Tetrahydrofuran; CASRN 109-99-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development 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.

STATUS OF DATA FOR Tetrahydrofuran

File First On-Line 02/21/2012

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	02/21/2012
Inhalation RfC (I.B.)	yes	02/21/2012
Carcinogenicity Assessment (II.)	yes	02/21/2012

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Substance Name – Tetrahydrofuran
CASRN – 109-99-9
Section I.A. Last Revised – 02/21/2012

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 IRIS Guidance Documents Web page 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 reproductive study** **Hellwig et al. (2002)/BASF (1996)**	$BMDL_{1SD}$: 928 mg/kg-day	1000	0.9 mg/kg-day

*Conversion Factors and Assumptions – 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, 2012) for more details. $BMDL_{1SD}$ = 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to a 1 SD (standard deviation) change from the control mean.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

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. The two-generation study was selected as the principal study for the RfD. It is a well-conducted, reproductive toxicity study and is considered to be more appropriate for use as the principal study, compared with the one-generation 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.

Decreased pup body weight gain in F1 and F2 pups observed in rats of the two-generation reproductive toxicity study was selected as the critical effect for RfD derivation. The decreases in body weight gain were consistently observed in both the F1 and F2 generation pups, and were most pronounced during PND 7–14. The decreases were dose-related, with a positive test

for trend ($p < 0.01$), for both male and female pups of both generations. Specifically, body weight gain was decreased by approximately 10–12% at the high dose in the F1 pups and 3–7% and 10% at the mid and high doses, respectively, in the F2 pups. The body weight gain decreases in F2 pups were accompanied by other developmental delays (i.e., delayed eye opening and increased incidence in sloped incisors). These changes occurred in the absence of significant maternal body weight changes or other overt signs of systemic toxicity. EPA concluded that these endpoints indicated delayed or altered growth following exposure to THF; an effect which is one of four major manifestations of developmental toxicity. These endpoints in pups are considered common markers of an adverse toxicological effect on development and are consistent with the principles and practices of the EPA's *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991).

Details of the dose-response modeling conducted for each endpoint are presented in Tables 5–2 and B–1 (Appendix B) of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012). A 1 standard deviation (SD) change in body weight gain compared with the control was selected as the BMR. In the case of a decreasing response, a 1 SD change from the control mean corresponds to 10% of an exposed population having larger decreases in body weight gain than the lowest 1% of the control group, when the data follow a normal distribution (U.S. EPA, 2000). The modeling was conducted following EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000) and the results are shown below in Table 1.

Table 1. BMD modeling results for pup body weight gain in the Wistar rat two-generation reproductive toxicity study (Hellwig et al. 2002/BASF, 1996)

Dataset	Selected Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$[a] (mg/kg-day)
F1 males, days 7–14	Linear	1257	928
F1 females, days 7–14	Linear	1559	1152
F2 males, days 7–14	Linear	1589	1131
F2 females, days 7–14	Linear	1661	1174

[a]$BMDL_{1SD}$ = 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to a 1 SD change from the control mean.

For pup body weight gain decreases induced by THF, the candidate points of departure (PODs), shown in Table 1, ranged from 928 to 1174 mg/kg-day. The decreased pup body weight gain in F1 males was selected as the basis for the POD for the RfD because this group corresponded to the lowest POD (i.e., 928 mg/kg-day).

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 exposure to THF 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 (U.S. EPA, 1991).

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 a 1 SD decrease from the control mean in body weight gain of F1 male rat pups was selected.

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. The two-generation study provided the results of histopathologic examinations limited to evaluations 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 via the oral route of exposure. Additionally, the database is lacking developmental toxicity studies. Although route-to-route extrapolation was not possible due to inadequate PBPK models (see

Section 3.6 and 5.1.1 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]), the inhalation database was considered. 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). The inhalation developmental studies provided evidence of effects on the fetus. 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 prenatally exposed fetuses may not be more sensitive than adult animals. Thus, the lack of studies examining endpoints other than reproductive toxicity (i.e., standard toxicity studies examining a comprehensive array of endpoints and developmental studies) following oral exposure is a database deficiency; 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.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

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

Study — Medium
Data Base — Low
RfD — Low-to-medium

A confidence level of high, medium, or low is assigned to the study used to derive the RfD, the overall database, and the RfD itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). There is medium confidence in the principal study (Hellwig et al., 2002; BASF, 1996); however, the overall 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. Therefore, the confidence in the RfD is characterized as low-to-medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

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

Source Document – *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012)

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, 2012). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

Agency Completion Date - 02/21/2012

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

Substance Name – Tetrahydrofuran
CASRN – 109-99-9
Section I.B. Last Revised – 02/21/2012

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 RfC
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 male $B6C3F_1$ 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 × 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, 2012) for more details.

