Scientific, External Technical Letter Peer Review of the TCEQ's Carbon Disulfide Development Support Document

Submitted to TCEQ by March 2014

Submitted by Toxicology Excellence for Risk Assessment (TERA)

TERA Contact: Jacqueline Patterson (patterson@tera.org)

Experts Selected by TERA to Provide a Technical Review of the Draft DSD for Carbon Disulfide

TERA independently selected the following three experts to provide technical review of the TCEQ document. Collectively, the group has significant expertise in epidemiology, toxicology, human health risk assessment, non-cancer risk methods, and familiarity with TCEQ risk methods. TERA has screened each expert for conflict of interest. None of the selected experts has a conflict of interest with the technical review of this document.

Kyle Steenland (Epidemiology and Risk Assessment)

Dr. Kyle Steenland is an environmental/occupational epidemiologist who has been a professor in the Environmental Health Department at the Rollins School of Health, Emory University since 2002. He has a Ph.D. in Epidemiology from the University of Pennsylvania. Prior to working at Emory, he worked for 20 years at the National Institute for Occupational Safety and Health (NIOSH) and spent a year at the International Agency for Research on Cancer (IARC). Dr. Steenland has published over 100 first-authored articles in the field, and edited two textbooks. He has conducted a large number of cohort studies, including both mortality and cancer incidence studies (e.g., cohorts of workers exposed to dioxin, ethylene oxide, welding fumes, sulfuric acid mists, silica, diesel fumes, and polychlorinated biphenyls). He is currently conducting two large cohort studies of community residents and workers exposed to perfluorooctanoic acid (PFOA), and to lead. He has also published a number of studies on epidemiologic methods, including exposure-response analyses, adjustment for multiple comparisons, the effect of measurement error, and the attributable fraction.

Penelope ("Penny") A. Fenner-Crisp (Risk Assessment, Non-cancer Methods, and Toxicology)

In August, 2004, Dr. Fenner-Crisp retired from her position as the Executive Director of the ILSI Risk Science Institute (RSI). Dr. Fenner-Crisp has since established a private consulting practice. Dr. Fenner-Crisp came to ILSI in December 2000 from U.S. EPA, having served in a variety of capacities over more than 22 years: Senior Science Advisor to the Director, the Deputy Director of the Office of Pesticide Programs (OPP) and the Director of its Health Effects Division; Special Assistant to the Assistant Administrator for Prevention, Pesticides and Toxic Substances; Director of the Health and Environmental Review Division of the Office of Pollution Prevention and Toxics (OPPT); and Senior Toxicologist in the Health Effects Branch of the Office of Drinking Water (ODW). Responsibilities included both the hands-on practice, and management oversight, of developing all components of both human health and ecological risk assessments related to drinking water contaminants, industrial chemicals and pesticides. Dr. Fenner-Crisp received her Ph.D. in Pharmacology from the University of Texas Medical Branch in Galveston. Her research interests encompassed the fields of neuro- and cardiovascular pharmacology. She completed a postdoctoral fellowship in Pharmacology-Morphology at the Georgetown University Schools of Medicine and Dentistry, with an emphasis on reproductive endocrinology (1971-1973). Before joining EPA in 1978, she was an Adjunct Instructor in the Anatomy Department and a Research Associate in the Pharmacology Department at

Georgetown. Dr. Fenner-Crisp is an active member of the Society of Toxicology (SOT) and the Society for Risk Analysis (SRA). In 1996, she was the recipient of the SRA's first Risk Practitioner award. She has been a Diplomate of the American Board of Toxicology since 1984. For the past decade-plus, her efforts have been focused primarily on the development and application of frameworks and guidance designed to facilitate the assessment of risk across life stages and for evaluating the mode of action of endpoints of concern observed in animal studies and their relevance to human health. She has served or chaired many expert panels on the national and international level.

Lynne Haber (Risk Assessment, Non-cancer Methods, TCEQ methods, and Toxicology)

Dr. Lynne Haber has 23 years of experience in conducting toxicological evaluations for substances, with application to drinking water standards, air criteria and contaminated sites risk assessment. She has led the development of numerous assessment documents, including primary author of more than 30 major documents for multiple EPA offices, other government regulatory agencies, and private sponsors, and has been a coauthor or reviewer of hundreds more. She has served as a panel chairperson or panel member for scientific peer reviews organized by *TERA*, EPA, and other U.S. and foreign government agencies. She has also served on two panels for the NAS/NRC. Dr. Haber is active in communicating her findings to the broader scientific community through participation in professional societies, routine publication of her work, authoring book chapters, service as an editorial reviewer for scientific journals, and through presentation of invited lectures. She was the lead author of the chapter on noncancer risk assessment for Patty's Toxicology (2001, 2011), and has performed technical meeting support. She has experience in benchmark concentration/ benchmark dose (BMC/BMD) modeling and categorical regression modeling, and served as a peer reviewer for EPA's BMD modeling guidelines. Other methods development work includes the combination of PBPK and BMD/BMC modeling in the development of RfDs and RfCs; research into methods for improving the scientific basis for uncertainty factors by addressing genetic polymorphisms and risk to children; consideration of mode of action in cancer risk assessment; and use of biomarker data in risk assessment. Dr. Haber received her Ph.D.in Molecular Biology from the Massachusetts Institute of Technology and has been a Diplomate of the American Board of Toxicology since 2004. She served as chair, vice president, and councilor of the SRA Dose-Response specialty group and as an officer of the SOT Risk Assessment Specialty Section (RASS), and is a Diplomate of the American Board of Toxicology. She is active in teaching basic and advanced risk assessment methods to diverse groups of risk assessors and at professional society meetings.

Reviewer One

Reviewer 1
Technical Review of the
Draft Carbon Disulfide Development Support Document
Review Guidelines

Background

The Toxicology Division of the Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that summarizes the hazard assessment and dose-response data and analyses used to derive health-protective Effects Screening Levels (ESLs) and Reference Values (ReV) for carbon disulfide. Within the draft DSD TCEQ has derived short-term and long-term toxicity values for human health, odor and vegetation endpoints. These toxicity values are used in the evaluation of air permit applications and ambient air data and were developed using RG-442 TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). The TCEQ guidelines can be found at http://www.tceq.texas.gov/publications/rg/rg-442.html. Reviewers are asked to familiarize themselves with the guidelines and consider the guidelines in formulating your comments and recommendations.

The TCEQ is seeking detailed peer input and guidance to further develop and finalize this DSD and welcomes all comments on the quality and content. *Note that the DSD document is designed to be a summary document and therefore does not provide as detailed descriptions as some other agency's toxicity assessments might. Reviewers should focus on the derivation of the Reference Values (ReVs) and not the Effects Screening Levels (ESLs). The ESLs are calculated by multiplying the ReV by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during an air permitting review. The 0.3 is a policy decision and reviewers are asked to not spend time commenting on this.*

Instructions

Please address each of the specific and general questions found below. For each response (including Yes/No responses), please explain your reasoning and considerations, discuss the scientific support for your comments and opinions, and identify the sources you consulted to construct your response. If a question is beyond your area of expertise, please indicate this. Please address each question by adding your answers to this Word document. In addition, feel free to annotate and comment within the draft TSD document using the Track Changes feature under the Review tab.

Due Date - Your written review should be returned to patterson@tera.org by email no later than January 9, 2014.

General Questions

1. What is your overall impression of the draft document? Please identify areas needing improvement and your suggestions to improve scientific quality and readability.

In general, I found this document to be easily readable. In most sections, it reflects an appropriate level of content and detail. I do have a few suggestions, however, regarding 1) moving some text from one place to another and 2) incorporating discussion of additional information. Some of these suggestions and others also are captured in the side-bar comments on the draft document itself.

Regarding area 1), I recommend that some text on pages 6 and 7 on the rationale for using the effects on metabolism of alcohol to be an appropriate representation of an effect of concern be moved to page 4 and expanded.

Regarding area 2), I recommend that some animal studies on the neurotoxicity of CS_2 be added to the discussion and summarized and, if appropriate, used to derive an animal data-based chronic ReV for comparison with the human-based ReV.

Also, I recommend that an animal data-based acute ReV be derived to compare with the human-based one.

2. Does the draft DSD clearly describe the data and approaches used by TCEQ to develop the toxicity values?

The document is very clear on which data and approaches have been chosen for the development of the toxicity values. However, there are some areas in which I am either in potential disagreement with, or at least am ambivalent about, the choices of the study selected for the POD.

3. Were procedures outlined in RG-442 *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) followed by the TCEQ in this assessment?

Given the choices made by TCEQ concerning the studies used to calculate or support the acute and chronic ReVs, I found no deviation from the basic procedures described in the Guidelines.

4. Please identify any additional relevant studies or data that you think should be included in this assessment. Please explain specifically how the studies/data could impact the assessment and toxicity values.

At the end of this charge document, I have listed a number of studies that should be (re)reviewed for suitability for deriving an animal-based chronic ReV to compare with the proposed human-based one. I also have recommended that an animal-based acute ReV be derived from the animal-based POD that was developed based upon the Saillenfait et al study. It is important to show that the chosen study/POD was the most appropriate one to use. Given that different uncertainty factors may be used for the animal studies, the resulting PODs/ReVs may not be as different as projected.

Specific Questions

5. Please comment on the following key decisions for derivation of the acute ReV. *For each element, please discuss if the TCEQ conclusions and choices are supported by the available data, and discuss any additional information or analyses that could improve the decision or related rationale*.

5A. Section 3.1.2 describes the key and supporting studies. Are these the most appropriate studies to use for the dose-response assessment? Have the key and supporting studies and the rationale for their selection been sufficiently described and supported in the DSD?

I am ambivalent about the choices made for the acute ReV derivation for two reasons. First, I find it rather unusual to characterize changes in toxicokinetic parameters as adverse effects. No other examples of this approach come to my mind at the moment. I have recommended that additional justification for making this choice be added to the document, in addition to moving it to an earlier part of the paper because I don't feel that the rationale for this choice has been adequately articulated.

However, if the decision is made to stick with study data identifying modification of toxicokinetic parameters as appropriate endpoints for derivation of an acute ReV, I would recommend using the Mack et al study results. These authors concluded that the lowest exposure concentration (10 ppm) produced a statistically significant reduction in free AAP levels. That's

two-fold lower than the lowest concentration (20 ppm) used in the Freundt et al study, which was also concluded by those authors to be an effect level. Reductions in both free AAP and total AAP were observed at all the higher doses (20. 40 and 80 ppm), exhibiting a dose response.

5B. Mode of Action (Section 3.1.3): Does the discussion on modes of action and metabolism correctly interpret the available data and are the conclusions supported by the data?

The explanation is a little thin, since it depends solely upon the brief discussion in NRC AEGL document. Some additional information can be found elsewhere in the literature, but it's probably not necessary to collect and review it for the purpose of this document.

5C.Point of Departure (POD) and Dosimetric Adjustment (Sections 3.1.5 and 3.1.6): TCEQ presents PODs from two studies with different endpoints (Freundt et al., 1976a and Saillenfait et al., 1989) and adjusts each for dose and human equivalency. Were the dosimetric adjustments correctly made and did they follow TCEQ 2012 guidance?

Yes. However, if one were to shift to the Mack study for derivation of the kinetics endpoint, one should apply a different factor to adjust from the experimental exposure period (6 hr) to a one-hour value. While the exposures in the Mack study were for 6 hrs, the first sampling occurred at Hour 3.

5D. Critical Effect (Section 3.1.6) Do you agree with the selection of inhibition of ethanol metabolism resulting in significantly increased blood acetaldehyde levels (Freundt et al., 1976a) to be the critical effect for derivation of the acute ReV?

No. I would prefer to use the results of the Mack study, given that they observed effects at 10 ppm after a 6 hr exposure.

5E. Uncertainty Factors (UFs) (Section 3.1.7): Did TCEQ select the appropriate uncertainty factors and provide sufficient rationale and support for the selections?

TCEQ used the appropriate UFs and provided the rationale and support for application to the Freundt data.

However, if one were to use the Mack data instead, I would consider increasing the UF_H, perhaps to 15-20. The reason I suggest that is that amidopyrine (*aka* aminopyrine) is a potassium channel blocker (its therapeutic mode of action). It is being used increasingly to treat

neurodegenerative diseases such as multiple sclerosis and myosthenia gravis. Drugs with this mode of action also are widely used to suppress certain types of cardiac arrhythmias, such as atrial fibrillation. Individuals suffering these conditions number in the multimillions in the U.S. and usually have additional underlying medical problems that compound the situation, constituting a sizeable sensitive population.

6. TCEQ evaluated available data for derivation of welfare-based acute and chronic (Sections 3.1.9 and 4.3) using the TCEQ guidelines (2012). Please comment on the appropriateness of the calculation of the $^{acute}ESL_{odor}$ value and decisions regarding sufficiency of data for the vegetation effects. Refer to Chapter 2 of the TCEQ (2012) for guidance.

The $^{acute}ESL_{odor}$ of 210 ppb was set in a manner consistent with the TQEC guideline criteria.

TQEC concluded that no data were available from which an ESL could be derived, based upon an inability to identify any LOAELs. However, the Kamel study concluded that, with regard to wheat
seeds

> The phytotoxic effect of CS_2 was rather lower than in the case of methyl bromide. Seeds having 9% m.c. were slightly impaired whatever the concentration of CS_2 was. The reduction in the percentage of germinated seeds was about 9% at 12% m.c. level, the bad effect increased steadily by the increase of the dose. The reduction in the percentage of germinated seeds was 5, 8 and 27% for doses of 200, 300 and 400 cc/m^3, respectively. At 15% m.c. level, the phytotoxic effect of the fumigant was much higher. Attia and Kamel (1953) indicated that CS_2 is quite a safe fumigant at the dose and period of exposure recommended for insect control. Longer periods of exposure may result in varietal differences.

I would suggest that one can identify a LOAEL from these data (probably, 8% at 300 cc/m^3) and derive a vegetation-based ESL, using that value.

7. Please comment on the following key decisions for derivation of the chronic ReV. ***For each element, please discuss if the TCEQ conclusions and choices are supported by***

the available data, and discuss any additional information or analyses that could improve the decision or related rationale.

7A. Critical Effect (Section 4.1): TCEQ identified the nervous system as the primary target of CS_2 based upon human epidemiological studies of workers exposed to CS2. Do you agree that this is the appropriate critical effect for derivation of the chronic ReV?

Based upon the current body of epidemiology data available for this exercise, effects on the nervous system do appear to be the best for deriving an ReV. However, there also is a body of literature that shows that CS_2 also has cardiovascular effects, some of which may involve alterations in the function of the nervous system, but with others associated with cholesterol/lipid imbalances. This literature on the purported cardiovascular effects should be reviewed with the goal of determining if any of these endpoints would be better suited for use in the derivation of a chronic ReV. Some of the more recent publications are listed at the end of this Charge document under Question #8. Others can be identified in more extensive literature search than I conducted. I looked only at PubMed.

7B. Key and Supporting Studies (Section 4.1.1.2): TCEQ identified Godderis et al. (2006) as the key study and several others as supporting studies. Are these the most appropriate studies to use for identification of critical effect and the dose-response assessment? Have the studies and the rationales for their selection been sufficiently described and supported in the DSD?

TCEQ identified the most appropriate study (Godderis et al) as the key study, given the requirement to use data which identify LOAELs . The Godderis LOAEL is lower than the Johnson et al LOAEL, although the latter study also identified a NOAEL. Those serving as support studies are also appropriately noted as such. They are all discussed in sufficient detail for the purpose of this document.

7C. Mode of Action (Section 4.1.2): Does the discussion on mode of action correctly interpret the available data? Do you agree that use of data on the parent compound is appropriate?

There are more studies on MOA than described in this section. Some are listed under Question #8. Some expanded discussion of MOA is warranted.

It is appropriate to use data on the parent compound in determining the dose metric.

7D. Point of Departure (POD): TCEQ identified a LOAEL of 8.9 mg/m^3 (2.84 ppm) for mild effects from Godderis et al. (2006), based on statistically significant reduced nerve conduction velocity in workers exposed for an average of 8.5 years (Standard Deviation 8.0). This study was not available when other agencies (e.g., Health Canada, US EPA, California EPA, ATSDR) developed their chronic values. Do you agree that 8.9 mg/m^3 (2.84 ppm) from Godderis et al. (2006) is the most appropriate POD among the available data and studies? TCEQ labels this a "LOAEL for mild effects," do you agree?

It is appropriate to use the Godderis et al LOAEL as the Johnson et al LOAEL is somewhat higher.

Yes, one can label it a "LOAEL for mild effects," as long as that is accommodated for in the application of the uncertainty factors .

7E. Dosimetric Adjustments (Section 4.1.3): Were the adjustments performed correctly and explained sufficiently?

Yes. All adjustments are consistent with the Guidelines.

7F. Uncertainty Factors (Section 4.1.4): Did TCEQ select the appropriate uncertainty factors and provide sufficient rationale and support for the selections?

Yes. All choices are consistent with the Guidelines.

Other Questions

8. Please identify any other relevant issues or questions that are important for the evaluation of this DSD and the toxicity values derived within it.

Additional references to consider:

<u>Neurotoxicity in animals and MOA papers</u>

The first 11 papers describe the NIEHS/EPA collaborative effort on characterizing the

neurotoxicity profile of inhaled carbon disulfide in rats. Some of the references (in red font) are listed in this draft document. I would recommend a (re)review of them to determine which, if any, can provide NOAELs/LOAELs for comparison with the human studies, as they represent a systematic approach to identify effects and possible MOAs.

1. Sills RC, Harry GJ, Valentine WM, Morgan DL. Interdisciplinary neurotoxicity inhalation studies: carbon disulfide and carbonyl sulfide research in F344 rats. Toxicol Appl Pharmacol. 2005 Sep 1;207(2 Suppl):245-50. Review.
2. Erve JC, Amarnath V, Sills RC, Morgan DL, Valentine WM. Characterization of a valine-lysine thiourea cross-link on rat globin produced by carbon disulfide or N,N-diethyldithiocarbamate in vivo. Chem Res Toxicol. 1998 Oct;11(10):1128-36.
3. Erve JC, Amarnath V, Graham DG, Sills RC, Morgan AL, Valentine WM. Carbon disulfide and N,N-diethyldithiocarbamate generate thiourea cross-links on erythrocyte spectrin in vivo. Chem Res Toxicol. 1998 May;11(5):544-9.
4. Harry GJ, Graham DG, Valentine WM, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VIII. Summary. Neurotoxicology. 1998 Feb;19(1):159-61.
5. Moser VC, Phillips PM, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VII. Behavioral evaluations using a functional observational battery. Neurotoxicology. 1998 Feb;19(1):147-57.
6. Herr DW, Vo KT, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VI. Electrophysiological examination of caudal tail nerve compound action potentials and nerve conduction velocity. Neurotoxicology. 1998 Feb;19(1):129-46.
7. Sills RC, Harry GJ, Morgan DL, Valentine WM, Graham DG. Carbon disulfide neurotoxicity in rats: V. Morphology of axonal swelling in the muscular branch of the posterior tibial nerve and spinal cord. Neurotoxicology. 1998 Feb;19(1):117-27.
8. Toews AD, Harry GJ, Lowrey KB, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: IV. Increased mRNA expression of low-affinity nerve growth factor receptor--a sensitive and early indicator of PNS damage. Neurotoxicology. 1998 Feb;19(1):109-16.
9. Valentine WM, Amarnath V, Amarnath K, Erve JC, Graham DG, Morgan DL, Sills RC. Covalent modification of hemoglobin by carbon disulfide: III. A potential biomarker of effect. Neurotoxicology. 1998 Feb;19(1):99-107.
10. Moorman MP, Sills RC, Collins BJ, Morgan DL. Carbon disulfide neurotoxicity in rats: II. Toxicokinetics. Neurotoxicology. 1998 Feb;19(1):89-97.
11. Sills RC, Morgan DL, Harry GJ. Carbon disulfide neurotoxicity in rats: I.

Introduction and study design. Neurotoxicology. 1998 Feb;19(1):83-7. No abstract available.

Additional papers describing effects in mice and possible MOAs include:

Sills RC, Valentine WM, Moser V, Graham DG, Morgan DL. Characterization of carbon disulfide neurotoxicity in C57BL6 mice: behavioral, morphologic, and molecular effects. Toxicol Pathol. 2000 Jan-Feb;28(1):142-8.

Song F, Zhang C, Wang Q, Zeng T, Xie K. Alterations in neurofilaments content and calpains activity of sciatic nerve of carbon disulfide-treated rats. Arch Toxicol. 2009 Jun;83(6):587-94.

Song F, Zhao X, Zhou G, Zhu Y, Xie K. Carbon disulfide-induced alterations of neurofilaments and calpains content in rat spinal cord. Neurochem Res. 2006 Dec;31(12):1491-9. Epub 2006 Nov 21.

Song F, Yu S, Zhao X, Zhang C, Xie K. Carbon disulfide-induced changes in cytoskeleton protein content of rat cerebral cortex. Neurochem Res. 2006 Jan;31(1):71-9.

Graham DG, Amarnath V, Valentine WM, Pyle SJ, Anthony DC. Pathogenetic studies of hexane and carbon disulfide neurotoxicity. Crit Rev Toxicol. 1995;25(2):91-112. Review.

Gottfried MR, Graham DG, Morgan M, Casey HW, Bus JS. The morphology of carbon disulfide neurotoxicity. Neurotoxicology. 1985 Winter;6(4):89-96.

Publications related to reproductive/developmental effects in humans

Le JY, Fu XM. 1996. Human sperm chromosome analysis—study on human sperm chromosome mutagenesis induced by carbon disulfide. Biomed Environ Sci 9(1):37–40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8721625.

Publications related to the potential for cardiovascular effects in humans

Kotseva K Occupational exposure to low concentrations of carbon disulfide as a risk factor for hypercholesterolaemia. Int Arch Occup Environ Health. 2001 Jan;74(1):38-42.

Bortkiewicz A, Gadzicka E, Szymczak W. 1997. Heart rate variability in workers exposed to carbon disulfide. J Auton Nerv Syst 66(1-2):62–68. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/9334994.

Chang SJ, Shih TS, Chou TC, et al. 2006. Electrocardiographic abnormality for workers exposed to carbon disulfide at a viscose rayon plant. J Occup Environ Med 48(4):394–99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16607194.

Jhun HJ, Yim SH, Kim R, et al. 2003. Heart-rate variability of carbon disulfide-poisoned subjects in Korea. Int Arch Occup Environ Health 76(2):156-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12733089.

Jian L, Hu D. 2000. Antioxidative stress response in workers exposed to carbon disulfide. Int Arch Occup Environ Health 73(7):503–06. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11057420.

Korinth G, Goen T, Ulm K, et al. 2003. Cardiovascular function of workers exposed to carbon disulphide. Int Arch Occup Environ Health 76(1):81–85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12592587.

Kotseva K. 2001. Occupational exposure to low concentrations of carbon disulfide as a risk factor for hypercholesterolaemia. Int Arch Occup Environ Health 74(1):38–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11196079.

Luo JC, Chang HY, Chang SJ, et al. 2003. Elevated triglyceride and decreased high density lipoprotein level in carbon disulfide workers in Taiwan. J Occup Environ Med 45(1):73–78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12553181.

Tan Xiaodong, Guanmin Chen et al. 2004. Cross-Sectional Study of Cardiovascular Effects of Carbon Disulfide Among Chinese Workers of a Viscose Factory. International Journal of Hygiene Environmental Health 206 (2004) 217–25.

Vanhoorne M, Comhaire F, De Bacquer D. 1994. Epidemiological study of the effects of carbon disulfide on male sexuality and reproduction. Arch Environ Health 49(4):273–78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8031184.

Wronska-Nofer T, Chojnowska-Jezierska J, Nofer JR, et al. 2002. Increased oxidative stress in subjects exposed to carbon disulfide (CS2)--an occupational coronary risk factor. Arch Toxicol 76(3):152-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11967620.

Wronska-Nofer T, Nofer JR, Stetkiewicz J, Wierzbicka M, Bolinska H, Fobker M, Schulte H, Assmann G, von Eckardstein A. Evidence for oxidative stress at elevated plasma thiol levels in chronic exposure to carbon disulfide (CS2) and coronary heart disease. Nutr Metab Cardiovasc Dis. 2007 Sep;17(7):546-53. Epub 2006 Jul 7.

Morvai V, Szakmáry E, Ungváry G. The effects of carbon disulfide and ethanol on the circulatory system of rats. J Toxicol Environ Health A. 2005 May 28;68(10):797-809.

Tan X, Chen G, Peng X, Wang F, Bi Y, Tao N, Wang C, Yan J, Ma S, Cao Z, He J, Yi P, Braeckman L, Vanhoorne M. Cross-sectional study of cardiovascular effects of carbon disulfide among Chinese workers of a viscose factory. Int J Hyg Environ Health. 2004 Jul;207(3):217-25.

Korinth G, Göen T, Ulm K, Hardt R, Hubmann M, Drexler H. Cardiovascular function of workers exposed to carbon disulphide. Int Arch Occup Environ Health. 2003 Feb;76(1):81-5. Epub 2002 Oct 12.

Tan X, Peng X, Wang F, Joyeux M, Hartemann P. Cardiovascular effects of carbon disulfide: meta-analysis of cohort studies. Int J Hyg Environ Health. 2002 Oct;205(6):473-7.

Sulsky SI, Hooven FH, Burch MT, Mundt KA. Critical review of the epidemiological literature on the potential cardiovascular effects of occupational carbon disulfide exposure. Int Arch Occup Environ Health. 2002 Aug;75(6):365-80. Epub 2002 Feb 13. Review.

Pepłlońska B, Sobala W, Szeszenia-Dabrowska N. Mortality pattern in the cohort of workers exposed to carbon disulfide. Int J Occup Med Environ Health. 2001;14(3):267-74.

Braeckman L, Kotseva K, Duprez D, De Bacquer D, De Buyzere M, Van De Veire N, Vanhoorne M. Vascular changes in workers exposed to carbon disulfide. Ann Acad Med Singapore. 2001 Sep;30(5):475-80.

Kotseva K, Braeckman L, Duprez D, De Bacquer D, De Buyzere M, Van De Veire N, Vanhoorne M. Decreased carotid artery distensibility as a sign of early atherosclerosis in viscose rayon workers. Occup Med (Lond). 2001 Jun;51(4):223-9.

Omae K, Takebayashi T, Nomiyama T, Ishizuka C, Nakashima H, Uemura T, Tanaka S, Yamauchi T, O'Uchi T, Horichi Y, Sakurai H. Cross sectional observation of the effects of carbon disulphide on arteriosclerosis in rayon manufacturing workers. Occup Environ Med. 1998 Jul;55(7):468-72.

Development Support Document
DRAFT, December 5, 2013

Carbon Disulfide

CAS Registry Number: 75-15-0

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Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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List of Acronyms and Abbreviations

List of Acronyms and Abbreviations

A	animals
AAP	aminoantipyrine
ACGIH	American Conference of Industrial Hygienists
ADH	alcohol dehydrogenase
AEGL	Acute Exposure Guideline Level
AIC	Akaike's Information Criterion
ALDH2	Aldehyde dehydrogenase2 (mitochondrial)
ADLH2(2)	Aldehyde dehydrogenase2*2 (mutant form of ALDH2 where a lysine residue replaces a glutamate in the active site at position 487 of ALDH2)
AMCV	Air Monitoring Comparison Value
ANCOVA	Analysis of variance controlling for co-variance
ANOVA	Analysis of variance
ASAT	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration 95% lower confidence limit
BMDS	Benchmark Dose Software
BRFSS	Behavioral Risk Factor Surveillance System survey
^{0} C	degrees centigrade
CES	critical effect size
CES_{05}	critical effect size corresponding to a 5% relative decrease in the mean when compared to controls
CNS	central nervous system
CS_2	Carbon disulfide
CYP450	cytochrome P-450
d	day(s)

List of Acronyms and Abbreviations

DSD	development support document
EG	exposure group
EMG	electromyography
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
ET	Extrathoracic
F	exposure frequency, days per week
GD	gestation day
g/L	grams per liter
h	hour(s)
H	Humans
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration

List of Acronyms and Abbreviations

Hg	mercury
HQ	hazard quotient
i.p.	intraperitoneal
kg	kilogram
LDH	lactate dehydrogenase
LOAEL	lowest-observed-adverse-effect-level
MCV	motor conduction velocity
µg	microgram
µg/m^3	micrograms per cubic meter
mg	milligrams
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
MRL	Minimal Risk Level
MW	molecular weight
n	number
N/A	Not applicable
NAC	National Advisory Committee
n-BA	n-butyl acetate
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OEHHA	Office of Environmental Health Hazard Assessment
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration

Deleted: MEK
Deleted: methyl ethyl ketone

List of Acronyms and Abbreviations

POD_{OC}	occupational point of departure
ppb	parts per billion
ppm	parts per million
REL	reference exposure level
ReV	reference value
RfC	inhalation reference concentration
RGDR	regional gas dose ratio
SA	surface area
SAR	structure-activity relationship
SCOB	scheduled-controlled operant behavior
SCV	sensory conduction velocity
SD	Sprague-Dawley
SMCs	self-reported multiple chemical sensitivity
SNAP	sensory nerve action potential
SPGT	serum glutamic-pyruvic transaminase
SSR	sympathetic skin response
TC	tolerable concentration
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TLV	Threshold Limit Value
TWA	time weighted average
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human (interspecies) uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor

Deleted: sural nerve sensible

Deleted: sural sensible nerve response amplitude

List of Acronyms and Abbreviations

USEPA	United States Environmental Protection Agency
V_E	minute volume

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of carbon disulfide (CS_2). Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) available at http://www.tceq.texas.gov/publications/rg/rg-442.html for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on carbon disulfide's physical/chemical data.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	Concentration	Notes
Acute ReV	1,300 ppb (4,100 µg/m^3) **Short-Term Health**	**Critical Effect(s):** Increase in blood acetaldehyde levels in humans with moderate intake of alcohol
$^{acute}ESL_{odor}$	210 ppb (650 µg/m^3) **Odor**	50% detection threshold; sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for impure CS_2
$^{acute}ESL_{veg}$	- - - **Short-Term Vegetation**	No data on vegetation effect levels; concentrations producing no observed effects were significantly above other short-term values
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	34 ppb (110 µg/m^3) **Long-Term Health**	**Critical Effect(s):** Statistically significant reductions in nerve conduction velocity in workers
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Carbon disulfide is not typically monitored for by the TCEQ's ambient air monitoring program (http://www5.tceq.state.tx.us/tamis/index.cfm?fuseaction=home.welcome), so only a limited amount of ambient air data are available to assess carbon disulfide's concentrations in Texas ambient air.

