Substance code
Tetrahydrofuran; CASRN 109-99-9; 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR Tetrahydrofuran

File First On-Line__/__/__

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	on-line	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Tetrahydrofuran
CASRN -- 109-99-9
Section I.A. Last Revised -- 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear

(presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr-d.htm for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This is the first IRIS assessment for THF; thus, no oral RfD was previously available on IRIS.

I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Decreased pup body weight gain Rat two-generation reproduction study Hellwig et al. (2002)/BASF (1996)	$BMDL_{0.05}$: 303 mg/kg-day	1000	0.3 mg/kg-day

* The animals were exposed via drinking water throughout gestation and lactation (7 days/week); thus, no adjustment for intermittent exposure was required. See Section 5.1.2 of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2011) for more details. $BMDL_{0.05}$ = 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to a change in the mean equal to 0.05 relative deviation (SD) from the control mean.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

The oral database for characterizing the potential hazards posed by THF in laboratory animals is limited. A one-generation reproductive toxicity (dose range-finding) study (BASF, 1994) and a two-generation reproductive toxicity study (Hellwig et al., 2002; BASF, 1996) in rats (both in drinking water) exist. Both of these studies identified increased kidney weight, decreased pup body weight gain, and delayed eye opening in F2 pups as the sensitive effects. The two-generation study is considered to be more appropriate for use as the principal study because it used a narrower range of exposure concentrations and larger group sizes, and is the more comprehensive of the two studies. The one-generation study was considered supportive.

Regarding kidney weight effects, increased relative kidney weight was observed at similar doses in the F0 males and females in both the one- and two-generation studies (less than 10% of the control mean). Treatment-related effects on absolute kidney weight were not as pronounced. For example, the only group for which both relative and absolute kidney weights were significantly increased ($p < 0.05$) was F0 males in the two-generation study, although smaller increases (that were not statistically significant) were noted in other groups. The observation that, at least for one group, both absolute and relative kidney weights were increased indicate that these changes reflect the effects of THF on the kidney itself and are not due solely to body weight changes. This conclusion is supported by the general absence of an effect of

THF on body weight gain in adult animals. Kidney weight changes that were observed in the F0 generation were not accompanied by gross kidney pathology, or clinical chemistry findings consistent with an effect on renal function (in the one-generation study) or by histopathological examination (in the two-generation reproductive toxicity study). In addition, exposure to THF had no effect on absolute or relative kidney weight in F1 generation adults. Thus, the kidney data were not considered further in the derivation of the RfD.

Decreases in pup body weight gain in F1 and F2 and delayed eye opening in F2 pups observed in rats of the two-generation reproductive toxicity study were considered candidate critical effects for RfD derivation. The decreases were consistently observed in both the F1 and F2 generation pups, and were most pronounced during PND 7-14. In F2 pups these changes were accompanied with other developmental delays (i.e., delayed eye opening). These changes occurred in the absence of significant maternal body weight changes or other overt signs of systemic toxicity. The candidate critical effects from the two-generation reproductive toxicity study (Hellwig et al., 2002; BASF, 1996) considered for benchmark dose (BMD) modeling were the F1 and F2 pup body weight gains during PND 7-14, as well as F2 delayed eye opening. However, visual inspection of the data set for delayed eye opening in F2 pups suggested that the results were not amenable to modeling. Therefore, this endpoint is represented by a NOAEL of 3000 ppm (385 mg/kg-day). The F1 and F2 pup weight gain data were deemed suitable for BMD modeling and results presented below.

Dataset	Selected Model	$BMD_{0.05}$ (mg/kg-day)	$BMDL_{0.05}$ (mg/kg-day)
F1 males, days 7–14	Linear	457	355
F1 females, days 7–14	Linear	513	376
F2 males, days 7–14	Linear	417	306
F2 females, days 7–14	Linear	440	303

[a]AIC = Akaike Information Criterion.
[b]BMDL = 95% lower bound of the BMD. Subscript denotes the specified benchmark response (BMR) level, 0.05 × (control mean).

Sources: Hellwig et al. (2002); BASF (1996).

The $BMDL_{05}$ of 303 mg/kg-day for reduced pup weight gain in F2 female Wistar rats exposed throughout gestation and lactation was selected as the POD in the derivation of the chronic RfD (Hellwig et al., 2002; BASF, 1996).