**The liver effects (increased liver weight and cytomegaly) and CNS effects in male mice are considered co-critical effects and the PODs for these effects are similar, ranging from 246-316 mg/m^3. The lowest of these three PODs, the $BMCL_{10}$ of 246 mg/m^3 based on increased absolute liver weight, was used to calculate the RfC.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

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 to comprehensive reporting in the subchronic study which better characterized the low-exposure effects associated with THF. As shown in Table 2, the designs of the subchronic and chronic exposure studies by NTP (1998) with respect to the exposure concentrations of THF and the examined parameters are somewhat different.

Table 2. Subchronic and chronic inhalation toxicity studies of THF in mice and rats (NTP, 1998): Exposure concentrations and examined non-neoplastic parameters

Study	Exposure Concentration	Parameters Evaluated
Subchronic (13-week) study: 10/sex/exposure group of rats or mice	0, 195, 590, 1,770, 5,310, 14,750 mg/m^3	Body weight, clinical observation, clinical chemistry, organ weights, complete histopathology for control and high concentration groups; gross lesions and potential target tissue histopathology for other exposure groups
Chronic (2-year) study: 50/sex/exposure group of rats or mice	0, 590, 1,770, 5,310 mg/m^3	Body weight, clinical observations, tissue histopathology

Following chronic exposure, no clinical findings were observed in female mice; however, 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 (NTP, 1998; chronic). 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 (NTP, 1998; subchronic). 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 (NTP, 1998; chronic). 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 by NTP (1998). 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 a slight increase in liver necrosis in the 5,310 mg/m^3 exposure group for female mice (from 3/50 in controls to 7/48) (NTP, 1998; chronic). No other non-neoplastic findings were seen in male or female mice or rats following chronic exposure. Subchronic exposure to THF (NTP, 1998; subchronic) 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 concentration-dependent and statistically significantly increased (7 – 36% above control) following exposure to concentrations of ≥1,770 mg/m^3. The increases in absolute and relative liver weights in male mice were supported by an increased incidence of centrilobular cytomegaly (graded mild), statistically significant at 14,750 mg/m^3 (7/10 compared to 0/10 in the next lower exposure group and the controls). Also, relative and absolute liver weights were significantly increased (6 – 14% above control) in female mice beginning at 5,310 mg/m^3 and were accompanied by centrilobular cytomegaly (graded minimal) at 14,750 mg/m^3 (10/10 animals compared to 0/10 in the next lower exposure group and the controls) (NTP, 1998; subchronic). The affected 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; subchronic). Liver tissues from male and female mice of the three lower exposure groups were not examined. Additionally, 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.

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 (U.S. EPA, 2002; 1998).

The most relevant endpoints for deriving the POD for the quantitative assessment were CNS effects, hepatic centrilobular cytomegaly, and increased liver weights in male mice in the NTP (1998) subchronic study. Data in mice, rather than rats, were modeled because mice were more sensitive to the THF-induced liver and CNS effects. The selection of the male mouse data was based on the fact that the liver weight increased more steadily from lower administered exposure in males than in females. Suitable data were available to model the

liver weight and liver histopathology findings using dose-response modeling methods (see Table 5-4 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]). Note that because there was very little effect on body weight until the highest exposure, the absolute and relative liver weight changes were essentially the same, and only the absolute liver weights were considered for modeling. For CNS effects, no incidence data were available from the NTP (1998) study, therefore dose-response modeling could not be conducted for this endpoint, and a NOAEL was identified for the candidate POD.

The dose-response modeling was conducted following EPA draft BMD technical guidance (U.S. EPA, 2000) and using similar to methods utilized for the RfD. For liver weights, a BMR of a 10% change relative to control mean was used, by analogy to its use in evaluating adult body weight changes. For centrilobular cytomegaly, no biological criterion for defining adversity was available, and a 10% extra risk was used under the assumption that is represents a minimal, biologically significant effect level.

Table 3. BMC[a] modeling results for noncancer liver effects in male mice resulting from subchronic inhalation exposure to THF (NTP, 1998)

Dataset	Selected Model	BMC_{10}[b]	$BMCL_{10}$[b]
Absolute liver weight	Power (unrestricted)	783	246
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_{10} and $BMCL_{10}$ refer to a BMR of 10% increase over the control mean; for centrilobular cytomegaly, BMC_{10} and $BMCL_{10}$ refer to 10% extra risk.

For CNS effects in male and female 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 liver effects (increased liver weight and cytomegaly) and CNS effects in male mice are considered co-critical effects and the PODs for these effects are similar, ranging from 246-316 mg/m^3. The lowest of these three PODs, the $BMCL_{10}$ of 246 mg/m^3 based on findings of increased absolute liver weight in male mice, was used to calculate 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 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 human variability relating to toxicodynamics and toxicokinetics in response to exposure to THF is not available.

