trans-1,2-Dichloroethylene; CASRN 156-60-5

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 trans-1,2-Dichloroethylene (trans-1,2-DCE)

File First On-Line 9/26/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/2010
Inhalation RfC (I.B.)	qualitative discussion	09/30/2010
Carcinogenicity Assessment (II.)	yes	09/30/2010

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE

Substance Name – trans-1,2-Dichloroethylene (trans-1,2-DCE)
CASRN – 156-60-5
Section I.A. Last Revised – 09/30/2010

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/backgrd.html 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.

The previous RfD of 0.02 mg/kg-day for trans-1,2-DCE was based on a 90-day subchronic drinking water study in mice (Barnes et al., 1985). The critical effect was increased serum ALP in male mice. A point of departure (POD) of 17 mg/kg-day (the no-observed-adverse-effect level [NOAEL] in this study) was identified and a composite uncertainty factor (UF) of 1,000 was applied, resulting in an RfD of 0.02 mg/kg-day. The UF of 1,000 accounted for the uncertainty in the extrapolation of dose levels from laboratory animals to humans, uncertainty in the threshold for sensitive humans, and uncertainty in extrapolating from subchronic to chronic exposure.

I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Decrease in number of antibody forming cells (AFCs) against sheep red blood cells (sRBCs) in male mice **Subchronic oral mouse study** **Shopp et al. (1985)**	$BMDL_{1SD}$: 65.0 mg/kg-day	3,000	0.02 mg/kg-day

*Conversion Factors and Assumptions - The $BMDL_{1SD}$ is the 95% lower confidence limit on the benchmark dose (BMD_{1SD}) corresponding to a change in mean response equal to one standard deviation from the control mean number of AFCs.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

Shopp et al. (1985) exposed male and female CD-1 mice (10 mice/group) to trans-1,2-DCE at concentrations of 0.1, 1.0, and 2.0 mg/mL in drinking water containing 1% emulphor for 90 days. These drinking water concentrations were equivalent to doses of 17, 175, and 387 mg/kg-day in male mice and 23, 224, 452 mg/kg-day in female mice. Three assays were conducted to evaluate humoral immune status: quantification of spleen AFCs directed against

sheep red blood cells (sRBCs) on days 4 and 5 after antigen presentation, hemagglutinin titers to sRBCs, and spleen cell response to the B cell mitogen lipopolysaccharide (LPS).

Body weight was not affected in male or female mice at any dose of trans-1,2-DCE following 90 days of exposure. The number of AFCs per 10^6 spleen cells was reduced by 26% in male mice exposed to trans-1,2-DCE at doses of 175 and 387 mg/kg-day (significantly different at $p < 0.05$ from control mice given deionized water). When expressed on a per spleen basis, the numbers of AFCs in male mice were significantly reduced at all exposure concentrations tested (equivalent to doses 17, 175, and 387 mg/kg-day). However, the expression of AFCs on a per spleen basis is affected by changes in the relative size of the spleen. Therefore, to avoid effects due to differences in relative spleen size, the number of AFCs per 10^6 spleen cells is considered the preferred measure. Spleen weights were not significantly affected by the treatments. Females responded normally except for mice in the 0.1 mg/mL group (23 mg/kg-day), which demonstrated a 32% decrease in AFC response on a total spleen basis.

Hemagglutinin titers in CD-1 mice exposed to trans-1,2-DCE at all dose levels were not significantly changed from control values. Spleen lymphocyte responsiveness to LPS was not altered in the males, but the female mice at the highest dose level demonstrated a statistically significantly enhanced spleen cell response to LPS.