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-

Commented [PFC1]: These two statements seem to be in conflict with one another. The first says "no data." The second claims NOELs above other short-term value which infers that relevant data exist. See Comment in Charge document on this topic. I think A number could be developed.

Commented [PFC2]: Given this statement, it would be appropriate to add some text which presents the rationale for carrying out the exercise of developing ReVs and ESLs for carbon disulfide. Is it the result of application of the chemical selection process described in Section 1.9 of the Guidelines?

based ESL; ^{acute}**ESL$_{veg}$**, acute vegetation-based ESL; ^{chronic}**ESL$_{threshold(nc)}$**, chronic health-based Effects Screening Level for threshold dose-response noncancer effects; ^{chronic}**ESL $_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; and ^{chronic}**ESL$_{veg}$**, chronic vegetation-based ESL

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
^{acute}ESL [1 h] (HQ = 0.3)	390 ppb (1,200 µg/m^3)[a]	**Critical Effect:** Increase in blood acetaldehyde levels in humans with moderate intake of alcohol
^{acute}ESL$_{odor}$	210 ppb (650 µg/m^3) **Odor** **Short-Term ESL for Air Permit Reviews**	50% detection threshold; sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for technical grade CS_2
^{acute}ESL$_{veg}$	--- **Short-Term Vegetation**	No data on vegetation effect levels; concentrations producing no observed effects were significantly above other short-term values
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	10 ppb (32 µg/m^3)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Statistically significant reductions in nerve conduction velocity in workers
^{chronic}ESL$_{nonthreshold(c)}$ ^{chronic}ESL$_{threshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
^{chronic}ESL$_{veg}$	---	No data found

[a] Based on the acute ReV of 1,300 ppb (4,100 µg/m^3) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 34 ppb (110 µg/m^3) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Commented [PFC3]: See comment #1

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	CS_2	ACGIH 2006
Chemical Structure	S=C=S	TCEQ 2013
Molecular Weight	76.14	ACGIH 2006
Physical State at 25°C	Liquid	ACGIH 2006
Color	Clear, colorless for pure CS_2; or faintly yellow for impure CS_2	ACGIH 2006
Odor	Sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for impure CS_2	ACGIH 2006 ATSDR 1996
CAS Registry Number	75-15-0	ACGIH 2006
Synonyms	Carbon sulfide, dithiocarbonic anhydride, sulphocarbonic anhydride, Weeviltox	ACGIH 2006
Solubility in water	Soluble, 2,300 mg/L @ 22°C	TCEQ 2012
Log K_{ow}	1.94	HSDB 2010
Vapor Pressure	260 mm Hg @ 20°C	ACGIH 2006
Relative Vapor Density (air = 1)	2.67	HSDB 2010
Melting Point	-112.1°C	HSDB 2010
Boiling Point	46.3°C @ 760 mm Hg	ACGIH 2006
Conversion Factors	1 $\mu g/m^3$ = 0.32 ppb 1 ppb = 3.13 $\mu g/m^3$ at 25°C	ACGIH 2006

Commented [PFC4]: This was a trade name for the compound when it was a registered pesticide. Should it be included?

Chapter 2 Major Sources and Uses

The most prominent industrial use of CS_2 is in the production of viscose rayon fibers; it is also used in the production of carbon tetrachloride and cellophane. CS_2 is used as a solvent for rubber, sulfur, oils, resins, and waxes, and has been used for soil fumigation and insect control in stored grain. Industrial processes that produce CS_2 as a by-product include coal blast furnaces and oil refining (ACGIH 2006; ATSDR 1996).

CS_2 is a minor component of the waste gases emitted from the processing of sour gas (Health Canada 2000). Continuous ambient monitoring data were collected over a two year period near a sour gas processing plant in Canada. The mean and maximum levels of CS_2 were 0.61 and 88 $\mu g/m^3$ (0.19 ppb and 28 ppb), respectively at an upwind location, and 1.40 and 156 $\mu g/m^3$ (0.44 and 49.9 ppb), respectively, at a downwind location (Legge et al. 1990a, b cited in Health Canada 2000). TCEQ has monitored for CS_2 in areas of oil and gas exploration in 2009, and detected levels from 0.06 ppb to 20 ppb in short-term, instantaneous grab samples (approximately 15-second duration).

Natural sources of CS_2 include wetlands, oceans, volcanic and geothermal activity, and microbial activity in soil (ATSDR 1996). In a small study conducted in New York, NY, CS_2 was detected in all of nine indoor air samples with a mean concentration of 0.63 $\mu g/m^3$, similar to the mean concentration detected in six outdoor air samples (0.3 $\mu g/m^3$) (Phillips 1992 in Health Canada 2000).

Commented [PFC5]: Add ppbs also, to be consistent with text in paragraph above.

Commented [PFC6]: See comment #5

Chapter 3 Acute Evaluation

Acute exposure to high doses of CS_2 causes central nervous system (CNS) effects in humans and animals. In humans, irritation of the eyes and throat, and CNS effects including dizziness and headache were observed at 180-240 ppm (NRC 2009). In humans, concentrations of approximately 2,000 ppm can cause nausea, vomiting, progressing dizziness, and beginning signs of central paralysis. In humans, concentrations from 2,000 ppm to above 3,000 ppm cause irregular respiration and narcosis. In animals, CNS effects include reduced activity and hyperexcitability, stupor, ataxia, tremor, convulsions, narcosis, respiratory arrest, and death (NRC 2009).

Commented [PFC7]: Add animal doses here to provide context and comparison with the human doses noted above.

Acute exposure to lower concentrations of CS_2 that does not cause notable CNS effects clearly causes inhibition of xenobiotic biotransformation reactions, inhibition of alcohol (ethanol) metabolism via the aldehyde dehydrogenase pathway, and alterations of carbohydrate and energy metabolism in the liver (NRC 2009).

CS_2 has also been identified as a reproductive and developmental toxicant in animals, but these effects are seen at much higher concentrations than those shown to cause inhibition of xenobiotic biotransformation reactions (the lowest LOAEL identified in an animal

Commented [PFC8]: An expanded discussion of why this effect is being considered an adverse effect and used for derivation of values is warranted. The paragraphs now at the bottom of Page 6 (beginning with "Based on guidance in ATSDR (2007).." and top of Page 7 could be moved here.

reproductive/developmental toxicity study was 400 ppm). Section 3.1.2 provides a review of available reproductive and developmental toxicity studies in humans and animals.

3.1 Health-Based Acute ReV and ^{acute}ESL

A comprehensive literature search was conducted regarding the acute inhalation toxicity of CS_2. Information from both human and animal studies regarding the acute toxicity of CS_2 was reviewed in detail by ATSDR (1996 and 2012), ACGIH (2006), OEHHA (1999), and NRC (2009). Well-conducted human studies demonstrate the acute effect of CS_2 inhalation on alcohol (ethanol) metabolism and xenobiotic biotransformation reactions, and since these effects occur at concentrations below those that cause other adverse effects they are preferentially used here to develop the acute toxicity factors such as the ReV and ESL. Numerous acute animal studies have been conducted on the effects of inhalation exposure to CS_2 and are discussed extensively in ATSDR (1996 and 2012) and NRC (2009). Acute animal inhalation studies support the findings of human studies.

3.1.1 Physical/Chemical Properties

Pure CS_2 is a clear, almost colorless liquid with a sweet, pleasant odor similar to chloroform. Technical grades of CS_2 have a strong, disagreeable odor similar to rotting radishes or overcooked cauliflower due to traces of hydrogen sulfide (ACGIH 2006). CS_2 is water soluble, evaporates readily at room temperature, explodes, and ignites easily. The main chemical and physical properties of CS_2 are summarized in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

Three human experimental studies with CS_2 conducted by Mack et al. (1974), Freundt and Lieberwirth (1974), and Freundt et al. (1976a) were identified as key and supporting studies for the acute evaluation of CS_2 and are summarized in Table 4.

3.1.2.1.1 Key Human Study (Freundt et al. 1976a)

Freundt et al. (1976a) conducted a study investigating the effect of CS_2 on ethanol metabolism in twelve healthy male volunteers, ages 20-32 years. Participants were asked not to take medications or alcohol for several days prior to the experiment and were fasted prior to exposure. Shortly before starting the experimental exposure, 2 milliliters (ml) of blood were drawn from each participant. At the beginning of the experiment, participants received 0.57 ml/kilogram (kg) ethanol in 3.01 ml/kg orange juice, with further doses of 0.047 ml/kg ethanol in 0.18 ml/kg orange juice given at 15-minute intervals throughout remainder of experimental period. For each study participant, a mean blood alcohol concentration of about 0.75 g/Liter (L) (0.075% blood alcohol concentration) was obtained and it remained fairly constant during the experiments (the legal blood alcohol concentration limit for intoxication in Texas is 0.08%). The blood acetaldehyde concentration was approximately 6×10^{-3} g/L in alcoholized control subjects.

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Participants were exposed to nominal concentrations of 0, 20, 40, or 80 ppm CS_2 for 8 hours (h) (analytical concentrations were not reported). Each participant served as his own control. Blood samples were drawn at hourly intervals during the 8 h exposure period to analyze for acetaldehyde and ethanol. The blood acetaldehyde concentration rose significantly by about 50% when subjects were exposed for 8 h to 20 ppm CS_2. Exposure for 8 h to 40 and 80 ppm CS_2 resulted in an additional slight increase in blood acetaldehyde concentration. A clear dose-response effect was observed. One h of exposure to 20 ppm CS_2 produced about a 50% increase in blood acetaldehyde levels, 40 ppm produced about an 80% increase, and 80 ppm produced about a 90% increase (estimates of percent increase are based on graphical representation of data).

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In an additional experiment, four volunteers were exposed to 20 ppm of CS_2 for 8 h. Exposed subjects were then given alcohol (about 0.5 g/L (0.05%) blood alcohol) beginning 16 h after termination of exposure to CS_2. Blood was collected at hourly intervals to analyze for acetaldehyde and alcohol. The blood acetaldehyde concentration in exposed participants reached slightly more than twice the control value indicating that effects can occur even when CS_2 exposure precedes alcohol intake. A similar effect was observed in volunteers repeatedly exposed to 20 ppm CS_2 8 h/d, for 5 days (d), then given alcohol simultaneously only on the last day.

Ethanol is oxidatively metabolized by two pathways in the liver, one by cytosolic alcohol dehydrogenase (ADH), and to a lesser extent by the cytochrome P-450 (CYP450) monooxygenase system in the liver (CYP2E1). Both result in the formation of acetaldehyde, which is further oxidized by mitochondrial aldehyde dehydrogenase (ALDH2) to acetate. Acetate then enters intermediary metabolism of the cell. CS_2 inhibits the metabolism of alcohol at the second step of the pathway (aldehyde dehydrogenase) which results in increased blood acetaldehyde levels. Some individuals have a mutation in the gene for the typical form of ALDH2 which results in the synthesis of ALDH2(2), which is a less active form of the enzyme. The presence of the ALDH2(2) mutation results in an excessive production of aldehyde after ingestion of alcohol. Individuals who are homozygous for the ALDH2(2) mutation are very sensitive to the effects of alcohol and develop an alcohol intolerance syndrome even after ingestion of only a small amount of alcohol.

The observed increase in acetaldehyde levels in Freundt et al. (1976a) occurred without any noticeable alcohol intolerance effect in participants (i.e., flushing, hypotension, and tachycardia). However, alcohol intolerance has been reported to occur in workers exposed to CS_2 (most likely at higher concentrations). Based on guidance in ATSDR (2007), the Toxicology Division (TD) determined that the increase in blood acetaldehyde levels seen after acute exposure to 20 ppm CS_2 is a mild adverse effect; it is a biochemical change caused by inhibition of liver enzymes that could potentially cause reversible, functional/clinical impairment in some individuals (i.e., individuals with a less active form of the enzyme responsible for metabolizing acetaldehyde to acetate [ALDH2(2)]).

The German Society for Occupational and Environmental Medicine identifies alcohol intolerance as an adverse effect induced by CS_2 (Drexler 1998 as cited in NRC 2009). Alcohol use is very common in the United States (US) (CDC 2013). According to the 2012, Behavioral Risk Factor Surveillance System (BRFSS) survey, approximately 55% of the adult US population drank alcohol in the past 30 days. Approximately 6% of the total population drank heavily, while 17% of the population binge drank. Because alcohol is used so prevalently in the US, the TD believes it is appropriate to consider alcohol intolerance inducted by CS_2 exposure to be a relevant endpoint for toxicity factor development.

Percent increases in blood acetaldehyde levels caused by CS_2 exposure were only shown graphically and were not amenable to benchmark dose modeling; therefore, 20 ppm was selected by the TD as the lowest-observed-adverse-effect-level (LOAEL). This study was selected as the key study for the potential critical health effect of increased blood acetaldehyde levels due to inhibition of ethanol metabolism. The LOAEL of 20 ppm was used as the point of departure (POD) to determine the POD human equivalent concentration (POD_{HEC}) for this potential critical health effect.

3.1.2.1.2 Supporting Human Studies

3.1.2.1.2.1 Freundt and Lieberwirth (1974)

Details of this study were obtained indirectly from NRC (2009) because the study was only available in German. Eleven healthy male volunteers (number in parentheses), ages 20-32 years, participated in a study conducted by Freundt and Lieberwirth (1974). Participants were asked not to take medicine or alcohol several days prior to the experiment and were exposed by inhalation to nominal concentrations of 0 (11), 40 (5), or 80 (4) ppm CS_2 for 8 h. Exposures were conducted in an 8 m^3 exposure chamber. Participants received alcohol and obtained a mean blood alcohol concentration of 0.7 g/L (0.07% blood alcohol) (range 0.58 to 0.85 g/L, or 0.05% to 0.085% blood alcohol). Details on when the alcohol was given to participants were not given in NRC (2009).

Subjects exposed to 40 ppm CS_2 and alcohol did not have significant changes of any serum parameters used as markers for effects on carbohydrate and energy metabolism in the liver (cholesterol, calcium, inorganic phosphate, total bilirubin, albumin, total protein, uric acid, urea-N, glucose, lactate dehydrogenase [LDH], alkaline phosphatase, and aspartate aminotransferase [ASAT]); however, the blood glucose level was about 13% lower at the end of the exposure period (although not statistically significant). Subjects exposed to 80 ppm CS_2 had a statistically significant decrease in blood glucose and a significant rise of the serum total bilirubin by 61% as compared with pre-exposure. The group that only received alcohol had a nearly identical serum total bilirubin concentration as the 80 ppm CS_2 group, although the increase was not statistically significant because the pre-exposure level in the alcohol-only group was higher than that in the 80 ppm group.

Four volunteers were exposed to 20 ppm CS_2 for 8 h without alcohol intake. A non-significant 30% decrease in blood glucose was observed after exposure. When this group received alcohol 16-24 h after CS_2 exposure, a 108% increase in serum total bilirubin concentration and slight non-statistically significant increases in serum albumin, total protein, uric acid, and alkaline phosphatase were observed.

A LOAEL of 80 ppm was identified in this study based on a statistically significant decrease in blood glucose and a significant rise of serum total bilirubin. A no-observed-adverse-effect-level (NOAEL) of 40 ppm was identified in this study.

3.1.2.1.2.2 Mack et al. (1974)

Mack et al. (1974) conducted a study to examine the inhibition of oxidative N-demethylation of amidopyrine by CS_2 (a measure of inhibition of Phase I biotransformation of amidopyrine). Nineteen healthy male adults, ages 21 to 40 years, participated in the experiment. Participants were instructed to discontinue medication intake and to restrict alcohol intake a few weeks prior to the experiment. Participants were exposed by inhalation to nominal concentrations of 0, 10, 20, 40, or 80 ppm CS_2 for 6 h. Each participant served as his own control.

Exposures were carried out in an 8 m^3 dynamic exposure chamber. At the start of the experiment, participants received amidopyrine orally at 7 mg/kg body weight. Urine samples were collected 3-33 h after the start of the exposure and were assayed for metabolites of amidopyrine (aminoantipyrine [AAP], 4-AAP, and N-acetyl-AAP). The lowest concentration tested (10 ppm) was sufficient to result in a significant deficit in the excretion of the free 4-AAP during the exposure. Exposure to 20, 40, and 80 ppm for 3 h resulted in a statistically significant dose-dependent reduction in free AAP, N-Acetyl AAP, and total AAP. The time of maximal depression as measured by the excreted total 4-AAP shifts from 6 h after 10 ppm to 12 h after 80 ppm, whereas the amount of maximal deficit ranges from 14% to nearly 50%. Specific percent changes for each endpoint at each concentration and time interval were not reported in the study. The excretion deficit was reversible and compensated for during the subsequent excretion phase. The intensity and the duration of the effect showed a well-defined dose-response relationship.

An additional experiment with exposure to 20 ppm CS_2 for 6 h showed the effect to be no longer detectable 18 h after exposure. A single 6 h exposure to 40 ppm CS_2 produced an identical inhibitory reaction compared to that seen after exposure to 20 ppm CS_2 for 6 h/d for 5 d.

After 3 h exposure to 10 ppm CS_2 (after 3 h of exposure) a statistically significant reduction in free AAP levels was observed in exposed individuals (indicating an inhibition of Phase I biotransformation of amidopyrine). A dose-response effect was observed after three hours of exposure, with 20, 40, and 80 ppm producing statistically significant, dose-related deficits in free AAP and total AAP levels greater than levels at 10 ppm. After three hours of exposure, 20, 40, and 80 ppm each produced statistically significant, dose-related deficits in free AAP and total AAP levels, greater than the deficits seen at 10 ppm. The deficits increased with dose level. While biochemical changes characterized by impairment of enzymes of the mixed function

oxidase system may be considered potentially adverse (ATSDR 2007), uncertainties in actual percent changes in free AAP levels observed at each exposure concentration and time interval, and no data showing any morphologic or clinical changes associated with the inhibition of Phase I biotransformation of amidopyrine, prevents TD from determining whether the observed effect was truly adverse. Therefore, a NOAEL or LOAEL could not be clearly identified and substantiated from the Mack et al. (1974) study. Results of the Mack et al. (1974) study support findings that CS_2 can inhibit metabolic processes at low concentrations.

Commented [PFC9]: My disagreement with this statement is noted here and elsewhere in greater detail.

Table 4. Summary of Key and Supporting Human Acute Inhalation Studies

Exposure Group	Concentration (ppm) and Duration	NOAEL	LOAEL	Critical Effect	Reference
12 healthy male volunteers, ages 20-32 years	0, 20, 40, or 80 ppm; 8 h	---	20 ppm[a]	Inhibition of ethanol metabolism resulting in significantly increased blood acetaldehyde levels	**Key Study:** Freundt et al. (1976a)
11 healthy male volunteers, ages 20-32 years	0, 40, or 80 ppm; 8 h	40 ppm	80 ppm[b]	Statistically significant decrease in blood glucose and significant rise of serum total bilirubin in alcoholized subjects	Supporting Study: Freundt and Lieberwirth (1974)
19 healthy male volunteers, ages 21-40 years	0, 10, 20, 40, or 80 ppm; 6 h		10 ppm?---	Inhibition of Phase I microsomal drug biotransformation	Supporting Study: Mack et al. (1974)

Deleted: 80 ppm[c]

[a] The LOAEL of 20 ppm identified in Freundt et al. (1976a) was used as the point-of-departure (POD) to derive a POD_{HEC} and subsequent Acute Rev and ESL.

[b] The LOAEL of 80 ppm identified in Freundt et al. (1974) was higher than the LOAEL of 20 ppm identified in the key study; therefore, Freundt et al. (1974) was used as a supporting study.

[c] Inhibition of Phase I microsomal drug biotransformation occurred at all concentrations tested in Mack et al. (1974); however, this effect could not clearly be classified as an adverse effect based on information provided in the study and guidance in ATSDR (2007) and TCEQ (2012). Mack et al. (1974) was used as a supporting study.

Commented [PFC10]: This statement seems inconsistent with the establishment of a LOAEL in Freundt et al 1976a. Each study measured a change in metabolism, albeit at different points in the pathway. I cannot rationalize calling the observed effects in Freundt "adverse" but not those in Mack.

3.1.2.2 Developmental/Reproductive Studies

Some human studies provide evidence that CS_2 may cause reproductive and developmental effects although limitations of the studies (i.e., poor exposure measurements, lack of appropriate control groups, concomitant exposure to other chemicals) prevent their use in the development of ReVs. Numerous animal studies provide evidence for CS_2-induced developmental and reproductive toxicity and are reviewed extensively in USEPA (1994), ATSDR (1996 and 2012), and NRC (2009). Reliable animal studies evaluating developmental/reproductive toxicity are summarized in Table 5.

3.1.2.2.1 Key Developmental Study (Saillenfait et al. 1989)

Saillenfait et al. (1989) exposed pregnant Sprague-Dawley rats (20-23/group) by inhalation to 0, 100, 200, 400, or 800 ppm CS_2, 6 h/d during gestational days 6-20. Maternal and fetal parameters were evaluated on day 21. Maternal toxicity (reduced maternal weight gain) and reduced fetal body weight was observed at 400 and 800 ppm. No effects were observed on implantations, resorptions, live fetuses, or fetal sex ratio. An increase in unossified sternebrae was observed in fetuses in the 800 ppm exposure group. A small, but not statistically significant incidence in club foot was observed in fetuses in the 400 and 800 ppm exposure groups. A LOAEL of 400 ppm was identified in this study for maternal toxicity and reduced fetal body weight. In the absence of acceptable human developmental toxicity studies, Saillenfait et al. (1989) was selected as the key study for the potential critical health effect of developmental and maternal toxicity. The NOAEL of 200 ppm was used as the POD to determine the POD_{HEC} for this potential critical health effect.

3.1.2.2.2 Supporting Studies

3.1.2.2.2.1 Belisles et al. (1980)

Belisles et al. (1980) exposed rats and rabbits (15-30/group) to 0, 20, or 40 ppm CS_2 for 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm CS_2 on days 0-18 or days 6-18 of gestation, and groups of rabbits not exposed pregestationally were exposed to 20 or 40 ppm on days 0-21 or days 7-21 of gestation. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during gestation days 0-18 or 6-18 (rats) or 0-21 or 7-21 (rabbits). Unexposed control animals were included for both pregestational and gestation periods. In rats, no maternal toxicity was observed and no embryotoxic, fetotoxic, or teratogenic effects were observed except for a slight nonsignificant increase in resorptions and reductions in live fetuses in two groups of exposed rats. A high degree of mortality was observed in the rabbit study, which was not exposure-related, and there was no evidence of exposure related maternal toxicity or developmental toxicity (authors report that the cause of death was unknown). A free-standing NOAEL of 40 ppm for maternal and developmental toxicity for both Sprague Dawley rats and New Zealand rabbits was identified in this study.

3.1.2.2.2.2 PAI (1991)

As described in NRC (2009), PAI (1991) exposed pregnant New Zealand rabbits (24/group) by inhalation to 0, 60, 100, 300, 600, or 1,200 ppm CS_2 for 6 h/d on gestation days 6-18. The uterine contents were examined on gestation day 29. Severe maternal toxicity including death was observed at 1,200 ppm. No maternal toxicity was observed at the lower doses. Embryotoxicity was observed at 600 and 1,200 ppm including postimplantation loss, number of live fetuses, and reduced fetal weight. In the lower dose groups and controls, 20-23 litters were examined and there were no signs of embryotoxicity. This study identified a LOAEL of 600 ppm for embryotoxicity in the absence of maternal toxicity.

3.1.2.2.2.3 WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993)

As described in NRC (2009) and Health Canada (2000), WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993) exposed female CD rats by inhalation to 0, 125, 250, or 500 ppm CS_2 for 6 h/d prior to mating through gestation day 19. The mothers were allowed to deliver and both mothers and pups were observed through day 21 of lactation. Maternal toxicity (irritation and reduced food consumption) and fetotoxicity (increased mortality, reduced pup viability, decreased litter size, and total litter loss) were observed at 500 ppm although no adverse maternal, reproductive, or fetal effects were noted in the lower dose groups. A NOAEL of 250 ppm for maternal toxicity, reproductive, and developmental effects was identified in this study.

3.1.2.2.2.4 Zenick et al. (1984)

Zenick et al. (1984) exposed male Long-Evans rats (12-14/group) by inhalation to 0 or 600 ppm CS_2 for 6 h/d, 5 d/week, for 10 weeks. No significant adverse effects on male reproductive parameters were observed after 1 week of exposure. Reproductive parameters including ejaculation latency, sperm count, and mount latency were affected after 4-10 weeks of exposure. No treatment related effects were observed on other parameters including hormone levels, histology of the reproductive organs, and organ weights (except lower prostate weight). A LOAEL of 600 ppm was identified in this study for reproductive effects. No treatment related effects were observed on epididymal sperm counts and reproductive organ weights after male rats were exposed by inhalation to 900 ppm CS_2 for 12 weeks in a pilot study conducted by Tepe and Zenick (1982) as reported in NRC (2009).

Table 5. Animal Reproductive and Developmental Studies

Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
Sprague-Dawley rats	0, 20, or 40 ppm; 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on GD 0-18 or GD 6-18. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during GD 0-18 or GD 6-18	40	---	Free-standing NOAEL for maternal and developmental toxicity	Belisles et al. (1980)
New Zealand rabbits	0, 20, or 40 ppm; 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on days GD 0-21 or GD 7-21. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during GD 0-21 or GD 7-21	40	---	Free-standing NOAEL for maternal and developmental toxicity	Belisles et al. (1980)
pregnant New Zealand rabbits	0, 60, 100, 300, 600, or 1200 ppm; 6 h/d on GD 6-18	300	600	Developmental toxicity (increased post-implantation loss) in the absence of maternal toxicity	PAI (1991)

Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
pregnant Sprague-Dawley rats	0, 100, 200, 400, or 800 ppm; 6 h/d during GD 6-20	200	400	Maternal toxicity and significant reductions in fetal body weight	Saillenfait et al. (1989)
female CD rats	0, 125, 250, or 500; 6 h/d prior to mating through GD 19	250	400	Maternal toxicity and reduced fetal body weight	WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993)
male Long-Evans rats	0 or 600; 6 h/d, 5 d/week, for 1 week	600	---	No adverse effects reported	Zenick et al. (1984)
male Long-Evans rats	0 or 600; 6 h/d, 5 d/week, for 10 weeks	---	600	ejaculation latency, sperm count, and mount latency affected after 4-10 weeks of exposure	Zenick et al. (1984)

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3.1.3 Metabolism and Mode-of-Action (MOA) Analysis

3.1.3.1 Metabolism

CS_2 can be metabolized in the liver by CYP450 to an unstable oxygen intermediate that either hydrolyzes to form atomic sulfur and monothiocarbamate, yielding carbonyl sulfate and carbon dioxide in breath and inorganic sulfates and organosulfur compounds in urine, or spontaneously generates atomic sulfur, carbonyl sulfide, and carbon dioxide. Conjugation of CS_2 or carbonyl sulfide with glutathione forms thiazolidine-2-thione-4-carboxylic acid and 2-oxythiazolidine-4-carboxylic acid, which are then excreted in urine. Figure 1 shows the proposed metabolic pathways for CS_2.

3.1.3.2 Absorption and Excretion

Human and animal studies have shown CS_2 to be rapidly and extensively absorbed through the respiratory tract (NRC 2009). Aqueous solutions of CS_2 have been shown to be absorbed by the skin in humans (NRC 2009). In both humans and animals, unmetabolized CS_2 is mainly excreted by the lungs while most of the absorbed CS_2 is metabolized and eliminated in the form of different metabolites by the kidney (NRC 2009).

3.1.3.3 Mode of Action (MOA) for Inhibition of Ethanol Metabolism and Phase I Xenobiotic Biotransformation

The reactive sulfur generated by CYP450 metabolism can bind macromolecules, including CYP450s, which is thought to be the mechanism responsible for inhibition of Phase I xenobiotic biotransformation observed in humans and animals (NRC 2009). CS_2 may also interact directly with amino acids to form dithiocarbamates. Low molecular weight dithiocarbamates are chelators of transition metal ions (e.g., Fe^{2+}, Cu^{2+}, Zn^{2+}) and formation of dithiocarbamates may inhibit enzymes that depend on transition metal ions for proper function (NRC 2009). This mechanism may explain the CS_2 induced inhibition of aldehyde dehydrogenase (ALDH2) in ethanol metabolism observed in humans and animals (Freundt et al. 1976a). Given the proposed mechanism of action of CS_2 outlined above, individuals with CYP450 or enzyme polymorphisms inhibited by CS_2 (i.e., individuals with ALDH2(2)) or individuals exposed to xeniobiotics (e.g., medications, ethanol) metabolized by CYP450s inhibited by CS_2 may be more sensitive to toxic effects.

3.1.3.4 MOA for Developmental Effects

In terms of the potential for developmental effects, a study in mice conducted by Danielsson et al. (1984) as cited in ATSDR (1996) provides evidence that CS_2 and its metabolites cross the placental barrier at all stages of gestation and localize selectively in tissues reported to be the target organs for CS_2 toxicity. The TD could not locate information regarding the possible MOA for CS_2-induced developmental toxicity.

3.1.4 Dose Metrics

Potential critical health effects identified were increased blood acetaldehyde levels due to inhibition of alcohol metabolism in animals and humans, and developmental and maternal toxicity in animals. In the key studies for each set of effects (Freundt et al. 1976a and Saillenfait et al. 1989), data on the exposure concentration of the parent chemical were available, whereas data on more specific dose metrics were not available. Thus, administered exposure concentrations of the parent chemicals were used as the dose metrics.

