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Provisional Peer-Reviewed Toxicity Values for

1,2,3-Trichlorobenzene
(CASRN 87-61-6)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
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 inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,2,3-TRICHLOROBENZENE (CASRN 87-61-6)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.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) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. 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 U.S. 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 U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. 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 U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

IRIS (U.S. EPA, 2009a), the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), and the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) do not report noncancer or cancer assessments for 1,2,3-trichlorobenzene. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) includes a Drinking Water Criteria Document (DWCD) for Trichlorobenzenes (U.S. EPA, 1988) and a Health Assessment Document (HAD) for Chlorinated Benzenes (U.S. EPA, 1985), neither of which derived toxicity values for 1,2,3-trichlorobenzene due to inadequate data. The World Health Organization (WHO) calculated a tolerable daily intake (TDI) of 0.02 mg/kg-day for 1,2,3-trichlorobenzene in an Environmental Health Criteria document (WHO, 1991), based on a NOEL reported as 7.7 mg/kg-day in a 13-week dietary study in rats (Côté et al., 1988), to which an UF of 500 was applied (basis for UF not reported). Health Canada (1993) derived a TDI of 0.00077 mg/kg-day using the same NOEL as the WHO (1991), but applied an UF of 10,000 (10 for intraspecies variation, 10 for interspecies variation, 10 for a less-than-chronic-duration study and 10 for lack of data on carcinogenicity or chronic toxicity). No occupational exposure limits have been established for 1,2,3-trichlorobenzene by the American Conference of Governmental Industrial Hygienists (ACGIH, 2007), National Institute of Occupational Safety and Health (NIOSH, 2005), or Occupational Safety and Health Administration (OSHA, 2008). The National Toxicology Program (NTP) has not assessed the toxicity or carcinogenicity of this compound (NTP, 2006) and it is not included in the 11th Report on Carcinogens (NTP, 2005). 1,2,3-Trichlorobenzene has not been the subject of a monograph by the International Agency for Research on Cancer (IARC, 2008) or a toxicological profile by the Agency for Toxic Substances Disease Registry (ATSDR, 2008).

To identify toxicological information pertinent to the derivation of provisional toxicity values for 1,2,3-trichlorobenzene, literature searches were conducted in December 2007 using the following databases: MEDLINE, TOXLINE, DART/ETIC, BIOSIS (January 2000−December 2007), Current Contents (prior 6 months), TSCATS1/2, GENETOX,

HSDB, and RTECS. Except where noted, the literature searches were not limited by date. A toxicity review on halogenated benzenes (Leber and Bus, 2001) was also consulted for relevant information. A final search for recently published toxicity studies was conducted for the period from January 2008 thru March 2009.

REVIEW OF PERTINENT DATA

Human Studies

Information regarding the toxicity or carcinogenicity of 1,2,3-trichlorobenzene in humans was not located.

Animal Studies

Oral Exposure

A subchronic toxicity study was conducted in which groups of 10 male and 10 female weanling Sprague-Dawley rats were fed 1,2,3-trichlorobenzene (>99% pure) in dietary concentrations of 0, 1, 10, 100, or 1000 ppm for 13 weeks (Côté et al., 1988). The diets were prepared by blending ground feed with corn oil solutions containing appropriate amounts of 1,2,3-trichlorobenzene. Reported approximate amounts of chemical ingested in the low- to high-dose groups were 0.08, 0.78, 7.7, and 78 mg/kg-day in the males and 0.13, 1.3, 12, and 113 mg/kg-day in the females. Endpoints evaluated throughout the study consisted of clinical signs (daily), body weight (weekly), food consumption (5 rats/dose/sex at weeks 1, 4, 8, and 12), and urinalysis (pH, protein, and nitrite in 5 rats/dose/sex at weeks 4, 8, and 12). Endpoints evaluated at the end of the 13-week feeding period included hematology (hemoglobin, packed cell volume, erythrocyte count, total and differential leukocyte counts, platelet count, prothrombin time, mean corpuscular hemoglobin [MCH] and mean corpuscular hemoglobin concentration [MCHC]), serum chemistry (sodium, potassium, inorganic phosphate, total bilirubin, alkaline phosphatase [ALP], aspartate aminotransferase [AST], total protein, calcium, cholesterol, glucose, uric acid and lactic dehydrogenase), hepatic microsomal aniline hydroxylase and aminopyrine demethylase activities, liver protein content, and femoral bone cytology. At necropsy, all animals were examined grossly, selected organs were weighed (liver, kidney, spleen, heart, and brain) and comprehensive histological examinations (41 tissues) were conducted.

