2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD); CASRN 1746-01-6

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. 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.

STATUS OF DATA FOR 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

File First On-Line 02/17/2012

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	02/17/2012
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	message	02/17/2012

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Substance Name – 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
CASRN – 1746-01-6
Section I.A. Last Revised – 02/17/2012

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.

There was no previous RfD for TCDD on the IRIS database.

For the assessment of human health risks posed by exposure to mixtures of TCDD and dioxin-like compounds (DLCs), including polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and dioxin-like polychlorinated biphenyls, and when data on a whole mixture or a sufficiently similar mixture are not available, EPA recommends use of the consensus mammalian Toxicity Equivalence Factor (TEF) values developed by the World Health Organization (U.S. EPA, 2010; Van den Berg et al., 2006).

I.A.1. Chronic Oral RfD Summary

Cocritical Effects	Point of Departure*	UF	Chronic RfD
Decreased sperm count and motility in men exposed to TCDD as boys **Epidemiologic cohort study** **Mocarelli et al., (2008)**	LOAEL[adjusted]: 0.020 ng/kg-day (2.0×10^{-8} mg/kg-day)	30	7×10^{-10} mg/kg-day
Increased TSH in neonates **Epidemiologic cohort study** **Baccarelli et al., (2008)**	LOAEL[adjusted]: 0.020 ng/kg-day (2.0×10^{-8} mg/kg-day)		

Conversion Factors and Assumptions – for both studies, physiologically based pharmacokinetic (PBPK) modeling was used to estimate oral intakes from TCDD exposures reported as serum concentrations. The details are presented in Methods of Analysis below. Data were not amenable to Benchmark Dose Modeling.

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

EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1 (Reanalysis Volume 1) reviews and summarizes the available data on noncancer effects caused by TCDD (for summary of the noncancer effects, see U.S. EPA (2012), Section 4). Adverse noncancer effects associated with oral TCDD exposure include hepatic, neurological, immunological, reproductive, endocrine, and developmental effects. As recommended by *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002), the RfD was developed based on consideration of all relevant and appropriate endpoints carried through to the derivation of "candidate" RfDs. Candidate RfDs were developed for all endpoints on the basis of PBPK model-derived internal dose (U.S. EPA [2012], Sections 3 and 4).

Two human epidemiologic studies (Baccarelli et al., (2008); Mocarelli et al., (2008) were chosen as the basis for deriving the RfD. Both of these studies are of a human population that was exposed to TCDD through an industrial accident in Seveso, Italy in 1976. Baccarelli et al. (2008) reported increased levels of thyroid stimulating hormone (TSH) in newborns exposed to TCDD in utero, indicating a possible dysregulation of thyroid hormone metabolism. The study authors related TCDD concentrations in maternal plasma to neonatal TSH levels using a multivariate linear regression model adjusting for a number of covariates including gender, birth weight, birth order, maternal age, hospital, and type of delivery. Based on this regression modeling, EPA defined the LOAEL for Baccarelli et al.(2008) to be the maternal TCDD lipid adjusted serum concentration (LASC) of 235 ppt (parts per trillion) at delivery, corresponding to a neonatal TSH level of 5 µU/mL. Using the Emond human PBPK model (Emond et al., 2005), the corresponding daily oral intake at the LOAEL is estimated to be 0.020 ng/kg day (see *Reanalysis Volume 1*, Section 4.2.3.1). The World Health Organization (WHO/UNICEF/ICCIDD, 1994) established the 5 µU/mL standard as an indicator of potential iodine deficiency and potential thyroid problems in neonates. The 5 µU/mL limit for TSH measurements in neonates was recommended by WHO (1994) for use in population surveillance programs as an indicator of iodine deficiency disease (IDD). For TCDD, the toxicological concern is not likely to be iodine uptake inhibition, but rather increased metabolism and clearance of the thyroid hormone, thyroxine (T4). Adequate levels of thyroid hormone are essential in the newborn and young infant as this is a period of active brain development (Zoeller and Rovet, 2004; Glinoer and Delange, 2000). Thyroid hormone disruption during pregnancy and in the neonatal period can lead to neurological deficiencies, particularly in the attention and memory domains (Oerbeck et al., 2005).

Mocarelli et al. (2008) reported decreased sperm concentrations and decreased motile sperm counts in men who were 1–9 years of age at the time of the Seveso accident (initial TCDD exposure event) in 1976. These results identify the first 10 years of life as a critical window of susceptibility for TCDD-induced sperm effects. Serum TCDD levels (as LASC) were measured in samples collected within one year of the initial exposure. Serum TCDD levels

and corresponding responses were reported by quartile, with a reference group of individuals assigned a TCDD LASC value of 15 ppt (the mean of the TCDD LASC reported in individuals outside the contaminated area). In the reference group, mean sperm concentrations and motile sperm counts were approximately 73 million sperm/mL and 41%, respectively. The lowest exposed group (1st quartile) TCDD LASC median was 68 ppt. In the 1st quartile, mean sperm concentrations of approximately 55 million sperm/mL and motile sperm counts of approximately 36% were reduced about 25 and 12%, respectively, from the reference group. Further decreases in these measures in the groups exposed to more than 68 ppt was minimal, with maximum reductions of 33% for sperm concentration and 25% for progressive sperm motility in the 4th and 3rd quartiles, respectively.