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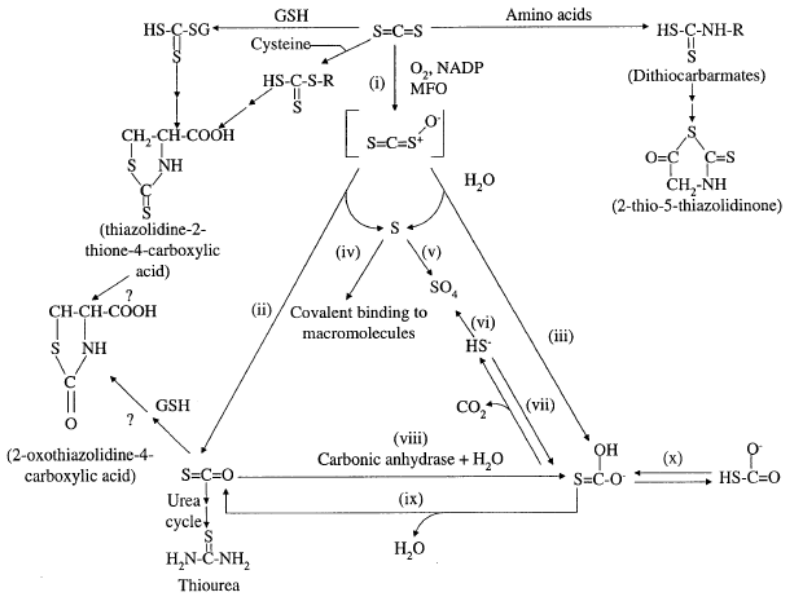

Figure 1. Proposed Metabolic Pathways for Carbon Disulfide (Figure 2-3 from ATSDR 1996)

3.1.5 PODs for Key Studies and Dosimetric Adjustments

The key studies selected for derivation of the POD_{HECs} are Freundt et al. (1976a) and Saillenfait et al. (1989). In Freundt et al. (1976a), humans exposed to 20 ppm CS_2 for 8 h had statistically significant increases in blood acetaldehyde levels; thus, the LOAEL of 20 ppm was used as the POD to derive the POD_{HEC}. The POD identified in Freundt et al. (1976a) was chosen over results from Mack et al. (1974) because a NOAEL or LOAEL could not be clearly identified and substantiated in Macke et al. (1974) based on the endpoint evaluated. However, results of the Mack et al. (1974) study support findings that CS_2 can inhibit metabolic processes at low concentrations.

Commented [PFC11]: Mack et al claimed effects at all concentrations, including the lowest (10ppm).

In the developmental study conducted by Saillenfait et al. (1989) in rats, maternal toxicity and significant reductions in fetal body weight were observed at 400 ppm but no adverse effects were observed at 200 ppm. The TD used the NOAEL of 200 ppm identified in this study as a POD to derive the POD_{HEC}. The NOAEL identified in Saillenfait et al. (1989) was selected over the free-standing NOAEL identified in Belisles et al. (1980) because the studies evaluated the same species and similar endpoints and Saillenfait et al. (1989) was able to identify a dose-response effect unlike Belisles et al. (1980).

3.1.5.1 Freundt et al. (1976a)

Freundt et al. (1976a) is a human study; therefore, no animal-to-human adjustment is necessary. The POD from the Freundt et al. (1976a) study is based on an 8 h exposure duration, so an exposure duration adjustment to 1 h must be considered. Experimental evidence presented in this DSD clearly indicate that CS_2 induced inhibition of alcohol metabolism is both concentration (C) and duration (T) dependent. Therefore, exposure duration adjustment for the Freundt et al. (1976a) study is appropriate. Default procedures discussed in TCEQ (2012) with n = 3 are used to adjust to a 1 h exposure duration for acute studies where both C and T play a role in toxicity.

$POD_{HEC\ ADJ} = C2 = [(C1)^3 \times (T1 / T2)]^{1/3} = [(20\ ppm)^3 \times (8\ h/1\ h)]^{1/3} = 40\ ppm$

3.1.5.2 Saillenfait et al. (1989)

The POD from Saillenfait et al. (1989) is based on effects observed in animals; therefore, an animal-to-human adjustment is necessary. The critical adverse effects caused by CS_2 are systemic effects and CS_2 is treated as a Category 3 gas (TCEQ 2012). For Category 3 gases, the default dosimetric adjustment from an animal concentration to a POD_{HEC} is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

The measured blood/air partition coefficient in humans ($(H_{b/g})_H$) for CS_2 is 0.36 (Soucek 1960 as cited in IPCS 1979). No measured or predicted blood/air partition coefficient in the rat ($(H_{b/g})_A$) was available. A default value of one is used as the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A$ / $(H_{b/g})_H$) as recommended by TCEQ (2012) for a vapor producing remote effects. The resulting POD_{HEC} from the POD of 200 ppm in the Saillenfait et al. (1989) study is 200 ppm:

POD_{HEC} = POD_{ADJ} x RGDR
= 200 ppm x 1
= 200 ppm

Since the POD from the Saillenfait et al. (1989) study is based on a developmental toxicity endpoint, no exposure duration adjustment is necessary.

3.1.6 Selection of the Critical Effect

As indicated in Section 3.1.2.1.1, data suggest that increased blood acetaldehyde levels caused by inhibition of alcohol (ethanol) metabolism via the aldehyde dehydrogenase pathway is the most sensitive and relevant endpoint for short-term exposure to CS_2. The specific critical effect of CS_2 exposure in Freundt et al. (1976a) was a statistically significant increase in blood acetaldehyde levels (approximately 50%) when human subjects were exposed for 8 h to 20 ppm

CS_2. The 20 ppm dose level from Freundt et al. (1976a) was identified as a LOAEL for mild effects and was used as the POD to derive a POD_{HEC} of 40 ppm. Since the POD_{HEC} of 40 ppm derived using the POD from the Freundt et al. (1976a) study was significantly lower than the POD_{HEC} of 200 ppm derived using the POD from the Saillenfait et al. (1989) study, it was selected as the critical effect and was used to derive the Acute ReV and ESL.

Commented [PFC12]: Given that this POD was derived, a potential acute ReV based upon it should be calculated to prove that the resulting value would be "significantly" higher than that resulting from use of the human data. Use of different assumptions and uncertainty factors will likely result in value that may be different from (and less than) the 10-fold difference in the respective POD_{HEC}s

3.1.7 Adjustments of the POD_{HEC}

The MOA by which CS_2 may produce toxicity is assumed to have a threshold/nonlinear MOA. Therefore, the POD_{HEC} from Freundt et al. (1976a) was divided by relevant uncertainty factors (UFs).

The following UFs were applied to the POD_{HEC} of 40 ppm from Freundt et al. (1976a):

- A UF_H of 10 was used for intrahuman variability to account for possible sensitive individuals within the human population (i.e., individuals with mutations in the ALDH2 gene, individuals taking disulfram).
- A UF_D of 1 was used because the overall database of acute toxicological studies with CS_2 is large (ATSDR 1996; NRC 2009). The acute studies consist of both human and animal studies as well as short-term reproductive/developmental studies.
- A LOAEL-to-NOAEL uncertainty factor (UF_L) of 3 was used because the POD_{HEC} of 40 ppm from Freundt et al. (1976a) was considered a LOAEL for mild effects based on reversible biochemical changes (increased blood acetaldehyde levels) that occurred in healthy human volunteers without any noticeable functional or clinical impairment.

A total UF of 30 was applied to the POD_{HEC} of 40 ppm to derive the acute ReV of 1.3 ppm (rounded to two significant figures).

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D \times UF_L)$$
$$= 40 \text{ ppm} / (10 \times 1 \times 3)$$
$$= 40 \text{ ppm} / 30$$
$$= 1.3 \text{ ppm}$$

3.1.8 Health-Based Acute ReV and ^{acute}ESL

The acute ReV of 1,300 ppb (4,100 µg/m^3) derived based on the Freundt et al. (1976a) study, was multiplied by 0.3 to calculate the ^{acute}ESL. At the target hazard quotient of 0.3, the ^{acute}ESL is 390 ppb (1,200 µg/m^3) (Table 6). Values were rounded to two significant figures at the end of all calculations.

Table 6. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Values and Descriptions
Study	Freundt et al. (1976a)
Study Population	Twelve healthy male adults, ages 20 to 32 years
Study Quality	Medium to High
Exposure Methods	Inhalation Chamber
POD_{HEC}	20 ppm, LOAEL for mild effects
Critical Effects	Increase in blood acetaldehyde levels in humans with moderate intake of alcohol (0.075% blood alcohol level)
Exposure Duration	8 h
Extrapolation to 1 h	TCEQ (2012) default procedure with n = 3
$POD_{HEC\ ADJ}$ (1 h)	40 ppm
Total UFs	30
Interspecies UF	Not Applicable (N/A)
Intraspecies UF	10
LOAEL UF	3 (mild effect)
Incomplete Database UF *Database Quality*	1 High
acute ReV [1 h] (HQ = 1)	**1,300 ppb (4,100 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**390 ppb (1,200 µg/m^3)**

3.1.9 Comparison of Acute ReV to Other Acute Regulatory Values

The acute ReV is slightly lower than the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Level (REL) of 2 ppm (6,200 µg/m^3) (OEHHA 1999) which is based on significant reductions in fetal body weight observed in Saillenfait et al. (1989). The acute ReV is lower than the 1-hour Acute Exposure Guideline Level-1 (AEGL-1) of 13 ppm (NRC 2009) based on Freundt et al. (1976a) by a factor of 10 because additional uncertainty factors were used to determine the ReV.

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Several studies have reported odor thresholds for CS_2. In Nagata (2003), the 50% odor detection threshold for CS_2 determined by the triangular odor bag method was 210 ppb. Amoore and Hautala (1983) reported a geometric mean odor threshold of 110 ppb, Leonardos et al. (1969) reported an odor recognition threshold of 210 ppb, and AIHA (1997) reported a range of all referenced odor values from 16 ppb to 420 ppb (reported in NRC 2009). The Nagata (2003) study is the only source of information for odor thresholds that meets the criteria in the TCEQ Guidelines (2012).

According to the TCEQ Guidelines (2012), odor detection values defined as the highest quality level of odor thresholds (Level 1) will be considered first in setting the $^{acute}ESL_{odor}$ values. The odor detection threshold reported by Nagata (2003) was determined by the standardized methods of measuring odor and is defined as Level 1 quality data. Therefore, the standardized odor detection threshold determined by Nagata (2003) was used to set the $^{acute}ESL_{odor}$. Accordingly, the $^{acute}ESL_{odor}$ for CS_2 is 210 ppb (650 µg/m^3).

3.2.2 Vegetation Effects

Three acute studies on the vegetation effects of CS_2 in air were located and are listed below:

- Taylor and Selvidge (1984) exposed bush beans (Phaseolus vulgaris) in a closed system to 420 to 5,600 mg/m^3 CS_2 for 6 h. No effects were observed on transpiration or photosynthesis at these concentrations. No visual injury was observed in beans exposed to 10,000 mg/m^3 CS_2 for 6 h.

- Kamel et al. (1975) exposed different species of seeds to CS_2. The most sensitive species was the seed of the wheat plant, Giza variety. Grains with a 15% moisture content suffered a 55% reduction in germination when exposed to 5.05 mg/L (5.05 x 10^8 µg/m^3) CS_2 for 24 h. Wheat seeds with a moisture content less than 15% can safely be exposed to CS_2 up to 2.53 x 10^8 µg/m^3 for 24 h.

- Verna et al. (1991) exposed seeds of multiple species to CS_2 up to 1,230 mg/L for 2 h. This exposure did not adversely affect germination.

None of the available acute studies on vegetation effects of CS_2 reported adverse effects. According to TCEQ Guidelines (2012), the vegetation-based ESL should be set at the lowest-observed–effect-level (LOEL). Since no LOEL was identified in any of the available studies, a vegetation-based ESL was not developed.

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3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

$^{acute}ESL_{odor}$ = 210 ppb (650 µg/m^3)
$^{acute}ESL$ = 390 ppb (1,200 µg/m^3)
acute ReV = 1,300 ppb (4,100 µg/m^3)

For the evaluation of ambient air monitoring data, the $^{acute}ESL_{odor}$ is lower than the acute ReV (Table 1), although both values may be used for the evaluation of air monitoring data. The short-term ESL for air permit evaluations is the $^{acute}ESL_{odor}$ of 210 ppb (650 µg/m^3) as it is lower than the health-based $^{acute}ESL$ (Table 2). The $^{acute}ESL$ (HQ = 0.3) is not used to evaluate ambient air monitoring data and will be used in air permitting applications.

3.4 Acute Inhalation Observed Adverse Effect Level

The acute inhalation observed adverse effect level would be the LOAEL from the key human study of 20 ppm (Freundt et al. 1976a). The $LOAEL_{HEC}$ determined from a human study, where inhibition of alcohol metabolism and the resulting increase in blood acetaldehyde levels, represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same (8 h) or longer durations as those used in the study. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity (i.e., individuals with a mutation in the ALDH2 gene would be expected to be more sensitive to effects of inhibition of alcohol metabolism). The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

A comprehensive literature search through July 2013 was conducted, and key studies were reviewed, regarding the chronic inhalation toxicity of CS_2. In addition, information presented in the ATSDR Toxicological Profile for CS_2 (1996), the ATSDR Addendum to the Toxicological Profile for CS_2 (2012), California's CS_2 RELs Document (OEHHA 1999), AEGLs (NRC 2009), American Conference of Industrial Hygienist's (ACGIH) Threshold Limit Value (TLV)-Time Weighted Average (TWA) support document (ACGIH 2006), and USEPA's IRIS Summary of CS_2 (1995) was evaluated.

The primary target of CS_2 is the nervous system. Numerous human epidemiological studies have been conducted using workers exposed to CS_2, and adverse health effects have been well characterized. Chronic exposure can cause neurophysiological and neuropathological changes (decreased peripheral nerve conduction velocity in motor and sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes). All other adverse effects caused by chronic CS_2 exposure including cardiovascular, reproductive, ophthalmologic, and renal, occur at higher concentrations than nervous system effects; therefore the key and supporting studies used to derive the chronic ReV are based on nervous system effects. Animal studies support the

findings of human studies and are described in detail elsewhere (USEPA 1995; ATSDR 1996 and 2012; OEHHA 2001).

4.1.1 Physical/Chemical Properties and Key Study

4.1.1.1 Physical/Chemical Properties

For physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.1.2 Human Studies

4.1.1.2.1 Key Human Study (Godderis et al. 2006)

Godderis et al. (2006) evaluated the neurobehavioral and clinical effects of CS_2 inhalation exposure on viscose rayon workers. The goal of the Godderis et al. (2006) study was to determine whether adverse effects occurred below the occupational TLV at that time of 31 mg/m^3 (10 ppm) set by the ACGIH (1994), using the same health outcomes evaluated in a study conducted by Vanhoorne et al. (1995). Workers were initially divided into two exposure groups: Exposure Group (EG)1, n=60 < 31 mg/m^3 (10 ppm) and EG2, n=25 > 31 mg/m^3 (10 ppm). The average yearly exposure to CS_2 for the exposure groups were: EG1= 8.9 mg/m^3 ± 1.1 (2.84 ppm) and EG2= 59.2 mg/m^3 ± 5.2 (18.9 ppm). Exposure groups were based on a cumulative exposure index calculated for each worker by multiplying the number of years in a job with the exposure concentration and adding up these products. Also the cumulative exposure index was reported as: EG1–59.5 years x mg/m^3 and EG2–746 years x mg/m^3. The estimated exposure levels for the jobs were based upon recent and historic monitoring for homogeneous exposure groups (spinners, bleach, stable, and post-preparation). The control group (n=66) consisted of workers from a plastic-processing factory, an assembly factory, and a starch-processing factory, and were not exposed to CS_2 or any other toxic compound in their work environment. Neurobehavioral and clinical effects were assessed using various approaches including standardized and validated questionnaires, clinical neurological examination, computer-assisted neurobehavioral tests, and neurophysiological examinations (nerve conduction and electromyography [EMG]). There was no mention of blinding the evaluators in any of these evaluations or tests. Confounding variables included age, race, educational level, personality score, smoking, alcohol use, motivation, shift work, and body mass index (BM I). Individuals who abused alcohol were excluded from the study.

Commented [PFC14]: How did they know who these people were? What was considered "abuse" ?

Disequilibrium complaints and sensory-motor complaints were statistically significantly higher for the total exposure group for the Q16 questionnaire results compared to controls. Multiple logistic regressions showed borderline significant differences between controls, EG1 and EG2 alone for the sensory-motor complaints after correction for different confounding variables ($p \leq 0.07$). The proportion of workers with absent sensation in one of five sensory functions (temperature, vibration, touch, pinprick or position) and the presence of positional tremor were higher in the total exposure group compared to controls. After correction for co-variables using multiple logistic regression, a significantly higher proportion of EG1 had positional tremor

compared to controls and significantly more individuals with abnormal sensation were in EG1 and EG2 compared to controls.

With respect to neurobehavioral examination system results, digital span backwards, finger-tapping dominant hand, and finger-tapping non-dominant hand were significantly worse in the total exposure group compared to controls. After correcting for confounding variables, only differences in finger tapping dominant and non-dominant hand were significant when comparing EG1, EG2, and controls. Four out of ten nerve conduction velocity tests were statistically significantly different from controls (Table 7). Analysis of variance (ANOVA) with Duncan's multiple range test showed significantly slower sural nerve sensible conduction velocity (SCV), longer sural sensory nerve response amplitude (SNAP) duration, and lower SNAP amplitude and sympathetic skin response (SSR) amplitude in EG1 and EG2 compared to controls ($p<0.05$). The same results were found after controlling for confounding variables using univariate analysis of co-variance (ANCOVA) (all $p<0.03$) (Table 8).

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Results clearly indicate an effect of CS_2 on various neurotoxicity endpoints. Because results showed that subclinincal and clinical effects occurred in individuals exposed to less than the TLV, Godderis et al. (2006) attempted to better predict the no-observed-effects-level (NOEL) by re-doing the ANCOVA and multiple logistic regression analyses using three subgroups of exposure: N1 group (n=34) exposed to $\leq$ 10 mg/m^3 (3.2 ppm), N2 group (n=25) exposed to 10.01 to 30.00 mg/m^3 (3.2 to 9.6 ppm), and N3 group (n=26) exposed to > 30 mg/m^3 (9.6 ppm).

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Regarding the statistically significant nerve conduction findings in the three exposed subgroups, Godderis et al. (2006) stated "Of the nerve conduction results, sural (SNAP) amplitude and duration and sural SCV were (borderline) significantly worse in all three subgroups…" (Table 9). SSR amplitude was only significantly diminished in N1 and N3, with no clear dose-response relationship. Based on the limited data presented for the three exposure subgroups, and the lack of a consistent dose-response relationship for the nerve conduction velocity results, the TD did not use data from the three subgroups to determine the POD. However, the information supports using the exposure estimate for EG1 (average yearly exposure [geometric mean] of 8.9 mg/m^3 [2.84 ppm]) as the POD.

A LOAEL of 8.9 mg/m^3 (2.84 ppm) for mild effects was identified in this study based on statistically significant reduced nerve conduction velocity in workers exposed for an average of 8.5 years (standard deviation 8.0). As noted above, 8.9 mg/m^3 (2.84 ppm) was the average yearly exposure concentration calculated for EG1. Reductions in nerve conduction velocity, while reduced compared to controls, were still within a range of clinically normal values so the effect is considered indicative of mild neurotoxicity and the LOAEL was considered a LOAEL for mild effects (ACGIH 2006). Godderis et al. (2006) was selected as the key study used to derive the chronic ReV because of the high quality of the study and the fact that adverse effects on nerve conduction were reported at lower concentrations than in other studies of similar quality (Johnson et al. 1983; Vanhoorne et al. 1995).

Table 7. Statistically Significant Peripheral Nerve Conduction Velocity Results (Godderis et al. 2006)

Nerve Conduction Velocity	Geometrical Mean (Standard Error)				Unit	P (t-test)
	Control Group	EG1 (n=60) < 10 ppm[a]	EG2 (n=25) > 10 ppm[b]	Total Exposed		
Log (sural SNAP amplitude)	10.50 (1.05)	5.58 (1.18)	2.86 (1.38)	4.57 (1.16)	µV	<0.001
Log (sural SCV)	55.58 (1.02)	41.39 (1.09)	27.6 (1.24)	36.81 (1.09)	m/s	<0.001
Log (sural SNAP duration)	1.93 (1.06)	3.43 (1.15)	5.29 (1.31)	3.90 (1.13)	ms	<0.001
Log (SSR amplitude)	768.60 (1.07)	379.75 (1.26)	418.60 (1.37)	390.84 (1.20)	µV	0.002

SNAP, sensory nerve response amplitude; **SCV**, conventional sensory nerve conduction velocity; **SSR**, sympathetic skin response

[a] EG1 had an average yearly exposure (geometric mean ±SE) of 8.9 mg/m^3 ± 1.1 and a cumulative exposure index of 746.6 years* mg/m^3 ± 17.1

[b] EG2 had an average yearly exposure of 59.2 mg/m^3 ± 5.2 and a cumulative exposure index of 746.6 years* mg/m^3 ± 116.1

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Table 8. Statistically Significant Results of ANCOVA (p≤0.03) on Nerve Conduction Velocity Studies Comparing Exposure Groups to Control Group (Godderis et al. 2006)

Nerve Conduction Velocity	Contrast Estimate (Standard Error)		
	EG1 (n=60) < 10 ppm	EG2 (n=25) > 10 ppm	Adjusting Covariates p≤0.05
Log (sural nerve SNAP amplitude)	–0.36 (0.09)	–0.41(0.13)	Race[a] (β = 0.04)
Log (sural nerve SCV)	–0.13 (0.05)	–0.18 (0.07)	None
Log (sural SNAP duration)	0.29 (0.08)	–0.29 (0.12)	None
Log (SSR amplitude)	–0.42 (0.13)	–0.481 (0.19)	None

SNAP, sensory nerve response amplitude; **SCV**, conventional sensory nerve conduction velocity; **SSR**, sympathetic skin response

[a] Dependent variable is increasing with confounding variable

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Table 9. Statistically Significant Results of ANCOVA on Nerve Conduction Velocity Results in Three Exposure Subgroups (Godderis et al. 2006)

Nerve Conduction Velocity	Contrast Estimate		
	N1 (n=34) ≤ 10 mg/m^3 (3.2 ppm)	**N2 (n=25) 10.01 - 30.00 mg/m^3 (3.2 - 9.6 ppm)**	**N3 (n=26) > 30 mg/m^3 (9.6 ppm)**
sural SNAP amplitude	–0.37, p=0.001	–0.26, p=0.041	–0.552, p<0.001
sural SNAP duration	0.23, p=0.019	0.35, p=0.002	0.423, p<0.001
sural nerve SCV	–0.118, p=0.043	–0.114, p=0.083	–0.226, p=0.001

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4.1.1.2.2 Supporting Human Studies

4.1.1.2.2.1 Johnson et al. (1983)

Johnson et al. (1983) studied the effects of CS_2 exposure on a cohort of male viscose rayon workers (n=145) compared to a group of non-exposed artificial fiber plant workers (n=212) located on the same premises. The mean exposure period was 12.1 ± 6.9 years. Exposed workers were divided into three groups based on previous exposure histories, job descriptions, and current carbon disulfide levels established on the basis of 8-hour personal monitors. The median CS_2 levels of exposed individuals were 1.4, 4.1, and 7.6 ppm. Workers were excluded on the basis of alcohol consumption, diabetes, or elevated blood lead levels to control for potential confounding factors. Maximum motor conduction velocity (MCV) was measured in the ulnar and peroneal nerves and SCV was measured in the sural nerve. Surface electrodes were used to measure nerve conduction velocity and both latency and amplitude ratios were calculated. Participants were also asked to answer a questionnaire with questions about central and peripheral nervous system symptoms. Neurophysiological results were compared between the three exposure groups plus an overall exposure group, and the non-exposed control group.

A small but significant ($p<0.05$) reduction in sural SCV and peroneal MCV was observed in the total exposed group compared to the control group. CS_2 exposure caused a dose-dependent decrease in peroneal nerve MCV, with a statistically significant difference ($p<0.05$) between the highest exposure group (7.6 ppm) and the control group. A reduction in the ratio of the amplitudes of muscle action potentials obtained from peroneal nerves stimulation was significant in the highest exposure group. A significant association was made between the cumulative exposure index for MCV and the decreased MCV in the total exposed group compared to the control group. No other endpoints evaluated in exposed individuals, including self-reported symptoms related to the peripheral nervous system, were found to be significantly different from controls. The LOAEL identified in this study was 7.6 ppm, based on significantly decreased peroneal nerve MCV.

USEPA (1995) used this study to derive the Inhalation Reference Concentration (RfC). This study was also used to derive the ATSDR (1996) chronic Minimal Risk Level (MRL), OEHHA (2001) chronic REL, and the Health Canada Tolerable Concentration (TC) (2000). The Godderis et al. (2006) study was published after these agencies derived their chronic inhalation CS_2 guidance values.

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4.1.1.2.2.2 Vanhoorne et al. (1995)

Vanhoorne et al. (1995) studied the effects of CS_2 exposure on a cohort of male workers in a Belgian viscose rayon factory (n=111) compared to a group of non-exposed individuals from other plants (n=74). CS_2 exposure concentrations associated with different jobs in the viscose rayon factory ranged from 4 to 112 mg/m^3 (time-weighted average for eight hours). Many of the jobs involved levels of exposure in excess of the TLV at that time of 31 mg/m^3 (10 ppm). Participants were evaluated using a self-administered questionnaire, a clinical neurological examination, and electroneuromyography. Data were analyzed with multiple regression methods and adjusted for a number of confounders.

With respect to the self-administered questionnaire, after adjusting for confounders, cumulative CS_2 exposure was significantly associated with symptoms consistent with polyneuropathy in the legs (i.e., increased leg pain ($p<0.01$), tingling ($p<0.007$), insensitive spots ($p<0.001$), and fatigue in legs ($p<0.003$)). Increased symptoms occurred with increasing cumulative CS_2 exposure.

No relationship was found between cumulative CS_2 exposure and the prevalence of abnormal neurologic findings from the physical examinations.

With respect to electroneuromyographic findings, exposed individuals had a significantly more prevalent abnormal recruitment pattern, and the prevalence of this finding increased with increasing CS_2 exposure. After adjusting for confounders in regression analysis, abnormal recruitment pattern was significantly associated with cumulative CS_2 exposure ($p<0.02$). All motor conduction velocities were significantly lower in the exposed than in the non-exposed subjects ($p<0.001$). A gradation of the effects of exposure was apparent, with a significant decrease in conduction velocities of those exposed to < 31 mg/m^3 ($p<0.01$). Regression analysis gave similar results, showing a negative association between cumulative CS_2 exposure and conduction velocities. The LOAEL identified in this study was 10 ppm (31 mg/m^3).

4.1.1.2.2.3 Other Supporting Human Studies

Hirata et al. (1984 as cited in ACGIH 2006) conducted a study of Chinese workers exposed to daily average CS_2 concentrations of 1.45 ppm. Exposed workers were found to have reduced ulnar nerve motor conduction velocities and slower motor fibers. Hirata et al. (1996) conducted another study of Japanese workers exposed to CS_2. Workers in the 1996 study were exposed to CS_2 at a mathematical average of 4.76 ppm and experienced statistically significantly reduced nerve conduction velocities in peroneal and sural nerves compared to controls. Reduced conduction velocities in the ulnar nerve were not found to be statistically significantly different

from controls in the 1996 study, contrary to findings in the 1984 study. Differences in reported effects were possibly due to uncertainties in exposure histories.

Vasilescu and Florescu (1980 as cited in ACGIH 2006) conducted a study on 30 male workers exposed to an average of 4.8 ppm CS_2 over a period of 10 to 16 years. Some workers were exposed to CS_2 concentrations as high as 224 ppm for short time intervals. Exposed individuals experienced decreased amplitude of sensory evoked potentials on stimulation of digital fibers, mild slowing of sensory conduction velocity, and decreased amplitude of sensory evoked potentials in distal muscles.

4.1.2 Mode of Action and Dose Metric

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With respect to long-term toxicity, the formation of reactive thiocarbamates seems to play a role in the development of lesions in the nervous system. It has been postulated that the axonal degeneration that underlies the neuropathy caused by CS_2 is the result of the reaction of CS_2 with protein amino groups to yield initial adducts (dithiocarbamate derivatives). Covalent binding of CS_2 with the formation of thiocarbamates and subsequent cross-linking of neurofilaments was demonstrated in rats after subacute to subchronic exposure (Erve et al. 1998a, b; Harry et al. 1998). Progressive crosslinking of the neurofilament is postulated to occur during its transport along the axon, and covalently crosslinked masses of neurofilaments may occlude axonal transport at the nodes of Ranvier, ultimately resulting in axonal swelling and degeneration (Health Canada 2000).

Exposure concentration of the parent chemical will be used as the default dose metric since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available.

4.1.3 POD for Key Study and Dosimetric Adjustments

In the key study by Godderis et al. (2006), workers exposed to 2.84 ppm CS_2 for an average of 8 years (± 8.0) had statistically significant reductions in nerve conduction velocity compared to controls. While exposed individuals had significantly lower nerve conduction velocities than controls, the reductions in nerve conduction velocities were found to be within a clinically normal range of values (ACGIH 2006; Johnson et al. 1983). However, nerve conduction velocity can vary widely so a decreased value may still be indicative of an adverse effect; therefore, the occupational point of departure (POD_{OC}) of 2.84 ppm is considered a LOAEL for mild neurotoxic effects.

