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Provisional Peer Reviewed Toxicity Values for

Thiophene
(CASRN 110-02-1)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR THIOPHENE (CASRN 110-02-1)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided

in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

INTRODUCTION

Computer searches of the following databases were conducted to identify studies regarding the oral and inhalation toxicity of thiophene: TOXLINE (1981-1994), TOXLINE65 (1965-1980), RTECS, TSCATS, DART, ETIC, CANCERLINE, CCRIS, EMIC, EMICBACK and GENETOX. Other sources of information that were consulted include the CARA data base (U.S. EPA, 1991, 1994b), IRIS (U.S. EPA, 1995a; 2007), the Quarterly Status Reports of the RfD/RfC and CRAVE Work Groups (U.S. EPA, 1995b), the HEAST (U.S. EPA, 1995c) and the Drinking Water Regulations and Health Advisories list (U.S. EPA, 1994a), the updated NTP Status Reports (NTP, 1994a, b), the Merck Index (Merck and Company, 1989) and Sax's Dangerous Properties of Industrial Materials (Sax, 1984). No ATSDR Toxicological Profiles for these compounds are available.

Occupational exposure limits for thiophene have not been adopted by ACGIH (1991a, 1993), OSHA (1989, 1993) or NIOSH (1992).

REVIEW OF PERTINENT LITERATURE

Human Studies

No studies were located regarding non-carcinogenic toxic effects in humans following subchronic or chronic oral exposure to thiophene.

Animal Studies

Oral Exposure

No studies were located regarding non-carcinogenic toxic effects in animals following subchronic or chronic oral exposure to thiophene.

Reviews of acute toxicity studies in animals of thiophene (including subacute exposure studies) follow. These studies have identified the nervous system and the liver as potential targets of the compound.

RTECS (1994) lists oral LD50s of 1400 mg/kg for rats and 420 mg/kg for mice; other acute lethality values include an intraperitoneal LD50 for mice of 100 mg/kg and a subcutaneous LD50 for rabbits of 830 mg/kg. Eli Lilly and Company (1992) reported that single oral doses of 500 mg/kg thiophene produced no deaths in 10 female ICR mice within 15 days of administration, but produced generalized leg weakness and tremors that disappeared within 3 days.

Albrechtsen et al. (1974) and Albrechtsen and Jensen (1973) reported that the destruction of small neurons occurs in the granular layer of the cerebellum of rats after 5-10 days of daily subcutaneous injections of 0.4 mL thiophene. Electron microscopic analysis revealed increased cross-sectional areas of mitochondria in Purkinje cells of rats treated with the same daily subcutaneous dosage of thiophene for 30 days. A dose of 2.1 g/kg is calculated based on the reported approximate body weight of the rats (0.2 kg) and a density of 1.05 g/mL for thiophene (Merck and Company, 1989). Several earlier reports also showed that subcutaneous injections of thiophene caused selective necrosis of granule cells in the cerebellum of rats (Herndon, 1968; Christomanos and Scholz, 1933).

McMurtry and Mitchell (1977) administered single i.p. doses of 250 mg/kg thiophene to groups of 10-15 male adult Swiss albino mice with or without pretreatments with phenobarbital (75 mg/kg, i.p., for 3 days), piperonyl butoxide (1360 mg/kg, i.p., 30 minutes before thiophene exposure) or cobaltous chloride ($CoCl_2$-6 H_2O, i.p., twice daily for 2 days). Phenobarbital is an inducer of cytochrome P-450 oxygenases, while piperonyl butoxide and cobaltous chloride are inhibitors of these enzymes. Mice were sacrificed 36 hours after thiophene administration. Livers and kidneys were examined microscopically and scored for degree of necrosis in hepatocytes or cortical and outer stripe renal tubular cells. The scoring system referred to the percentage of cells with necrosis as follows: 0 = no necrosis; 1+ = 1% to 6% necrotic; 2+ = 6% to 25% necrotic; 3+ = 26% to 50% necrotic; 4+ = > 50% necrotic. Renal necrosis was not found