I.A.3. UNCERTAINTY FACTORS

UF = 1,000

A default UF of 10 was applied for inter-individual variability (UF_H) to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of THF in humans. Although a human PBPK model based on inhalation exposure of volunteers (Droz et al., 1999) is available, information on the

human variability in response to THF exposure in humans is not available.

A default UF of 10 was applied for interspecies extrapolation (UF_A) to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability) because information was unavailable to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans for THF.

An UF of 1 was applied to account for subchronic to chronic extrapolation (UF_S) because developmental toxicity resulting from a narrow period of exposure was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure.

An UF of 1 was applied for LOAEL-to-NOAEL extrapolation (UF_L) because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of 5% change in pup body weight gain in F2 female rats was selected under an assumption that it represents a minimal biologically significant change.

An UF of 10 was selected to account for deficiencies in the oral database (UF_D). The oral database for THF contains a two-generation reproductive toxicity study and a range-finding one-generation reproductive study (Hellwig et al., 2002; BASF, 1996, 1994). The one-generation study did not include a histopathological examination of tissues and the two-generation study provided the results of histopathologic examinations of the liver, kidney, digestive, and reproductive organs in male and female rats. There are no available human occupational or epidemiological studies or standard toxicity studies, including developmental toxicity studies, in animals via the oral route of exposure. Following inhalation exposure, there are developmental toxicity studies (no two-generation reproductive toxicity studies are available) and chronic and subchronic studies available in rats and mice (NTP, 1998; Mast et al., 1992; DuPont Haskell Laboratory, 1980) which may be informative with respect to the potential oral toxicity of THF. The inhalation developmental studies provided evidence of effects on the fetus, although these studies are limited as they did not provide an evaluation of postnatal development. The subchronic and chronic studies reported systemic toxicity (CNS effects and liver weight changes) at exposure concentrations lower than those inducing developmental toxicity; suggesting that fetuses and weanling animals may not be more sensitive than adult animals. Thus, the lack of studies examining endpoints other than reproductive and developmental toxicity following oral exposure is a database deficiency. Therefore, due to the absence of a developmental toxicity study and other toxicity studies examining a comprehensive array of endpoints following oral exposure to THF, a 10-fold UF was applied.

I.A.4. ADDITIONAL STUDIES/COMMENTS

There are no other subchronic or chronic THF toxicity studies by the oral route.

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study -- Medium

Data Base -- Low
RfD – Low-to-medium

The overall confidence in this RfD assessment is low-to-medium. There is medium confidence in the principal study (Hellwig et al., 2002/BASF, 1996), however, the confidence in the oral THF database is low, with several key data gaps identified, including lack of a full systemic toxicity study and developmental toxicity studies.

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document – U.S. EPA, 2011

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2011).

Agency Completion Date -- __/__/__

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Tetrahydrofuran
CASRN – 109-99-9
Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can

also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This is the first IRIS assessment for THF; thus, no inhalation RfC was previously available on IRIS.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Increased liver weight and centrilobular cytomegaly; CNS effects (narcosis) Subchronic mouse study NTP (1998)	$BMCL_{10}$: 246 mg/m^3	100	2 mg/m^3

*Conversion Factors and Assumptions – Increased absolute liver weight and incidence of centrilobular cytomegaly in female $B6C3F_1$ mice exposed to THF are extrarespiratory tract effects consistent with properties of category 3 gases. The POD was converted to a POD_{ADJ} as follows: POD × hours of daily exposure/24 hours x 5 days/week. The POD_{HEC} was calculated based on the POD_{ADJ} × regional gas dose ratio (RGDR). The RGDR for extrarespiratory effects is calculated by using a default value of 1 for the ratio of the animal-to-human blood:gas (air) partition coefficients because there is no available THF partition coefficient value for mice. See Sections 5.2.2 and 5.2.3 of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2011) for more details.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Animal studies are available that examine inhalation effects of THF following subchronic exposure in rats and mice (NTP, 1998; DuPont Haskell Laboratory, 1996b; Horiguchi et al., 1984; Kawata and Ito, 1984; Stasenkova and Kochetkova, 1963) and 2-year exposure in rats and mice (NTP, 1998), in addition to developmental toxicity studies in both mice (Mast et al., 1992) and rats (Mast et al., 1992; DuPont Haskell Laboratory, 1980). Several of these studies reported portal-of-entry findings, including irritation of the nasal and respiratory tracts (Horiguchi et al., 1984; Kawata and Ito, 1984; Stasenkova and Kochetkova, 1963) but were not considered suitable for RfC derivation due to concerns about lack of consistency among study findings, reporting of these effects, and study design.