4.1.3.1 Default Exposure Duration Adjustments

The POD_{OC} of 2.84 ppm was obtained from a human occupational study. Since workers are assumed to be exposed for 8 h/d, 5 d/week, it was necessary to adjust the POD_{OC} to a continuous exposure concentration using the following dosimetric adjustments:

$$POD_{HEC} = POD_{OC} \times \left(\frac{VE_{ho}}{VE_{h}}\right) \times \left(\frac{days/week_{oc}}{days/week_{res}}\right)$$

Where:

POD_{HEC} = human equivalent concentration POD applicable to the general public
POD_{OC} = occupational time-weighted average POD
VE_{ho} = default occupational ventilation rate for an eight-hour day (10 m^3/day)
VE_h = default non-occupational ventilation rate for a 24-hour day (20 m^3/day)
$days/week_{oc}$ = occupational exposure frequency, usually 5 days/week
$days/week_{res}$ = residential exposure frequency; usually 7 days/week

Therefore:

POD_{HEC} = 2.84 ppm x 10/20 x 5/7
POD_{HEC} = 1.014 ppm

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4.1.4 Adjustments of the POD_{HEC}

The critical effect identified in Godderis et al. (2006) is reduced nerve conduction velocity and is considered a mild neurotoxic effect. This effect is assumed to have a threshold; therefore, UFs were applied to the POD_{HEC} to derive the chronic ReV (i.e., assume a threshold/nonlinear MOA).

- A UF_H of 10 was applied to account for human variability and sensitive subpopulations (i.e., children, the elderly, individuals with pre-existing conditions) to the effects of CS_2.
- A UF_D of 1 was used because the database for CS_2 was considered complete and of high quality.
- A UF_L of 3 was used because the POD was considered a LOAEL for mild effects. Reductions in nerve conduction velocity observed at the POD, although reduced compared to controls, were still within range of clinically normal values; therefore, these effects are indicative of mild neurotoxicity.
- A UF_{sub} was not used because workers exposed to the POD were employed for an average of 8.5 (±8.0) years which is considered a chronic exposure duration.
- A UF_A was not used because a human occupational study was used as the key study.

A total UF of 30 was applied to the POD_{HEC} of 1.014 ppm to derive the chronic ReV of 34 ppb (rounded to two significant figures):

Chronic ReV = $POD_{HEC}/(UF_H \times UF_D \times UF_L)$
= 1.014 ppm /(10 x 1 x 3)
= 1.014 ppm/30

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= 0.0338 ppm
= 34 ppb (rounded to two significant figures)

4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

The chronic ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 34 ppb (110 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 10 ppb (32 µg/m^3) (Table 10).

Table 10. Derivation of the Chronic ReV and $^{chronic}ESL$

Parameter	Values and Descriptions
Study	Godderis et al. (2006)
Study Population	85 exposed male workers (EG1: < 10 ppm , n = 60 and EG2: >10 ppm, n = 25); further divided into three subgroups of average exposure, N1: ≤ 10 mg/m^3 (n = 34), N2: 10.01 to 30.00 mg/m^3 (n = 25), and N3: > 30 mg/m^3 (n = 26)
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Statistically significant reductions in nerve conduction velocity
POD_{OC}	2.84 ppm
Exposure Duration	8 h/d, 5 d/week, for an average of 8.5 (±8.0) years
Extrapolation to continuous exposure (POD_{ADJ})	1.014 ppm
POD_{HEC}	1.014 ppm
Total UFs	30
Interspecies UF	Not Applicable
Intraspecies UF	10
LOAEL UF	3
Subchronic to chronic UF	Not Applicable

Incomplete Database UF *Database Quality*	1 High
Chronic ReV (HQ = 1)	**34 ppb (110 µg/m^3)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**10 ppb (32 µg/m^3)**

4.1.6 Comparison of TCEQ's Chronic ReV to other Long-Term, Health Protective Comparison Levels from Other Agencies

Table 11 presents a comparison of the TCEQ chronic ReV to long-term, health protective comparison values developed by other agencies. Note that all agencies besides TCEQ developed chronic inhalation toxicity factors before Godderis et al. (2006) was published, although a recent addendum to the ATSDR Toxicological Profile for CS_2 (ATSDR 2012) reviews the Godderis et al. (2006) study. The TCEQ chronic ReV is similar to the TC developed by Health Canada (2000) and is an order of magnitude or more lower than values developed by ATSDR, USEPA, and OEHHA.

Table 11. Long-Term, Health Protective Comparison Levels Developed by TCEQ and Other Agencies

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value (ppb)	POD_{HEC}	Total Uncertainty Factor	Key Study and Critical Effect
TCEQ (2013)	Reference Value (ReV)	34	1,014 ppb LOAEL	30	Godderis et al. (2006); minimal decrease in nerve conduction velocity
USEPA (1995)	Reference Concentration (RfC)	224	6,304 ppb BMC_{10} [NOAEL (mean) of 5,100 ppb]	30	Johnson et al. (1983); minimal decrease in nerve conduction velocity
ATSDR (1996)	Minimal Risk Level (MRL)	300	7,600 ppb LOAEL [NOAEL (median) of 4,100 ppb]	30	Johnson et al. (1983); minimal decrease in nerve conduction

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value (ppb)	POD_{HEC}	Total Uncertainty Factor	Key Study and Critical Effect
					velocity
Health Canada (2000)	Tolerable Concentration (TC)	32	1,600 ppb $BMCL_{05}$ [NOEL of 4,160 ppb]	50	Johnson et al. (1983); minimal decrease in nerve conduction velocity
OEHHA (2001)	Reference Exposure Level (REL)	300	2,540 ppb $BMCL_{05}$	10	Johnson et al. (1983); minimal decrease in nerve conduction velocity

4.2 Carcinogenic Potential

There are no data available to determine whether or not CS_2 has carcinogenic potential so a chronic carcinogenic value was not developed.

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4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects of CS_2.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values:

- Chronic ReV 34 ppb (110 µg/m^3)
- $^{chronic}ESL_{threshold(nc)}$ 10 ppb (32 µg/m^3)

The chronic ReV of 34 ppb (110 µg/m^3) will be used for the evaluation of ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ of 10 ppb (32 µg/m^3) is the long-term ESL used for air permit reviews (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is not used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Level

The chronic inhalation observed adverse effect level would be the LOAEL from the key human study (TCEQ 2012). In Godderis et al. (2006), workers exposed to 2.84 ppm CS_2 for an average of 8.5 years (± 8.0) had statistically significant reductions in nerve conduction velocity. The relevant POD_{OC} was 2.84 ppm and isconsidered a LOAEL for mild neurotoxic effects. The POD_{HEC} of 1.014 ppm calculated from the human study (Godderis et al. 2006) was associated with a reduction in nerve conduction velocity and represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same or longer durations as those used in the study. Importantly, effects are not a certainty due to intraspecies differences in sensitivity. The inhalation observed adverse effect level isprovided for informational purposes only (TCEQ 2012).

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Appendix A

Commented [PFC22]: If the/an Appendix is included to summarize the relevant animal studies supporting the human data-derived acute ReV, then it should be expanded to include summaries of the relevant animal studies related to the derivation of the chronic ReV.

Appendix A and Table 12 contains a summary of acute animal inhalation studies that support the acute human inhalation studies described in section 3.1.2.1.

Freundt and Dreher (1969) examined the effect of CS_2 on metabolism of various drugs (hexobarbital-Na, aminophenazone, and procaine-HCl) by the liver. Female Wistar rats were exposed by inhalation to 0, 20, 50, 100, 200, or 400 ppm CS_2 for 8 h. Rats were injected with 100 mg/kg hexobarbital-Na immediately after exposure. Rats exposed to 20 ppm CS_2 for 8 h had twice the sleep duration as controls while exposure to 400 ppm for 8 h caused an increase in sleep duration by a factor of 5.5. Exposure to 100 ppm for 1 h doubled sleep duration. Inhibition of hexobarbital metabolism continually increased during the 100 ppm/8 h exposure, and then decreased exponentially after exposure ended. Inhibition was no longer present 24 h after exposure. Inhibition of metabolism of aminophenazone was determined by measuring urinary excretion of total 4-aminoantipyrine for 24 h. The excretion of 4-aminoantipyrine was inhibited by 70% during the first 6 h after exposure to 50 ppm CS_2. Metabolism of procaine-HCl was only slightly inhibited. Ordinary liver function tests (BSP clearance measured in the bile, SLDH, SGDT, and SGOT) remained normal even at the highest exposure concentration (400 ppm/8 h). Experimental methods and results were only briefly described in this study.

Freundt and Kurzinger (1975) exposed female Wistar rats by inhalation to 0, 20, 100, 200, or 400 ppm CS_2 for 8 h. A significant, dose-related decrease in liver glycogen content was observed in all exposed groups. The decrease developed slowly and steadily and was rapidly reversible after exposure ended. The decrease in liver glycogen content was associated with an increase of hepatic lactate and a decrease of serum potassium and calcium concentrations. A dose-dependent and rapidly reversible rise in inorganic phosphate concentrations was also observed. Body temperature fell significantly at 100 ppm and above. Oxygen consumption of the liver tissue *ex vivo* was elevated after exposure to 400 ppm/8 h. Significant decreases in relative liver weight occurred at all concentrations although liver weight decreases were similar between 20 ppm and 100 ppm groups with greater (and dose-dependent) decreases observed in 200 ppm and 400 ppm groups. The maximum relative liver weight decrease occurred at 400 ppm and was approximately 20%. Body weights (less than 1%), intake of food and water, and fecal excretion were decreased after 8 h exposure to both 100 ppm and 400 ppm. No significant change was noted in liver function tests (Bromsulphalein (BSP) clearance measured in the bile, serum lactate dehydrogenase (SLDH), serum glutamic-pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT)) at any of the exposure concentrations up to the highest concentration tested (400 ppm/8 h).

Freundt et al. (1976a) exposed female Wistar rats by inhalation to 0, 20, or 400 ppm CS_2 for 8 hours or to 400 ppm CS_2 for 8 hours, every other night, for a total of 12 exposures. Rats were given 2g/kg ethanol by intraperitoneal injection (i.p.) and then exposed to CS_2 again until blood collection. Blood ethanol concentrations decreased linearly in a similar fashion in both CS_2 exposed animals and controls. At the time of onset of ethanol elimination from the blood, acetaldehyde levels rose to reach a plateau after 30 minutes to an hour. Blood acetaldehyde

levels were significantly elevated in CS_2 exposed animals (difference between 20 and 400 ppm was not significant). A similar effect was observed in humans as discussed in Section 3.1.2.1.1 (Freundt et al. 1976a). After rats were exposed to 400 ppm CS_2 for 8 hours, 1.25 g/kg of acetaldehyde was administered by i.p. injection. Acetaldehyde was eliminated rapidly in both exposed and control animals although CS_2 exposed animals had a significantly lower rate of elimination and a prolonged excretion half-life.

Freundt et al. (1976b) exposed female Wistar rats and female NMRI mice to 0, 20, 50, 100, 200, or 400 ppm CS_2 for 8 h. Immediately after termination of exposure, animals were treated with various xeniobiotics and subsequently tested for the excretion of xenobiotics metabolites. At all experimental concentration of CS_2, the excretion of the following metabolites was significantly delayed indicating inhibition of Phase I metabolism: 4-OH-antipyrine from antipyrine, acetaminophenol from acetanalid and phenacetin, 4-aminoantipyrine from aminopyrine, and trichloroethanol and trichloroacetic acid from trichloroethene. Phase II N-acetylation and glucuronidation pathways were not significantly affected up to 400 ppm CS_2. Phase I inhibitory effects were reversible from 6 to 36 hours post-exposure. In addition, CS_2 exposure significantly increased hexobarbital-induced sleep duration in rats in a dose-dependent manner.

McKenna and DiStefano (1977) exposed Male Sprague-Dawley rats to 0.1 – 2.0 mg/L (32 – 640 ppm) CS_2 for 4, 6, and 8 h. Exposure to a minimum concentration of 64 ppm for 8 h caused a decrease of dopamine in the brain. Neither signs of toxicity, nor the absence of toxic effects were reported in the study. Increasing exposure led to decreased activity of dopamine β-carboxylase. The effect of CS_2 was attributed to the formation of dithiocarbamates, which complex with copper, since in vitro inhibition of purified dopamine-β-hydroxylase by carbon disulfide was dependent on preincubation with amines capable of dithiocarbamate formation. The inhibition of dopamine-β-hydroxylase decreased progressively with increasing Cu^{2+} concentration, and equimolar concentrations of Cu^{2+} and inhibitor were without effect, suggesting that the inhibition occurred through the binding of enzymic copper.

Acute exposure to higher concentrations of CS_2 (> 100 ppm) has resulted in more severe adverse effects in animals including developmental/reproductive toxicity (see Section 3.1.2.3), CNS effects (reduced activity and hyperexcitability, stupor, ataxia, tremor, convulsions, narcosis, respiratory arrest), decreased body weight, and death (ATSDR 1996; NRC 2009).

Table 12. Summary of Acute Animal Inhalation Studies Noting Adverse Effects Below 100 ppm (POD_{HEC} = 20 ppm).

Animal Strain	Concentration (ppm) and Duration (h)	Critical Effect	Reference[a]
female Wistar rats	0, 20, 50, 100, 200, or 400; 8 h	Inhibition of microsomal drug biotransformation; ≥ 20 ppm	Freundt and Dreher (1969)
female Wistar rats	0, 20, 100, 200, or 400; 8 h	Liver effects, increase in whole-body oxygen uptake, fall in body temperature, decrease of body weight; ≥ 20 ppm	Freundt and Kurzinger (1975)
female Wistar rats and female NMRI mice	0, 20, 50, 100, 200, or 400; 8 h	Inhibition of Phase I microsomal drug biotransformation; ≥ 20 ppm	Freundt et al. (1976b)
male Sprague-Dawley rats	32 - 640; 8 h	Decrease of brain noradrenaline in adrenal glands of heart; ≥ 64 ppm	McKenna and DiStefano (1977)

Reviewer Two

Reviewer 2
Technical Review of the
Draft Carbon Disulfide Development Support Document
Review Guidelines

Background

The Toxicology Division of the Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that summarizes the hazard assessment and dose-response data and analyses used to derive health-protective Effects Screening Levels (ESLs) and Reference Values (ReV) for carbon disulfide. Within the draft DSD TCEQ has derived short-term and long-term toxicity values for human health, odor and vegetation endpoints. These toxicity values are used in the evaluation of air permit applications and ambient air data and were developed using RG-442 TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). The TCEQ guidelines can be found at http://www.tceq.texas.gov/publications/rg/rg-442.html. Reviewers are asked to familiarize themselves with the guidelines and consider the guidelines in formulating your comments and recommendations.

The TCEQ is seeking detailed peer input and guidance to further develop and finalize this DSD and welcomes all comments on the quality and content. *Note that the DSD document is designed to be a summary document and therefore does not provide as detailed descriptions as some other agency's toxicity assessments might. Reviewers should focus on the derivation of the Reference Values (ReVs) and not the Effects Screening Levels (ESLs). The ESLs are calculated by multiplying the ReV by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during an air permitting review. The 0.3 is a policy decision and reviewers are asked to not spend time commenting on this.*

Instructions

Please address each of the specific and general questions found below. For each response (including Yes/No responses), please explain your reasoning and considerations, discuss the scientific support for your comments and opinions, and identify the sources you consulted to construct your response. If a question is beyond your area of expertise, please indicate this. Please address each question by adding your answers to this Word document. In addition, feel free to annotate and comment within the draft TSD document using the Track Changes feature under the Review tab.

Due Date - Your written review should be returned to patterson@tera.org by email no later than January 9, 2014.

General Questions

1. **What is your overall impression of the draft document? Please identify areas needing improvement and your suggestions to improve scientific quality and readability.**

My general impression is that it is readable. I think an executive summary would be helpful. It would be good to state the motivation for this work. Is Texas concerned about environmental exposures to CS2, presumably from gas/oil exploration (as per section on Sources)? Alternatively, is Texas embarked on setting environmental levels for a series of identified chemicals (how identified?), of which CS2 is just one.

Most exposure to CS2 is presumably occupational, not environmental. It would seem that further air sampling of environmental levels might be worthwhile to document a potential problem. The 'Source' section says only 15 minutes grab samples in oil/gas areas have been collected in 2009 (how many? What was the mean and median?).

2. **Does the draft DSD clearly describe the data and approaches used by TCEQ to develop the toxicity values?**

Yes, although the use of uncertainty factors should be explained with more detail. Some introductory explanation about the UFs is in order. Also in specific instances, their application could be further explained. Is the use of a UF_L supposed to set an exposure level where there is likely to be no measureable effect? In the adjustments of the PODHEC for chronic exposure, a UF_L of 3 was used because the observed effect in humans was mild and within clinical range. I don't understand the logic here.

3. **Were procedures outlined in RG-442 *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) followed by the TCEQ in this assessment?**

Yes.

4. **Please identify any additional relevant studies or data that you think should be included in this assessment. Please explain specifically how the studies/data could impact the assessment and toxicity values.**

None

Specific Questions

5. Please comment on the following key decisions for derivation of the acute ReV. *For each element, please discuss if the TCEQ conclusions and choices are supported by the available data, and discuss any additional information or analyses that could improve the decision or related rationale*.

5A. Section 3.1.2 describes the key and supporting studies. Are these the most appropriate studies to use for the dose-response assessment? Have the key and supporting studies and the rationale for their selection been sufficiently described and supported in the DSD?

I am not clear about the acute adverse effect – increased intolerance to the effects of alcohol? The document says no symptoms of alcohol intolerance were observed in Freundt et al. when aldehyde levels went up. Quoting this section (page 6): 'based on guidance in ATSDR (2007), the Toxicology Division (TD) determined that the increase in blood acetaldehyde levels seen after acute exposure to 20 ppm CS2 is a mild adverse effect; it is a biochemical change caused by inhibition of liver enzymes that could potentially cause reversible, functional/clinical impairment in some individuals (i.e., individuals with a less active form of the enzyme responsible for metabolizing acetaldehyde to acetate [ALDH2(2)]).' What impairment exactly is being discussed here?

5B. Mode of Action (Section 3.1.3): Does the discussion on modes of action and metabolism correctly interpret the available data and are the conclusions supported by the data?

This level of toxicological/mechanistic detail is beyond my expertise (epidemiology).

5C.Point of Departure (POD) and Dosimetric Adjustment (Sections 3.1.5 and 3.1.6): TCEQ presents PODs from two studies with different endpoints (Freundt et al., 1976a and Saillenfait et al., 1989) and adjusts each for dose and human equivalency. Were the dosimetric adjustments correctly made and did they follow TCEQ 2012 guidance?

These seem reasonably done.

5D. Critical Effect (Section 3.1.6) Do you agree with the selection of inhibition of ethanol metabolism resulting in significantly increased blood acetaldehyde levels (Freundt et al., 1976a) to be the critical effect for derivation of the acute ReV?

I am not clear about this. It seems that Saillenfait et al. identified a more severe endpoint (developmental toxicity), albeit with a higher NOAEL, than Freundt et al. (increased blood aldehydes when intoxicated, without alcohol intolerance symptoms). It would seem a better case would need to be made why Freundt et al. was chosen over Saillenfait et al.

5E. Uncertainty Factors (UFs) (Section 3.1.7): Did TCEQ select the appropriate uncertainty factors and provide sufficient rationale and support for the selections?

See my comments below for UFs for chronic effects. I would like to see a bit more discussion of the basis of choice of UFs in general (are some simply by convention) and in particular I don't understand the logic for the choice of UF_L.

6. TCEQ evaluated available data for derivation of welfare-based acute and chronic (Sections 3.1.9 and 4.3) using the TCEQ guidelines (2012). Please comment on the appropriateness of the calculation of the $^{acute}ESL_{odor}$ value and decisions regarding sufficiency of data for the vegetation effects. Refer to Chapter 2 of the TCEQ (2012) for guidance.

These sections (odor threshold, no vegetation effect) seem fine as is.

7. Please comment on the following key decisions for derivation of the chronic ReV. ***For each element, please discuss if the TCEQ conclusions and choices are supported by the available data, and discuss any additional information or analyses that could improve the decision or related rationale*****.**

7A. Critical Effect (Section 4.1): TCEQ identified the nervous system as the primary target of CS_2 based upon human epidemiological studies of workers exposed to CS2. Do you agree that this is the appropriate critical effect for derivation of the chronic ReV?

Yes, the literature documents nervous system effects.

7B. Key and Supporting Studies (Section 4.1.1.2): TCEQ identified Godderis et al.

(2006) as the key study and several others as supporting studies. Are these the most appropriate studies to use for identification of critical effect and the dose-response assessment? Have the studies and the rationales for their selection been sufficiently described and supported in the DSD?

Yes and yes. However, it should be noted that a weakness of the Godderis et al. study is that there are no tests for trend in exposure-response, although the point estimates by increasing exposure often do show increasing effects. The TCEQ document should also make more mention of exposure-response trends when present, or when absent, as this bears on causality.

7C. Mode of Action (Section 4.1.2): Does the discussion on mode of action correctly interpret the available data? Do you agree that use of data on the parent compound is appropriate?

This question pertains to toxicology and is beyond my expertise (epidemiology).

7D. Point of Departure (POD): TCEQ identified a LOAEL of 8.9 mg/m^3 (2.84 ppm) for mild effects from Godderis et al. (2006), based on statistically significant reduced nerve conduction velocity in workers exposed for an average of 8.5 years (Standard Deviation 8.0). This study was not available when other agencies (e.g., Health Canada, US EPA, California EPA, ATSDR) developed their chronic values. Do you agree that 8.9 mg/m^3 (2.84 ppm) from Godderis et al. (2006) is the most appropriate POD among the available data and studies? TCEQ labels this a "LOAEL for mild effects," do you agree?

It seems that TCEQ is taking as the LOAEL and POD the lowest level in Godderis et al. in which significant (a p=0.05) effects are seen in sub-clinical nerve conduction velocities, when the exposed group is divided into two (<30 mg/m^3, 30+ mg/m^3). This seems reasonable, but perhaps should be clearly stated.

It is not entirely clear to me, however, why the data from dividing the exposed into 3 groups (<10, 10-30, 30+ mg/m^3) are not used. Godderis et al. explicity added these analyses to try to derive a better LOAEL. The document says there was no clear exposure-response in these analyses. Yet for the sural nerve endpoints, there was a monotonic exposure response for duration, and not monotonic (but nearly so) for amplification and velocity, with statistically significant worsening in the <10 mg/m^3 group for all 3 endpoints, as shown in the TCEQ document's Table 9. Arguably the POD should be taken from the <10 mg/m^3 group. Indeed

Godderis et al. note 'NOEL-estimation analysis suggested that even average exposures of <10 mg/m3 may be not entirely safe'. A disadvantage to using the <10 mg/m^3 group is that there is no mean or median exposure level given for this group. However, a reasonable estimate might be 1/3 of the mean for the <30 mg/m^3 group.

7E. Dosimetric Adjustments (Section 4.1.3): Were the adjustments performed correctly and explained sufficiently?

These seem to be correct; I presume they are standard in converting occupational to residential exposures. Perhaps this could be clearly stated. However, there is an implicit assumption here that duration of exposure is not important, and that average intensity of exposures is the key metric. Is an exposure of 8.5 years to a worker at 2.84 ppm (8.9 mg/m^3) equivalent to a lifetime environmental exposure for a resident exposed as the equivalent intensity? It would seem this warrants some discussion.

Generally in occupational studies chronic conditions (and peripheral neuropathy is assumed to be an irreversible chronic condition, which perhaps should be explicitly stated somewhere), cumulative exposure tends to be a preferable metric to average exposure. In one of the key supporting studies, Johnson et al. (1983), we see that a cumulative exposure index is a significant predictor of peroneal and sural nerve conduction velocity (but not ulnar), although no clear data are shown on whether average (exposure group) or cumulative exposure are stronger predictors of nerve endpoints, and models with cumulative exposure also incorrectly adjusted for length of employment (a component of cumulative exposure). In the other key supporting study (Vanhoorne et al. 1985), again a cumulative exposure index shows a clear exposure-response pattern in Figure 1 (peroneal nerve conduction velocity).

7F. Uncertainty Factors (Section 4.1.4): Did TCEQ select the appropriate uncertainty factors and provide sufficient rationale and support for the selections?

See comment above. More discussion/explanation on these factors is in order. The document states in this Section, 'this effect is assumed to have a threshold ; therefore, UFs were applied to the POD_{HEC} to derive the chronic ReV (i.e., assume a threshold/nonlinear MOA)'. This is not clear to me. Why is the peripheral neuropathy effect assumed to have a threshold (simply because the endpoint is not cancer)? What would that threshold be?

Other Questions

8. Please identify any other relevant issues or questions that are important for the

evaluation of this DSD and the toxicity values derived within it.

Perhaps some mention should be made that while mild subclinical nerve conduction effects in Godderis et al. are chosen as the endpoint of interest, there is some evidence in this study and in other studies that symptoms of Parkinsonism (clinical effects) have been seen in CS2 exposed workers. Godderis et al. note, 'In our study not only the neurophysiological examinations revealed abnormalities, the questionnaire and clinical neurological examination revealed increased sensorimotor complaints and sensory abnormalities in both exposed groups, even after correction for confounding factors. Our results suggest that the current TLV does not protect from clinical PNP.'

Minor points

In Table 7 it should be made clear that the p-value is for the entire exposed group vs controls. In general it would be good for each Table presented to indicate from which Table in Godderis et al. the data were taken. There is a mistake in Table 7 - footnote 'a' regarding cumulative exposure for the low exposed group (it is not 746). There is a typo in Table 8 for SNAP duration in the high exposed group (should be 0.29 not -0.29). I suggest that 'multiple logistic regression' (I assume this is supposed to mean multivariate logistic regression) be called as conventionally simply 'logistic regression'. I believe in Table 9 that the outcomes were log transformed, so they should be re-labelled. A footnote might indicate that these analyses were adjusted for covariates when such covariates were significant. The right hand column of Table 8 is confusing ('adjusting covariates'). It might be eliminated and a footnote added that the regressions were adjusted for covariates which were significant at the p=0.05, and that the first endpoint was adjusted for race only and there were no covariates included in the models for the 2nd and 3rd endpoints.

In section 4.5 I did not understand the sentence 'Importantly, effects are not a certainty due to intraspecies differences in sensitivity.', as I believe the authors have been discussion Godderis et al., which is a human study, and hence there was no intraspecies differences.

Development Support Document
DRAFT, December 5, 2013

Carbon Disulfide

CAS Registry Number: 75-15-0

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Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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List of Acronyms and Abbreviations

List of Acronyms and Abbreviations

A	animals
AAP	aminoantipyrine
ACGIH	American Conference of Industrial Hygienists
ADH	alcohol dehydrogenase
AEGL	Acute Exposure Guideline Level
AIC	Akaike's Information Criterion
ALDH2	Aldehyde dehydrogenase2 (mitochondrial)
ADLH2(2)	Aldehyde dehydrogenase2*2 (mutant form of ALDH2 where a lysine residue replaces a glutamate in the active site at position 487 of ALDH2)
AMCV	Air Monitoring Comparison Value
ANCOVA	Analysis of variance controlling for co-variance
ANOVA	Analysis of variance
ASAT	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration 95% lower confidence limit
BMDS	Benchmark Dose Software
BRFSS	Behavioral Risk Factor Surveillance System survey
^{0} C	degrees centigrade
CES	critical effect size
CES_{05}	critical effect size corresponding to a 5% relative decrease in the mean when compared to controls
CNS	central nervous system
CS_2	Carbon disulfide
CYP450	cytochrome P-450
d	day(s)

List of Acronyms and Abbreviations

DSD	development support document
EG	exposure group
EMG	electromyography
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
ET	Extrathoracic
F	exposure frequency, days per week
GD	gestation day
g/L	grams per liter
h	hour(s)
H	Humans
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration

List of Acronyms and Abbreviations

Hg	mercury
HQ	hazard quotient
i.p.	intraperitoneal
kg	kilogram
LDH	lactate dehydrogenase
LOAEL	lowest-observed-adverse-effect-level
MCV	motor conduction velocity
MEK	methyl ethyl ketone
µg	microgram
µg/m^3	micrograms per cubic meter
mg	milligrams
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
MRL	Minimal Risk Level
MW	molecular weight
n	number
N/A	Not applicable
NAC	National Advisory Committee
n-BA	n-butyl acetate
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OEHHA	Office of Environmental Health Hazard Assessment
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration

List of Acronyms and Abbreviations

POD_{OC}	occupational point of departure
ppb	parts per billion
ppm	parts per million
REL	reference exposure level
ReV	reference value
RfC	inhalation reference concentration
RGDR	regional gas dose ratio
SA	surface area
SAR	structure-activity relationship
SCOB	scheduled-controlled operant behavior
SCV	sural nerve sensible conduction velocity
SD	Sprague-Dawley
SMCs	self-reported multiple chemical sensitivity
SNAP	sural sensible nerve response amplitude
SPGT	serum glutamic-pyruvic transaminase
SSR	sympathetic skin response
TC	tolerable concentration
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TLV	Threshold Limit Value
TWA	time weighted average
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human (interspecies) uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor

List of Acronyms and Abbreviations

USEPA	United States Environmental Protection Agency
V_E	minute volume

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of carbon disulfide (CS_2). Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) available at http://www.tceq.texas.gov/publications/rg/rg-442.html for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on carbon disulfide's physical/chemical data.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	**Concentration**	**Notes**
Acute ReV	1,300 ppb (4,100 µg/m^3) **Short-Term Health**	**Critical Effect(s):** Increase in blood acetaldehyde levels in humans with moderate intake of alcohol
$^{acute}ESL_{odor}$	210 ppb (650 µg/m^3) **Odor**	50% detection threshold; sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for impure CS_2
$^{acute}ESL_{veg}$	- - - **Short-Term Vegetation**	No data on vegetation effect levels; concentrations producing no observed effects were significantly above other short-term values
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	34 ppb (110 µg/m^3) **Long-Term Health**	**Critical Effect(s):** Statistically significant reductions in nerve conduction velocity in workers
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Carbon disulfide is not typically monitored for by the TCEQ's ambient air monitoring program (http://www5.tceq.state.tx.us/tamis/index.cfm?fuseaction=home.welcome), so only a limited amount of ambient air data are available to assess carbon disulfide's concentrations in Texas ambient air.