Body-weight gain was 5.1, 9.8, 2.4, and 10.2% less than controls in males at 0.08, 0.78, 7.7, and 78 mg/kg-day, respectively; the decreases in the 0.78 and 78 mg/kg-day animals were statistically ($p < 0.05$) significant (Côté et al., 1988). Because of the lack of clear dose-response, the authors concluded that the effect at 0.78 mg/kg-day was probably an incidental finding. There were no significant decreases in body-weight gain in the females or food consumption in either sex. Relative liver weight was significantly ($p < 0.05$) increased in males at 78 mg/kg-day (12.5% higher than controls) and relative kidney weight was significantly increased in males at 0.08, 0.78, and 78 mg/kg-day (14.2, 14.2, and 21.4% higher than controls); absolute organ weights were unchanged. The increases in kidney weight were not accompanied by renal histopathology or abnormal urinalysis. Hematology, serum chemistry, and hepatic microsomal enzymes were not affected by exposure. The only other exposure-related effects were histopathological changes in the liver and thyroid. These effects were qualitatively described in a general manner that also pertained to other trichlorobenzenes in the study. The effects were

considered by the researchers to be generally mild in nature, biologically significant only at the highest dose level and more severe in males than females. Hepatic changes in "most treated groups consisted of a mild-to-moderate increase in cytoplasmic volume and anisokaryosis of hepatocytes observed mostly in perivenous and midzone areas." High-dose rats had mild hepatic changes "characterized by aggregated basophilia as well as widespread midzonal vacuolation due to fatty infiltration." Thyroid changes "were characterized by reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape and reduced colloid density." The severity of the thyroid changes "varied from minimal in the low-dose groups to mild and moderate in the high-dose groups." Other information regarding the liver and thyroid lesions (e.g., incidence data) was not reported. Based on the mild-to-moderate histopathological changes in the liver and thyroid of the high-dose male rats, this study identified a NOAEL of 7.7 mg/kg-day and LOAEL of 78 mg/kg-day.

A developmental toxicity study was conducted in which groups of 13−14 female Sprague-Dawley rats were administered 1,2,3-trichlorobenzene (99.5% pure) in corn oil by gavage in doses of 0 (vehicle control), 150, 300, or 600 mg/kg-day on Gestation Days (GDs) 6−15 (Black et al., 1988). The dams were sacrificed on GD 22. Clinical signs were monitored throughout the study. Maternal endpoints evaluated at termination included body weight, hematology (hemoglobin concentration, hematocrit value, erythrocyte count, total and differential leukocyte counts, mean corpuscular volume [MCV], MCH and MCHC), serum chemistry (sodium, potassium, inorganic phosphorus, total bilirubin, ALP, AST, total protein, calcium, cholesterol, glucose, uric acid and lactic dehydrogenase), hepatic microsomal aniline hydroxylase and aminopyrine-N-demethylase activities, liver protein concentration, organ weights (liver, kidney, spleen, heart and brain), and histopathology (25 tissues). Developmental endpoints included resorptions and dead fetuses, litter size, fetal body weight, gross birth defects and skeletal (approximately two-thirds of each litter), and visceral (remaining fetuses) malformations and variations. Effects in the maternal rats included statistically significant ($p < 0.05$) increases in the weight of the liver (relative to body weight) at 600 mg/kg-day (13.7% higher than controls, with no changes in absolute liver weight or body weight) and hepatic microsomal aminopyrine-N-demethylase activity at 600 mg/kg-day (19.7% higher than controls) and decreases in hemoglobin concentration at 300 and 600 mg/kg-day (5.0 and 5.8% less than controls) and hematocrit level at 600 mg/kg-day (10.5% less than controls). The authors concluded that the changes in hemoglobin concentration and hematocrit indicated a very mild anemia. Other maternal effects included histopathological changes in the liver and thyroid. These effects were qualitatively described in a general manner that also pertained to other trichlorobenzenes in the study. The hepatic changes were mild, consisted largely of increased periportal cytoplasmic eosinophilia and mild anisokaryosis of hepatocellular nuclei and apparently occurred at ≥300 mg/kg-day. The thyroid changes were mild and consisted of reduced follicle size (often accompanied by angular collapse) at ≥300 mg/kg-day and increased epithelial height and cytoplasmic vacuolation at 600 mg/kg-day. Other information regarding the liver and thyroid lesions (e.g., incidence data) was not reported. There were no indications of 1,2,3-trichlorobenzene-induced developmental toxicity. Based on decreased hemoglobin concentration and histopathological changes in the liver and thyroid, this study identified a NOAEL of 150 mg/kg-day and LOAEL of 300 mg/kg-day for maternal toxicity. A NOAEL of 600 mg/kg-day and no LOAEL were identified for developmental toxicity.

Additional toxicity studies (unpublished) may be among the Toxic Substances Control Act (TSCA) confidential submissions that are noted in the TSCATS Low Detail Report (U.S. EPA, 2008b) but they could not be obtained in a reasonable period of time.