Three assays were also used to evaluate the status of cellular immunity: (1) delayed-type hypersensitivity (DTH) response to sRBCs challenge, (2) popliteal lymph node proliferation in response to sRBCs, and (3) spleen cell response to concanavalin A (Con A). Male mice exposed to trans-1,2-DCE did not show changes in either the DTH or popliteal lymph node proliferation response to sRBCs, but females exposed to 1.0 mg/mL had a slight increase in the DTH response. No alterations in spleen lymphocyte response to Con A were noted. In addition, the ability of bone marrow cells from mice exposed to trans-1,2-DCE for 90 days to incorporate ^{125}I-labeled deoxyuridine was essentially unaffected by the treatments.

Shopp et al. (1985) concluded that there was marked suppression in humoral immune status in male mice and that the decrease in AFCs was significantly decreased in these mice. The authors also suggested, however, that the decrease in AFCs was not severe enough to depress the functional ability of the humoral immune system because there was no change in hemagglutination titers to sRBCs or lymphoproliferative response of spleen cells to the B-cell mitogen LPS. Overall, the authors concluded that the immune system of CD-1 mice was not overly sensitive to the effects of trans-1,2-DCE and that the effects observed were probably the result of general toxicity rather than specific target organ toxicity.

EPA evaluated the findings from Shopp et al. (1985) and determined, in contrast to the study authors, that the 26% suppression in the number of sRBC-specific AFCs per 10^6 spleen cells

of male mice in Shopp et al. (1985) is a biologically significant measure indicating suppressed immune function associated with oral exposure to trans-1,2-DCE that is not contradicted by a lack of observed change in the hemagglutination assay to sRBCs or proliferative response to LPS. See the *Toxicological Review of cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* (U.S. EPA, 2010), Section 4.6.1.2, for further discussion of the immune endpoint findings.

Method of Analysis. Decreased number of AFCs against sRBCs in male mice (Shopp et al., 1985) was selected as the critical effect. BMD modeling methodology (U.S. EPA, 2000) was employed 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). Little information exists concerning the biological significance of particular changes in AFC levels in rodents, and what these changes would correspond to in humans. Therefore, as recommended for continuous data in the *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000), a change in the mean response equal to one standard deviation from the control mean was used as the benchmark response (BMR) to facilitate a consistent basis of comparison across assessments for this endpoint in the absence of information regarding the level of change considered to be biologically significant. In this case, a BMR of 1 standard deviation corresponds to a 20% decrease in AFCs per 10^6 spleen cells.

All of the available continuous models in BMDS (i.e., linear, polynominal, power, and Hill models) were fit to this data set. The best-fitting model was chosen from those models exhibiting adequate fit by selecting the model with the lowest Akaike Information Criteria (AIC) value, as well as evaluating how well each model visually fit the data, especially in the region of the curve near the BMD. Based on these model selection criteria, a second-degree polynomial model provided the best fit to these data, yielding a BMD_{1SD} of 125.6 mg/kg-day and a $BMDL_{1SD}$ of 65.0 mg/kg-day. The $BMDL_{1SD}$ of 65.0 mg/kg-day was identified as the POD for the trans-1,2-DCE RfD.

I.A.3. UNCERTAINTY FACTORS

UF = 3,000

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 trans-1,2-DCE in the human population. Factors that could contribute to a range of human response to trans-1,2-DCE are 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 trans-1,2-DCE to reactive metabolites has been documented. This variation in CYP450 could alter susceptibility to trans-1,2-DCE

toxicity. Individual variability in nutritional status, alcohol consumption, or the presence of underlying disease could also alter metabolism of trans-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 trans-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 1 standard deviation in spleen cell antibody production was selected under an assumption that it represents a minimal biologically significant change.

An UF of 10 was used to account for extrapolating from a POD for a subchronic exposure duration to estimate chronic exposure conditions (UF_S).

An UF of 3 was used to account for database deficiencies (UF_D). There are several subchronic oral studies of trans-1,2-DCE (NTP, 2002; Hayes, 1987; Barnes, 1985; Shopp, 1985). One study investigated developmental toxicity of trans-1,2-DCE via inhalation (DuPont, 1988) and showed few developmental parameters to be affected by treatment. In this study developmental toxicity was manifest only in high-dose groups. Developmental toxicity potential for trans-1,2-DCE is also informed by a series of oral range-finding studies of the developmental toxicity of a mixture of 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, and number of fetuses [live/dead], implantation sites, and resorptions). The database for trans-1,2-DCE is missing studies of reproductive toxicity, including a two-generation reproductive toxicity study.

