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Provisional Peer-Reviewed Toxicity Values for

cis-1,2-Dichloroethylene
(CASRN 156-59-2)

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Note: Because the subchronic p-RfD presented in this document is based solely on the 2010 IRIS information, no external review was performed. All of the information provided in this PPRTV document was available to peer reviewers during the standard IRIS peer review process.

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *CIS*-1,2-DICHLOROETHYLENE (CASRN 156-59-2)

BACKGROUND

HISTORY

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

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All of the information provided in this PPRTV document was available to peer reviewers during the standard IRIS peer review process. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

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

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

On September 30, 2010, IRIS (U.S. EPA, 2010) posted a chronic RfD of 0.002 mg/kg-day for *cis*-1,2-dichloroethylene based on a subchronic-duration oral rat study (90 days) by McCauley et al. (1995, 1990), using a point of departure (POD) from a benchmark dose level ($BMDL_{10}$) of 5.1 mg/kg-day and a combined UF of 3000 (UF_H = 10; UF_A = 10; UF_L = 1; UF_S = 10; and UF_D = 3). Development of the subchronic p-RfD in this PPRTV document has been accomplished using only information provided in the IRIS toxicological review of *cis*-1,2-dichloroethylene (CASRN 156-59-2) (U.S. EPA, 2010). All of the information provided in this PPRTV document was available to peer reviewers during the standard IRIS peer review process.

IRIS does not generally post subchronic-duration values. However, because the IRIS chronic value was developed from a subchronic-duration study by utilizing the UF_S of 10, a subchronic p-RfD is presented in this PPRTV document based on this same study. The PPRTV duplicates only the key information necessary to succinctly support the derivation of a subchronic p-RfD. Full details are available on the IRIS database (see the References section—U.S. EPA [2010]), but omits much of the detailed information and the reader is directed to the IRIS online document for details.

HUMAN AND ANIMAL STUDIES

Refer to the IRIS toxicological review of *cis*-1,2-dichloroethylene (U.S. EPA, 2010) for summaries of human and animal studies.

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF PROVISIONAL ORAL REFERENCE DOSES

On September 30, 2010, IRIS (U.S. EPA, 2010) posted an RfD of 0.002 mg/kg-day based on a subchronic-duration oral rat study (90 days) by McCauley et al. (1995, 1990), using a POD from a $BMDL_{10}$ of 5.1 mg/kg-day and a combined UF of 3000 (UF_H = 10; UF_A = 10; UF_L = 1; UF_S = 10; and UF_D = 3).

Background on the principal study provided in the IRIS file (i.e., EPA [2010], Section I.A.2) is indicated below:

> *McCauley et al. (1995, 1990) administered 0, 32, 97, 291, or 872 mg/kg-day cis-1,2-DCE by corn oil gavage to male and female Sprague-Dawley rats (10 rats/sex/group) for 90 days. At the end of the 90-day exposure period, animals were sacrificed and the brain, gonads, heart, kidneys, adrenals, liver, spleen, and thymus were weighed and examined for gross pathology. Blood samples were collected for hematological and clinical chemistry examinations. Tissues from controls and the high-dose group animals were examined for histopathologic changes.*
>
> *Clinical observations during the study were reported by the authors as minimal and not compound-related. Gavage deaths were present in both the treated and control groups (1/10 female rats at 32 mg/kg-day; 1/10 female rats at 97 mg/kg-day; 1/10 male controls; 3/10 male rats at 291 mg/kg-day; 4/10 male rats at 872 mg/kg-day). Terminal body weights in male rats at the two highest dose groups were lower than controls by 10−11%, but were not considered by the author as statistically significant; no treatment-related effects on body weight were reported in female rats.*
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> *Absolute liver weights were statistically significantly increased by 10, 15[,] and 24% in female rats at doses of 97, 291, and 872 mg/kg-day, respectively. The increases in absolute liver weight of 6, 13, 5[,] and 15% in male rats of the 32[-], 97[-], 291[-] and 872[-]mg/kg-day dose groups, respectively, were not statistically significant nor dose related. Relative liver weights were statistically significantly increased in a dose-related manner in males and females. The increases were 15, 17, and 32% for males and 14, 19, and 30% for females at 97, 291, and 872 mg/kg-day, respectively. Histopathological evaluation revealed no specific hepatic injury. The authors concluded that there was a consistent, dose-related increase in relative liver weight in both sexes and that this effect, in light of the negative histopathology findings, may reflect hypertrophy and hyperplasia.*
>
> *Absolute kidney weights in female rats were increased by 3, 16, 17, and 17% compared to the control at doses of 32, 97, 291, and 872 mg/kg-day, respectively, but were not statistically significant. In male rats increases in absolute kidney weight of 9, 17, 7, and 14% for the 32, 97, 291, and 872 mg/kg-day dose groups, respectively, were not statistically significantly elevated compared to the control*

