg/day, or 0.1 mg/day for a 70 kg man. A medium level of confidence in the RfD reflects the confidence in the key study and the total data base for furan.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The effects of subchronic oral exposure to furan were discussed in Section 6.1.2.1. and data for derivation of CSs are summarized in Table 9-1. These data indicate three types of toxic effects associated with exposure to furan. Mortality occurred in rats of both sexes in the 60 mg/kg group. Degenerative, necrotic and hyperplastic liver lesions, assigned an RV_e of 8, occurred in male and female rats at 8 mg/kg, in male mice at 8 mg/kg and in female mice at 15 mg/kg. Minimal or mild liver lesions, assigned an RV_e of 6, occurred in male and female rats at 4 mg/kg. CSs are calculated for each of these effects in Table 9-2 using the data that generate the lowest equivalent human dose. The largest CS, 37.6, which corresponds to an RQ of 100 pounds and is associated with degenerative, necrotic and hyperplastic liver lesions in male mice, is chosen to represent the chronic toxicity of furan (Table 9-3).

9.2. BASED ON CARCINOGENICITY

Pertinent data regarding the carcinogenicity of furan could not be located in the available literature as cited in Appendix A. Because histopathology from a 2-year oral gavage study using rats and mice is currently in progress, the data are unavailable (NTP, 1987). Therefore, insufficient data preclude the derivation of carcinogenic potency factors. Furan is assigned to EPA Group D, not classifiable as to carcinogenicity. Hazard ranking based on carcinogenicity is not possible.

TABLE 9-1

Oral Toxicity Summary for Furan

Species/ Strain	Sex/ Number	Average Body Weight[a] (kg)	Purity/ Vehicle	Exposure	Transformed Animal Dose[b] (mg/kg/day)	Equivalent Human Dose[c] (mg/kg/day)	Response	Reference
Rat/Fischer 344	M/10	0.165	>98%/ corn oil	60 mg/kg, 5 days/week, 13 weeks	42.9	5.71	Mortality	SRI, 1982a
Rat/Fischer 344	M/10	0.296	>98%/ corn oil	8 mg/kg, 5 days/week, 13 weeks	5.7	0.92	Degenerative, necrotic, hyperplastic lesions in liver	SRI, 1982a
Rat/Fischer 344	M/10	0.298	>98%/ corn oil	4 mg/kg, 5 days/week, 13 weeks	2.9	0.47	Mild liver lesions	SRI, 1982a
Rat/Fischer 344	F/10	0.151	>98%/ corn oil	60 mg/kg, 5 days/week, 13 weeks	42.9	5.54	Mortality	SRI, 1982a
Rat/Fischer 344	F/10	0.183	>98%/ corn oil	8 mg/kg, 5 days/week, 13 weeks	5.7	0.79	Degenerative, necrotic, hyperplastic lesions in liver	SRI, 1982a
Rat/Fischer 344	F/10	0.179	>98%/ corn oil	4 mg/kg, 5 days/week, 13 weeks	2.9	0.40	Mild liver lesions	SRI, 1982a
Mouse/B6C3F1	M/10	0.034	>98%/ corn oil	8 mg/kg, 5 days/week, 13 weeks	5.7	0.45	Degenerative, necrotic, hyperplastic lesions in liver	SRI, 1982b
Mouse/B6C3F1	F/10	0.025	>98%/ corn oil	15 mg/kg, 5 days/week, 13 weeks	10.7	0.76	Degenerative, necrotic, hyperplastic lesions in liver	SRI, 1982b

[a]Calculated from weekly group average body weight data provided by investigators.

[b]Transformed dosage calculated by expanding treatment over a 7-day week.

[c]Calculated by multiplying the animal dosage by the cube root of the ratio of the animal to human reference body weight (70 kg).

TABLE 9-2

Oral Composite Scores for Furan

Species	Animal Dose (mg/kg/day)	Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rat	42.9	38.8	3.1	Mortality	10	31	100	SRI, 1982a
Mouse	5.7	3.2	4.7	Degenerative, necrotic, hyperplastic liver lesions	8	37.6	100	SRI, 1982b
Rat	2.9	2.8	4.8	Mild liver lesions	6	28.8	100	SRI, 1982a

*Calculated by multiplying the equivalent human dose expressed in mg/kg/day by 70 kg and applying a factor of 10 to expand from subchronic to chronic exposure.

TABLE 9-3

Furan

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral/gavage
Dose*:	3.2 mg/day
Effect:	degenerative, necrotic, hyperplastic liver lesions
Reference:	SRI, 1982b
RV_d:	4.7
RV_e:	8
Composite Score:	37.6
RQ:	100

*Equivalent human dose

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in February, 1987. In addition, hand searches were made of Chemical Abstracts (Collective Indices 5-9), and the following secondary sources should be reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

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APPENDIX B

Summary Table for Furan

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Carcinogenicity	ID	ID	ID	ID	ID
Oral Exposure					
Subchronic	mice	2 mg/kg, 5 days/week, 13 weeks	toxic hepatitis	1 mg/day	SRI, 1982b
Chronic	mice	2 mg/kg, 5 days/week, 13 weeks	toxic hepatitis	0.1 mg/day	SRI, 1982b
Carcinogenicity	ID	ID	ID	ID	ID
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		100			SRI, 1982b
Based on Carcinogenicity:		ID			

ID = Insufficient data