I.A.4. ADDITIONAL STUDIES/COMMENTS

No studies of the effects of oral exposure to trans-1,2-DCE in humans were identified.

The oral toxicity of trans-1,2-DCE was evaluated in four subchronic toxicity studies—NTP (2002) (rats and mice), Barnes et al. (1985) (mice), Hayes et al. (1987) (rats), and Shopp et al. (1985) (mice). The drinking water study by Barnes et al. (1985) exposed mice at doses up to approximately 400 mg/kg-day, whereas the drinking water study by Hayes et al. (1987) and dietary study by NTP (2002) exposed mice and rats to doses almost an order of magnitude higher. These three studies identified a range of effects associated with trans-1,2-DCE

exposure, including decreased body weight gain, effects on organ weights (liver, kidney, thymus, and lung), minimal changes in liver function enzymes, decreased mean body weight, and minimal decreases in hematological parameters. Shopp et al. (1985), identified as the principal study for RfD derivation, evaluated the immunotoxic potential of trans-1,2-DCE. No chronic bioassays of trans-1,2-DCE toxicity have been performed.

Statistically significant effects on the liver were observed by Barnes et al. (1985) and NTP (2002), but not Hayes et al. (1987). In the 90-day Barnes et al. (1985) study, male and female mice were exposed to trans-1,2-DCE in drinking water at doses up to 387 mg/kg-day for males and up to 452 mg/kg-day for females. A significant increase in mean liver weights was noted at the mid-dose (175 mg/kg-day), but not at the highest dose, in male mice. No DCE-induced changes in terminal body weight were observed. Significant increases in serum alkaline phosphatase (ALP) levels of 62 and 33% were reported at the 175 and 387 mg/kg-day doses, respectively, in male mice. These increases showed no dose-response relationship, were within the normal range for this mouse strain, and were not observed in female mice. In female mice, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were depressed at all doses, with statistical significance at the two highest dose levels. Increases in ALT and AST levels are indications of liver damage; the implication of decreases in these enzymes is unknown. The findings of Barnes et al. (1985) suggest that trans-1,2-DCE, via drinking water, does not induce hepatotoxicity at doses up to 387 mg/kg-day in male mice and up to 452 mg/kg-day in female mice.

NTP (2002) conducted a 14-week dietary study of trans-1,2-DCE in rats and mice at doses ranging from approximately 190 to 3,200 mg/kg-day in rats and approximately 450 to 8,000 mg/kg-day in mice. Absolute and relative liver weights of female rats exposed to ≥395 mg/kg-day were statistically significantly higher by 8–17% and 6–10%, respectively, than those of the vehicle controls; liver weights of male rats were not affected by trans-1,2-DCE exposure. In mice, relative liver weights were statistically significantly increased over controls in males (by 9–15%) exposed to doses of ≥1,900 mg/kg-day and in females (by 11%) exposed to doses of ≥3,760 mg/kg-day. Clinical chemistry data did not suggest hepatotoxicity in either species. Statistically significant decreases in serum ALP activities were reported in female rats exposed to the three highest doses compared with the vehicle controls; these decreases were minimal in severity (<13%) and transient (i.e., present at day 21 but not week 14). No exposure-related changes in ALP activities were observed in male rats or mice of either sex. No changes were observed in other clinical chemistry parameters, including cholesterol, ALT, and sorbitol dehydrogenase (SDH) levels, in rats or mice of either sex.

The increased liver weight observed in NTP (2002) and Barnes et al. (1985) was related to administration of trans-1,2-DCE; however, in the absence of elevated liver enzymes or histopathology, the change in liver weight is difficult to interpret.