Inhalation Exposure

No pertinent inhalation studies were located.

Other Studies

Gavage administration of 1,2,3-trichlorobenzene in liquid paraffin to rats at a dose level of 780 mg/kg-day for 7 days induced nonnecrotic liver cell degeneration in the central, midzonal, and periportal regions, as well as increases in hepatic uroporphyrin, urinary coproporphyrin, and urinary porphobilinogen levels (Rimington and Ziegler, 1963).

A limited amount of information is available on the genotoxicity of 1,2,3-trichlorobenzene. 1,2,3-Trichlorobenzene did not induce reverse mutations in *Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 (Haworth et al., 1983; Nohmi et al., 1985) or DNA repairing genes (*umuDC*) in *S. typhimurium* TA1535/pSK1002 (Ono et al., 1992), when tested with or without metabolic activation. 1,2,3-Trichlorobenzene did not induce chromosome aberrations in cultured Chinese hamster lung fibroblast cells when tested with or without metabolic activation (Sofuni et al., 1985). In vivo, intraperitoneal administration of 1,2,3-trichlorobenzene to male NMRI mice caused a dose-related increase in micronucleus formation in bone marrow polychromatic erythrocytes (Mohtashamipur et al., 1987). In this study, two doses of 125, 250, 375, or 500 mg/kg were injected 24 hours apart and evaluations were performed on bone marrow samples taken 30 hours after the first injection. Total doses (i.e., 250, 500, 750, and 1000 mg/kg) ranged from 18−72% of the single dose intraperitoneal LD_{50} (1390 mg/kg).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,2,3-TRICHLOROBENZENE

Information relevant to oral RfD derivation is available from one subchronic toxicity study and one developmental toxicity study. In this subchronic toxicity study, Côté et al. (1988), exposed male and female rats to 1,2,3-trichlorobenzene (0.0, 0.08, 0.78, 7.7, and 78 mg/kg-day in males; 0.0, 0.13, 1.3, 12, and 113 mg/kg-day in females) in the diet for 13 weeks. The main effects included a statistically significant ($p < 0.05$) reduction in male rat body weight gain as well as mild-to-moderate histopathological changes in the liver (aggregated basophilia and widespread midzonal vacuolation due to fatty infiltration) and thyroid (reduced follicular size and colloid density and increased epithelial height) in the high-dose animals. The study authors noted that the observed effects were generally more severe in males than females. Based on the body weight, liver effects, and thyroid effects in the male rat, this study identified a NOAEL of 7.7 mg/kg-day and LOAEL of 78 mg/kg-day for subchronic oral toxicity. In the developmental toxicity study (Black et al., 1988), female rats were exposed to 150, 300, or 600 mg/kg-day of 1,2,3-trichlorobenzene by gavage on GDs 6−15. Effects in the dams included decreased hemoglobin concentration and histopathological changes in the liver and thyroid; based on these

effects, this study identifies a NOAEL of 150 mg/kg-day and LOAEL of 300 mg/kg-day for maternal toxicity. No fetotoxic or teratogenic effects were observed, indicating that a NOAEL of 600 mg/kg-day and no LOAEL were identified for developmental toxicity.

Subchronic p-RfD

The NOAEL of 7.7 mg/kg-day for a reduction in male body weight gain, as well as liver and thyroid histopathology in rats exposed to 1,2,3-trichlorobenzene for 13 weeks (Côté et al., 1988), is used to derive the subchronic p-RfD. Benchmark dose (BMD) analysis is precluded because the incidence of lesions was not reported. Derivation of the subchronic p-RfD involves dividing the NOAEL by a UF of 1000. The **subchronic p-RfD** is calculated as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 7.7 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{0.008 \text{ or } 8 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

The composite UF of 1000 includes component UF factors of 10 for extrapolation from rats to humans, 10 for human variability, and 10 for database insufficiencies, as explained below.

- A 10-fold UF is applied to account for laboratory animal-to-human interspecies differences because no information is available on the toxicity of 1,2,3-trichlorobenzene in humans. No other information is available to assess possible differences between animals and humans in pharmacokinetic and pharmacodynamic responses to 1,2,3-trichlorobenzene.
- A 10-fold UF for intraspecies differences is applied to account for potentially susceptible human subpopulations. In the absence of information on the variability in response of humans to 1,2,3-trichlorobenzene, the full value of 10 is used.
- A 10-fold UF is applied to account for deficiencies in the available 1,2,3-trichlorobenzene database. The oral database is limited to one subchronic (13-week) toxicity study in rats and one developmental toxicity study in fetal rats where no effects were observed. These studies have reporting insufficiencies and testing in only one species. The database additionally lacks studies on reproductive toxicity, neurotoxicity, immunotoxicity and studies with a second species.