Following chronic exposure, no effects or clinical findings were observed in female mice, except for a slight increase in liver necrosis in the 5,310 mg/m^{3}exposure group (from 3/50 in controls to 7/48) (NTP, 1998). Clinical signs of CNS toxicity (narcosis) were the only effects observed in male mice during and up to 1 hour after cessation of exposure to THF at 5,310

mg/m^3. Similar effects were observed following subchronic exposure to THF in which CNS toxicity (narcosis) was reported in both male and female rats at 14,750 mg/m^3 THF and mice at ≥ 5,310 mg/m^3, respectively. Immediately after exposure, both male and female rats in the high exposure group showed ataxia (irregular movement with lack of coordination). Male and female mice exposed to 5,310, and 14,750 mg/m^3 were in a state of narcosis (stupor) during exposure, but were alert and fully awake immediately after exposure to 5,310 mg/m^3 while mice in the 14,750 mg/m^3 group required up to 2 hours for recovery. It should be noted that it is possible that the rats and mice may have developed a tolerance to THF exposure considering the effects were observed at similar concentrations (5,310 mg/m^3) in the subchronic and chronic studies. However, this cannot be determined due to the lack of reporting of incidence data for these effects and because the chronic study did not include the higher exposure group (14,750 mg/m^3) for comparison.

Chronic exposure to THF resulted in liver necrosis in the 5,310 mg/m^3 exposure group for female mice (NTP, 1998). Subchronic exposure to THF (NTP, 1998) provided evidence of increased liver weights (both absolute and relative) in the 14,750 mg/m^3 female rats and this finding was accompanied by increased serum bile acid concentration in the absence of cholestasis or hepatocellular necrosis. The study authors indicated that these changes were consistent with decreased or altered hepatic function. In male mice, absolute and relative liver weights were statistically significantly increased following exposure to concentrations of ≥1,770 mg/m^3. The increases in absolute and relative liver weights in male mice were corroborated by increased incidence of centrilobular cytomegaly, statistically significant at 14,750 mg/m^3 (7/10 compared to 0/10 in controls). Also, relative and absolute liver weights were statistically significantly increased in female mice beginning at 5,310 mg/m^3 and were accompanied by centrilobular cytomegaly (10/10 animals compared to 0/10 in controls) at 14,750 mg/m^3. The hepatocytes were additionally described as having slight karyomegaly (enlarged nucleus), increased cytoplasmic volume, and granular cytoplasm with less vacuolation than that of midzonal and periportal hepatocytes (NTP, 1998). No clinical chemistry measurements were performed in mice; however, the finding of increased bile acids in rats, in the absence of increased serum liver enzymes, was interpreted as possibly signifying decreased or altered hepatocellular function in the 14,750 mg/m^3 exposure group.

In consideration of the available studies reporting effects of chronic and subchronic THF exposure in animals, the NTP (1998) study was chosen as the principal study. The subchronic phase, rather than the chronic phase, of this study was selected to serve as the principal study due comprehensive reporting in the subchronic study which better characterized the low-dose effects associated with THF. Sensitive endpoints identified in this study, the effects in the CNS and liver, were selected as the co-critical effects. The CNS effects were observed in rats and mice (at concentrations ≥5,310 mg/m^3) and the liver effects were observed in rats (at concentrations of 14,750 mg/m^3) and mice (at concentrations ≥590 mg/m^3). The toxicological significance of the observed liver weight changes was considered to be uncertain at the low concentrations (590-1,770 mg/m^3), where the changes were of minimal severity and were not accompanied by other signs of liver toxicity. The increases in absolute and relative liver weights at 5,310 mg/m^3 were greater than 10% above controls (statistically significant) and were accompanied by minimal increases in histopathology findings (1/10 incidence in centrilobular cytomegaly) that progressed with increases in THF concentration. The liver and CNS effects observed at the exposure

concentration of ≥5,310 mg/m^3 were considered biologically significant and representative of adverse effects.