In the 90-day drinking water study by Hayes et al. (1987), kidney weight (absolute and relative to body weight) was statistically significantly increased in female rats (by 11 to 13%) at doses of 1,257 and 2,809 mg/kg-day trans-1,2-DCE, but not in male rats in any dose groups. The kidney weight changes in female rats were not accompanied by histopathologic changes. In the dietary study by NTP (2002), absolute kidney weight was decreased (up to 9%) in female rats (1,580 and 3,245 mg/kg-day) and female mice (7,925 mg/kg-day), but relative kidney weight was similar to controls in all dosed groups. No gross or histopathological lesions in the kidney were observed in rats or mice that were attributed to exposure to trans-1,2-DCE (NTP, 2002). Similarly, clinical chemistry findings, blood urea nitrogen (BUN), creatinine, total protein, and albumin levels, did not provide evidence of any functional changes in the kidney. NTP (2002) observed that sporadic differences in clinical chemistry parameters at various time points generally did not demonstrate an exposure response relationship or were inconsistent between males and females. Overall, the findings from Hayes et al. (1987) and NTP (2002) provide limited evidence that trans-1,2-DCE affects the kidney. The findings from these two studies are inconsistent, with Hayes et al. (1987) reporting an increase in relative kidney weight and NTP (2002) reporting a decrease. Neither NTP (2002) nor Hayes et al. (1987) found any treatment-related histopathological changes of the kidney in rats and mice. Additionally, NTP (2002) did not find any clinical chemistry changes indicative of nephrotoxicity. Therefore, the kidney weight data are difficult to interpret.

There is limited evidence in the trans-1,2-DCE database for effects on the thymus. In a 90-day drinking water study, Barnes et al. (1985) reported decreased relative and absolute thymus weight in mid- (224 mg/kg-day) and high-dose (452 mg/kg-day) female mice, but not in any of the treated male mice. Hayes et al. (1987) reported no changes in absolute and relative thymus weight or histopathologic changes in the thymus at doses almost 10-fold higher than the doses used in Barnes et al. (1985). NTP (2002) reported no changes in absolute and relative thymus weight in rats and mice, except for a statistically significant increase in absolute (27%) and relative (25%) thymus weight in female mice at the low dose, and no significant histopathologic lesions.

Inconsistent hematological findings have been associated with trans-1,2-DCE exposure. In a 90-day drinking water study, Barnes et al. (1985) reported sporadic changes in hematology parameters (prothrombin time, leukocytes, and polymorphonuclear leukocytes) in mice; changes in these parameters were not dose-related or consistent across sexes. In a second subchronic drinking water study of trans-1,2-DCE, Hayes et al. (1987) reported no treatment-related effects on hematologic parameters in rats at doses up to approximately 3,000 mg/kg-day. NTP (2002) reported mild decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts at week 14 in male and female rats in all (380–3,245 mg/kg-day) but the lowest dose groups (190 mg/kg-day). Only decreased RBC counts showed a dose-

response and statistical significance. This effect was demonstrated in male rats with significant decreases at doses ≥380 mg/kg-day ($p \leq 0.05$), although the maximum decrease in RBC was only 7% in males and 5% in females at the highest dose (3,210 and 3,245 mg/kg-day for males and females, respectively). NTP (2002) concluded that the trans-isomer may have an effect on hematologic endpoints but more consistency between studies is necessary before the biological significance (if any) is known.