in thiophene-exposed mice, regardless of pretreatment. Thiophene without pretreatment produced hepatic necrosis; the percentages of treated mice were 10%, 10%, 30%, 50% and 0% in the 0, 1+, 2+, 3+ and 4+ categories, respectively. Phenobarbital pretreatment enhanced the hepatotoxic effect; 100% of phenobarbital pretreated mice showed livers with 4+ necrosis. Piperonyl butoxide inhibited the hepatotoxic effect; 93% of mice exposed to thiophene and piperonyl butoxide showed no liver necrosis and only 7% showed a 2+ necrosis. Cobaltous chloride pretreatment also inhibited the hepatotoxic effect of thiophene, but to a lesser extent than the piperonyl butoxide treatment. Percentages of mice treated with thiophene and cobaltous chloride were 46%, 27%, 18%, 9% and 0% in the 0, 1+, 2+, 3+ and 4+ categories, respectively. These results suggest that the hepatotoxic effect of thiophene is mediated through a metabolic intermediate produced, either directly or indirectly, via cytochrome P-450 monooxygenases.

Metabolism

The disposition and metabolism of thiophene has been studied in animals. The results, reviewed in the following paragraph, suggest that thiophene is eliminated from rats and rabbits predominately as the unchanged compound in exhaled air and as a few metabolites in the urine (Bray et al., 1971; Nomeir et al., 1993). A detailed chemical analysis of the major metabolite in rat urine indicated that it was a 2,5-dihydrothiophene sulfoxide bearing a N-acetyl-cysteinyl group on position 2 (Dansette et al., 1992). A metabolic scheme was proposed involving: 1) an initial S-oxidation of thiophene, presumably by cytochrome P-450; 2) an addition of glutathione at position 2 of thiophene-S-oxide; and 3) transformation of the glutathione conjugate to an N-acetylcysteine conjugate. Although the proposed thiophene-S-oxide intermediate has not been isolated, Dansette et al. (1992) have speculated that, because of its highly reactive nature, this proposed intermediate may be responsible for the toxic effects of thiophene.

Bray et al. (1971) found that rats given single oral doses of 200-300 mg/kg thiophene excreted 32% of the dose unchanged in the expired air, < 1% in the feces and 40% in the urine as metabolites. The major metabolite was tentatively identified as 3-hydroxy 2,3-dihydro-2-thienyl mercapturic acid and a minor metabolite was identified as 2-thienyl mercapturic acid. Similar results were found with rabbits (Bray et al., 1971). In experiments with male Fischer 344 rats exposed by nose-only inhalation to radiolabeled thiophene for 1 hour at a concentration of 8000 ppm, Nomeir et al. (1993) found that 16.3% of inhaled thiophene was absorbed by the respiratory tract and that, within 72 hours, 99% of retained thiophene equivalents was excreted, primarily as unchanged thiophene in exhaled air (73.9% of excreted radioactivity) or as metabolites in urine (24.8%). Fecal elimination represented a minor excretory pathway (0.6%). HPLC analysis of methanol extracts of urine indicated that three radioactive metabolites were present, but they were not identified (Nomeir et al., 1993). Dansette et al. (1992) identified a urinary metabolite from rats given single i.p. injections of radiolabeled thiophene that accounted for 94% of the total radioactivity found in urine collected within 50 hours of thiophene injection. The authors reported that an analysis of its ^{1}H and ^{14}C NMR, IR and mass spectra indicated that the metabolite was a 2,5-dihydrothiophene sulfoxide bearing a N-acetyl-cysteinyl group on position 2.

Mutagenicity

Several laboratories found that thiophene did not produce reverse mutations in several strains of Salmonella typhimurium in the presence or absence of rat metabolic activation systems (Florin et al., 1980; Zeiger et al., 1987; Aeschbacher et al., 1989). Additional information regarding the possible mutagenicity or carcinogenicity of thiophene was not located.