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-

based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{threshold(nc)}$**, chronic health-based Effects Screening Level for threshold dose-response noncancer effects; **$^{chronic}ESL_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	390 ppb (1,200 µg/m^3)[a]	**Critical Effect:** Increase in blood acetaldehyde levels in humans with moderate intake of alcohol
$^{acute}ESL_{odor}$	210 ppb (650 µg/m^3) **Odor** **Short-Term ESL for Air Permit Reviews**	50% detection threshold; sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for technical grade CS_2
$^{acute}ESL_{veg}$	--- **Short-Term Vegetation**	No data on vegetation effect levels; concentrations producing no observed effects were significantly above other short-term values
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	10 ppb (32 µg/m^3)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Statistically significant reductions in nerve conduction velocity in workers
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 1,300 ppb (4,100 µg/m^3) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 34 ppb (110 µg/m^3) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	CS_2	ACGIH 2006
Chemical Structure	S=C=S	TCEQ 2013
Molecular Weight	76.14	ACGIH 2006
Physical State at 25°C	Liquid	ACGIH 2006
Color	Clear, colorless for pure CS_2; or faintly yellow for impure CS_2	ACGIH 2006
Odor	Sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for impure CS_2	ACGIH 2006 ATSDR 1996
CAS Registry Number	75-15-0	ACGIH 2006
Synonyms	Carbon sulfide, dithiocarbonic anhydride, sulphocarbonic anhydride, Weeviltox	ACGIH 2006
Solubility in water	Soluble, 2,300 mg/L @ 22°C	TCEQ 2012
Log K_{ow}	1.94	HSDB 2010
Vapor Pressure	260 mm Hg @ 20°C	ACGIH 2006
Relative Vapor Density (air = 1)	2.67	HSDB 2010
Melting Point	-112.1°C	HSDB 2010
Boiling Point	46.3°C @ 760 mm Hg	ACGIH 2006
Conversion Factors	1 $\mu g/m^3$ = 0.32 ppb 1 ppb = 3.13 $\mu g/m^3$ at 25°C	ACGIH 2006

Chapter 2 Major Sources and Uses

The most prominent industrial use of CS_2 is in the production of viscose rayon fibers; it is also used in the production of carbon tetrachloride and cellophane. CS_2 is used as a solvent for rubber, sulfur, oils, resins, and waxes, and has been used for soil fumigation and insect control in stored grain. Industrial processes that produce CS_2 as a by-product include coal blast furnaces and oil refining (ACGIH 2006; ATSDR 1996).

CS_2 is a minor component of the waste gases emitted from the processing of sour gas (Health Canada 2000). Continuous ambient monitoring data were collected over a two year period near a sour gas processing plant in Canada. The mean and maximum levels of CS_2 were 0.61 and 88 $\mu g/m^3$ (0.19 ppb and 28 ppb), respectively at an upwind location, and 1.40 and 156 $\mu g/m^3$ (0.44 and 49.9 ppb), respectively, at a downwind location (Legge et al. 1990a, b cited in Health Canada 2000). TCEQ has monitored for CS_2 in areas of oil and gas exploration in 2009, and detected levels from 0.06 ppb to 20 ppb in short-term, instantaneous grab samples (approximately 15-second duration).

Natural sources of CS_2 include wetlands, oceans, volcanic and geothermal activity, and microbial activity in soil (ATSDR 1996). In a small study conducted in New York, NY, CS_2 was detected in all of nine indoor air samples with a mean concentration of 0.63 $\mu g/m^3$, similar to the mean concentration detected in six outdoor air samples (0.3 $\mu g/m^3$) (Phillips 1992 in Health Canada 2000).

Chapter 3 Acute Evaluation

Acute exposure to high doses of CS_2 causes central nervous system (CNS) effects in humans and animals. In humans, irritation of the eyes and throat, and CNS effects including dizziness and headache were observed at 180-240 ppm (NRC 2009). In humans, concentrations of approximately 2,000 ppm can cause nausea, vomiting, progressing dizziness, and beginning signs of central paralysis. In humans, concentrations from 2,000 ppm to above 3,000 ppm cause irregular respiration and narcosis. In animals, CNS effects include reduced activity and hyperexcitability, stupor, ataxia, tremor, convulsions, narcosis, respiratory arrest, and death (NRC 2009).

Acute exposure to lower concentrations of CS_2 that does not cause notable CNS effects clearly causes inhibition of xenobiotic biotransformation reactions, inhibition of alcohol (ethanol) metabolism via the aldehyde dehydrogenase pathway, and alterations of carbohydrate and energy metabolism in the liver (NRC 2009).

CS_2 has also been identified as a reproductive and developmental toxicant in animals, but these effects are seen at much higher concentrations than those shown to cause inhibition of xenobiotic biotransformation reactions (the lowest LOAEL identified in an animal

reproductive/developmental toxicity study was 400 ppm). Section 3.1.2 provides a review of available reproductive and developmental toxicity studies in humans and animals.

3.1 Health-Based Acute ReV and ^{acute}ESL

A comprehensive literature search was conducted regarding the acute inhalation toxicity of CS_2. Information from both human and animal studies regarding the acute toxicity of CS_2 was reviewed in detail by ATSDR (1996 and 2012), ACGIH (2006), OEHHA (1999), and NRC (2009). Well-conducted human studies demonstrate the acute effect of CS_2 inhalation on alcohol (ethanol) metabolism and xenobiotic biotransformation reactions, and since these effects occur at concentrations below those that cause other adverse effects they are preferentially used here to develop the acute toxicity factors such as the ReV and ESL. Numerous acute animal studies have been conducted on the effects of inhalation exposure to CS_2 and are discussed extensively in ATSDR (1996 and 2012) and NRC (2009). Acute animal inhalation studies support the findings of human studies.

3.1.1 Physical/Chemical Properties

Pure CS_2 is a clear, almost colorless liquid with a sweet, pleasant odor similar to chloroform. Technical grades of CS_2 have a strong, disagreeable odor similar to rotting radishes or overcooked cauliflower due to traces of hydrogen sulfide (ACGIH 2006). CS_2 is water soluble, evaporates readily at room temperature, explodes, and ignites easily. The main chemical and physical properties of CS_2 are summarized in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

Three human experimental studies with CS_2 conducted by Mack et al. (1974), Freundt and Lieberwirth (1974), and Freundt et al. (1976a) were identified as key and supporting studies for the acute evaluation of CS_2 and are summarized in Table 4.

3.1.2.1.1 Key Human Study (Freundt et al. 1976a)

Freundt et al. (1976a) conducted a study investigating the effect of CS_2 on ethanol metabolism in twelve healthy male volunteers, ages 20-32 years. Participants were asked not to take medications or alcohol several days prior to the experiment and were fasted prior to exposure. Shortly before starting the experimental exposure, 2 milliliters (ml) of blood were drawn from each participant. At the beginning of the experiment, participants received 0.57 ml/kilogram (kg) ethanol in 3.01 ml/kg orange juice, with further doses of 0.047 ml/kg ethanol in 0.18 ml/kg orange juice given at 15-minute intervals throughout remainder of experimental period. For each study participant, a mean blood alcohol concentration of about 0.75 g/Liter (L) (0.075% blood alcohol concentration) was obtained and it remained fairly constant during the experiments (the legal blood alcohol concentration limit for intoxication in Texas is 0.08%). The blood acetaldehyde concentration was approximately 6×10^{-3} g/L in alcoholized control subjects.

Participants were exposed to nominal concentrations of 0, 20, 40, and 80 ppm CS_2 for 8 hours (h) (analytical concentrations were not reported). Each participant served as his own control. Blood samples were drawn from participants at hourly intervals during the 8 h exposure period to analyze for acetaldehyde and ethanol. The blood acetaldehyde concentration rose significantly by about 50% when subjects were exposed for 8 h to 20 ppm CS_2. Exposure for 8 h to 40 and 80 ppm CS_2 resulted in an additional slight increase in blood acetaldehyde concentration. A clear dose-response effect was observed. One h of exposure to 20 ppm CS_2 produced about a 50% increase in blood acetaldehyde levels, 40 ppm produced about an 80% increase, and 80 ppm produced about a 90% increase (estimates of percent increase are based on graphical representation of data).

In an additional experiment, four volunteers were exposed to 20 ppm of CS_2 for 8 h. Exposed subjects were then given alcohol (about 0.5 g/L (0.05%) blood alcohol) beginning 16 h after termination of exposure to CS_2. Blood was collected at hourly intervals to analyze for acetaldehyde and alcohol. The blood acetaldehyde concentration in exposed participants reached slightly more than twice the control value indicating that effects can occur even when CS_2 exposure precedes alcohol intake. A similar effect was observed in volunteers repeatedly exposed to 20 ppm CS_2 8 h/d, for 5 days (d), then given alcohol simultaneously only on the last day.

Ethanol is oxidatively metabolized by two pathways in the liver, one by cytosolic alcohol dehydrogenase (ADH), and to a lesser extent by the cytochrome P-450 (CYP450) monooxygenase system in the liver (CYP2E1). Both result in the formation of acetaldehyde, which is further oxidized by mitochondrial aldehyde dehydrogenase (ALDH2) to acetate. Acetate then enters intermediary metabolism of the cell. CS_2 inhibits the metabolism of alcohol at the second step of the pathway (aldehyde dehydrogenase) which results in increased blood acetaldehyde levels. Some individuals have a mutation in the gene for the typical form of ALDH2 which results in the synthesis of ALDH2(2), which is a less active form of the enzyme. The presence of the ALDH2(2) mutation results in an excessive production of aldehyde after ingestion of alcohol. Individuals who are homozygous for the ALDH2(2) mutation are very sensitive to the effects of alcohol and develop an alcohol intolerance syndrome even after ingestion of only a small amount of alcohol.

The observed increase in acetaldehyde levels in Freundt et al. (1976a) occurred without any noticeable alcohol intolerance effect in participants (i.e., flushing, hypotension, and tachycardia). However, alcohol intolerance has been reported to occur in workers exposed to CS_2 (most likely higher concentrations). Based on guidance in ATSDR (2007), the Toxicology Division (TD) determined that the increase in blood acetaldehyde levels seen after acute exposure to 20 ppm CS_2 is a mild adverse effect; it is a biochemical change caused by inhibition of liver enzymes that could potentially cause reversible, functional/clinical impairment in some individuals (i.e., individuals with a less active form of the enzyme responsible for metabolizing acetaldehyde to acetate [ALDH2(2)]).

The German Society for Occupational and Environmental Medicine identifies alcohol intolerance as an adverse effect induced by CS_2 (Drexler 1998 as cited in NRC 2009). Alcohol use is very common in the United States (US) (CDC 2013). According to the 2012, Behavioral Risk Factor Surveillance System (BRFSS) survey, approximately 55% of the adult US population drank alcohol in the past 30 days. Approximately 6% of the total population drank heavily, while 17% of the population binge drank. Because alcohol is used so prevalently in the US, the TD believes it is appropriate to consider alcohol intolerance inducted by CS_2 exposure to be a relevant endpoint for toxicity factor development.

Percent increases in blood acetaldehyde levels caused by CS_2 exposure were only shown graphically and were not amenable to benchmark dose modeling; therefore, 20 ppm was selected by the TD as the lowest-observed-adverse-effect-level (LOAEL). This study was selected as the key study for the potential critical health effect of increased blood acetaldehyde levels due to inhibition of ethanol metabolism. The LOAEL of 20 ppm was used as the point of departure (POD) to determine the POD human equivalent concentration (POD_{HEC}) for this potential critical health effect.

3.1.2.1.2 Supporting Human Studies

3.1.2.1.2.1 Freundt and Lieberwirth (1974)

Details of this study were obtained directly from NRC (2009) because the study was only available in German. Eleven healthy male volunteers (number in parentheses), ages 20-32 years, participated in a study conducted by Freundt and Lieberwirth (1974). Participants were asked not to take medicine or alcohol several days prior to the experiment and were exposed by inhalation to nominal concentrations of 0 (11), 40 (5), or 80 (4) ppm CS_2 for 8 h. Exposures were conducted in an 8 m^3 exposure chamber. Participants received alcohol and obtained a mean blood alcohol concentration of 0.7 g/L (0.07% blood alcohol) (range 0.58 to 0.85 g/L, or 0.05% to 0.085% blood alcohol). Details on when the alcohol was given to participants were not given in NRC (2009).

Subjects exposed to 40 ppm CS_2 and alcohol did not have significant changes of any serum parameters used as markers for effects on carbohydrate and energy metabolism in the liver (cholesterol, calcium, inorganic phosphate, total bilirubin, albumin, total protein, uric acid, urea-N, glucose, lactate dehydrogenase [LDH], alkaline phosphatase, and aspartate aminotransferase [ASAT]); however, the blood glucose level was about 13% lower at the end of the exposure period (although not statistically significant). Subjects exposed to 80 ppm CS_2 had a statistically significant decrease in blood glucose and a significant rise of the serum total bilirubin by 61% as compared with pre-exposure. The group that only received alcohol had a nearly identical serum total bilirubin concentration as the 80 ppm CS_2 group, although the increase was not statistically significant because the pre-exposure level in the alcohol-only group was higher than that in the 80 ppm group.

Four volunteers were exposed to 20 ppm CS_2 for 8 h without alcohol intake. A non-significant 30% decrease in blood glucose was observed after exposure. When this group received alcohol 16-24 h after CS_2 exposure, a 108% increase in serum total bilirubin concentration and slight non-statistically significant increases in serum albumin, total protein, uric acid, and alkaline phosphatase were observed.

A LOAEL of 80 ppm was identified in this study based on a statistically significant decrease in blood glucose and a significant rise of serum total bilirubin. A no-observed-adverse-effect-level (NOAEL) of 40 ppm was identified in this study.

3.1.2.1.2.2 Mack et al. (1974)

Mack et al. (1974) conducted a study to examine the inhibition of oxidative N-demethylation of amidopyrine by CS_2 (a measure of inhibition of Phase I biotransformation of amidopyrine). Nineteen healthy male adults, ages 21 to 40 years, participated in the experiment. Participants were instructed to discontinue medication intake and to restrict alcohol intake a few weeks prior to the experiment. Participants were exposed by inhalation to nominal concentrations of 0, 10, 20, 40, or 80 ppm CS_2 for 6 h. Each participant served as his own control.

Exposures were carried out in an 8 m^3 dynamic exposure chamber. At the start of the experiment, participants received amidopyrine orally at 7 mg/kg body weight. Urine samples were collected 3-33 h after the start of the exposure and were assayed for metabolites of amidopyrine (aminoantipyrine [AAP], 4-AAP, and N-acetyl-AAP). The lowest concentration tested (10 ppm) was sufficient to result in a significant deficit in the excretion of the free 4-AAP during the exposure. Exposure to 20, 40, and 80 ppm for 3 h resulted in a statistically significant dose-dependent reduction in free AAP, N-Acetyl AAP, and total AAP. The time of maximal depression as measured by the excreted total 4-AAP shifts from 6 h after 10 ppm to 12 h after 80 ppm, whereas the amount of maximal deficit ranges from 14% to nearly 50%. Specific percent changes for each endpoint at each concentration and time interval were not reported in the study. The excretion deficit was reversible and compensated for during the subsequent excretion phase. The intensity and the duration of the effect showed a well-defined dose-response relationship.

An additional experiment with exposure to 20 ppm CS_2 for 6 h showed the effect to be no longer detectable 18 h after exposure. A single 6 h exposure to 40 ppm CS_2 produced an identical inhibitory reaction compared to that seen after exposure to 20 ppm CS_2 for 6 h/d for 5 d.

After 3 h exposure to 10 ppm CS_2 (after 3 h of exposure) a statistically significant reduction in free AAP levels was observed in exposed individuals (indicating an inhibition of Phase I biotransformation of amidopyrine). A dose-response effect was observed after three hours of exposure, with 20, 40, and 80 ppm producing statistically significant, dose-related deficits in free AAP and total AAP levels greater than levels at 10 ppm. After three hours of exposure, 20, 40, and 80 ppm each produced statistically significant, dose-related deficits in free AAP and total AAP levels, greater than the deficits seen at 10 ppm. The deficits increased with dose level. While biochemical changes characterized by impairment of enzymes of the mixed function

oxidase system may be considered potentially adverse (ATSDR 2007), uncertainties in actual percent changes in free AAP levels observed at each exposure concentration and time interval, and no data showing any morphologic or clinical changes associated with the inhibition of Phase I biotransformation of amidopyrine, prevents TD from determining whether the observed effect was truly adverse. Therefore, a NOAEL or LOAEL could not be clearly identified and substantiated from the Mack et al. (1974) study. Results of the Mack et al. (1974) study support findings that CS_2 can inhibit metabolic processes at low concentrations.

Table 4. Summary of Key and Supporting Human Acute Inhalation Studies

Exposure Group	Concentration (ppm) and Duration	NOAEL	LOAEL	Critical Effect	Reference
12 healthy male volunteers, ages 20-32 years	0, 20, 40, or 80 ppm; 8 h	---	20 ppm[a]	Inhibition of ethanol metabolism resulting in significantly increased blood acetaldehyde levels	**Key Study:** Freundt et al. (1976a)
11 healthy male volunteers, ages 20-32 years	0, 40, or 80 ppm; 8 h	40 ppm	80 ppm[b]	Statistically significant decrease in blood glucose and significant rise of serum total bilirubin in alcoholized subjects	Supporting Study: Freundt and Lieberwirth (1974)
19 healthy male volunteers, ages 21-40 years	0, 10, 20, 40, or 80 ppm; 6 h	80 ppm[c]	---	Inhibition of Phase I microsomal drug biotransformation	Supporting Study: Mack et al. (1974)

[a] The LOAEL of 20 ppm identified in Freundt et al. (1976a) was used as the point-of-departure (POD) to derive a POD_{HEC} and subsequent Acute Rev and ESL.

[b] The LOAEL of 80 ppm identified in Freundt et al. (1974) was higher than the LOAEL of 20 ppm identified in the key study; therefore, Freundt et al. (1974) was used as a supporting study.

[c] Inhibition of Phase I microsomal drug biotransformation occurred at all concentrations tested in Mack et al. (1974); however, this effect could not clearly be classified as an adverse effect based on information provided in the study and guidance in ATSDR (2007) and TCEQ (2012). Mack et al. (1974) was used as a supporting study.

3.1.2.2 Developmental/Reproductive Studies

Some human studies provide evidence that CS_2 may cause reproductive and developmental effects although limitations of the studies (i.e., poor exposure measurements, lack of appropriate control groups, concomitant exposure to other chemicals) prevent their use in the development of ReVs. Numerous animal studies provide evidence for CS_2-induced developmental and reproductive toxicity and are reviewed extensively in USEPA (1994), ATSDR (1996 and 2012), and NRC (2009). Reliable animal studies evaluating developmental/reproductive toxicity are summarized in Table 5.

3.1.2.2.1 Key Developmental Study (Saillenfait et al. 1989)

Saillenfait et al. (1989) exposed pregnant Sprague-Dawley rats (20-23/group) by inhalation to 0, 100, 200, 400, or 800 ppm CS_2, 6 h/d during gestational days 6-20. Maternal and fetal parameters were evaluated on day 21. Maternal toxicity (reduced maternal weight gain) and reduced fetal body weight was observed at 400 and 800 ppm. No effects were observed on implantations, resorptions, live fetuses, or fetal sex ratio. An increase in unossified sternebrae was observed in fetuses in the 800 ppm exposure group. A small, but not statistically significant incidence in club foot was observed in fetuses in the 400 and 800 ppm exposure groups. A LOAEL of 400 ppm was identified in this study for maternal toxicity and reduced fetal body weight. In the absence of acceptable human developmental toxicity studies, Saillenfait et al. (1989) was selected as the key study for the potential critical health effect of developmental and maternal toxicity. The NOAEL of 200 ppm was used as the POD to determine the POD_{HEC} for this potential critical health effect.

3.1.2.2.2 Supporting Studies

3.1.2.2.2.1 Belisles et al. (1980)

Belisles et al. (1980) exposed rats and rabbits (15-30/group) to 0, 20, or 40 ppm CS_2 for 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm CS_2 on days 0-18 or days 6-18 of gestation, and groups of rabbits not exposed pregestationally were exposed to 20 or 40 ppm on days 0-21 or days 7-21 of gestation. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during gestation days 0-18 or 6-18 (rats) or 0-21 or 7-21 (rabbits). Unexposed control animals were included for both pregestational and gestation periods. In rats, no maternal toxicity was observed and no embryotoxic, fetotoxic, or teratogenic effects were observed except for a slight nonsignificant increase in resorptions and reductions in live fetuses in two groups of exposed rats. A high degree of mortality was observed in the rabbit study, which was not exposure-related, and there was no evidence of exposure related maternal toxicity or developmental toxicity (authors report that the cause of death was unknown). A free-standing NOAEL of 40 ppm for maternal and developmental toxicity for both Sprague Dawley rats and New Zealand rabbits was identified in this study.

3.1.2.2.2.2 PAI (1991)

As described in NRC (2009), PAI (1991) exposed pregnant New Zealand rabbits (24/group) by inhalation to 0, 60, 100, 300, 600, or 1,200 ppm CS_2 for 6 h/d on gestation days 6-18. The uterine contents were examined on gestation day 29. Severe maternal toxicity including death was observed at 1,200 ppm. No maternal toxicity was observed at the lower doses. Embryotoxicity was observed at 600 and 1,200 ppm including postimplantation loss, number of live fetuses, and reduced fetal weight. In the lower dose groups and controls, 20-23 litters were examined and there were no signs of embryotoxicity. This study identified a LOAEL of 600 ppm for embryotoxicity in the absence of maternal toxicity.

3.1.2.2.2.3 WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993)

As described in NRC (2009) and Health Canada (2000), WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993) exposed female CD rats by inhalation to 0, 125, 250, or 500 ppm CS_2 for 6 h/d prior to mating through gestation day 19. The mothers were allowed to deliver and both mothers and pups were observed through day 21 of lactation. Maternal toxicity (irritation and reduced food consumption) and fetotoxicity (increased mortality, reduced pup viability, decreased litter size, and total litter loss) were observed at 500 ppm although no adverse maternal, reproductive, or fetal effects were noted in the lower dose groups. A NOAEL of 250 ppm for maternal toxicity, reproductive, and developmental effects was identified in this study.

3.1.2.2.2.4 Zenick et al. (1984)

Zenick et al. (1984) exposed male Long-Evans rats (12-14/group) by inhalation to 0 or 600 ppm CS_2 for 6 h/d, 5 d/week, for 10 weeks. No significant adverse effects on male reproductive parameters were observed after 1 week of exposure. Reproductive parameters including ejaculation latency, sperm count, and mount latency were affected after 4-10 weeks of exposure. No treatment related effects were observed on other parameters including hormone levels, histology of the reproductive organs, and organ weights (except lower prostate weight). A LOAEL of 600 ppm was identified in this study for reproductive effects. No treatment related effects were observed on epididymal sperm counts and reproductive organ weights after male rats were exposed by inhalation to 900 ppm CS_2 for 12 weeks in a pilot study conducted by Tepe and Zenick (1982) as reported in NRC (2009).

Table 5. Animal Reproductive and Developmental Studies

Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
Sprague-Dawley rats	0, 20, or 40 ppm; 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on GD 0-18 or GD 6-18. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during GD 0-18 or GD 6-18	40	---	Free-standing NOAEL for maternal and developmental toxicity	Belisles et al. (1980)
New Zealand rabbits	0, 20, or 40 ppm; 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on days GD 0-21 or GD 7-21. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during GD 0-21 or GD 7-21	40	---	Free-standing NOAEL for maternal and developmental toxicity	Belisles et al. (1980)
pregnant New Zealand rabbits	0, 60, 100, 300, 600, or 1200 ppm; 6 h/d on GD 6-18	300	600	Developmental toxicity (increased post-implantation loss) in the absence of maternal toxicity	PAI (1991)

Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
pregnant Sprague-Dawley rats	0, 100, 200, 400, or 800 ppm; 6 h/d during GD 6-20	200	400	Maternal toxicity and significant reductions in fetal body weight	Saillenfait et al. (1989)
female CD rats	0, 125, 250, and 500; 6 h/d prior to mating through GD 19	250	400	Maternal toxicity and reduced fetal body weight	WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993)
male Long-Evans rats	0 or 600; 6 h/d, 5 d/week, for 1 week	600	---	No adverse effects reported	Zenick et al. (1984)
male Long-Evans rats	0 or 600; 6 h/d, 5 d/week, for 10 weeks	---	600	ejaculation latency, sperm count, and mount latency affected after 4-10 weeks of exposure	Zenick et al. (1984)

3.1.3 Metabolism and Mode-of-Action (MOA) Analysis

3.1.3.1 Metabolism

CS_2 can be metabolized in the liver by CYP450 to an unstable oxygen intermediate that either hydrolyzes to form atomic sulfur and monothiocarbamate, yielding carbonyl sulfate and carbon dioxide in breath and inorganic sulfates and organosulfur compounds in urine, or spontaneously generates atomic sulfur, carbonyl sulfide, and carbon dioxide. Conjugation of CS_2 or carbonyl sulfide with glutathione forms thiazolidine-2-thione-4-carboxylic acid and 2-oxythiazolidine-4-carboxylic acid, which are then excreted in urine. Figure 1 shows the proposed metabolic pathways for CS_2.

3.1.3.2 Absorption and Excretion

Human and animal studies have shown CS_2 to be rapidly and extensively absorbed through the respiratory tract (NRC 2009). Aqueous solutions of CS_2 have been shown to be absorbed by the skin in humans (NRC 2009). In both humans and animals, unmetabolized CS_2 is mainly excreted by the lungs while most of the absorbed CS_2 is metabolized and eliminated in the form of different metabolites by the kidney (NRC 2009).

3.1.3.3 Mode of Action (MOA) for Inhibition of Ethanol Metabolism and Phase I Xenobiotic Biotransformation

The reactive sulfur generated by CYP450 metabolism can bind macromolecules, including CYP450s, which is thought to be the mechanism responsible for inhibition of Phase I xenobiotic biotransformation observed in humans and animals (NRC 2009). CS_2 may also interact directly with amino acids to form dithiocarbamates. Low molecular weight dithiocarbamates are chelators of transition metal ions (e.g., Fe^{2+}, Cu^{2+}, Zn^{2+}) and formation of dithiocarbamates may inhibit enzymes that depend on transition metal ions for proper function (NRC 2009). This mechanism may explain the CS_2 induced inhibition of aldehyde dehydrogenase (ALDH2) in ethanol metabolism observed in humans and animals (Freundt et al. 1976a). Given the proposed mechanism of action of CS_2 outlined above, individuals with CYP450 or enzyme polymorphisms inhibited by CS_2 (i.e., individuals with ALDH2(2)) or individuals exposed to xeniobiotics (e.g., medications, ethanol) metabolized by CYP450s inhibited by CS_2 may be more sensitive to toxic effects.

3.1.3.4 MOA for Developmental Effects

In terms of the potential for developmental effects, a study in mice conducted by Danielsson et al. (1984) as cited in ATSDR (1996) provides evidence that CS_2 and its metabolites cross the placental barrier at all stages of gestation and localize selectively in tissues reported to be the target organs for CS_2 toxicity. The TD could not locate information regarding the possible MOA for CS_2-induced developmental toxicity.

3.1.4 Dose Metrics

Potential critical health effects identified were increased blood acetaldehyde levels due to inhibition of alcohol metabolism, and developmental and maternal toxicity. In both key studies (Freundt et al. 1976a and Saillenfait et al. 1989), data on the exposure concentration of the parent chemical were available, whereas data on more specific dose metrics were not available. Thus, exposure concentrations of the parent chemicals were used as the dose metrics.

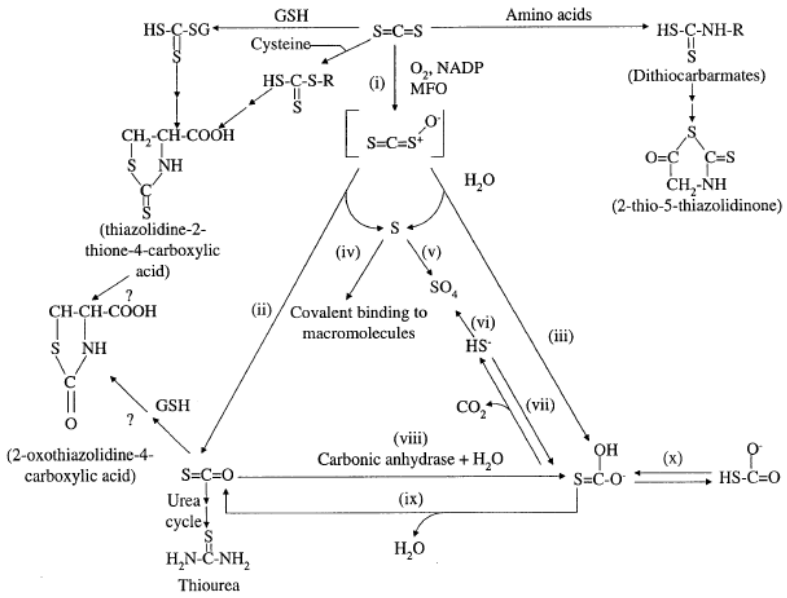

Figure 1. Proposed Metabolic Pathways for Carbon Disulfide (Figure 2-3 from ATSDR 1996)

3.1.5 PODs for Key Studies and Dosimetric Adjustments

The key studies selected for derivation of the POD_{HECs} are Freundt et al. (1976a) and Saillenfait et al. (1989). In Freundt et al. (1976a), humans exposed to 20 ppm CS_2 for 8 h had statistically significant increases in blood acetaldehyde levels; thus, the LOAEL of 20 ppm was used as the POD to derive the POD_{HEC}. The POD identified in Freundt et al. (1976a) was chosen over results from Mack et al. (1974) because a NOAEL or LOAEL could not be clearly identified and substantiated in Macke et al. (1974) based on the endpoint evaluated. However, results of the Mack et al. (1974) study support findings that CS_2 can inhibit metabolic processes at low concentrations.

In the developmental study conducted by Saillenfait et al. (1989) in rats, maternal toxicity and significant reductions in fetal body weight were observed at 400 ppm but no adverse effects were observed at 200 ppm. The TD used the NOAEL of 200 ppm identified in this study as a POD to derive the POD_{HEC}. The NOAEL identified in Saillenfait et al. (1989) was selected over the free-standing NOAEL identified in Belisles et al. (1980) because the studies evaluated the same species and similar endpoints and Saillenfait et al. (1989) was able to identify a dose-response effect unlike Belisles et al. (1980).