The immunotoxicity associated with oral exposure to trans-1,2-DCE was investigated in mice treated for 14 or 90 days (Shopp et al., 1985; Munson et al., 1982). In male CD-1 mice administered trans-1,2-DCE for 14 consecutive days at doses up to 222 mg/kg-day by gavage, Munson et al. (1982) evaluated humoral immune function as indicated by the ability of spleen cells to produce IgM AFCs following challenge with sRBCs. Munson et al. (1982) also assessed cell-mediated immune function as indicated by the DTH response to sRBCs. The authors described the antibody response to sRBCs as the number of AFCs per spleen and per 10^6 spleen cells. Munson et al. (1982) reported a trend toward suppression of the number of AFCs expressed on a per spleen basis (significant at $p < 0.1$), but this response was not statistically significant at the $p < 0.05$ level or when expressed per 10^6 spleen cells. The authors concluded that mice exposed to trans-1,2-DCE for 14 consecutive days at doses up to 222 mg/kg-day showed no significant change in cell-mediated or humoral immunity (Munson et al., 1982). As described in Section I.A.2, Shopp et al. (1985) provide some evidence of an effect of trans-1,2-DCE on humoral immune response.

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 to medium
RfD – Low

The overall confidence in this RfD assessment is low. Confidence in the principal study (Shopp et al., 1985) is medium. This 90-day immunotoxicity study of oral exposure of male and female CD-1 mice to trans-1,2-DCE (administered in drinking water) is a well-conducted, peer reviewed study. The Shopp et al. (1985) study included three dose groups as well as a vehicle control group. Animals were evaluated for humoral immune status as measured by the ability of spleen cells from these mice to produce splenic IgM AFCs against sRBC, hemagglutination titers to sRBC, and by spleen cell response to LPS.

Confidence in the oral database is low to medium. Four subchronic studies were considered in the evaluation of oral exposure to trans-1,2-DCE (NTP, 2002; Hayes, et al., 1987; Barnes et al., 1985; Shopp et al., 1985). These studies evaluated a wide range of toxicity endpoints, including hematology, urinalysis, clinical chemistry, histopathology, and immune system function. Developmental toxicity potential for trans-1,2-DCE is informed by a series of oral range-finding studies of a mixture of 1,2-DCE isomers (NTP, 1991a, b, c) that showed no evidence of developmental toxicity. There are no chronic studies of trans-1,2-DCE toxicity.

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 – U.S. EPA, 2010

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 cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* (U.S. EPA, 2010). ***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 -- 09/30/2010

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 – trans-1,2-Dichloroethylene (trans-1,2-DCE)
CASRN – 156-60-5
Section I.B. Last Revised – 09/30/2010

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.

An inhalation RfC for trans-1,2-DCE was not previously available on IRIS.

I.B.1. CHRONIC INHALATION RfC SUMMARY

No epidemiological studies of the effects of inhalation exposure to trans-1,2-DCE in humans are available, and case reports involving acute exposure to 1,2-DCE do not provide data useful for derivation of an RfC. There are two 90-day or longer duration studies using trans-1,2-DCE (DuPont, 1998; Freundt et al., 1977). The Freundt et al. (1977) subchronic study is a one-concentration study with liver endpoint data collected over several exposure durations and the DuPont (1998) report is available only as an unpublished study.

Freundt et al. (1977) exposed six rats/group for 8 hours/day, 5 days/week to air containing 792 mg/m^3 (200 ppm) trans-1,2-DCE for 1, 2, 8, and 16 weeks. Histological changes included slight to severe fatty accumulation in the liver lobules and Kupffer cells after exposure to 792 mg/m^3 for 1, 2, 8, and 16 weeks. For each of the exposure durations there was no statistically significant difference between the controls and the exposed groups with respect to the

incidence of liver effects (fat accumulation). In general, however, the incidence and severity of fat accumulation increased with increasing exposure duration.

In the DuPont (1998) study, male and female rats (15/sex/dose) were exposed to 0, 792, 3,960, or 15,800 mg/m^3 (0, 200, 1,000, or 4,000 ppm) trans-1,2-DCE for 6 hours/day, 5 days/week for 90 days. No exposure-related effects were seen in clinical or pathology parameters or on liver cell proliferation. In general, no statistically significant changes were seen in organ weight changes. The only hematological changes that showed dose-related trends at both 45 and 90 days in male and female rats were changes in white blood cell (WBC) and lymphocyte counts. WBC counts decreased by up to 18 to 20% in male and female rats, and lymphocyte levels decreased by up to 22 to 25%.