Inhalation Exposure

No studies were located regarding non-carcinogenic toxic effects in animals or humans following subchronic or chronic inhalation exposure to thiophene.

Nomeir et al. (1993) stated that thiophene has been reported to cause neurotoxic and cardiovascular system effects in occupationally exposed workers, and to alter light sensitivity of the eyes, but did not cite the original reports. In an earlier review, O'Donoghue (1985) stated that human neurotoxicity due to thiophene had not been reported, but that there are Soviet reports of workers engaged in the synthesis of sulfur-containing compounds including thiophenes who showed changes in the nervous system, the cardiovascular system and particularly the liver (Mukhametova et al., 1974). According to O'Donoghue's review (1985), Soviet experiments showed effects on the light sensitivity of human eyes down to a concentration of about 1 mg/m3, but not at 0.8 or 0.6 mg/m3 (Knikmatullayeva, 1967). Further information concerning toxic effects in humans exposed to thiophene was not located.

Reviews of acute toxicity studies in animals of thiophene (including subacute exposure studies) follow. These studies have identified the nervous system and the liver as potential targets of the compound. RTECS (1994) lists an inhalation LC50 of 9500 mg/m^3 for mice.

NTP (1994c) has sponsored studies of rats and mice exposed to vapors of thiophene, 6 hours/day on weekdays for a total of 12 exposures in whole-body inhalation chambers. Accounts of these studies are only available as abstracts prepared by the laboratory that conducted the study.

In the rat study (NTP, 1994c), Fischer rats of both sexes (the number of rats was not specified) were exposed to thiophene concentrations of 0, 2000, 4000 and 8000 ppm by the aforementioned protocol. Death occurred in all rats exposed to 8000 ppm following one exposure. During the first week of the study, deaths also occurred in the 4000- and 2000-ppm groups, but the incidence of death was not specified. Clinical signs of toxicity were reported to have been observed at the 4000 ppm exposure level including rough haircoat, ocular discharge, nasal discharge, dyspnea and staggering gait. The occurrence of clinical signs of toxicity in the 2000-ppm group was not mentioned. Other thiophene-exposure related effects were described as follows. "Thiophene exposure produced a dose-related depression in group mean body weight relative to control in rats of both sexes. Microscopic examination revealed chronic active inflammation of the lung in rats at the 4000 ppm exposure level and necrotizing inflammation of the liver in all exposure groups with severity increasing with dose. All dose groups of both sexes

surviving until study termination showed a decrease in the absolute lung weight and in the lung to brain weight ratio."

In the mouse study (NTP, 1994c), groups of 10 male and 10 female B6C3F1 mice were exposed by the same protocol to thiophene concentrations of 0, 500, 1000, 2000, 4000 or 8000 ppm. Five mice/sex/group were designated for necropsy and histopathologic evaluation, and five mice/sex/group were included for a neuropathology evaluation. Male mice at all thiophene exposure levels died or were moribund following single exposures. All female mice died in the 4000- and 8000-ppm groups, while 2/10 females died in the 2000-ppm group. In surviving female mice, liver absolute and relative organ weights were increased compared with controls, and thymus organ weight parameters were decreased. No exposure-related effects on body weight or lung weights were found. Mortality was attributed to liver toxicity; centrilobular degeneration of hepatocytes occurred in mice that died within hours of the first exposure. Surviving female mice showed centrilobular necrosis of hepatocytes at all exposure levels. Exposure-related necrotizing inflammation of the nose and nasal cavity also was found. This lesion was more severe in surviving mice than in those that died after the first exposure. The authors reported that no other exposure-related microscopic lesions were found.