3.1.5.1 Freundt et al. (1976a)

Freundt et al. (1976a) is a human study; therefore, no animal-to-human adjustment is necessary. The POD from the Freundt et al. (1976a) study is based on an 8 h exposure duration, so an exposure duration adjustment to 1 h must be considered. Experimental evidence presented in this DSD clearly indicate that CS_2 induced inhibition of alcohol metabolism is both concentration (C) and duration (T) dependent. Therefore, exposure duration adjustment for the Freundt et al. (1976a) study is appropriate. Default procedures discussed in TCEQ (2012) with n = 3 are used to adjust to a 1 h exposure duration for acute studies where both C and T play a role in toxicity.

$POD_{HEC\ ADJ} = C2 = [(C1)^3 \times (T1 / T2)]^{1/3} = [(20\ ppm)^3 \times (8\ h/1\ h)]^{1/3} = 40\ ppm$

3.1.5.2 Saillenfait et al. (1989)

The POD from Saillenfait et al. (1989) is based on effects observed in animals; therefore, an animal-to-human adjustment is necessary. The critical adverse effects caused by CS_2 are systemic effects and CS_2 is treated as a Category 3 gas (TCEQ 2012). For Category 3 gases, the default dosimetric adjustment from an animal concentration to a POD_{HEC} is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

The measured blood/air partition coefficient in humans ($(H_{b/g})_H$) for CS_2 is 0.36 (Soucek 1960 as cited in IPCS 1979). No measured or predicted blood/air partition coefficient in the rat ($(H_{b/g})_A$) was available. A default value of one is used as the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A$ / $(H_{b/g})_H$) as recommended by TCEQ (2012) for a vapor producing remote effects. The resulting POD_{HEC} from the POD of 200 ppm in the Saillenfait et al. (1989) study is 200 ppm:

POD_{HEC} = POD_{ADJ} x RGDR
= 200 ppm x 1
= 200 ppm

Since the POD from the Saillenfait et al. (1989) study is based on a developmental toxicity endpoint, no exposure duration adjustment is necessary.

3.1.6 Selection of the Critical Effect

As indicated in Section 3.1.2.1.1, data suggest that increased blood acetaldehyde levels caused by inhibition of alcohol (ethanol) metabolism via the aldehyde dehydrogenase pathway is the most sensitive and relevant endpoint for short-term exposure to CS_2. The specific critical effect of CS_2 exposure in Freundt et al. (1976a) was a statistically significant increase in blood acetaldehyde levels (approximately 50%) when human subjects were exposed for 8 h to 20 ppm

CS_2. The 20 ppm dose level from Freundt et al. (1976a) was identified as a LOAEL for mild effects and was used as the POD to derive a POD_{HEC} of 40 ppm. Since the POD_{HEC} of 40 ppm derived using the POD from the Freundt et al. (1976a) study was significantly lower than the POD_{HEC} of 200 ppm derived using the POD from the Saillenfait et al. (1989) study, it was selected as the critical effect and was used to derive the Acute ReV and ESL.

3.1.7 Adjustments of the POD_{HEC}

The MOA by which CS_2 may produce toxicity is assumed to have a threshold/nonlinear MOA. Therefore, the POD_{HEC} from Freundt et al. (1976a) was divided by relevant uncertainty factors (UFs).

The following UFs were applied to the POD_{HEC} of 40 ppm from Freundt et al. (1976a):

- A UF_H of 10 was used for intrahuman variability to account for possible sensitive individuals within the human population (i.e., individuals with mutations in the ALDH2 gene, individuals taking disulfram).

- A UF_D of 1 was used because the overall database of acute toxicological studies with CS_2 is large (ATSDR 1996; NRC 2009). The acute studies consist of both human and animal studies as well as short-term reproductive/developmental studies.

- A LOAEL-to-NOAEL uncertainty factor (UF_L) of 3 was used because the POD_{HEC} of 40 ppm from Freundt et al. (1976a) was considered a LOAEL for mild effects based on reversible biochemical changes (increased blood acetaldehyde levels) that occurred in healthy human volunteers without any noticeable functional or clinical impairment.

A total UF of 30 was applied to the POD_{HEC} of 40 ppm to derive the acute ReV of 1.3 ppm (rounded to two significant figures).

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D \times UF_L)$$
$$= 40 \text{ ppm} / (10 \times 1 \times 3)$$
$$= 40 \text{ ppm} / 30$$
$$= 1.3 \text{ ppm}$$

3.1.8 Health-Based Acute ReV and ^{acute}ESL

The acute ReV of 1,300 ppb (4,100 µg/m^3) derived based on the Freundt et al. (1976a) study, was multiplied by 0.3 to calculate the ^{acute}ESL. At the target hazard quotient of 0.3, the ^{acute}ESL is 390 ppb (1,200 µg/m^3) (Table 6). Values were rounded to two significant figures at the end of all calculations.

Table 6. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Values and Descriptions
Study	Freundt et al. (1976a)
Study Population	Twelve healthy male adults, ages 20 to 32 years
Study Quality	Medium to High
Exposure Methods	Inhalation Chamber
POD_{HEC}	20 ppm, LOAEL for mild effects
Critical Effects	Increase in blood acetaldehyde levels in humans with moderate intake of alcohol (0.075% blood alcohol level)
Exposure Duration	8 h
Extrapolation to 1 h	TCEQ (2012) default procedure with n = 3
$POD_{HEC\ ADJ}$ (1 h)	40 ppm
Total UFs	30
Interspecies UF	Not Applicable (N/A)
Intraspecies UF	10
LOAEL UF	3 (mild effect)
Incomplete Database UF *Database Quality*	1 High
acute ReV [1 h] (HQ = 1)	**1,300 ppb (4,100 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**390 ppb (1,200 µg/m^3)**

3.1.9 Comparison of Acute ReV to Other Acute Regulatory Values

The acute ReV is slightly lower than the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Level (REL) of 2 ppm (6,200 µg/m^3) (OEHHA 1999) which is based on significant reductions in fetal body weight observed in Saillenfait et al. (1989). The acute ReV is lower than the 1-hour Acute Exposure Guideline Level-1 (AEGL-1) of 13 ppm (NRC 2009) based on Freundt et al. (1976a) by a factor of 10 because additional uncertainty factors were used to determine the ReV.

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Several studies have reported odor thresholds for CS_2. In Nagata (2003), the 50% odor detection threshold for CS_2 determined by the triangular odor bag method was 210 ppb. Amoore and Hautala (1983) reported a geometric mean odor threshold of 110 ppb, Leonardos et al. (1969) reported an odor recognition threshold of 210 ppb, and AIHA (1997) reported a range of all referenced odor values from 16 ppb to 420 ppb (reported in NRC 2009). The Nagata (2003) study is the only source of information for odor thresholds that meets the criteria in the TCEQ Guidelines (2012).

According to the TCEQ Guidelines (2012), odor detection values defined as the highest quality level of odor thresholds (Level 1) will be considered first in setting the $^{acute}ESL_{odor}$ values. The odor detection threshold reported by Nagata (2003) was determined by the standardized methods of measuring odor and is defined as Level 1 quality data. Therefore, the standardized odor detection threshold determined by Nagata (2003) was used to set the $^{acute}ESL_{odor}$. Accordingly, the $^{acute}ESL_{odor}$ for CS_2 is 210 ppb (650 µg/m^3).

3.2.2 Vegetation Effects

Three acute studies on the vegetation effects of CS_2 in air were located and are listed below:

- Taylor and Selvidge (1984) exposed bush beans (Phaseolus vulgaris) in a closed system to 420 to 5,600 mg/m^3 CS_2 for 6 h. No effects were observed on transpiration or photosynthesis at these concentrations. No visual injury was observed in beans exposed to 10,000 mg/m^3 CS_2 for 6 h.

- Kamel et al. (1975) exposed different species of seeds to CS_2. The most sensitive species was the seed of the wheat plant, Giza variety. Grains with a 15% moisture content suffered a 55% reduction in germination when exposed to 5.05 mg/L (5.05 x 10^8 µg/m^3) CS_2 for 24 h. Wheat seeds with a moisture content less than 15% can safely be exposed to CS_2 up to 2.53 x 10^8 µg/m^3 for 24 h.

- Verna et al. (1991) exposed seeds of multiple species to CS_2 up to 1,230 mg/L for 2 h. This exposure did not adversely affect germination.

None of the available acute studies on vegetation effects of CS_2 reported adverse effects. According to TCEQ Guidelines (2012), the vegetation-based ESL should be set at the lowest-observed–effect-level (LOEL). Since a LOEL was not reported, a vegetation-based ESL was not developed.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

$^{acute}ESL_{odor}$ = 210 ppb (650 µg/m^3)
$^{acute}ESL$ = 390 ppb (1,200 µg/m^3)
acute ReV = 1,300 ppb (4,100 µg/m^3)

For the evaluation of ambient air monitoring data, the $^{acute}ESL_{odor}$ is lower than the acute ReV (Table 1), although both values may be used for the evaluation of air monitoring data. The short-term ESL for air permit evaluations is the $^{acute}ESL_{odor}$ of 210 ppb (650 µg/m^3) as it is lower than the health-based $^{acute}ESL$ (Table 2). The $^{acute}ESL$ (HQ = 0.3) is not used to evaluate ambient air monitoring data and will be used in air permitting applications.

3.4 Acute Inhalation Observed Adverse Effect Level

The acute inhalation observed adverse effect level would be the LOAEL from the key human study of 20 ppm (Freundt et al. 1976a). The $LOAEL_{HEC}$ determined from a human study, where inhibition of alcohol metabolism and the resulting increase in blood acetaldehyde levels, represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same (8 h) or longer durations as those used in the study. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity (i.e., individuals with a mutation in the ALDH2 gene would be expected to be more sensitive to effects of inhibition of alcohol metabolism). The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

A comprehensive literature search through July 2013 was conducted, and key studies were reviewed, regarding the chronic inhalation toxicity of CS_2. In addition, information presented in the ATSDR Toxicological Profile for CS_2 (1996), the ATSDR Addendum to the Toxicological Profile for CS_2 (2012), California's CS_2 RELs Document (OEHHA 1999), AEGLs (NRC 2009), American Conference of Industrial Hygienist's (ACGIH) Threshold Limit Value (TLV)-Time Weighted Average (TWA) support document (ACGIH 2006), and USEPA's IRIS Summary of CS_2 (1995) was evaluated.

The primary target of CS_2 is the nervous system. Numerous human epidemiological studies have been conducted using workers exposed to CS_2, and adverse health effects have been well characterized. Chronic exposure can cause neurophysiological and neuropathological changes (decreased peripheral nerve conduction velocity in motor and sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes). All other adverse effects caused by chronic CS_2 exposure including cardiovascular, reproductive, ophthalmologic, and renal, occur at higher concentrations than nervous system effects; therefore the key and supporting studies used to derive the chronic ReV are based on nervous system effects. Animal studies support the

findings of human studies and are described in detail elsewhere (USEPA 1995; ATSDR 1996 and 2012; OEHHA 2001).

4.1.1 Physical/Chemical Properties and Key Study

4.1.1.1 Physical/Chemical Properties

For physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.1.2 Human Studies

4.1.1.2.1 Key Human Study (Godderis et al. 2006)

Godderis et al. (2006) evaluated the neurobehavioral and clinical effects of CS_2 inhalation exposure on viscose rayon workers. The goal of the Godderis et al. (2006) study was to determine whether adverse effects occurred below the occupational TLV at that time of 31 mg/m^3 (10 ppm) set by the ACGIH (1994), using the same health outcomes evaluated in a study conducted by Vanhoorne et al. (1995). Workers were initially divided into two exposure groups: Exposure Group (EG)1, n=60 < 31 mg/m^3 (10 ppm) and EG2, n=25 > 31 mg/m^3 (10 ppm). The average yearly exposure to CS_2 for the exposure groups were: EG1= 8.9 mg/m^3 ± 1.1 (2.84 ppm) and EG2= 59.2 mg/m^3 ± 5.2 (18.9 ppm). Exposure groups were based on a cumulative exposure index calculated for each worker by multiplying the number of years in a job with the exposure concentration and adding up these products. Also the cumulative exposure index was reported as: EG1–59.5 years x mg/m^3 and EG2–746 years x mg/m^3. The estimated exposure levels for the jobs were based upon recent and historic monitoring for homogeneous exposure groups (spinners, bleach, stable, and post-preparation). The control group (n=66) consisted of workers from a plastic-processing factory, an assembly factory, and a starch-processing factory, and were not exposed to CS_2 or any other toxic compound in their work environment. Neurobehavioral and clinical effects were assessed using various approaches including standardized and validated questionnaires, clinical neurological examination, computer-assisted neurobehavioral tests, and neurophysiological examinations (nerve conduction and electromyography [EMG]). There was no mention of blinding the evaluators in any of these evaluations or tests. Confounding variables included age, race, educational level, personality score, smoking, alcohol use, motivation, shift work, and body mass index (BM I). Individuals who abused alcohol were excluded from the study.

Disequilibrium complaints and sensory-motor complaints were statistically significantly higher for the total exposure group for the Q16 questionnaire results compared to controls. Multiple logistic regressions showed borderline significant differences between controls, EG1 and EG2 alone for the sensory-motor complaints after correction for different confounding variables ($p \leq 0.07$). The proportion of workers with absent sensation in one of five sensory functions (temperature, vibration, touch, pinprick or position) and the presence of positional tremor were higher in the total exposure group compared to controls. After correction for co-variables using multiple logistic regression, a significantly higher proportion of EG1 had positional tremor

Commented [KS1]: P value for what? EG1 vs controls. EG2 p<0.0001

compared to controls and significantly more individuals with abnormal sensation were in EG1 and EG2 compared to controls.

Commented [KS2]: But not EG2? Right, p=.4

Commented [KS3]: Any exposure response? Yes some, but not tested

With respect to neurobehavioral examination system results, digital span backwards, finger-tapping dominant hand, and finger-tapping non-dominant hand were significantly worse in the total exposure group compared to controls. After correcting for confounding variables, only differences in finger tapping dominant and non-dominant hand were significant when comparing EG1, EG2, and controls. Four out of ten nerve conduction velocity tests were statistically significantly different from controls (Table 7). Analysis of variance (ANOVA) with Duncan's multiple range test showed significantly slower sural nerve sensible conduction velocity (SCV), longer sural sensible nerve response amplitude (SNAP) duration, and lower SNAP amplitude and sympathetic skin response (SSR) amplitude in EG1 and EG2 compared to controls ($p<0.05$). The same results were found after controlling for confounding variables using univariate analysis of co-variance (ANCOVA) (all $p<0.03$) (Table 8).

Commented [KS4]: Clarify that this for the entire exposed group vs controls..

The main effect relied on here is motor effects.

Results clearly indicate an effect of CS_2 on various neurotoxicity endpoints. Because results showed that subclinincal and clinical effects occurred in individuals exposed to less than the TLV, Godderis et al. (2006) attempted to better predict the no–observed-effects-level (NOEL) by re-doing the ANCOVA and multiple logistic regression analyses using three subgroups of exposure: N1 group (n=34) exposed to ≤ 10 mg/m^3 (3.2 ppm), N2 group (n=25) exposed to 10.01 to 30.00 mg/m^3 (3.2 to 9.6 ppm), and N3 group (n=26) exposed to > 30 mg/m^3 (9.6 ppm).

Commented [KS5]: Leave out 'multiple'

Regarding the statistically significant nerve conduction findings in the three subgroups, Godderis et al. (2006) stated "Of the nerve conduction results, sural (SNAP) amplitude and duration and sural SCV were (borderline) significantly worse in all three subgroups…" (Table 9). SSR amplitude was only significantly diminished in N1 and N3, with no clear dose-response relationship. Based on the limited data presented for the three exposure subgroups, and the lack of a consistent dose-response relationship for the nerve conduction velocity results, the TD did not use data from the three subgroups to determine the POD. However, the information supports using the exposure estimate for EG1 (average yearly exposure [geometric mean] of 8.9 mg/m^3 [2.84 ppm]) as the POD.

A LOAEL of 8.9 mg/m^3 (2.84 ppm) for mild effects was identified in this study based on statistically significant reduced nerve conduction velocity in workers exposed for an average of 8.5 years (standard deviation 8.0). As noted above, 8.9 mg/m^3 (2.84 ppm) was the average yearly exposure concentration calculated for EG1. Reductions in nerve conduction velocity, while reduced compared to controls, were still within a range of clinically normal values so the effect is considered indicative of mild neurotoxicity and the LOAEL was considered a LOAEL for mild effects (ACGIH 2006). Godderis et al. (2006) was selected as the key study used to derive the chronic ReV because of the high quality of the study and the fact that adverse effects on nerve conduction were reported at lower concentrations than in other studies of similar quality (Johnson et al. 1983; Vanhoorne et al. 1995).

Table 7. Statistically Significant Peripheral Nerve Conduction Velocity Results (Godderis et al. 2006)

Nerve Conduction Velocity	Geometrical Mean (Standard Error)				Unit	P (t-test)
	Control Group	EG1 (n=60) < 10 ppm[a]	EG2 (n=25) > 10 ppm[b]	Total Exposed		
Log (sural SNAP amplitude)	10.50 (1.05)	5.58 (1.18)	2.86 (1.38)	4.57 (1.16)	µV	<0.001
Log (sural SCV)	55.58 (1.02)	41.39 (1.09)	27.6 (1.24)	36.81 (1.09)	m/s	<0.001
Log (sural SNAP duration)	1.93 (1.06)	3.43 (1.15)	5.29 (1.31)	3.90 (1.13)	ms	<0.001
Log (SSR amplitude)	768.60 (1.07)	379.75 (1.26)	418.60 (1.37)	390.84 (1.20)	µV	0.002

SNAP, sensible nerve response amplitude; **SCV**, conventional sensible nerve conduction velocity; **SSR**, sympathetic skin response

[a] EG1 had an average yearly exposure (geometric mean ±SE) of 8.9 mg/m^3 ± 1.1 and a cumulative exposure index of 746.6 years* mg/m^3 ± 17.1

[b] EG2 had an average yearly exposure of 59.2 mg/m^3 ± 5.2 and a cumulative exposure index of 746.6 years* mg/m^3 ± 116.1

Commented [KS6]: P value for what? Combined exp group vs nonexp, unadjusted for covariates

Commented [KS7]: a typo here on 746

Commented [KS8]: Note: no analyses by cumulative exposure? ? Give descriptives.

Commented [KS9]: More reasonable, duration of about 12 years

Table 8. Statistically Significant Results of ANCOVA (p≤0.03) on Nerve Conduction Velocity Studies Comparing Exposure Groups to Control Group (Godderis et al. 2006)

Nerve Conduction Velocity	Contrast Estimate (Standard Error)		
	EG1 (n=60) < 10 ppm	EG2 (n=25) > 10 ppm	Adjusting Covariates p≤0.05
Log (sural nerve SNAP amplitude)	–0.36 (0.09)	–0.41(0.13)	Race[a] (β = 0.04)
Log (sural nerve SCV)	–0.13 (0.05)	–0.18 (0.07)	None
Log (sural SNAP duration)	0.29 (0.08)	–0.29 (0.12)	None
Log (SSR amplitude)	–0.42 (0.13)	–0.481 (0.19)	None

SNAP, sensible nerve response amplitude; **SCV**, conventional sensible nerve conduction velocity; **SSR**, sympathetic skin response

[a] Dependent variable is increasing with confounding variable

Commented [KS10]: What does this mean? Put covariates in footnote

Commented [KS11]: Typo should be +29, from Table 6a

Table 9. Statistically Significant Results of ANCOVA on Nerve Conduction Velocity Results in Three Exposure Subgroups (Godderis et al. 2006)

Nerve Conduction Velocity	Contrast Estimate		
	N1 (n=34) ≤ 10 mg/m^3 (3.2 ppm)	**N2 (n=25) 10.01 - 30.00 mg/m^3 (3.2 - 9.6 ppm)**	**N3 (n=26) > 30 mg/m^3 (9.6 ppm)**
sural nerve SNAP amplitude	–0.37, p=0.001	–0.26, p=0.041	–0.552, p<0.001
sural SNAP duration	0.23, p=0.019	0.35, p=0.002	0.423, p<0.001
sural nerve SCV	–0.118, p=0.043	–0.114, p=0.083	–0.226, p=0.001

Commented [KS12]: What covariates were controlled for. It appears this is from a multiple regression of a logged outcome, 3 exposure groups

4.1.1.2.2 Supporting Human Studies

4.1.1.2.2.1 Johnson et al. (1983)

Johnson et al. (1983) studied the effects of CS_2 exposure on a cohort of male viscose rayon workers (n=145) compared to a group of non-exposed artificial fiber plant workers (n=212) located on the same premises. The mean exposure period was 12.1 ± 6.9 years. Exposed workers were divided into three groups based on previous exposure histories, job descriptions, and current carbon disulfide levels established on the basis of 8-hour personal monitors. The median CS_2 levels of exposed individuals were 1.4, 4.1, and 7.6 ppm. Workers were excluded on the basis of alcohol consumption, diabetes, or elevated blood lead levels to control for potential confounding factors. Maximum motor conduction velocity (MCV) was measured in the ulnar and peroneal nerves and SCV was measured in the sural nerve. Surface electrodes were used to measure nerve conduction velocity and both latency and amplitude ratios were calculated. Participants were also asked to answer a questionnaire with questions about central and peripheral nervous system symptoms. Neurophysiological results were compared between the three exposure groups plus an overall exposure group, and the non-exposed control group.

Commented [KS13]: Lower exposure in this one

A small but significant ($p<0.05$) reduction in sural SCV and peroneal MCV was observed in the total exposed group compared to the control group. CS_2 exposure caused a dose-dependent decrease in peroneal nerve MCV, with a statistically significant difference ($p<0.05$) between the highest exposure group (7.6 ppm) and the control group. A reduction in the ratio of the amplitudes of muscle action potentials obtained from peroneal nerves stimulation was significant in the highest exposure group. A significant association was made between the cumulative exposure index for MCV and the decreased MCV in the total exposed group compared to the control group. No other endpoints evaluated in exposed individuals, including self-reported symptoms related to the peripheral nervous system, were found to be significantly different from controls. The LOAEL identified in this study was 7.6 ppm, based on significantly decreased peroneal nerve MCV.

Commented [KS14]: Did cumexp perform better than average exp. Adjusted for confounders/

USEPA (1995) used this study to derive the Inhalation Reference Concentration (RfC). This study was also used to derive the ATSDR (1996) chronic Minimal Risk Level (MRL), OEHHA (2001) chronic REL, and the Health Canada Tolerable Concentration (TC) (2000). The Godderis et al. (2006) study was published after these agencies derived chronic inhalation CS_2 regulatory values.

4.1.1.2.2.2 Vanhoorne et al. (1995)

Vanhoorne et al. (1995) studied the effects of CS_2 exposure on a cohort of male workers in a Belgian viscose rayon factory (n=111) compared to a group of non-exposed individuals from other plants (n=74). CS_2 exposure concentrations associated with different jobs in the viscose rayon factory ranged from 4 to 112 mg/m^3 (time-weighted average for eight hours). Many of the jobs involved levels of exposure in excess of the TLV at that time of 31 mg/m^3 (10 ppm). Participants were evaluated using a self-administered questionnaire, a clinical neurological examination, and electroneuromyography. Data were analyzed with multiple regression methods and adjusted for a number of confounders.

With respect to the self-administered questionnaire, after adjusting for confounders, cumulative CS_2 exposure was significantly associated with symptoms consistent with polyneuropathy in the legs (i.e., increased leg pain ($p<0.01$), tingling ($p<0.007$), insensitive spots ($p<0.001$), and fatigue in legs ($p<0.003$)). Increased symptoms occurred with increasing cumulative CS_2 exposure.

No relationship was found between cumulative CS_2 exposure and the prevalence of abnormal neurologic findings from the physical examinations.

With respect to electroneuromyographic findings, exposed individuals had a significantly more prevalent abnormal recruitment pattern, and the prevalence of this finding increased with increasing CS_2 exposure. After adjusting for confounders in regression analysis, abnormal recruitment pattern was significantly associated with cumulative CS_2 exposure ($p<0.02$). All motor conduction velocities were significantly lower in the exposed than in the non-exposed subjects ($p<0.001$). A gradation of the effects of exposure was apparent, with a significant decrease in conduction velocities of those exposed to < 31 mg/m^3 ($p<0.01$). Regression analysis gave similar results, showing a negative association between cumulative CS_2 exposure and conduction velocities. The LOAEL identified in this study was 10 ppm (31 mg/m^3).

Commented [KS15]: What is this?

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4.1.1.2.2.3 Other Supporting Human Studies

Hirata et al. (1984 as cited in ACGIH 2006) conducted a study of Chinese workers exposed to daily average CS_2 concentrations of 1.45 ppm. Exposed workers were found to have reduced ulnar nerve motor conduction velocities and slower motor fibers. Hirata et al. (1996) conducted another study of Japanese workers exposed to CS_2. Workers in the 1996 study were exposed to CS_2 at a mathematical average of 4.76 ppm and experienced statistically significantly reduced nerve conduction velocities in peroneal and sural nerves compared to controls. Reduced conduction velocities in the ulnar nerve were not found to be statistically significantly different

from controls in the 1996 study, contrary to findings in the 1984 study. Differences in reported effects were possibly due to uncertainties in exposure histories.

Vasilescu and Florescu (1980 as cited in ACGIH 2006) conducted a study on 30 male workers exposed to an average of 4.8 ppm CS_2 over a period of 10 to 16 years. Some workers were exposed to CS_2 concentrations as high as 224 ppm for short time intervals. Exposed individuals experienced decreased amplitude of sensory evoked potentials on stimulation of digital fibers, mild slowing of sensory conduction velocity, and decreased amplitude of sensory evoked potentials in distal muscles.

4.1.2 Mode of Action and Dose Metric

With respect to long-term toxicity, the formation of reactive thiocarbamates seems to play a role in the development of lesions in the nervous system. It has been postulated that the axonal degeneration that underlies the neuropathy caused by CS_2 is the result of the reaction of CS_2 with protein amino groups to yield initial adducts (dithiocarbamate derivatives). Covalent binding of CS_2 with the formation of thiocarbamates and subsequent cross-linking of neurofilaments was demonstrated in rats after subacute to subchronic exposure (Erve et al. 1998a, b; Harry et al. 1998). Progressive crosslinking of the neurofilament is postulated to occur during its transport along the axon, and covalently crosslinked masses of neurofilaments may occlude axonal transport at the nodes of Ranvier, ultimately resulting in axonal swelling and degeneration (Health Canada 2000).

Exposure concentration of the parent chemical will be used as the default dose metric since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available.

Commented [KS18]: Why? Cumexp was used in one and perhaps two studies?

4.1.3 POD for Key Study and Dosimetric Adjustments

In the key study by Godderis et al. (2006), workers exposed to 2.84 ppm CS_2 for an average of 8 years (± 8.0) had statistically significant reductions in nerve conduction velocity compared to controls. While exposed individuals had significantly lower nerve conduction velocities than controls, the reductions in nerve conduction velocities were found to be within a clinically normal range of values (ACGIH 2006; Johnson et al. 1983). However, nerve conduction velocity can vary widely so a decreased value may still be indicative of an adverse effect; therefore, the occupational point of departure (POD_{OC}) of 2.84 ppm is considered a LOAEL for mild neurotoxic effects.

4.1.3.1 Default Exposure Duration Adjustments

The POD_{OC} of 2.84 ppm was obtained from a human occupational study. Since workers are assumed to be exposed for 8 h/d, 5 d/week, it was necessary to adjust the POD_{OC} to a continuous exposure concentration using the following dosimetric adjustments:

$$POD_{HEC} = POD_{OC} \times \left(\frac{VE_{ho}}{VE_{h}}\right) \times \left(\frac{days/week_{oc}}{days/week_{res}}\right)$$

Where:

POD_{HEC} = human equivalent concentration POD applicable to the general public
POD_{OC} = occupational time-weighted average POD
VE_{ho} = default occupational ventilation rate for an eight-hour day (10 m^3/day)
VE_h = default non-occupational ventilation rate for a 24-hour day (20 m^3/day)
$days/week_{oc}$ = occupational exposure frequency, usually 5 days/week
$days/week_{res}$ = residential exposure frequency; usually 7 days/week

Therefore:

POD_{HEC} = 2.84 ppm x 10/20 x 5/7
POD_{HEC} = 1.014 ppm

4.1.4 Adjustments of the POD_{HEC}

The critical effect identified in Godderis et al. (2006) is reduced nerve conduction velocity and is considered a mild neurotoxic effect. This effect is assumed to have a threshold; therefore, UFs were applied to the POD_{HEC} to derive the chronic ReV (i.e., assume a threshold/nonlinear MOA).

Commented [KS19]: Why?

- A UF_H of 10 was applied to account for human variability and sensitive subpopulations (i.e., children, the elderly, individuals with pre-existing conditions) to the effects of CS_2.
- A UF_D of 1 was used because the database for CS_2 was considered complete and of high quality.
- A UF_L of 3 was used because the POD was considered a LOAEL for mild effects. Reductions in nerve conduction velocity observed at the POD, although reduced compared to controls, were still within range of clinically normal values; therefore, these effects are indicative of mild neurotoxicity.
- A UF_{sub} was not used because workers exposed to the POD were employed for an average of 8.5 (±8.0) years which is considered a chronic exposure duration.
- A UF_A was not used because a human occupational study was used as the key study.

A total UF of 30 was applied to the POD_{HEC} of 1.014 ppm to derive the chronic ReV of 34 ppb (rounded to two significant figures):

Chronic ReV = $POD_{HEC}/(UF_H \times UF_D \times UF_L)$
= 1.014 ppm /(10 x 1 x 3)
= 1.014 ppm/30

= 0.0338 ppm
= 34 ppb (rounded to two significant figures)

4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

The chronic ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 34 ppb (110 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 10 ppb (32 µg/m^3) (Table 10).