Although Freundt et al. (1977) reported histopathologic changes in the liver of rats, the DuPont (1998) study did not corroborate the Freundt et al. study findings. DuPont (1998) reported relatively small increases in relative and absolute liver weight (1 to 8%) and no gross or microscopic changes of the liver attributable to trans-1,2-DCE at an exposure concentration 20-fold higher than that used in the Freundt et al. (1977) study. NTP (2002) similarly found no histopathologic changes in the liver when trans-1,2-DCE was administered for 90 days by the oral route at dietary concentrations as high as 50,000 ppm. In light of the results of DuPont (1998) and NTP (2002), it is difficult to explain the liver findings in the single-exposure concentration study by Freundt et al. (1977). Given the limitations of the Freundt et al. (1977) study (i.e., small sample size, use of only one exposure concentration, and observation of fatty accumulation in the liver lobules and Kupfer cells in control animals at some exposure durations) and lack of corroboration from other studies, the Freundt et al. (1977) study was not used as the basis for deriving an RfC for trans-1,2-DCE.

The findings from the DuPont (1998) study were also considered as the basis for RfC derivation. The decreases in WBC and lymphocyte count reported in DuPont (1998), while treatment related, are of uncertain toxicological significance. The study authors suggested that the decreases in WBC and lymphocyte counts were attributable to the release of endogenous glucocorticoids that can cause redistribution of lymphocytes from the circulation into the lymphoid tissue and may, therefore, be considered a secondary effect associated with stress (Jensen, 1969; Brondeau et al., 1990). While plausible, specific support for this hypothesis was not provided. The lack of histopathological changes of the spleen and thymus in the DuPont (1998) study are not consistent with a direct effect of trans-1,2-DCE on lymphocytes. Further, the hematological findings from oral toxicity studies of trans-1,2-DCE do not support a determination that trans-1,2-DCE induces toxicologically significant effects on these hematologic parameters (see the *Toxicological Review of cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* [U.S. EPA, 2010], Section 5.2.2).

Thus, the available inhalation data from Freundt et al. (1977) and DuPont (1998) were considered insufficient to support reference value derivation and an RfC for trans-1,2-DCE was not derived.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

I.B.3. UNCERTAINTY FACTORS

Not applicable.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

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

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

Not applicable.

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 – U.S. EPA, 2010

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 cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* (U.S. EPA, 2010). ***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 -- 09/30/2010

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 – trans-1,2-Dichloroethylene (trans-1,2-DCE)
CASRN – 156-60-5
Section II. Last Revised – 09/30/2010

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.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

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

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is "inadequate information to assess the carcinogenic potential" of trans-1,2-DCE. This cancer descriptor is

based on the absence of epidemiological studies in humans and lack of animal studies designed to evaluate the carcinogenic potential of trans-1,2-DCE.

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

No epidemiologic studies evaluating possible long-term health effects of trans-1,2-DCE or a mixture of cis- and trans-1,2-DCE were identified.

II.A.3. ANIMAL CARCINOGENICITY DATA

No cancer bioassays of trans-1,2-DCE are available.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Evidence from genotoxicity and mutagenicity studies is inconclusive. Trans-1,2-DCE and mixtures of cis- and trans-1,2-DCE have been mostly nonpositive in bacterial genotoxicity assays for gene reversion or DNA damage but gave positive results in some bacterial assays for mitotic recombination or aneuploidy, frequently in the absence of metabolic activation by S9. Results for chromosomal aberrations or sister chromatid exchanges in mammalian cells in culture were mixed, providing positive findings in the presence or absence of metabolic activation. In vivo assays in mice that looked for chromosomal aberrations, micronuclei, and sister chromatid exchange were negative.