A UF for extrapolating from a subchronic- to a chronic-duration exposure is not applied because the POD is based upon a subchronic-duration exposure to 1,2,3-trichlorobenzene. Also a UF for extrapolating from a LOAEL to a NOAEL is not applied because a NOAEL is identified as the POD in the critical study.

The overall confidence in this RfD assessment is medium-to-low. Confidence in the principal study is **medium**. The principal study examined relevant systemic toxicity endpoints in rats of both sexes exposed to four dose levels and identifies a NOAEL and LOAEL, but it is limited by qualitative and generalized reporting of critical results. Confidence in the database is **low**, as discussed above. Reflecting the medium confidence in the principal study and low confidence in the database, confidence in the subchronic p-RfD is **low**.

Chronic p-RfD

No chronic oral toxicity study of 1,2,3-trimethylbenzene was located, indicating that the subchronic p-RfD provides the only basis for derivation of a chronic p-RfD. A chronic p-RfD is not derived because the application of an additional UF of 10 for extrapolation from a subchronic duration study demonstrates a level of uncertainty that is inconsistent with U.S. EPA risk assessment methods. However, the Appendix of this document contains a screening-level value that may be useful in certain instances. Please see the attached Appendix for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,2,3-TRICHLOROBENZENE

No subchronic toxicity, chronic toxicity, or other relevant inhalation studies of 1,2,3-trichlorobenzene were located. RfC derivation is precluded by the lack of data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,2,3-TRICHLOROBENZENE

There are no human or animal carcinogenicity data for 1,2,3-trichlorobenzene. A limited amount of genotoxicity data suggest that 1,2,3-trichlorobenzene is not mutagenic, but may be clastogenic. When tested in vitro, with or without metabolic activation, 1,2,3-trichlorobenzene did not induce reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 (Haworth et al., 1983; Nohmi et al., 1985), DNA repairing genes (*umuDC*) in *S. typhimurium* TA1535/pSK1002 (Ono et al., 1992) or chromosome aberrations in Chinese hamster lung fibroblast cells (Sofuni et al., 1985). When tested in vivo by i.p. injection in mice, 1,2,3-trichlorobenzene induced micronuclei in bone marrow polychromatic erythrocytes (Mohtashamipur et al., 1987).

In accordance with current EPA cancer guidelines (U.S. EPA, 2005), the available data are inadequate for an assessment of human carcinogenic potential.

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APPENDIX. DERIVATION OF A SCREENING VALUE FOR 1,2,3-TRICHLOROBENZENE

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for 1,2,3-trichlorobenzene. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Screening Chronic p-RfD

No chronic oral toxicity studies of 1,2,3-trichlorobenzene were located. Consequently, the NOAEL of 7.7 mg/kg-day for a reduction in male body weight gain as well as liver and thyroid histopathology in rats exposed to 1,2,3-trichlorobenzene for 13 weeks (Côté et al., 1988) was used to derive the chronic oral screening value. Benchmark dose (BMD) analysis is precluded because the incidence of lesions was unreported. Derivation of the provisional chronic oral screening value involves dividing the NOAEL by a composite UF of 10,000. The **screening chronic p-RfD** is calculated as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 7.7 \text{ mg/kg-day} \div 10{,}000 \\ &= \mathbf{0.0008 \text{ or } 8 \times 10^{-4} \text{ mg/kg-day}} \end{aligned}$$

The composite UF of 10,000 includes component UF factors of 10 for extrapolation from rats to humans, 10 for human variability, 10 for extrapolation from a subchronic study, and 10 for database insufficiencies, as explained below.

- A 10-fold UF is applied to account for laboratory animal-to-human interspecies differences because no information is available on the toxicity of 1,2,3-trichlorobenzene in humans. No other information is available to assess possible differences between animals and humans in pharmacokinetic and pharmacodynamic responses to 1,2,3-trichlorobenzene.
- A 10-fold UF for intraspecies differences is applied to account for potentially susceptible human subpopulations. In the absence of information on the variability in response of humans to 1,2,3-trichlorobenzene, the full value of 10 is used.
- A 10-fold UF for extrapolation from a subchronic study is applied in the absence of chronic oral toxicity studies.
- A 10-fold UF is applied to account for deficiencies in the available 1,2,3-trichlorobenzene database. The oral database is limited to one subchronic (13-week) toxicity study in rats and one developmental toxicity study in fetal rats where no effects were observed. These studies have reporting insufficiencies and testing in only

one species. The database additionally lacks studies on reproductive toxicity, neurotoxicity, immunotoxicity and studies in a second species.

An UF for extrapolating from a LOAEL to a NOAEL is not applied because a NOAEL was identified as the POD in the critical study.