The lowest exposure group (TCDD LASC = 68 ppt) in Mocarelli et al. (2008) is designated as a LOAEL. Using the Emond PBPK model (Emond et al., 2005), EPA estimated both the peak initial exposure and the average exposure over the critical window. Because of the uncertainty in the influence of the peak exposure relative to the average exposure over the entire 10 year window, the LOAEL of 0.020 ng/kg day was calculated as the average of the peak exposure (0.032 ng/kg day) and the average exposure across the critical exposure window (0.008 ng/kg day) (see *Reanalysis Volume 1*, Section 4.2.3.2).

Supporting Studies

Mocarelli et al. (2011), also reported reductions in sperm concentrations for men who were exposed to TCDD in utero and by lactation; the effects were very similar to those in men exposed as boys from the coprincipal study by Mocarelli et al. (2008). The maternal TCDD exposures associated with the effects reported by Mocarelli et al. (2011) are somewhat lower than the exposures in the LOAEL group in Mocarelli et al. (2008), but quantifying either a NOAEL or LOAEL is complicated by large uncertainties arising from relativelyhigh background exposures to DLCs in this study population. Reduced sperm concentration associated with TCDD exposure has been reported in rodent studies (Simanainen et al., 2004; Latchoumycandane et al., 2002) and overt male reproductive effects have also been shown for rodents (Ikeda et al., 2005; Ohsako et al., 2001) (see *Reanalysis Volume 1*, Section 4.3.6.2). In addition to the effects of TCDD on neonatal TSH levels, TCDD has been associated with reductions in thyroid hormone (thyroxine, T4) levels in a number of animal studies (Crofton et al., 2005; Seo et al., 1995; Sewall et al., 1995; Van Birgelen et al., 1995a; Van Birgelen et al., 1995b) (see *Reanalysis Volume 1*, Section 4.3.6.1.).

Methods of Analysis

For both coprincipal studies, PBPK modeling was used to estimate continuous daily oral intakes from TCDD (lipid adjusted) serum concentrations (LASC) (see *Reanalysis Volume 1*,

Section 4.2.3). Additional PBPK modeling was conducted for Mocarelli et al. (2008) to adjust for the changing LASC time profile, characterized by a high initial exposure followed by slow elimination of TCDD over an average 3 year period. For Mocarelli et al. (2008), the lowest exposure group (TCDD LASC = 68 ppt) was designated as a LOAEL and the Emond PBPK model (Emond et al., 2005) was used to determine a LOAEL[adjusted] of 0.020 ng/kg day. The LOAEL[adjusted] was calculated as the average of the peak exposure intake and the average intake over a critical exposure window of susceptibility of 10 years (the first 10 years of life). For Baccarelli et al.(2008), the maternal TCDD LASC of 235 ppt at delivery associated with a neonatal TSH level of 5 µU/ml, as modeled by the study authors, was determined to be a LOAEL; a corresponding 30 year continuous oral intake of 0.020 ng/kg day was estimated using the Emond PBPK model (Emond et al., 2005) and assigned as the LOAEL[adjusted]. TCDD LASC was assumed to be constant during pregnancy.

I.A.3. UNCERTAINTY FACTORS

UF = 30

An uncertainty factor (UF) of 10 was applied for LOAEL to NOAEL extrapolation as a NOAEL could not be identified for either coprincipal study.

An UF of 3 was applied for interindividual variability to account for human to human variability in susceptibility. The individuals evaluated in the two principal studies included infants (exposed in utero) and adults who were exposed when they were less than 10 years of age, groups that are considered to represent sensitive lifestages. These studies considered together associate TCDD exposures with health effects in potentially vulnerable lifestage subgroups. An UF of 1 was not applied because the sample sizes for the lifestages studied were relatively small, which, combined with uncertainty in exposure estimation, may not fully capture the range of interindividual variability. In addition, potential chronic effects were not fully elucidated for humans and could possibly be more sensitive.

An UF of 1 for interspecies extrapolation was applied because human data were utilized for derivation of the RfD.

An UF of 1for study duration was applied because, although chronic effect levels are not well defined for humans, animal bioassays indicate that duration of exposure is not likely to be a determining factor in toxicological outcomes. Developmental effects and other short term effects occur at doses similar to effects noted in chronic studies.

An UF of 1for database deficiencies was applied because the database for TCDD contains an extensive range of human and animal studies that examine a comprehensive set of endpoints. There is no evidence to suggest that additional data would result in a lower RfD.