The candidate critical effects from the subchronic toxicity study (NTP, 1998) considered for benchmark dose (BMD) modeling were the liver and CNS effects in female mice. For CNS effects in mice, no incidence data were available, and a NOAEL of 1,770 mg/m^3 was identified as the POD. The adjustment for human equivalent continuous concentration corresponds to a candidate POD of 316 mg/m^3. The increased liver weight and centrilobular cytomegaly were amenable for BMC modeling and results are presented below.

Dataset	**Selected Model**	**$BMC_{0.10}$[b]**	**$BMCL_{0.10}$[b]**
Absolute liver weight	Power (unrestricted)	783	246
		BMC_{10}	**$BMCL_{10}$**
Centrilobular cytomegaly	Multistage, degree 2 (coefficients ≥0)	805	256

[a]Concentrations used in the modeling were the HECs in mg/m^3.
[b]For liver weights, $BMC_{0.10}$ and $BMCL_{0.10}$ refer to a BMR of 10% increase in the control mean, while for centrilobular cytomegaly, BMC_{10} and $BMCL_{10}$ refer to 10% extra risk.

Data Source: NTP (1998).

Of the three candidate PODs, the $BMCL_{10}$ of 246 mg/m^3 based on findings of increased absolute liver weight in male mice, was selected as the POD for deriving the RfC because it was the most sensitive endpoint.

I.B.3. UNCERTAINTY FACTORS

UF = 100

A default UF of 10 was applied for inter-individual variability (UF_H) to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the pharmacokinetics and pharmacodynamics of THF in humans. Although a human PBPK model based on inhalation exposure of volunteers (Droz et al., 1999) is available, information on human variability relating to toxicodynamics and toxicokinetics in response to exposure to THF is not available.

A default UF of 3 was applied for interspecies extrapolation (UF_A) to account for the uncertainty in extrapolating from laboratory animals to humans. This value is adopted by convention where an adjustment from an animal-specific POD_{ADJ} to a POD_{HEC} has been incorporated. Application of an UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component associated with exposure to THF is mostly addressed by the determination of an HEC as described in the RfC methodology (U.S. EPA, 1994b). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method and an UF of 3 is retained to account for residual uncertainty regarding the toxicodynamic differences between mice and humans.

An UF of 1 was applied to account for extrapolation from subchronic-to-chronic exposure (UF_S), due to the lack of evidence that increased duration of exposure to THF may not increase the incidence or severity of these effects. The 14-week study for THF (NTP, 1998), selected as the principal study, reported critical findings of CNS effects and increased liver weight which was supported by hepatic centrilobular cytomegaly. In the chronic exposure phase of the study, while no organ weights were taken, no hepatic cytomegaly was identified at any exposure level including the high exposure group of 5,310 mg/m^3. However, the incidence of liver necrosis in the female mice of the 5,310 mg/m^3 exposure group was increased (although not statistically significant) from 3/50 in the control to 7/48. The available chronic information suggests that liver damage observed in rodents following subchronic exposure to THF (NTP, 1998) may not progress to more severe effects following chronic exposures near the POD, considering that cytomegaly was not reported at chronic exposures ≤ 5,310 mg/m^3 and that necrosis was only observed at 5,310 mg/m^3 (the highest concentration), the same concentration as the LOAEL for the CNS and liver effects in the subchronic study. Additionally, the CNS effects were observed following exposure to 5,310 mg/m^3 in both the subchronic and chronic studies but with no evidence of effects at lower concentrations in the chronic study. A full comparison of the studies is not possible given the incidence data were not reported for these effects in either study. However, the available evidence suggests that increased duration of exposure to THF may not increase the incidence or severity of these effects; thus, a 1-fold UF was applied.

An UF of 1 was applied for LOAEL-to-NOAEL extrapolation (UF_L) because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of 10% change in absolute liver weight in male mice was selected under an assumption that it represents a minimal biologically significant change.