DERIVATION OF PROVISONAL SUBCHRONIC AND CHRONIC RFDs FOR THIOPHENE

The acute and subacute toxicity data for thiophene in animals identify the nervous system and the liver as target organs for its toxicity. Metabolic studies indicate that thiophene's acute hepatotoxicity may be mediated by a metabolic intermediate produced by cytochrome P-450 oxygenases. However, the complete lack of exposure-response data following subchronic or chronic exposure by any route precludes the derivation of systemic toxicity values (an RfD) for this compound.

Thiophene is structurally similar to furan, a compound for which an oral RfD, based on a subchronic NOAEL for hepatic lesions in mice, is available on IRIS (U.S. EPA, 1989a). Furan is a 5-membered heterocyclic ring with one oxygen atom, while thiophene's non-carbon cyclic member is a sulfur atom. McMurtry and Mitchell's (1977) comparison of the effects in mice of intraperitoneal injections of these compounds showed that similar dosage levels of either compound (300 mg/kg, furan and 250 mg/kg, thiophene) caused a similar degree of hepatic necrosis. Percentages of furan-treated mice were 0, 29%, 0%, 54% and 19% in the 0, 1+, 2+, 3+ and 4+ necrosis categories; these are similar to results for thiophene cited in the previous section of this paper. Another similarity between the two compounds is that their hepatotoxic effects were diminished by cytochrome P-450 inhibitors and enhanced by a cytochrome P-450 inducing agent. Nevertheless, there are dissimilarities between the biological behavior of the 2 compounds including: 1) the observation that furan produces renal necrosis, but thiophene does not (McMurtry and Mitchell, 1977; NTP 1993), and 2) the evidence that furan's hepatotoxicity may involve cytochrome P-450-mediated formation of a furan epoxide intermediate, while thiophene's hepatotoxicity may involve a thiophene sulfoxide intermediate formed by the same family of enzymes (Dansette et al., 1992). Furan is not recommended as a surrogate for

thiophene in RfD derivation, because it is unknown how these dissimilarities in biological behavior may affect relative differences between exposure-response relationships for the two compounds.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RFCs FOR THIOPHENE

The acute and subacute toxicity data for thiophene in animals identify the nervous system and the liver as target organs for its toxicity. Metabolic studies indicate that thiophene's acute hepatotoxicity may be mediated by a metabolic intermediate produced by cytochrome P-450 oxygenases. However, the complete lack of exposure-response data following subchronic or chronic exposure by any route precludes the derivation of systemic toxicity values (an RfC) for this compound.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR THIOPHENE

Weight-of-Evidence Classification

No studies were located regarding the carcinogenicity of thiophene in animals or humans. Information regarding the genotoxic potential of thiophene is restricted to the finding that thiophene did not produce reverse mutations in several Ames assay tests. On the basis of no human data and inadequate evidence of carcinogenicity in animals, a cancer classification of Group D - Not Classifiable as to Human Carcinogenicity is appropriate. Neither oral slope factors nor inhalation unit risks are derived for Group D chemicals.

In 2007, the available cancer literature was reviewed. No additional cancer data were available. Consequently, the Weight-of-Evidence descriptor was revised to reflect the Agency's revised cancer guidelines. Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) "there is inadequate information to assess the carcinogenic potential of thiophene."

Mode of Action Discussion

A recently completed NTP (1993) lifetime gavage exposure study with rats and mice treated with furan found "clear evidence of carcinogenic activity" of furan in male and female F344/N rats and male and female B6C3F1 mice. Increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and increased incidences of mononuclear cell leukemia were found in furan-treated rats. Increased incidences of hepatocellular neoplasms and benign pheochromocytomas of the adrenal gland were also found in furan-treated mice. It is unknown if lifetime exposure to thiophene would produce similar carcinogenic responses. Although there are some similarities in the behavior of furan and thiophene in biological systems as previously discussed, there are also dissimilarities. How the balance of similar and dissimilar metabolic and toxicologic properties may influence the potential of thiophene to produce cancer, like that produced by furan, is unknown.

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