Table 10. Derivation of the Chronic ReV and $^{chronic}ESL$

Parameter	Values and Descriptions
Study	Godderis et al. (2006)
Study Population	85 exposed male workers (EG1: < 10 ppm , n = 60 and EG2: >10 ppm, n = 25); further divided into three subgroups of average exposure, N1: ≤ 10 mg/m^3 (n = 34), N2: 10.01 to 30.00 mg/m^3 (n = 25), and N3: > 30 mg/m^3 (n = 26)
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Statistically significant reductions in nerve conduction velocity
POD_{OC}	2.84 ppm
Exposure Duration	8 h/d, 5 d/week, for an average of 8.5 (±8.0) years
Extrapolation to continuous exposure (POD_{ADJ})	1.014 ppm
POD_{HEC}	1.014 ppm
Total UFs	30
Interspecies UF	Not Applicable
Intraspecies UF	10
LOAEL UF	3
Subchronic to chronic UF	Not Applicable

Incomplete Database UF *Database Quality*	1 High
Chronic ReV (HQ = 1)	**34 ppb (110 µg/m^3)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**10 ppb (32 µg/m^3)**

4.1.6 Comparison of TCEQ's Chronic ReV to other Long-Term, Health Protective Comparison Levels from Other Agencies

Table 11 presents a comparison of the TCEQ chronic ReV to long-term, health protective comparison values developed by other agencies. Note that all agencies besides TCEQ developed chronic inhalation toxicity factors before Godderis et al. (2006) was published, although a recent addendum to the ATSDR Toxicological Profile for CS_2 (ATSDR 2012) reviews the Godderis et al. (2006) study. The TCEQ chronic ReV is similar to the TC developed by Health Canada (2000) and is an order of magnitude or more lower than values developed by ATSDR, USEPA, and OEHHA.

Table 11. Long-Term, Health Protective Comparison Levels Developed by TCEQ and Other Agencies

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value (ppb)	POD_{HEC}	Total Uncertainty Factor	Key Study and Critical Effect
TCEQ (2013)	Reference Value (ReV)	34	1,014 ppb LOAEL	30	Godderis et al. (2006); minimal decrease in nerve conduction velocity
USEPA (1995)	Reference Concentration (RfC)	224	6,304 ppb BMC_{10} [NOAEL (mean) of 5,100 ppb]	30	Johnson et al. (1983); minimal decrease in nerve conduction velocity
ATSDR (1996)	Minimal Risk Level (MRL)	300	7,600 ppb LOAEL [NOAEL (median) of 4,100 ppb]	30	Johnson et al. (1983); minimal decrease in nerve conduction

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value (ppb)	POD_{HEC}	Total Uncertainty Factor	Key Study and Critical Effect
					velocity
Health Canada (2000)	Tolerable Concentration (TC)	32	1,600 ppb $BMCL_{05}$ [NOEL of 4,160 ppb]	50	Johnson et al. (1983); minimal decrease in nerve conduction velocity
OEHHA (2001)	Reference Exposure Level (REL)	300	2,540 ppb $BMCL_{05}$	10	Johnson et al. (1983); minimal decrease in nerve conduction velocity

4.2 Carcinogenic Potential

There is no definitive evidence that CS_2 has carcinogenic potential so a chronic carcinogenic value was not developed.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects of CS_2.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values:

- Chronic ReV 34 ppb (110 µg/m^3)
- $^{chronic}ESL_{threshold(nc)}$ 10 ppb (32 µg/m^3)

The chronic ReV of 34 ppb (110 µg/m^3) will be used for the evaluation of ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ of 10 ppb (32 µg/m^3) is the long-term ESL used for air permit reviews (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is not used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Level

The chronic inhalation observed adverse effect level would be the LOAEL from the key human study (TCEQ 2012). In Godderis et al. (2006), workers exposed to 2.84 ppm CS_2 for an average of 8.5 years (± 8.0) had statistically significant reductions in nerve conduction velocity. The relevant POD_{OC} was 2.84 ppm and is considered a LOAEL for mild neurotoxic effects. The POD_{HEC} of 1.014 ppm calculated from the human study (Godderis et al. 2006) was associated with a reduction in nerve conduction velocity and represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same or longer durations as those used in the study. Importantly, effects are not a certainty due to intraspecies differences in sensitivity. The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

Commented [KS20]: Intraspecies?

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Appendix A

Appendix A and Table 12 contains a summary of acute animal inhalation studies that support the acute human inhalation studies described in section 3.1.2.1.

Freundt and Dreher (1969) examined the effect of CS_2 on metabolism of various drugs (hexobarbital-Na, aminophenazone, and procaine-HCl) by the liver. Female Wistar rats were exposed by inhalation to 0, 20, 50, 100, 200, or 400 ppm CS_2 for 8 h. Rats were injected with 100 mg/kg hexobarbital-Na immediately after exposure. Rats exposed to 20 ppm CS_2 for 8 h had twice the sleep duration as controls while exposure to 400 ppm for 8 h caused an increase in sleep duration by a factor of 5.5. Exposure to 100 ppm for 1 h doubled sleep duration. Inhibition of hexobarbital metabolism continually increased during the 100 ppm/8 h exposure, and then decreased exponentially after exposure ended. Inhibition was no longer present 24 h after exposure. Inhibition of metabolism of aminophenazone was determined by measuring urinary excretion of total 4-aminoantipyrine for 24 h. The excretion of 4-aminoantipyrine was inhibited by 70% during the first 6 h after exposure to 50 ppm CS_2. Metabolism of procaine-HCl was only slightly inhibited. Ordinary liver function tests (BSP clearance measured in the bile, SLDH, SGDT, and SGOT) remained normal even at the highest exposure concentration (400 ppm/8 h). Experimental methods and results were only briefly described in this study.

Freundt and Kurzinger (1975) exposed female Wistar rats by inhalation to 0, 20, 100, 200, or 400 ppm CS_2 for 8 h. A significant, dose-related decrease in liver glycogen content was observed in all exposed groups. The decrease developed slowly and steadily and was rapidly reversible after exposure ended. The decrease in liver glycogen content was associated with an increase of hepatic lactate and a decrease of serum potassium and calcium concentrations. A dose-dependent and rapidly reversible rise in inorganic phosphate concentrations was also observed. Body temperature fell significantly at 100 ppm and above. Oxygen consumption of the liver tissue *ex vivo* was elevated after exposure to 400 ppm/8 h. Significant decreases in relative liver weight occurred at all concentrations although liver weight decreases were similar between 20 ppm and 100 ppm groups with greater (and dose-dependent) decreases observed in 200 ppm and 400 ppm groups. The maximum relative liver weight decrease occurred at 400 ppm and was approximately 20%. Body weights (less than 1%), intake of food and water, and fecal excretion were decreased after 8 h exposure to both 100 ppm and 400 ppm. No significant change was noted in liver function tests (Bromsulphalein (BSP) clearance measured in the bile, serum lactate dehydrogenase (SLDH), serum glutamic-pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT)) at any of the exposure concentrations up to the highest concentration tested (400 ppm/8 h).

Freundt et al. (1976a) exposed female Wistar rats by inhalation to 0, 20, or 400 ppm CS_2 for 8 hours or to 400 ppm CS_2 for 8 hours, every other night, for a total of 12 exposures. Rats were given 2g/kg ethanol by intraperitoneal injection (i.p.) and then exposed to CS_2 again until blood collection. Blood ethanol concentrations decreased linearly in a similar fashion in both CS_2 exposed animals and controls. At the time of onset of ethanol elimination from the blood, acetaldehyde levels rose to reach a plateau after 30 minutes to an hour. Blood acetaldehyde

levels were significantly elevated in CS_2 exposed animals (difference between 20 and 400 ppm was not significant). A similar effect was observed in humans as discussed in Section 3.1.2.1.1 (Freundt et al. 1976a). After rats were exposed to 400 ppm CS_2 for 8 hours, 1.25 g/kg of acetaldehyde was administered by i.p. injection. Acetaldehyde was eliminated rapidly in both exposed and control animals although CS_2 exposed animals had a significantly lower rate of elimination and a prolonged excretion half-life.

Freundt et al. (1976b) exposed female Wistar rats and female NMRI mice to 0, 20, 50, 100, 200, or 400 ppm CS_2 for 8 h. Immediately after termination of exposure, animals were treated with various xeniobiotics and subsequently tested for the excretion of xenobiotics metabolites. At all experimental concentration of CS_2, the excretion of the following metabolites was significantly delayed indicating inhibition of Phase I metabolism: 4-OH-antipyrine from antipyrine, acetaminophenol from acetanalid and phenacetin, 4-aminoantipyrine from aminopyrine, and trichloroethanol and trichloroacetic acid from trichloroethene. Phase II N-acetylation and glucuronidation pathways were not significantly affected up to 400 ppm CS_2. Phase I inhibitory effects were reversible from 6 to 36 hours post-exposure. In addition, CS_2 exposure significantly increased hexobarbital-induced sleep duration in rats in a dose-dependent manner.

McKenna and DiStefano (1977) exposed Male Sprague-Dawley rats to 0.1 – 2.0 mg/L (32 – 640 ppm) CS_2 for 4, 6, and 8 h. Exposure to a minimum concentration of 64 ppm for 8 h caused a decrease of dopamine in the brain. Neither signs of toxicity, nor the absence of toxic effects were reported in the study. Increasing exposure led to decreased activity of dopamine β-carboxylase. The effect of CS_2 was attributed to the formation of dithiocarbamates, which complex with copper, since in vitro inhibition of purified dopamine-β-hydroxylase by carbon disulfide was dependent on preincubation with amines capable of dithiocarbamate formation. The inhibition of dopamine-β-hydroxylase decreased progressively with increasing Cu^{2+} concentration, and equimolar concentrations of Cu^{2+} and inhibitor were without effect, suggesting that the inhibition occurred through the binding of enzymic copper.

Acute exposure to higher concentrations of CS_2 (> 100 ppm) has resulted in more severe adverse effects in animals including developmental/reproductive toxicity (see Section 3.1.2.3), CNS effects (reduced activity and hyperexcitability, stupor, ataxia, tremor, convulsions, narcosis, respiratory arrest), decreased body weight, and death (ATSDR 1996; NRC 2009).

Table 12. Summary of Acute Animal Inhalation Studies Noting Adverse Effects Below 100 ppm (POD_{HEC} = 20 ppm).

Animal Strain	Concentration (ppm) and Duration (h)	Critical Effect	Reference[a]

Animal Strain	Concentration (ppm) and Duration (h)	Critical Effect	Reference[a]
female Wistar rats	0, 20, 50, 100, 200, or 400; 8 h	Inhibition of microsomal drug biotransformation; ≥ 20 ppm	Freundt and Dreher (1969)
female Wistar rats	0, 20, 100, 200, or 400; 8 h	Liver effects, increase in whole-body oxygen uptake, fall in body temperature, decrease of body weight; ≥ 20 ppm	Freundt and Kurzinger (1975)
female Wistar rats and female NMRI mice	0, 20, 50, 100, 200, or 400; 8 h	Inhibition of Phase I microsomal drug biotransformation; ≥ 20 ppm	Freundt et al. (1976b)
male Sprague-Dawley rats	32 - 640; 8 h	Decrease of brain noradrenaline in adrenal glands of heart; ≥ 64 ppm	McKenna and DiStefano (1977)

Reviewer Three

Technical Review of the
Draft Carbon Disulfide Development Support Document
Review Guidelines

Background

The Toxicology Division of the Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that summarizes the hazard assessment and dose-response data and analyses used to derive health-protective Effects Screening Levels (ESLs) and Reference Values (ReV) for carbon disulfide. Within the draft DSD TCEQ has derived short-term and long-term toxicity values for human health, odor and vegetation endpoints. These toxicity values are used in the evaluation of air permit applications and ambient air data and were developed using RG-442 TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). The TCEQ guidelines can be found at http://www.tceq.texas.gov/publications/rg/rg-442.html. Reviewers are asked to familiarize themselves with the guidelines and consider the guidelines in formulating your comments and recommendations.

The TCEQ is seeking detailed peer input and guidance to further develop and finalize this DSD and welcomes all comments on the quality and content. *Note that the DSD document is designed to be a summary document and therefore does not provide as detailed descriptions as some other agency's toxicity assessments might. Reviewers should focus on the derivation of the Reference Values (ReVs) and not the Effects Screening Levels (ESLs). The ESLs are calculated by multiplying the ReV by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during an air permitting review. The 0.3 is a policy decision and reviewers are asked to not spend time commenting on this.*

Instructions

Please address each of the specific and general questions found below. For each response (including Yes/No responses), please explain your reasoning and considerations, discuss the scientific support for your comments and opinions, and identify the sources you consulted to construct your response. If a question is beyond your area of expertise, please indicate this. Please address each question by adding your answers to this Word document. In addition, feel free to annotate and comment within the draft TSD document using the Track Changes feature under the Review tab.

Due Date - Your written review should be returned to patterson@tera.org by email no later than January 9, 2014.

General Questions

1. What is your overall impression of the draft document? Please identify areas needing improvement and your suggestions to improve scientific quality and readability.

Overall, the document is generally clear and appropriately documented, within the parameters and general approach used by TCEQ. However, there are a number of areas where additional transparency would be useful, as noted on my edit of the report. In addition, there are a number of sentences that I flagged where the meaning was unclear. Finally, to aid in communication, it would be useful for the author to not simply report findings, but include additional text about the meaning and significance of the findings.

2. Does the draft DSD clearly describe the data and approaches used by TCEQ to develop the toxicity values?

The data are generally well described, with some exceptions as noted in my markups to the document. The TCEQ approaches (e.g., with regard to uncertainty factors) are described more by reference to the guidance than being explicitly described here. However, I do not think that it is necessary to describe the methods in detail in each DSD, except where they differ from "standard" – e.g., U.S. EPA methods. As described in more detail in the context of the specific charge questions, more explanation and transparency is needed with regard to the choice of the POD.

3. Were procedures outlined in RG-442 *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) followed by the TCEQ in this assessment?

The procedures are generally followed. I have some comments about the duration adjustment and choice of uncertainty factors for the acute assessment, as described in more detail below. In addition, more contextual information is needed in the presentation of the observed adverse effect level.

4. Please identify any additional relevant studies or data that you think should be included in this assessment. Please explain specifically how the studies/data could impact the assessment and toxicity values.

I am not aware of any important relevant studies that were missed.

Specific Questions

5. Please comment on the following key decisions for derivation of the acute ReV. *For each element, please discuss if the TCEQ conclusions and choices are supported by the available data, and discuss any additional information or analyses that could improve the decision or related rationale*.

5A. Section 3.1.2 describes the key and supporting studies. Are these the most appropriate studies to use for the dose-response assessment? Have the key and supporting studies and the rationale for their selection been sufficiently described and supported in the DSD?

It is very unusual to use changes in levels of a metabolic enzyme as the basis for the POD. This choice may be appropriate, particularly as a policy choice, but as my graduate school teachers taught, "extraordinary claims require extraordinary evidence." The DSD choice of the POD is perhaps not quite extraordinary, but the choice is unusual enough that substantially better documentation and more transparency is needed.

More explicit documentation is needed on why the DSD considers 20 ppm to be a LOAEL. The degree of change from control is noted, but no information is provided on whether the acetaldehyde levels reached biologically meaningful (adverse) levels. As noted, Freundt et al. reported there was no noticeable alcohol intolerance at the CS2 exposure levels tested. The finding that alcohol intolerance occurs in workers at higher concentrations does not mean that all increases in acetaldehyde (or the ones observed in the Freundt study) are adverse. However, it is of note that the blood levels in the study were below the legal intoxication level in Texas. Since clearly many people experience blood ethanol levels well above the legal intoxication level, is part of the thinking that the LOAEL is aimed to protect people who have had higher doses of ethanol? If that is the case, the key question is at what concentration of carbon disulfide and dose of ethanol are the effects of the acetaldehyde of greater concern than the effects from the ethanol alone. Would the acetaldehyde levels (at 20 ppm carbon disulfide) resulting from ethanol doses somewhat above the legal intoxication limit be sufficient to cause greater adverse effects than those from the ethanol itself?

The DSD cites ATSDR guidance as part of the support for the choice of the POD, but it is not clear what aspect of the guidance is intended. Based on the discussion of the Mack et al. paper, it appears that the judgment is based on the ATSDR determination that impairment of mixed function oxidases may be adverse. If this is so, the full ATSDR guidance on the topic should be considered:

> Modifications occurring in the mixed function oxidase system as a consequence of the adaptive response may potentiate or inhibit toxic responses to other exogenous substances. Agents that induce chemical metabolizing enzyme systems generally tend to potentiate hepatic injury produced by compounds such as chloroform, carbon tetrachloride, or halothane…The borderline between adaptive physiology and toxicity (functional impairment) is not always well delineated. The following guidance provides general direction for assessing hepatic adaptive responses; although this guidance will be appropriate in most cases, there may be exceptions. However, for the purpose of assessing the biological significance of adaptive responses in the liver, the following criteria should be used: Biochemical changes characterized by induction of enzymes of the mixed function oxidase system along with morphologic changes of hepatocellular hypertrophy and proliferation of smooth endoplasmic reticulum should be considered potentially adverse and should be classified as a less serious LOAEL. Other supportive changes that may be observed include increased organ weight, hepatic enlargement, and accentuated cytoplasmic eosinophilia. To maximize the accuracy of assessing hepatic (or other) adaptive responses, in addition to the guidance given here, this interpretive process must be accompanied by insightful case-by-case analysis.

Thus, there are two key considerations. First – the reason that changes in enzyme levels may be considered adverse is because of concern that they could increase the toxicity from exposure to other chemicals. In this case, one concern is whether carbon disulfide would increase the toxicity of ethanol, as discussed above. It also appears that TCEQ may also be concerned about the impact of carbon disulfide exposure on metabolism of drugs, based on the effects on phase I enzymes. If this is of concern and part of the basis for the choice of the POD, the reasoning needs to be more explicit.

The second key consideration from ATSDR is that not all changes in enzyme levels are adverse; the changes are considered appropriate as a POD based on the degree of change, when the degree of change in enzyme levels is of sufficient magnitude to also cause other changes. The DSD has not documented that the degree of change of acetaldehyde levels is of sufficient magnitude to be considered a LOAEL. It is also noteworthy that ATSDR did not consider the Freundt study to have identified a LOAEL – either in the 1996 profile or the 2012 addendum. Although the 2007 guidance was published after the 1996 profile, ATSDR has had similar guidance with regard to changes in metabolic enzymes for many years. Therefore, if TCEQ chooses to use the POD based on changes in acetaldehyde level, the justification for the choice needs to be made more explicit, as well as explicitly noting that, even though the choice was informed by the ATSDR guidance, ATSDR itself came to a different conclusion.

5B. Mode of Action (Section 3.1.3): Does the discussion on modes of action and metabolism correctly interpret the available data and are the conclusions supported by the data?

The MOA data are well presented and the conclusions are generally reasonable. The MOA text says that carbon disulfide can bind CYP450s, presumably resulting in enzyme inhibition, but this enzyme is not explicitly mentioned in the discussion of effects. Are any of the chemicals evaluated in the Mack study metabolized by a CYP450? It is also of note that CYP450 2E1 – one of the major isozymes, is present in the liver at large excess. Polymorphisms (or induction) of this enzyme affect metabolism of xenobiotics only at very high doses of chemicals; at lower doses, metabolism is limited by flow to the liver. See for example, work by Lipscomb with trichloroethylene.

5C.Point of Departure (POD) and Dosimetric Adjustment (Sections 3.1.5 and 3.1.6): TCEQ presents PODs from two studies with different endpoints (Freundt et al., 1976a and Saillenfait et al., 1989) and adjusts each for dose and human equivalency. Were the dosimetric adjustments correctly made and did they follow TCEQ 2012 guidance?

For the Freundt study, data are available on the increased blood acetaldehyde levels after 1 hour of exposure to carbon disulfide, and (based on the published graph) there does not appear a progression of increased acetaldehyde levels with longer exposure duration. Rather than using the data from 8 hours of exposure and then back extrapolating to 1 hour of exposure, the 1-hour exposure data should be used directly. If TCEQ considers the change at 20 ppm to be adverse, then the POD should be 20 ppm.

If the Saillenfait study were to be used for the POD, the absence of a duration adjustment is appropriate. However, the document should note, as described in the TCEQ guidance, "The averaging time for ReV and ESL values based on reproductive or developmental effects is the number of hours of the single day of exposure, not a 1-h averaging time as is typical for 1-h ReVs."

5D. Critical Effect (Section 3.1.6) Do you agree with the selection of inhibition of ethanol metabolism resulting in significantly increased blood acetaldehyde levels (Freundt et al., 1976a) to be the critical effect for derivation of the acute ReV?

See response to 5A.

The Saillenfait study appears to be a reasonable alternative if TCEQ chooses to not use the Freundt study in the final document, but more documentation of the effects in the Saillenfait study would be needed.

5E. Uncertainty Factors (UFs) (Section 3.1.7): Did TCEQ select the appropriate

uncertainty factors and provide sufficient rationale and support for the selections?

The UFs for intraspecies variability and database deficiency are appropriate and adequately documented. For the LOAEL to NOAEL UF, TCEQ guidance is to use a value of 2 to 3 when extrapolating from a minimal LOAEL. Based on the considerations described in 5A, a factor of 2 seems more appropriate than a factor of 3 for this UF.

For transparency, it would be useful to not only include the duration adjustment for the Saillenfait study, but to carry the calculation through to an acute ReV based on the animal data. Using UFH=10, UFA=3, and other UFs =1, I calculate an acute ReV of 6.7 ppm.

6. TCEQ evaluated available data for derivation of welfare-based acute and chronic (Sections 3.1.9 and 4.3) using the TCEQ guidelines (2012). Please comment on the appropriateness of the calculation of the $^{acute}ESL_{odor}$ value and decisions regarding sufficiency of data for the vegetation effects. Refer to Chapter 2 of the TCEQ (2012) for guidance.

These calculations and decisions appear to be appropriate.

7. Please comment on the following key decisions for derivation of the chronic ReV. ***For each element, please discuss if the TCEQ conclusions and choices are supported by the available data, and discuss any additional information or analyses that could improve the decision or related rationale*****.**

7A. Critical Effect (Section 4.1): TCEQ identified the nervous system as the primary target of CS_2 based upon human epidemiological studies of workers exposed to CS2. Do you agree that this is the appropriate critical effect for derivation of the chronic ReV?

Yes. There is strong and consistent evidence that the nervous system is the primary target.

7B. Key and Supporting Studies (Section 4.1.1.2): TCEQ identified Godderis et al. (2006) as the key study and several others as supporting studies. Are these the most appropriate studies to use for identification of critical effect and the dose-response assessment? Have the studies and the rationales for their selection been sufficiently described and supported in the DSD?

Godderis seems appropriate as the key study. It was well conducted and identified the lowest POD. As noted in the attached markup, there are several aspects of the description of the Godderis where additional clarity in presentation would be useful. Additional information however, is needed on the method for exposure evaluation in the Godderis and Vanhoorne studies.

7C. Mode of Action (Section 4.1.2): Does the discussion on mode of action correctly interpret the available data? Do you agree that use of data on the parent compound is appropriate?

The mode of action discussion is appropriate, and the parent chemical concentration is an appropriate dose metric.

7D. Point of Departure (POD): TCEQ identified a LOAEL of 8.9 mg/m^3 (2.84 ppm) for mild effects from Godderis et al. (2006), based on statistically significant reduced nerve conduction velocity in workers exposed for an average of 8.5 years (Standard Deviation 8.0). This study was not available when other agencies (e.g., Health Canada, US EPA, California EPA, ATSDR) developed their chronic values. Do you agree that 8.9 mg/m^3 (2.84 ppm) from Godderis et al. (2006) is the most appropriate POD among the available data and studies? TCEQ labels this a "LOAEL for mild effects," do you agree?

I agree that 8.9 mg/m3 can be considered a LOAEL for a mild effect. I did not fully understand the presentation of the three subgroup analysis. What key information was missing that TCEQ considered "limited data" to be a reason for not using the three subgroup analysis as a basis for the POD? Also, the statistics in Table 9 are beyond me. It would be useful to provide additional information on what the "contrast estimate" is. Was only the statistical analysis provided for the three subgroup analysis, and no primary results? It may be useful to consult a neurologist or neurotoxicologist to aid in interpretation of the adversity of the findings in the low concentration group.

7E. Dosimetric Adjustments (Section 4.1.3): Were the adjustments performed correctly and explained sufficiently?

Yes, this is a standard approach.

7F. Uncertainty Factors (Section 4.1.4): Did TCEQ select the appropriate uncertainty factors and provide sufficient rationale and support for the selections?

The average exposure duration at the POD was 8 years (± 8.0), indicating that there is large variability in the duration of exposure. This is an uncertainty related to the exposure duration and onset of the effect that should be noted. However, I do not think that this uncertainty means that a subchronic-to-chronic factor other than 1 is needed, in light of other conservative aspects of the derivation.

The other UFs appear appropriate. One might be able to argue for a factor of 2 for a minimal LOAEL, considering that the changes were still within a normal range. However, this conservatism balances the uncertainty and variability with regard to the exposure duration.

Other Questions

8. Please identify any other relevant issues or questions that are important for the evaluation of this DSD and the toxicity values derived within it.

Rather than "dose," the term concentration should be used in describing the concentration in air that people or animals were exposed to. "Dose" for inhalation studies should be used only for internal dose, or sometimes for the cumulative exposure, expressed as the product of concentration and time.

With regard to the documentation of the "observed adverse effect level," the writeup needs additional context and explanation. As described in the TCEQ guidelines, the documentation "will include a narrative putting the observed effect levels and their associated uncertainties and caveats (e.g., data limitations, potential inter/intraspecies differences in sensitivity) into proper context. One such caveat is that exceedance of an observed effect level is meaningful only for exposure scenarios that are similar or greater in duration." Furthermore, TCEQ's presentation to the Alliance for Risk Assessment panel that reviewed the method included the statement that "the effect levels should not be interpreted to mean that effects will not occur at lower concentrations, rather that dose-response data showing effects at lower concentrations are not available." The panel also recommended that the document present appropriate context (e.g., distinguishing information based on extrapolation from observation, predictive values based on maximum likelihood estimates vs. health-protective values based on confidence limits) on why the health-protective value is lower than the observed adverse effect level.

Development Support Document
DRAFT, December 5, 2013

Carbon Disulfide

CAS Registry Number: 75-15-0

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Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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List of Acronyms and Abbreviations

A	animals
AAP	aminoantipyrine
ACGIH	American Conference of Industrial Hygienists
ADH	alcohol dehydrogenase
AEGL	Acute Exposure Guideline Level
AIC	Akaike's Information Criterion
ALDH2	Aldehyde dehydrogenase2 (mitochondrial)
ADLH2(2)	Aldehyde dehydrogenase2*2 (mutant form of ALDH2 where a lysine residue replaces a glutamate in the active site at position 487 of ALDH2)
AMCV	Air Monitoring Comparison Value
ANCOVA	Analysis of variance controlling for co-variance
ANOVA	Analysis of variance
ASAT	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration 95% lower confidence limit
BMDS	Benchmark Dose Software
BRFSS	Behavioral Risk Factor Surveillance System survey
^{0} C	degrees centigrade
CES	critical effect size
CES_{05}	critical effect size corresponding to a 5% relative decrease in the mean when compared to controls
CNS	central nervous system
CS_2	Carbon disulfide
CYP450	cytochrome P-450
d	day(s)

List of Acronyms and Abbreviations

DSD	development support document
EG	exposure group
EMG	electromyography
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
ET	Extrathoracic
F	exposure frequency, days per week
GD	gestation day
g/L	grams per liter
h	hour(s)
H	Humans
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration

List of Acronyms and Abbreviations

Hg	mercury
HQ	hazard quotient
i.p.	intraperitoneal
kg	kilogram
LDH	lactate dehydrogenase
LOAEL	lowest-observed-adverse-effect-level
MCV	motor conduction velocity
MEK	methyl ethyl ketone
µg	microgram
µg/m^3	micrograms per cubic meter
mg	milligrams
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
MRL	Minimal Risk Level
MW	molecular weight
n	number
N/A	Not applicable
NAC	National Advisory Committee
n-BA	n-butyl acetate
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OEHHA	Office of Environmental Health Hazard Assessment
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration

List of Acronyms and Abbreviations

POD_{OC}	occupational point of departure
ppb	parts per billion
ppm	parts per million
REL	reference exposure level
ReV	reference value
RfC	inhalation reference concentration
RGDR	regional gas dose ratio
SA	surface area
SAR	structure-activity relationship
SCOB	scheduled-controlled operant behavior
SCV	sural nerve sensible conduction velocity
SD	Sprague-Dawley
SMCs	self-reported multiple chemical sensitivity
SNAP	sural sensible nerve response amplitude
SPGT	serum glutamic-pyruvic transaminase
SSR	sympathetic skin response
TC	tolerable concentration
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TLV	Threshold Limit Value
TWA	time weighted average
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human (interspecies) uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor

List of Acronyms and Abbreviations

USEPA	United States Environmental Protection Agency
V_E	minute volume

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of carbon disulfide (CS_2). Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) available at http://www.tceq.texas.gov/publications/rg/rg-442.html for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on carbon disulfide's physical/chemical data.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	Concentration	Notes
Acute ReV	1,300 ppb (4,100 µg/m^3) **Short-Term Health**	**Critical Effect(s):** Increase in blood acetaldehyde levels in humans with moderate intake of alcohol
$^{acute}ESL_{odor}$	210 ppb (650 µg/m^3) **Odor**	50% detection threshold; sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for impure CS_2
$^{acute}ESL_{veg}$	- - - **Short-Term Vegetation**	No data on vegetation effect levels; concentrations producing no observed effects were significantly above other short-term values
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	34 ppb (110 µg/m^3) **Long-Term Health**	**Critical Effect(s):** Statistically significant reductions in nerve conduction velocity in workers
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Carbon disulfide is not typically monitored for by the TCEQ's ambient air monitoring program (http://www5.tceq.state.tx.us/tamis/index.cfm?fuseaction=home.welcome), so only a limited amount of ambient air data are available to assess carbon disulfide's concentrations in Texas ambient air.