An UF of 3 was applied to account for deficiencies in the database (UF_D) for THF. Chronic and subchronic inhalation bioassays and developmental toxicity studies are available in rats and mice (NTP, 1998; Mast et al., 1992; DuPont Haskell Laboratory, 1980). No two-generation reproductive toxicity study by the inhalation route is available. The inhalation data for THF suggest that fetuses and weanling animals may not be more sensitive than adult animals given that the observed LOAELs for developmental effects were greater than the LOAELs for systemic toxicity (CNS and liver weight changes) in adult animals. However, the inhalation developmental studies are limited, since they did not provide an evaluation of postnatal development. In the oral two-generation reproductive toxicity study for THF, postnatal development (decreased pup body weight gain, in addition to delayed eye opening and increased incidence of sloped incisors) was affected at drinking water concentrations that had minimal effects on the dams. Therefore, a database UF of 3 was applied to account for the lack of a two-generational reproductive study.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Further support for THF-induced CNS effects is provided by neurotoxicity, developmental, acute, and short-term studies. The only findings in a neurotoxicity study were sedative effects in male and female rats at 4,425 and 8,850 mg/m^3 (DuPont Haskell Laboratory,

1996b; Malley et al., 2001). Developmental studies conducted in both rats and mice reported maternal toxicity including CNS effects (Mast et al., 1992). Following acute and short-term exposure, symptoms of CNS toxicity, including sedation, coma, altered respiration, and decreased response to external stimuli, were observed in dogs (Stoughton and Robbins, 1936), mice (Stasenkova and Kochetkova, 1963; Stoughton and Robbins, 1936), and rats (Horiguchi et al., 1984; DuPont Haskell Laboratory, 1979; Stasenkova and Kochetkova, 1963). Additionally, human CNS effects may result from THF occupational exposure. Based on the above findings, the CNS toxicity was further considered as a candidate critical effect in the derivation of the RfC.

Further support in the database exists for liver effects following THF exposure. Specifically, fatty liver degeneration (or infiltration) which was observed following short-term inhalation exposure in female mice (Gamer et al., 2002; BASF, 2001a) is a likely adverse effect since certain drugs which evoke fatty liver changes may predispose the liver to oxidative stress, lipid peroxidation, and possible mitochondrial and organ damage (Begriche et al., 2006; Letteron et al., 1996). In another subchronic inhalation toxicity study, Horiguchi et al. (1984) reported mild liver toxicity in male rats in the form of increased serum liver enzymes, bilirubin, and cholesterol at THF exposure concentrations of 2,950 and 14,750 mg/m^3 in addition to increased relative liver weight at 14,750 mg/m^3 but no liver histopathology findings were reported. Some earlier studies also reported liver effects when THF was administered in animals using exposure routes other than inhalation (Stasenkova and Kochetkova, 1963; Komsta et al., 1988). The human liver also may be a target organ for THF occupational exposure settings. While the reported liver findings may be confounded by the likelihood of coexposure to other chemicals, it is reasonable to conclude that repeated occupational exposure to high concentrations of THF may have contributed to the large increases in serum liver enzymes and the palpable liver findings in some of the human studies (Garnier et al., 1989; Horiuchi et al., 1967).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study -- High
Data Base – Medium-to-high
RfC – Medium-to-high

The overall confidence in this RfC assessment is medium to high. Although chronic toxicity studies and developmental toxicity studies were available for the inhalation route, no multigeneration reproduction toxicity study by the inhalation route is available; thus, the confidence in the database is medium-to-high. Based on high confidence in the well-conducted critical study and medium-to-high confidence in the database, the overall confidence in the RfC can be characterized as medium-to-high.

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – U.S. EPA, 2011

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments

received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2011).

Agency Completion Date -- __/__/__

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Tetrahydrofuran
CASRN – 109-99-9
Section II. Last Revised -- 00/00/0000

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per μg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

This is the first IRIS assessment for THF. Therefore, no previous characterization of cancer potential or quantitative cancer evaluation exists.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for THF provides "suggestive evidence of carcinogenic potential." No human data are

available to assess the carcinogenic potential of THF. A 2-year NTP (1998) inhalation cancer bioassay reported a marginally increased incidence of renal tubule adenomas and carcinomas in male F344/N rats (statistically significant exposure-response trend) and an increased incidence of hepatocellular adenomas and carcinomas in female $B6C3F_1$ mice (statistically significant trend and increase incidence at the highest concentration tested) following inhalation exposure. No other treatment-related increases in tumor incidence were observed. NTP (1998) concluded that the data provided *some evidence* for THF carcinogenicity in male rats (renal tubular adenomas and carcinomas) and *clear evidence* of carcinogenicity in female mice (hepatocellular adenomas and carcinomas). There was no evidence of carcinogenic activity in female rats. Likewise, in male mice there was no evidence of carcinogenicity reported by NTP (1998).