nor dose related. Statistically significant increases in relative kidney weights were recorded in male rats in all dose groups (14, 19, 19, and 27% at 32, 97, 291, and 872 mg/kg-day, respectively). Female rats exhibited increased (although not statistically significant) relative kidney weights in the three highest doses (19, 23, and 23% at 97, 291, and 872 mg/kg-day, respectively). Relatively large variances in the female dose groups may explain why relative kidney weight increases in females were not statistically significant. Histopathological findings for kidney effects were negative, leading the authors to hypothesize that the increases in relative kidney weight may be due at least in part to decreased body weight gain.

Sporadic changes (although noted as statistically significant) in some clinical chemistry parameters were observed. Blood urea nitrogen (BUN) levels were significantly decreased (40%) at the highest dose in males but not in females. Serum calcium levels were significantly elevated by 8 and 10% in males at the 32 and 97 mg/kg-day doses, respectively, and serum phosphorus was significantly decreased by 14% in males exposed to 32 mg/kg-day. In females, serum phosphorus was significantly increased by 34 and 25% in the groups dosed with 97 and 291 mg/kg-day, respectively. No significant changes were reported in AST activity. Hemoglobin and hematocrit level, and red blood cell (RBC) count were significantly decreased in female rats dosed at 291 mg/kg-day, while only hematocrit was significantly decreased in females dosed with 872 mg/kg-day. In males, similar decreases (ranging from 6 to 10% compared with the control) occurred in hemoglobin in the 291[-] and 872[-]mg/kg-day groups and in hematocrit in the 97[-], 291[-] and 872[-]mg/kg-day groups. Overall, the changes in clinical chemistry and hematology parameters were considered by the authors to be marginal and of questionable biological significance. No noteworthy compound-related histopathological changes were observed in any dose group.

IRIS utilized a BMD approach to develop the POD as indicated below:

Increased relative kidney weight in male and female rats (McCauley et al. (1995, 1990) was identified as the critical effect. Benchmark dose (BMD) modeling methodology (U.S. EPA, 2000) was used to determine the point of departure (POD) by estimating the effective dose at a specified level of response (BMDx) and its 95% lower confidence limit (BMDLx). A 10% change in relative kidney weight compared with the control was selected as the benchmark response (BMR) level. A BMR of 10% change in relative kidney weight was selected by analogy to body weight, for which a 10% change is generally recognized as a minimally biologically significant change (U.S. EPA, 2000).

All of the models for continuous data (i.e., linear, polynomial, power, and Hill models) in U.S. EPA's BMDS (version 2.1) were fit to relative kidney weight data. For the male rat, BMDS modeling of relative kidney weight data showed that only the Hill model adequately fit the data (test 4 χ^2 $p > 0.1$). The other continuous models fit to these data, the polynomial (linear and degree>2) and power models, exhibited significant lack of fit. The Hill model predicted a BMD_{10} and $BMDL_{10}$ of 19.8 and 5.1 mg/kg-day, respectively. For the female rat, the Hill model

provided the best fit of the relative kidney weight data (based on the model with the lowest Akaike Information Criteria (AIC) value and adequate visual fit of the data). The Hill model predicted a BMD_{10} and $BMDL_{10}$ of 55.2 and 10.4 mg/kg-day, respectively. The POD for the RfD for cis-1,2-DCE was selected as 5.1 mg/kg-day based on male rat relative kidney weight, the lower of the male and female $BMDL_{10}$ values for this endpoint.