An UF of 3 (i.e., $10^{1/2}$ = 3.16 rounded to 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, 1994). 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 the remaining 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 increase the incidence or severity of these effects. The 14-week study for THF (NTP, 1998; subchronic), 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 (NTP, 1998; chronic) 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 $\leq$ 5,310 mg/m^3 and that necrosis was only observed at 5,310 mg/m^3 (the highest concentration in chronic study), 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, an UF of 1 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 as 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). The inhalation data for THF suggest that fetuses 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. 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. No two-generation reproductive toxicity study by the inhalation route is available. Therefore, a database UF of 3 was applied to account for the lack of a two-generation 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,1996; 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, as reported in Section 4.1 of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012), human CNS effects may result from THF occupational exposure.

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, 2001), 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 (Section 4.2.1.2 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]). Some earlier studies also reported liver effects when THF was administered in animals using exposure routes other than inhalation (Komsta et al., 1988; Stasenkova and Kochetkova, 1963). As reported in Section 4.1 of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012), 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).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

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

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

As noted above, a confidence level of high, medium, or low is assigned to the study used to derive the RfC, the overall database, and the RfC itself, as described in EPA (U.S. EPA, 1994), Section 4.3.9.2. The principal study used to derive the RfC (NTP, 1998) was a well-conducted and documented study reflecting high confidence. The study included subchronic and chronic exposure duration components in two species by the relevant route of exposure, evaluated a comprehensive array of tissues, and covered a well-spaced concentration range. Confidence in the supporting database is medium to high. Although chronic toxicity studies (NTP, 1998) and developmental toxicity studies (Mast et al., 1992; DuPont Haskell Laboratory, 1980) were available for the inhalation route, no multigeneration reproductive toxicity study by the inhalation route is available. Both the inhalation developmental toxicity studies (Mast et al., 1992; DuPont Haskell Laboratory, 1980) and the oral two-generation reproductive toxicity study (Hellwig et al., 2002; BASF, 1996) show that effects in fetuses and pups occur at exposures that cause at least minimal maternal effects and that these concentrations are higher than the NOAEL for organ weight changes in mice (NTP, 1998). Based on high confidence in the well-conducted principal study and medium-to-high confidence in the database, the overall confidence in the RfC can be characterized as medium to high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

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

Source Document - *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012).

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, 2012). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date - 02/21/2012

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

Substance Name – Tetrahydrofuran
CASRN – 109-99-9
Section II. Last Revised – 02/21/2012

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 µg/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 an 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). 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 or male mice reported by NTP (1998).

There are some data suggesting that the observed renal tumors in the male rats may be secondary to α_{2u}-globulin accumulation; however, a review of the data available for THF indicates that the data do not support an α_{2u}-globulin-related mode of action (MOA) (Section 4.7.3.1 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012].). Another consideration regarding the renal tumors is the possibility that advanced chronic progressive nephropathy (CPN), a spontaneous age-related renal disease of laboratory rodents, may play a role in the incidence of atypical tubule hyperplasia (ATH) and perhaps the THF-induced kidney tumors in male rat kidneys. The NTP 2-year carcinogenicity study on THF (1998) reported no difference in the incidence or severity of CPN in the control versus treated male rats. 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 in support of 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 identified and the available data are insufficient to establish a mode of action for the THF liver tumor induction (Section 4.7.3.2 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]). Thus, the liver tumors observed in female mice are considered relevant to the assessment of the carcinogenic potential of THF to humans.

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 toxicokinetic data that absorption does not occur by other routes. 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

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 exceeded 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 increase in 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 significant increase in incidences 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 and mutagenicity studies for THF are mostly negative and provide very limited evidence to suggest a mutagenic mode of action. All bacterial mutation assays were negative for THF. In vitro genotoxicity assays with eukaryotic cells were also negative with the exception of a slight increase in chromosomal aberrations in Chinese hamster ovary cells with metabolic activation (Galloway et al., 1987). In vivo studies suggest that THF is not likely to be mutagenic; however, studies have not been conducted in target tissues.

Both renal and hepatocellular adenomas and carcinomas are observed following inhalation exposure to THF (NTP, 1998). There are mechanistic data suggesting that the induction of kidney tumors in male rats and liver tumors in female mice may involve the accumulation of α_{2u}-globulin in the kidney and increased cell proliferation in the liver, respectively. However, an analysis of the data indicates that there is insufficient evidence to establish the roles of α_{2u}-globulin in THF-induced kidney tumors or cell proliferation in THF-induced liver tumors. THF is not likely to be genotoxic, as the results of the genotoxicity and mutagenicity assays provide little evidence of genotoxic or mutagenic activity, with most data determined to be conclusively negative (Section 4.5 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]). Therefore, the mode of carcinogenic action of THF has not been established.