U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information, e.g., pharmacokinetic data that absorption does not occur by another route. Information available on the carcinogenic effects of THF via the inhalation route demonstrates that tumors occur in tissues remote from the site of absorption. Information on the carcinogenic effects of THF via the oral and dermal routes in humans or animals is not available. Based on the observance of systemic tumors following inhalation exposure, and in the absence of information to indicate otherwise, it is assumed that an internal dose will be achieved regardless of the route of exposure. Therefore, there is "suggestive evidence of carcinogenic potential" following exposure to THF by all routes of exposure.

II.A.2. HUMAN CARCINOGENICITY DATA

None.

II.A.3. ANIMAL CARCINOGENICITY DATA

The NTP (1998) chronic inhalation exposure bioassay in laboratory animals was adequately designed to assess the carcinogenic potential of lifetime inhalation exposure to THF. This study involved exposure of F344/N rats (50/sex/group) and $B6C3F_1$ mice (50/sex/group) to 0, 200, 600, and 1,800 ppm (0, 590, 1,770, and 5,310 mg/m^3) THF for 6 hours/day, 5 days/week for 105 weeks. For the male rats, a statistically significant treatment-related trend was observed for combined incidences of renal tubular epithelial adenomas or carcinomas (1/50, 1/50, 4/50, and 5/50) (NTP, 1998). The response was predominantly benign except for two carcinomas present at the high exposure concentration. The individual incidences of the kidney adenomas or carcinomas in the high exposure male rats appeared to exceed the incidence of these tumors in F344/N historical controls (rate: 0.9 ± 1.3%; range: 0–4%) but were not statistically significant when compared with the concurrent controls (NTP, 1998).

In female mice there was a statistically significant increased incidences of hepatocellular adenomas or carcinomas at the high concentration (1,800 ppm) and a positive trend for these hepatocellular neoplasms across exposure to 200, 600, and 1,800 ppm THF compared with controls (17/50, 24/50, 26/50, and 41/48) (NTP, 1998). The females also showed a statistically

significant positive trend in hepatocellular carcinomas (albeit not a significantly increased incidence; 6/50, 10/50, 10/50, and 16/48). There was no statistically significantly increased incidence of hepatocellular adenomas or carcinomas in male mice (35/50, 31/50, 30/50, and 18/50), even after adjustment for differential survival.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Results from genotoxicity studies for THF are mostly negative and provide very limited evidence to suggest a genotoxic mode of action. All bacterial mutation assays were negative for THF genotoxicity. In vitro genotoxicity assays with eukaryotic cells also proved to be negative with the exception of a slight increase in chromosomal aberrations in Chinese hamster ovary cells with metabolic activation. In vivo studies suggest that THF is not likely to be mutagenic; however, studies have not been conducted in target tissues.

There are some data suggesting that the observed renal tumors in the male rats may be secondary to α_{2u}-globulin accumulation. A review of the data available for THF indicates that the data do not support an α_{2u}-globulin-related MOA. Another consideration regarding the renal tumors is the possibility that advanced chronic progressive nephropathy (CPN) may play a role in the incidence of atypical tubule hyperplasia (ATH) and perhaps the THF-induced kidney tumors in male rat kidneys). CPN is an age-related renal disease of laboratory rodents that occurs spontaneously. There was no difference in the incidence or severity of CPN in the control versus treated male rats of the NTP 2-year carcinogenicity study on THF. Therefore, although THF did not exacerbate development of CPN, it is possible that it may have exacerbated the development of proliferative lesions within CPN-affected tissue; however, there is no direct evidence to support this. Thus, the kidney tumors observed in male rats are considered relevant to the assessment of the carcinogenic potential of THF to humans.

For the liver tumors in mice, some mechanistic data suggest that THF may induce cell proliferation and lead to a promotion in the growth of pre-initiated cells. However, key precursor events linked to observed cell proliferation have not been clearly identified and the available data are insufficient to establish a mode of action for the THF liver tumor induction. Thus, the liver tumors observed in female mice are considered relevant to the assessment of the carcinogenic potential of THF to humans.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

No oral slope factor for THF was derived. Cancer bioassays involving oral exposure to THF are not available, and a route-to-route extrapolation is not recommended due to the lack of physiologically based pharmacokinetic models for THF.