A subchronic p-RfD is developed from IRIS's (2010) reporting of McAuley et al. (1995, 1990) (omitting the extrapolation to chronic duration, i.e., UF_S of 10).

Subchronic p-RfD = $BMDL_{10} \div UF_C$
= 5.1 mg/kg-day ÷ 300
= 0.017 or 2×10^{-2} mg/kg-day

The discussion of the uncertainty factors utilized by IRIS is shown below:

An intraspecies UF (UF_H) of 10 was applied to account for potentially sensitive human subpopulations in the absence of quantitative information on the variability of response to cis-1,2-DCE in the human population. Factors that could contribute to a range of human response to cis-1,2-DCE were discussed in Section 4.8 of the Toxicological Review of cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene (U.S. EPA, 2010). Intrahuman variability in CYP450 levels that are responsible for metabolism of cis-1,2-DCE to reactive metabolites has been documented. This variation in CYP450 could alter susceptibility to cis-1,2-DCE toxicity. Individual variability in nutritional status, alcohol consumption, or the presence of underlying disease could also alter metabolism of cis-1,2-DCE. To account for these uncertainties, a factor of 10 was included for individual variability.

An interspecies UF (UF_A) of 10 was applied to account for the variability in extrapolating from laboratory animals to humans. No information was available to characterize the toxicokinetic or toxicodynamic differences between experimental animals and humans for cis-1,2-DCE.

An UF of 1 was used for extrapolation from a LOAEL to a NOAEL (UF_L) because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% change in relative kidney weight compared with the control was selected under an assumption that it represents a minimally biologically significant change.

An UF of 3 was used to account for database deficiencies (UF_D). The study used in this RfD derivation, McCauley et al. (1995, 1990), is the only study of repeat-dose toxicity available for cis-1,2-DCE. The database for this isomer is missing studies of reproductive toxicity, including a two-generation reproductive toxicity study, and developmental toxicity; however, the developmental toxicity potential for cis-1,2-DCE is informed by a series of range-finding studies of the developmental toxicity of a mixture of cis-1,2-DCE isomers (composition of isomers unknown) (NTP, 1991a, b, c). No evidence of developmental toxicity was

observed in mice or rats based on the parameters evaluated in these range-finding studies (gravid uterus weight, fetal body weight, number of fetuses [live/dead], implantation sites, and resorptions).

An UF of 1 was used since a subchronic exposure was utilized to develop a subchronic value (UF_S).

Confidence in the subchronic p-RfD value is identical to that of the chronic RfD value: low, based on a study confidence of medium and a database confidence of low.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

There is no suitable information for developing RfC values. IRIS did not develop an RfC value as indicated below:

The inhalation toxicity database for cis-1,2-DCE does not support derivation of an RfC. No studies of the effects of cis-1,2-DCE by inhalation exposure in humans were identified. In experimental animals, investigation of the inhalation toxicity of cis-1,2-DCE is limited to an acute 4-hour inhalation LC_{50} study in rats (DuPont, 1999). There are no inhalation studies of subchronic, chronic, reproductive, or developmental toxicity of cis-1,2-DCE. Therefore, no inhalation RfC values were derived for cis-1,2-DCE.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

The cancer WOE descriptor for *cis*-1,2-dichloroethylene is provided in the IRIS toxicological review of *cis*-1,2-dichloroethylene (U.S. EPA, 2010) as "*Inadequate Information to Assess Carcinogenic Potential (both oral and inhalation)*." This descriptor is based on the absence of epidemiological studies in humans and the lack of animal studies designed to evaluate the carcinogenic potential.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

As indicated in the IRIS toxicological review of *cis*-1,2-dichloroethylene (U.S. EPA, 2010), the lack of data on carcinogenicity precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. REFERENCES

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