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

A 2-year NTP (1998) inhalation cancer bioassay reported an increased incidence of hepatocellular adenomas and carcinomas in female $B6C3F_1$ mice (statistically significant trend) and an increased incidence of renal tubule adenomas and carcinomas in male F344/N rats (statistically significant trend) following inhalation exposure to 200, 600, and 1,800 ppm THF (NTP, 1998) (see Section 4.7.2 of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]).

The U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates."

In this case, the NTP (1998) cancer bioassay for THF is a well-conducted study showing hepatocellular adenoma or carcinomas in female mice that were increased in a dose-related manner, starting at an approximate 15% increase over controls at the lowest exposure. The adjusted rate of renal adenoma or carcinoma in male rats was also increased in a dose-related manner, starting at an approximate 9% increase over controls at the lowest exposure. The data from this study are amenable to modeling; EPA would generally derive a cancer risk estimate from such data.

However, a majority of the external peer review panel members (see Appendix A: Summary of External Peer Review and Public Comments and Disposition of the *Toxicological Review of Tetrahydrofuran* [U.S. EPA, 2012]) stated that derivation of an inhalation unit risk (IUR) for THF would result in an overestimation of cancer risk if a linear low-dose extrapolation approach was utilized. Although the reviewers agreed with EPA's conclusion that based on the available data the modes of action for both liver and kidney tumors induced by THF are not well understood, they suggested that THF is a weak, nongenotoxic carcinogen that would have

a threshold. Specifically, they stated that THF does not appear to be genotoxic, does not produce irreversible damage and/or proliferative lesions that are preneoplastic, is rapidly metabolized, and is not bioaccumulative, and thus recommended the use of a nonlinear extrapolation approach to quantify cancer risk for THF. The reviewers who recommended a nonlinear approach suggested that a nongenotoxic carcinogen would consequently have a nonlinear cancer response at low dose. This concept is recognized as controversial in the scientific community.

The U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) recommend that the method used to characterize and quantify cancer risk for a chemical is determined by what is known about the mode of action of the carcinogen and the shape of the cancer dose-response curve. The linear approach is recommended if the mode of action of carcinogenicity is not understood (U.S. EPA, 2005a). In the case of THF, very little data are available to inform the mode of action and no data are available to indicate the shape of the dose-response curve at low doses. If data were available to better inform the mode of action, and the data were indicative of a threshold response, then a reference value could be derived based on a precursor endpoint (i.e., key event in the mode of action) and considered for the RfC for THF. In such a case, the reference value would be considered protective against tumor development following inhalation exposures. For THF, there were no reported noncancer effects that could serve as a precursor endpoint upon which to base a nonlinear analysis. EPA considered whether the cell proliferation reported in the livers of mice following short-term exposure to THF was a potential key event in the development of female mouse liver tumors; however, given the absence of proliferation data in any of the subchronic or chronic studies, the use of this endpoint is not supported. Thus, the nonlinear analysis recommended by the peer reviewers cannot be readily implemented.

Based on the peer reviewers' concern for the potential overestimation of risk in deriving an IUR for THF using a linear low-dose extrapolation approach combined with the uncertainty associated with the carcinogenic potential for THF, EPA did not derive an IUR. However, because there may be some circumstances for which a cancer risk estimate for THF would be useful, EPA has presented what the inhalation cancer risk estimate would be if it were derived using a linear low-dose approach. This derivation can be found in Appendix B of the *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012). Risk assessors should use caution when considering the use of this value due to the uncertainty associated with the potential overestimation of risk related to the linear low-dose extrapolation approach employed in its derivation and the suggestive nature of the tumorigenic response.

II.C.1. SUMMARY OF RISK ESTIMATES

Not applicable.

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

II.D.1. EPA DOCUMENTATION

Source Document - *Toxicological Review of Tetrahydrofuran* (U.S. EPA, 2012).

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, 2012). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

II.D.2. EPA REVIEW

Agency Completion Date - 02/21/2012

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

Substance Name – Tetrahydrofuran
CASRN – 109-99-9

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VII. REVISION HISTORY

Tetrahydrofuran
CASRN – 109-99-9
File First On-Line – 02/21/2012

Date	Section	Description
02/21/2012	I., II., VI.	RfD, RfC, and cancer assessment added.

VIII. SYNONYMS

Tetrahydrofuran
CASRN – 109-99-9
Section VIII. Last Revised – 02/21/2012

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