II.B.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

II.C.1.1. Inhalation Unit Risk - 3×10^{-6} per $\mu g/m^3$

The inhalation unit risk is derived from the HEC $BMCL_{10}$, the 95% lower bound on the exposure associated with a 10% extra cancer risk of liver tumors in female $B6C3F_1$ mice, by dividing the risk (as a fraction) by the $BMCL_{10}$, and represents an upper bound, continuous lifetime exposure risk estimate:

$BMCL_{10}$, lower 95% bound on exposure at 10% extra risk - 35 mg/m^3
BMC_{10}, central estimate of exposure at 10% extra risk - 52 mg/m^3

The slope of the linear extrapolation from the central estimate BMC_{10} is $0.1/(52\ mg/m^3) = 2 \times 10^{-6}$ per $\mu g/m^3$.

The unit risk for THF should not be used with exposures exceeding the point of departure ($BMCL_{10}$ or 35 mg/m^3), because, above this level, the modeled dose-response better characterizes what is known about the carcinogenicity of THF than the inhalation unit risk.

Air Concentrations at Specified Risk Levels:

Risk Level	Lower Bound on Concentration Estimate
E-4 (1 in 10,000)	35 $\mu g/m^3$
E-5 (1 in 100,000)	3.5 $\mu g/m^3$
E-6 (1 in 1,000,000)	0.35 $\mu g/m^3$

II.C.1.2. Extrapolation Method

Multistage model with linear extrapolation from the point of departure ($BMCL_{10}$).

II.C.2. DOSE-RESPONSE DATA

Tumor type – Liver hepatocellular adenomas or carcinomas
Test species – Female $B6C3F_1$ mice
Route – Inhalation
References – NTP, 1998

Lesion	Concentration (ppm)			
	0	200	600	1,800
Female B6C3F$_1$ mice				
Hepatocellular adenoma or carcinoma				
Overall incidence[a]	17/50	24/50	26/50	41/48
Adjusted rate[b]	46.3%	61.3%	69.1%	93.0%
Adjusted incidence[c]	17/37	24/39	26/38	41/44
Trend test p-values[d]	$p < 0.001$			

[a]Number of animals with tumors per number of animals examined.
[b]Kaplan-Meier estimated tumor incidence at the end of the study, incorporating an adjustment for intercurrent mortality.
[c]Adjusted denominator estimated by dividing numerator (tumors) by the adjusted rate expressed as a proportion (e.g., 0.083 rather than 8.3%).
[d]Trend tests: logistic regression

Source: NTP (1998).

II.C.3. ADDITIONAL COMMENTS

Exposures were converted to human equivalent exposures considering inhalation dosimetry (U.S. EPA, 1994). An upper limit for each unit risk was estimated by linear extrapolation from the lower confidence limit on exposure at the POD. The data for female mouse liver tumors were selected for the derivation of the POD for the quantitative concentration-response assessment since the data provided the strongest carcinogenic response to inhalation exposure in animals. The resulting (upper bound) unit risk included adjustment for continuous exposure. See the *Toxicological Review of Tetrahydrofuran* for more information (U.S. EPA, 2011).

II.C.4. DISCUSSION OF CONFIDENCE

Though some mode-of-action information is available, the weight of evidence evaluation is insufficient to establish the mode of action for THF-induced kidney and liver tumors. The lack of activity in a number of mutagenicity assays indicates that a genotoxic mode of carcinogenic action is most likely not responsible for the tumorigenic activity of THF. Additional studies exploring other mode(s) of action for THF-induced kidney and liver tumors were also inconclusive.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA, 2011

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2011).

II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Tetrahydrofuran
CASRN – 109-99-9
Section VI. Last Revised -- 00/00/0000

VI.A. ORAL RfD REFERENCES

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VII. REVISION HISTORY

Tetrahydrofuran
CASRN – 109-99-9
File First On-Line __/__/__

Date	Section	Description
__/__/__	I., II, and VI.	RfD and RfC added; cancer assessment added.

VIII. SYNONYMS

Tetrahydrofuran
CASRN – 109-99-9
Last Revised -- 00/00/0000

109-99-9
THF
diethyleneoxide
tetramethyleneoxide
1,4-epoxy butane
furanidine;
oxacyclopentane