Trans-1,2-DCE is converted into reactive epoxides (oxiranes) by CYP450 enzymes. It is likely that epoxides are responsible for the inactivation of CYP2E1 by binding to its heme moiety, and protein adduct formation via sulfhydryl groups of amino acids has been shown to occur with 1,2-DCE (Maiorino et al., 1982; Sipes and Gandolfi, 1980). However, DNA adduct formation has not been demonstrated. DNA binding of 1,2-DCE was negative in an in vitro assay where other chlorinated hydrocarbons gave positive results (Sipes and Gandolfi, 1980).

Positive results have been obtained with trans-1,2-DCE in several genotoxicity assays in the absence of metabolic activation, suggesting that the C=C double bond positioned next to two chlorine substituents might be reactive on its own. However, Henschler (1977), in an

evaluation of the mutagenicity of halogenated olefins, pointed out that asymmetric distribution of chlorine substituents across the C–C bond, such as exists in 1,1-DCE, was far more likely to give rise to mutagenic events because the resulting epoxides are unstable, as compared with a symmetric distribution of the chlorines as exists in trans-1,2-DCE. Evidence for other effects that could potentially lead to tumor formation, such as redox cycling, GSH depletion, or lipid peroxidation, has not been shown for trans-1,2-DCE.

The fact that both cis- and trans-1,2-DCE form epoxides and/or radicals as active metabolites raises the question of whether these intermediates represent structural alerts. Laurence et al. (1984) performed a computational study of the reactivities of vinyl chloride and trans-1,2-DCE by evaluating the bond energies of protonated chlorine or oxygen in the corresponding chlorooxiranes. Their assessment indicated that the oxirane from trans-1,2-DCE should form a guanine N_7 adduct analogous to the one found after vinyl chloride exposure that is thought to be the cause of vinyl chloride-related cancer. However, this evaluation also predicted that the trans-1,2-DCE oxirane would be far more reactive than the one formed by vinyl chloride, rapidly reacting with other cellular nucleophiles before sufficient quantities could reach critical targets in the DNA, and thus predicting a lack of carcinogenicity associated with trans-1,2-DCE.

Carcinogenic activity of a metabolite of trans-1,2-DCE, dichloroacetic acid, has been established in several animal bioassays but not in humans (U.S. EPA, 2003).

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

II.B.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.B.2. DOSE-RESPONSE DATA

Not applicable.

II.B.3. ADDITIONAL COMMENTS

Not applicable.

II.B.4. DISCUSSION OF CONFIDENCE

Not applicable.

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

II.C.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.C.2. DOSE-RESPONSE DATA

Not applicable.

II.C.3. ADDITIONAL COMMENTS

Not applicable.

II.C.4. DISCUSSION OF CONFIDENCE

Not applicable.

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

II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA, 2010

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 cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* (U.S. EPA, 2010). ***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 -- 09/30/2010

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 (internet address).

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

VI. BIBLIOGRAPHY

Substance Name – trans-1,2-Dichloroethylene (trans-1,2-DCE)
CASRN – 156-60-5

VI.A. ORAL RfD REFERENCES

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VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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VII. REVISION HISTORY

Substance Name – trans-1,2-Dichloroethylene (trans-1,2-DCE)
CASRN – 156-60-5
Section VII. Last Revised – 09/30/2010

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary on-line
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.
09/30/2010	I., II., VI	RfD assessment added; RfC and cancer assessment sections revised. Screening-Level Literature Review Findings message has been removed.

VIII. SYNONYMS

Substance Name – trans-1,2-Dichloroethylene (trans-1,2-DCE)
CASRN – 156-60-5
Section VIII. Last Revised – 09/30/2010

- 156-60-5
- acetylene dichloride, trans-
- dichloroethylene, trans-
- 1,2-dichloroethylene, trans-
- ethylene, 1,2-dichloro-, (E)-
- RCRA waste number U079
- trans-acetylene dichloride
- trans-dichloroethylene
- trans-1,2-dichloroethylene