I.A.4. ADDITIONAL STUDIES/COMMENTS

Other outcomes reported in humans include female reproductive effects (Eskenazi et al., 2007; Warner et al., 2007; Eskenazi et al., 2005; Warner et al., 2004; Eskenazi et al., 2002), subtle changes in immune system components (Baccarelli et al., 2004; Baccarelli et al., 2002), development dental defects (Alaluusua et al., 2004), and diabetes (Michalek and Pavuk, 2008). Most of these effects occur at higher doses than the cocritical effects of semen quality and neonatal TSH; also, for many of these studies, the quantification of an adverse response level is too uncertain to define meaningful NOAELs or LOAELs. Diabetes may be a sensitive outcome as a result of TCDD exposure in humans, but the relevant exposures could not be quantified for the purposes of RfD development (see *Reanalysis Volume 1*, Appendix C for discussion).

Although human data are preferred, Table 4 5 in *Reanalysis Volume 1* (U.S. EPA, 2012) presents candidate RfDs for a number of animal bioassays, many of which are lower than the human RfD. Adverse noncancer effects reported in these studies include hepatic, neurological, immunological, reproductive, endocrine, and developmental effects. PBPK modeling (Emond et al., 2005) was used for interspecies toxicokinetic extrapolation of all rodent bioassays, assuming that whole blood TCDD concentration was the relevant dose metric; a 1st-order body burden model was used for other species for which no PBPK model was available. Two of the rodent bioassays among this group of studies–Bell et al. (2007) (candidate RfD = 8.9E-8 mg/kg-day based on delay in the onset of puberty) and NTP (2006) (candidate RfD = 4.6E-10 mg/kg day day based on liver and lung lesions)–are of particular note. Both studies were well designed and conducted, using 30 or more animals per dose group. Bell et al. (2007) evaluated several reproductive and developmental endpoints, initiating TCDD exposures well before mating and continuing through gestation. NTP (2006) is the most comprehensive evaluation of TCDD chronic toxicity in rodents to date, evaluating dozens of endpoints at several time points in all major tissues.

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

Study — High
Data Base — High
RfD — High

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). The overall confidence in this RfD assessment is high. Confidence in the coprincipal studies is high. The two principal studies were well conducted and show health effects in humans. Exposure assessment is a limitation of Mocarelli et al. (2008) because of the atypical exposure profile (high dose exposure followed by gradual elimination). However, the use of PBPK modeling to estimate internal exposures over the critical window and to account for the potential influence of the initial high peak exposure is considered to mitigate this limitation. The maternal exposures reported in Baccarelli et al. (2008) were not subject to large fluctuations, since the maternal blood measurements occurred several years following the accident and the newborns were exposed over a much narrower critical window (i.e., during pregnancy); there is, however, some uncertainty in the extrapolation of serum TCDD concentrations from the time of measurement to the time of pregnancy.

Confidence in the database is high. The TCDD database is extensive, covering a myriad of endpoints and exposure durations in both sexes of many species, including humans. Analogous effects have been observed in animal bioassays and in human epidemiologic studies, increasing the overall confidence in the relevance to humans of the effects reported in rodents and the association of TCDD exposure with the effects reported in humans.

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

Source Document – *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1* (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 *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1* (PDF) (1,521 pp, 13.5M) (U.S. EPA, 2012).

Agency Completion Date - 02/17/2012

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 – 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
CASRN – 1746-01-6
Section I.B. Last Revised – 02/17/2012

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.

There was no previous inhalation RfC for TCDD on the IRIS database.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Not available. An RfC was not derived for TCDD.

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

Not applicable

I.B.3. UNCERTAINTY FACTORS

Not applicable

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable

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

Not applicable

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

Not applicable

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 – 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
CASRN – 1746-01-6
Section I.A. Last Revised – 02/17/2012

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 $\mu g/m^3$ 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.

There was no previous cancer assessment for TCDD on the IRIS database.

MESSAGE: On August 29, 2011 EPA announced a plan to separate the *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* into two volumes: Volume 1 (noncancer assessment) and Volume 2 (cancer assessment and uncertainty analysis). The noncancer assessment and TCDD RfD are provided in this document. EPA will finalize Volume 2 as expeditiously as possible.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

Not applicable

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

Not applicable

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

Not applicable

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

II.D.1. EPA DOCUMENTATION

Not applicable

The cancer assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is currently underway.

II.D.2. EPA REVIEW

Not applicable

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

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CASRN – 1746-01-6

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VI.B. INHALATION RfC REFERENCES

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

VII. REVISION HISTORY

Substance Name – 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
CASRN – 1746-01-6
File First On-Line – 02/17/2012

Date	Section	Description
02/17/2012	I.A.	RfD added

VIII. SYNONYMS

Substance Name – 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
CASRN – 1746-01-6
Section VIII. Last Revised – 02/17/2012

- Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-
- Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-
- TCDD
- 2,3,7,8-TCDD
- Tetrachlorodibenzodioxin
- 2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin
- 2,3,7,8-Tetrachlorodibenzo-1,4-dioxin
- Tetradioxin
- Dioxin