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-

based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{threshold(nc)}$**, chronic health-based Effects Screening Level for threshold dose-response noncancer effects; **$^{chronic}ESL_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	390 ppb (1,200 µg/m^3)[a]	**Critical Effect:** Increase in blood acetaldehyde levels in humans with moderate intake of alcohol
$^{acute}ESL_{odor}$	210 ppb (650 µg/m^3) **Odor** **Short-Term ESL for Air Permit Reviews**	50% detection threshold; sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for technical grade CS_2
$^{acute}ESL_{veg}$	--- **Short-Term Vegetation**	No data on vegetation effect levels; concentrations producing no observed effects were significantly above other short-term values
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	10 ppb (32 µg/m^3)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Statistically significant reductions in nerve conduction velocity in workers
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 1,300 ppb (4,100 µg/m^3) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 34 ppb (110 µg/m^3) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	CS_2	ACGIH 2006
Chemical Structure	S=C=S	TCEQ 2013
Molecular Weight	76.14	ACGIH 2006
Physical State at 25°C	Liquid	ACGIH 2006
Color	Clear, colorless for pure CS_2; or faintly yellow for impure CS_2	ACGIH 2006
Odor	Sweet, pleasant, ethereal odor for pure CS_2; or unpleasant, rotting radishes for impure CS_2	ACGIH 2006 ATSDR 1996
CAS Registry Number	75-15-0	ACGIH 2006
Synonyms	Carbon sulfide, dithiocarbonic anhydride, sulphocarbonic anhydride, Weeviltox	ACGIH 2006
Solubility in water	Soluble, 2,300 mg/L @ 22°C	TCEQ 2012
Log K_{ow}	1.94	HSDB 2010
Vapor Pressure	260 mm Hg @ 20°C	ACGIH 2006
Relative Vapor Density (air = 1)	2.67	HSDB 2010
Melting Point	-112.1°C	HSDB 2010
Boiling Point	46.3°C @ 760 mm Hg	ACGIH 2006
Conversion Factors	1 $\mu g/m^3$ = 0.32 ppb 1 ppb = 3.13 $\mu g/m^3$ at 25°C	ACGIH 2006

Chapter 2 Major Sources and Uses

The most prominent industrial use of CS_2 is in the production of viscose rayon fibers; it is also used in the production of carbon tetrachloride and cellophane. CS_2 is used as a solvent for rubber, sulfur, oils, resins, and waxes, and has been used for soil fumigation and insect control in stored grain. Industrial processes that produce CS_2 as a by-product include coal blast furnaces and oil refining (ACGIH 2006; ATSDR 1996).

CS_2 is a minor component of the waste gases emitted from the processing of sour gas (Health Canada 2000). Continuous ambient monitoring data were collected over a two year period near a sour gas processing plant in Canada. The mean and maximum levels of CS_2 were 0.61 and 88 $\mu g/m^3$ (0.19 ppb and 28 ppb), respectively at an upwind location, and 1.40 and 156 $\mu g/m^3$ (0.44 and 49.9 ppb), respectively, at a downwind location (Legge et al. 1990a, b cited in Health Canada 2000). TCEQ has monitored for CS_2 in areas of oil and gas exploration in 2009, and detected levels from 0.06 ppb to 20 ppb in short-term, instantaneous grab samples (approximately 15-second duration).

Natural sources of CS_2 include wetlands, oceans, volcanic and geothermal activity, and microbial activity in soil (ATSDR 1996). In a small study conducted in New York, NY, CS_2 was detected in all of nine indoor air samples with a mean concentration of 0.63 $\mu g/m^3$, similar to the mean concentration detected in six outdoor air samples (0.3 $\mu g/m^3$) (Phillips 1992 in Health Canada 2000).

Chapter 3 Acute Evaluation

Acute exposure to high doses of CS_2 causes central nervous system (CNS) effects in humans and animals. In humans, irritation of the eyes and throat, and CNS effects including dizziness and headache were observed at 180-240 ppm (NRC 2009). In humans, concentrations of approximately 2,000 ppm can cause nausea, vomiting, progressing dizziness, and beginning signs of central paralysis. In humans, concentrations from 2,000 ppm to above 3,000 ppm cause irregular respiration and narcosis. In animals, CNS effects include reduced activity and hyperexcitability, stupor, ataxia, tremor, convulsions, narcosis, respiratory arrest, and death (NRC 2009).

Acute exposure to lower concentrations of CS_2 that does not cause notable CNS effects clearly causes inhibition of xenobiotic biotransformation reactions, inhibition of alcohol (ethanol) metabolism via the aldehyde dehydrogenase pathway, and alterations of carbohydrate and energy metabolism in the liver (NRC 2009).

CS_2 has also been identified as a reproductive and developmental toxicant in animals, but these effects are seen at much higher concentrations than those shown to cause inhibition of xenobiotic biotransformation reactions (the lowest LOAEL identified in an animal

reproductive/developmental toxicity study was 400 ppm). Section 3.1.2 provides a review of available reproductive and developmental toxicity studies in humans and animals.

3.1 Health-Based Acute ReV and ^{acute}ESL

A comprehensive literature search was conducted regarding the acute inhalation toxicity of CS_2. Information from both human and animal studies regarding the acute toxicity of CS_2 was reviewed in detail by ATSDR (1996 and 2012), ACGIH (2006), OEHHA (1999), and NRC (2009). Well-conducted human studies demonstrate the acute effect of CS_2 inhalation on alcohol (ethanol) metabolism and xenobiotic biotransformation reactions, and since these effects occur at concentrations below those that cause other adverse effects they are preferentially used here to develop the acute toxicity factors such as the ReV and ESL. Numerous acute animal studies have been conducted on the effects of inhalation exposure to CS_2 and are discussed extensively in ATSDR (1996 and 2012) and NRC (2009). Acute animal inhalation studies support the findings of human studies.

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3.1.1 Physical/Chemical Properties

Pure CS_2 is a clear, almost colorless liquid with a sweet, pleasant odor similar to chloroform. Technical grades of CS_2 have a strong, disagreeable odor similar to rotting radishes or overcooked cauliflower due to traces of hydrogen sulfide (ACGIH 2006). CS_2 is water soluble, evaporates readily at room temperature, explodes, and ignites easily. The main chemical and physical properties of CS_2 are summarized in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

Three human experimental studies with CS_2 conducted by Mack et al. (1974), Freundt and Lieberwirth (1974), and Freundt et al. (1976a) were identified as key and supporting studies for the acute evaluation of CS_2 and are summarized in Table 4.

3.1.2.1.1 Key Human Study (Freundt et al. 1976a)

Freundt et al. (1976a) conducted a study investigating the effect of CS_2 on ethanol metabolism in twelve healthy male volunteers, ages 20-32 years. Participants were asked not to take medications or alcohol several days prior to the experiment and were fasted prior to exposure. Shortly before starting the experimental exposure, 2 milliliters (ml) of blood were drawn from each participant. At the beginning of the experiment, participants received 0.57 ml/kilogram (kg) ethanol in 3.01 ml/kg orange juice, with further doses of 0.047 ml/kg ethanol in 0.18 ml/kg orange juice given at 15-minute intervals throughout remainder of experimental period. For each study participant, a mean blood alcohol concentration of about 0.75 g/Liter (L) (0.075% blood alcohol concentration) was obtained and it remained fairly constant during the experiments (the legal blood alcohol concentration limit for intoxication in Texas is 0.08%). The blood acetaldehyde concentration was approximately 6×10^{-3} g/L in alcoholized control subjects.

Participants were exposed to nominal concentrations of 0, 20, 40, and 80 ppm CS_2 for 8 hours (h) (analytical concentrations were not reported). Each participant served as his own control. Blood samples were drawn from participants at hourly intervals during the 8 h exposure period to analyze for acetaldehyde and ethanol. The blood acetaldehyde concentration rose significantly by about 50% when subjects were exposed for 8 h to 20 ppm CS_2. Exposure for 8 h to 40 and 80 ppm CS_2 resulted in an additional slight increase in blood acetaldehyde concentration. A clear dose-response effect was observed. One h of exposure to 20 ppm CS_2 produced about a 50% increase in blood acetaldehyde levels, 40 ppm produced about an 80% increase, and 80 ppm produced about a 90% increase (estimates of percent increase are based on graphical representation of data).

In an additional experiment, four volunteers were exposed to 20 ppm of CS_2 for 8 h. Exposed subjects were then given alcohol (about 0.5 g/L (0.05%) blood alcohol) beginning 16 h after termination of exposure to CS_2. Blood was collected at hourly intervals to analyze for acetaldehyde and alcohol. The blood acetaldehyde concentration in exposed participants reached slightly more than twice the control value indicating that effects can occur even when CS_2 exposure precedes alcohol intake. A similar effect was observed in volunteers repeatedly exposed to 20 ppm CS_2 8 h/d, for 5 days (d), then given alcohol simultaneously only on the last day.

Ethanol is oxidatively metabolized by two pathways in the liver, one by cytosolic alcohol dehydrogenase (ADH), and to a lesser extent by the cytochrome P-450 (CYP450) monooxygenase system in the liver (CYP2E1). Both result in the formation of acetaldehyde, which is further oxidized by mitochondrial aldehyde dehydrogenase (ALDH2) to acetate. Acetate then enters intermediary metabolism of the cell. CS_2 inhibits the metabolism of alcohol at the second step of the pathway (aldehyde dehydrogenase) which results in increased blood acetaldehyde levels. Some individuals have a mutation in the gene for the typical form of ALDH2 which results in the synthesis of ALDH2(2), which is a less active form of the enzyme. The presence of the ALDH2(2) mutation results in an excessive production of aldehyde after ingestion of alcohol. Individuals who are homozygous for the ALDH2(2) mutation are very sensitive to the effects of alcohol and develop an alcohol intolerance syndrome even after ingestion of only a small amount of alcohol.

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The observed increase in acetaldehyde levels in Freundt et al. (1976a) occurred without any noticeable alcohol intolerance effect in participants (i.e., flushing, hypotension, and tachycardia). However, alcohol intolerance has been reported to occur in workers exposed to CS_2 (most likely higher concentrations). Based on guidance in ATSDR (2007), the Toxicology Division (TD) determined that the increase in blood acetaldehyde levels seen after acute exposure to 20 ppm CS_2 is a mild adverse effect; it is a biochemical change caused by inhibition of liver enzymes that could potentially cause reversible, functional/clinical impairment in some individuals (i.e., individuals with a less active form of the enzyme responsible for metabolizing acetaldehyde to acetate [ALDH2(2)]).

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The German Society for Occupational and Environmental Medicine identifies alcohol intolerance as an adverse effect induced by CS_2 (Drexler 1998 as cited in NRC 2009). Alcohol use is very common in the United States (US) (CDC 2013). According to the 2012, Behavioral Risk Factor Surveillance System (BRFSS) survey, approximately 55% of the adult US population drank alcohol in the past 30 days. Approximately 6% of the total population drank heavily, while 17% of the population binge drank. Because alcohol is consumed so prevalently in the US, the TD believes it is appropriate to consider alcohol intolerance inducted by CS_2 exposure to be a relevant endpoint for toxicity factor development.

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Percent increases in blood acetaldehyde levels caused by CS_2 exposure were only shown graphically and were not amenable to benchmark dose modeling; therefore, 20 ppm was selected by the TD as the lowest-observed-adverse-effect-level (LOAEL). This study was selected as the key study for the potential critical health effect of increased blood acetaldehyde levels due to inhibition of ethanol metabolism. The LOAEL of 20 ppm was used as the point of departure (POD) to determine the POD human equivalent concentration (POD_{HEC}) for this potential critical health effect.

3.1.2.1.2 Supporting Human Studies

3.1.2.1.2.1 Freundt and Lieberwirth (1974)

Details of this study were obtained directly from NRC (2009) because the study was only available in German. Eleven healthy male volunteers ages 20-32 years, participated in a study conducted by Freundt and Lieberwirth (1974). Participants (number in parentheses), were asked not to take medicine or alcohol several days prior to the experiment and were exposed by inhalation to nominal concentrations of 0 (11), 40 (5), or 80 (4) ppm CS_2 for 8 h. Exposures were conducted in an 8 m^3 exposure chamber. Participants received alcohol and obtained a mean blood alcohol concentration of 0.7 g/L (0.07% blood alcohol) (range 0.58 to 0.85 g/L, or 0.05% to 0.085% blood alcohol). Details on when the alcohol was given to participants were not given in NRC (2009).

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Subjects exposed to 40 ppm CS_2 and alcohol did not have significant changes of any serum parameters used as markers for effects on carbohydrate and energy metabolism in the liver (cholesterol, calcium, inorganic phosphate, total bilirubin, albumin, total protein, uric acid, urea-N, glucose, lactate dehydrogenase [LDH], alkaline phosphatase, and aspartate aminotransferase [ASAT]); however, the blood glucose level was about 13% lower at the end of the exposure period (although not statistically significant). Subjects exposed to 80 ppm CS_2 had a statistically significant decrease in blood glucose and a significant rise of the serum total bilirubin by 61% as compared with pre-exposure. The group that only received alcohol had a nearly identical serum total bilirubin concentration as the 80 ppm CS_2 group, although the increase was not statistically significant because the pre-exposure level in the alcohol-only group was higher than that in the 80 ppm group.

Four volunteers were exposed to 20 ppm CS_2 for 8 h without alcohol intake. A non-significant 30% decrease in blood glucose was observed after exposure. When this group received alcohol 16-24 h after CS_2 exposure, a 108% increase in serum total bilirubin concentration and slight non-statistically significant increases in serum albumin, total protein, uric acid, and alkaline phosphatase were observed.

A LOAEL of 80 ppm was identified in this study based on a statistically significant decrease in blood glucose and a significant rise of serum total bilirubin. A no-observed-adverse-effect-level (NOAEL) of 40 ppm was identified in this study.

3.1.2.1.2.2 Mack et al. (1974)

Mack et al. (1974) conducted a study to examine the inhibition of oxidative N-demethylation of amidopyrine by CS_2 (a measure of inhibition of Phase I biotransformation of amidopyrine). Nineteen healthy male adults, ages 21 to 40 years, participated in the experiment. Participants were instructed to discontinue medication intake and to restrict alcohol intake a few weeks prior to the experiment. Participants were exposed by inhalation to nominal concentrations of 0, 10, 20, 40, or 80 ppm CS_2 for 6 h. Each participant served as his own control.

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Exposures were carried out in an 8 m^3 dynamic exposure chamber. At the start of the experiment, participants received amidopyrine orally at 7 mg/kg body weight. Urine samples were collected 3-33 h after the start of the exposure and were assayed for metabolites of amidopyrine (aminoantipyrine [AAP], 4-AAP, and N-acetyl-AAP). The lowest concentration tested (10 ppm) was sufficient to result in a significant deficit in the excretion of the free 4-AAP during the exposure. Exposure to 20, 40, and 80 ppm for 3 h resulted in a statistically significant dose-dependent reduction in free AAP, N-Acetyl AAP, and total AAP. The time of maximal depression as measured by the excreted total 4-AAP shifts from 6 h after 10 ppm to 12 h after 80 ppm, whereas the amount of maximal deficit ranges from 14% to nearly 50%. Specific percent changes for each endpoint at each concentration and time interval were not reported in the study. The excretion deficit was reversible and compensated for during the subsequent excretion phase. The intensity and the duration of the effect showed a well-defined dose-response relationship.

An additional experiment with exposure to 20 ppm CS_2 for 6 h showed the effect to be no longer detectable 18 h after exposure. A single 6 h exposure to 40 ppm CS_2 produced an identical inhibitory reaction compared to that seen after exposure to 20 ppm CS_2 for 6 h/d for 5 d.

After 3 h exposure to 10 ppm CS_2 (after 3 h of exposure) a statistically significant reduction in free AAP levels was observed in exposed individuals (indicating an inhibition of Phase I biotransformation of amidopyrine). A dose-response effect was observed after three hours of exposure, with 20, 40, and 80 ppm producing statistically significant, dose-related deficits in free AAP and total AAP levels greater than levels at 10 ppm. After three hours of exposure, 20, 40, and 80 ppm each produced statistically significant, dose-related deficits in free AAP and total AAP levels, greater than the deficits seen at 10 ppm. The deficits increased with dose level. While biochemical changes characterized by impairment of enzymes of the mixed function

oxidase system may be considered potentially adverse (ATSDR 2007), uncertainties in actual percent changes in free AAP levels observed at each exposure concentration and time interval, and no data showing any morphologic or clinical changes associated with the inhibition of Phase I biotransformation of amidopyrine, prevents TD from determining whether the observed effect was truly adverse. Therefore, a NOAEL or LOAEL could not be clearly identified and substantiated from the Mack et al. (1974) study. Results of the Mack et al. (1974) study support findings that CS_2 can inhibit metabolic processes at low concentrations.

Table 4. Summary of Key and Supporting Human Acute Inhalation Studies

Exposure Group	Concentration (ppm) and Duration	NOAEL	LOAEL	Critical Effect	Reference
12 healthy male volunteers, ages 20-32 years	0, 20, 40, or 80 ppm; 8 h	---	20 ppm[a]	Inhibition of ethanol metabolism resulting in significantly increased blood acetaldehyde levels	**Key Study:** Freundt et al. (1976a)
11 healthy male volunteers, ages 20-32 years	0, 40, or 80 ppm; 8 h	40 ppm	80 ppm[b]	Statistically significant decrease in blood glucose and significant rise of serum total bilirubin in alcoholized subjects	Supporting Study: Freundt and Lieberwirth (1974)
19 healthy male volunteers, ages 21-40 years	0, 10, 20, 40, or 80 ppm; 6 h	80 ppm[c]	---	Inhibition of Phase I microsomal drug biotransformation	Supporting Study: Mack et al. (1974)

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[a] The LOAEL of 20 ppm identified in Freundt et al. (1976a) was used as the point-of-departure (POD) to derive a POD_{HEC} and subsequent Acute Rev and ESL.

[b] The LOAEL of 80 ppm identified in Freundt et al. (1974) was higher than the LOAEL of 20 ppm identified in the key study; therefore, Freundt et al. (1974) was used as a supporting study.

[c] Inhibition of Phase I microsomal drug biotransformation occurred at all concentrations tested in Mack et al. (1974); however, this effect could not clearly be classified as an adverse effect based on information provided in the study and guidance in ATSDR (2007) and TCEQ (2012). Mack et al. (1974) was used as a supporting study.

3.1.2.2 Developmental/Reproductive Studies

Some human studies provide evidence that CS_2 may cause reproductive and developmental effects although limitations of the studies (i.e., poor exposure measurements, lack of appropriate control groups, concomitant exposure to other chemicals) prevent their use in the development of ReVs. Numerous animal studies provide evidence for CS_2-induced developmental and reproductive toxicity and are reviewed extensively in USEPA (1994), ATSDR (1996 and 2012), and NRC (2009). Reliable animal studies evaluating developmental/reproductive toxicity are summarized in Table 5.

3.1.2.2.1 Key Developmental Study (Saillenfait et al. 1989)

Saillenfait et al. (1989) exposed pregnant Sprague-Dawley rats (20-23/group) by inhalation to 0, 100, 200, 400, or 800 ppm CS_2, 6 h/d during gestational days 6-20. Maternal and fetal parameters were evaluated on day 21. Maternal toxicity (reduced maternal weight gain) and reduced fetal body weight was observed at 400 and 800 ppm. No effects were observed on implantations, resorptions, live fetuses, or fetal sex ratio. An increase in unossified sternebrae was observed in fetuses in the 800 ppm exposure group. A small, but not statistically significant incidence in club foot was observed in fetuses in the 400 and 800 ppm exposure groups. A LOAEL of 400 ppm was identified in this study for maternal toxicity and reduced fetal body weight. In the absence of acceptable human developmental toxicity studies, Saillenfait et al. (1989) was selected as the key study for the potential critical health effect of developmental and maternal toxicity. The NOAEL of 200 ppm was used as the POD to determine the POD_{HEC} for this potential critical health effect.

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Commented [h8]: Concentration-related?

3.1.2.2.2 Supporting Studies

3.1.2.2.2.1 Belisles et al. (1980)

Belisles et al. (1980) exposed rats and rabbits (15-30/group) to 0, 20, or 40 ppm CS_2 for 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm CS_2 on days 0-18 or days 6-18 of gestation, and groups of rabbits not exposed pregestationally were exposed to 20 or 40 ppm on days 0-21 or days 7-21 of gestation. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during gestation days 0-18 or 6-18 (rats) or 0-21 or 7-21 (rabbits). Unexposed control animals were included for both pregestational and gestation periods. In rats, no maternal toxicity was observed and no embryotoxic, fetotoxic, or teratogenic effects were observed except for a slight nonsignificant increase in resorptions and reductions in live fetuses in two groups of exposed rats. A high degree of mortality was observed in the rabbit study, which was not exposure-related, and there was no evidence of exposure related maternal toxicity or developmental toxicity (authors report that the cause of death was unknown). A free-standing NOAEL of 40 ppm for maternal and developmental toxicity for both Sprague Dawley rats and New Zealand rabbits was identified in this study.

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Commented [h10]: Concentation related? Looks not chemical-related, especially based on low concentrations tested, but a bit more information would be useful, in light of the severity of the endpoints.

3.1.2.2.2.2 PAI (1991)

As described in NRC (2009), PAI (1991) exposed pregnant New Zealand rabbits (24/group) by inhalation to 0, 60, 100, 300, 600, or 1,200 ppm CS_2 for 6 h/d on gestation days 6-18. The uterine contents were examined on gestation day 29. Severe maternal toxicity including death was observed at 1,200 ppm. No maternal toxicity was observed at the lower concentrations. Embryotoxicity was observed at 600 and 1,200 ppm including postimplantation loss, number of live fetuses, and reduced fetal weight. In the lower dose groups and controls, 20-23 litters were examined and there were no signs of embryotoxicity. This study identified a LOAEL of 600 ppm for embryotoxicity in the absence of maternal toxicity.

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3.1.2.2.2.3 WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993)

As described in NRC (2009) and Health Canada (2000), WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993) exposed female CD rats by inhalation to 0, 125, 250, or 500 ppm CS_2 for 6 h/d prior to mating through gestation day 19. The mothers were allowed to deliver and both mothers and pups were observed through day 21 of lactation. Maternal toxicity (irritation and reduced food consumption) and fetotoxicity (increased mortality, reduced pup viability, decreased litter size, and total litter loss) were observed at 500 ppm although no adverse maternal, reproductive, or fetal effects were noted in the lower dose groups. A NOAEL of 250 ppm for maternal toxicity, reproductive, and developmental effects was identified in this study.

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3.1.2.2.2.4 Zenick et al. (1984)

Zenick et al. (1984) exposed male Long-Evans rats (12-14/group) by inhalation to 0 or 600 ppm CS_2 for 6 h/d, 5 d/week, for 10 weeks and xx parameters were evaluated weekly (?). No significant adverse effects on male reproductive parameters were observed after 1 week of exposure. Reproductive parameters including ejaculation latency, sperm count, and mount latency were affected after 4-10 weeks of exposure. No treatment related effects were observed on other parameters including hormone levels, histology of the reproductive organs, and organ weights (except lower prostate weight). A LOAEL of 600 ppm was identified in this study for reproductive effects. No treatment related effects were observed on epididymal sperm counts and reproductive organ weights after male rats were exposed by inhalation to 900 ppm CS_2 for 12 weeks in a pilot study conducted by Tepe and Zenick (1982) as reported in NRC (2009).

Table 5. Animal Reproductive and Developmental Studies

Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
Sprague-Dawley rats	0, 20, or 40 ppm; 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on GD 0-18 or GD 6-18. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during GD 0-18 or GD 6-18	40	---	Free-standing NOAEL for maternal and developmental toxicity	Belisles et al. (1980)
New Zealand rabbits	0, 20, or 40 ppm; 7 h/d, 5 d/week for 3 weeks prior to mating. After mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on days GD 0-21 or GD 7-21. Animals exposed pregestationally were divided into two groups and exposed to 20 or 40 ppm during GD 0-21 or GD 7-21	40	---	Free-standing NOAEL for maternal and developmental toxicity	Belisles et al. (1980)
pregnant New Zealand rabbits	0, 60, 100, 300, 600, or 1200 ppm; 6 h/d on GD 6-18	300	600	Developmental toxicity (increased post-implantation loss) in the absence of maternal toxicity	PAI (1991)

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Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
pregnant Sprague-Dawley rats	0, 100, 200, 400, or 800 ppm; 6 h/d during GD 6-20	200	400	Maternal toxicity and significant reductions in fetal body weight	Saillenfait et al. (1989)
female CD rats	0, 125, 250, and 500; 6 h/d prior to mating through GD 19	250	400	Maternal toxicity and reduced fetal body weight	WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993)
male Long-Evans rats	0 or 600; 6 h/d, 5 d/week, for 1 week	600	---	No adverse effects reported	Zenick et al. (1984)
male Long-Evans rats	0 or 600; 6 h/d, 5 d/week, for 10 weeks	---	600	ejaculation latency, sperm count, and mount latency affected after 4-10 weeks of exposure	Zenick et al. (1984)

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3.1.3 Metabolism and Mode-of-Action (MOA) Analysis

3.1.3.1 Metabolism

CS_2 can be metabolized in the liver by CYP450 to an unstable oxygen intermediate that either hydrolyzes to form atomic sulfur and monothiocarbamate, yielding carbonyl sulfate and carbon dioxide in breath, and inorganic sulfates and organosulfur compounds in urine, or spontaneously generates atomic sulfur, carbonyl sulfide, and carbon dioxide. Conjugation of CS_2 or carbonyl sulfide with glutathione forms thiazolidine-2-thione-4-carboxylic acid and 2-oxythiazolidine-4-carboxylic acid, which are then excreted in urine. Figure 1 shows the proposed metabolic pathways for CS_2.

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3.1.3.2 Absorption and Excretion

Human and animal studies have shown CS_2 to be rapidly and extensively absorbed through the respiratory tract (NRC 2009). Aqueous solutions of CS_2 have been shown to be absorbed by the skin in humans (NRC 2009). In both humans and animals, unmetabolized CS_2 is mainly excreted by the lungs while most of the absorbed CS_2 is metabolized and eliminated by the kidney in the form of different metabolites (NRC 2009).

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3.1.3.3 Mode of Action (MOA) for Inhibition of Ethanol Metabolism and Phase I Xenobiotic Biotransformation

The reactive sulfur generated by CYP450 metabolism can bind macromolecules, including CYP450s, which is thought to be the mechanism responsible for inhibition of Phase I xenobiotic biotransformation observed in humans and animals (NRC 2009). CS_2 may also interact directly with amino acids to form dithiocarbamates. Low molecular weight dithiocarbamates are chelators of transition metal ions (e.g., Fe^{2+}, Cu^{2+}, Zn^{2+}) and formation of dithiocarbamates may inhibit enzymes that depend on transition metal ions for proper function (NRC 2009). This mechanism may explain the CS_2 induced inhibition of aldehyde dehydrogenase (ALDH2) in ethanol metabolism observed in humans and animals (Freundt et al. 1976a). Given the proposed mechanism of action of CS_2 outlined above, individuals with CYP450 polymorphisms or polymorphisms in enzymes that are inhibited by CS_2 (i.e., individuals with ALDH2(2)) or individuals exposed to xeniobiotics (e.g., medications, ethanol) metabolized by CYP450s inhibited by CS_2 may be more sensitive to toxic effects.

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3.1.3.4 MOA for Developmental Effects

In terms of the potential for developmental effects, a study in mice conducted by Danielsson et al. (1984) as cited in ATSDR (1996) provides evidence that CS_2 and its metabolites cross the placental barrier at all stages of gestation and localize selectively in tissues reported to be the target organs for CS_2 toxicity. The TD could not locate information regarding the possible MOA for CS_2-induced developmental toxicity.

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3.1.4 Dose Metrics

Potential critical health effects identified were increased blood acetaldehyde levels due to inhibition of alcohol metabolism, and developmental and maternal toxicity. In both key studies (Freundt et al. 1976a and Saillenfait et al. 1989), data on the exposure concentration of the parent chemical were available, whereas data on more specific dose metrics were not available. Thus, exposure concentration of the parent chemicals was used as the dose metric.

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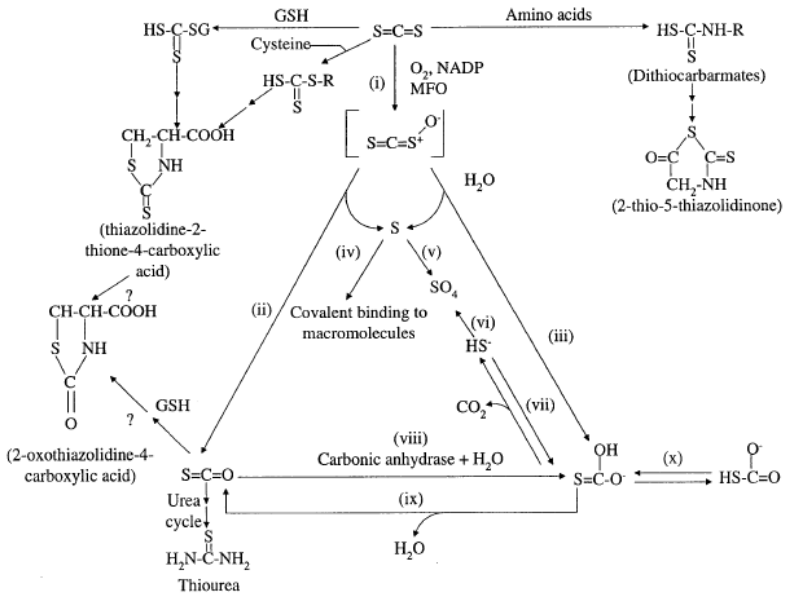

Figure 1. Proposed Metabolic Pathways for Carbon Disulfide (Figure 2-3 from ATSDR 1996)

3.1.5 PODs for Key Studies and Dosimetric Adjustments

The key studies selected for derivation of the POD_{HECs} are Freundt et al. (1976a) and Saillenfait et al. (1989). In Freundt et al. (1976a), humans exposed to 20 ppm CS_2 for 8 h had statistically significant increases in blood acetaldehyde levels; thus, the LOAEL of 20 ppm was used as the POD to derive the POD_{HEC}. The POD identified in Freundt et al. (1976a) was chosen over results from Mack et al. (1974) because a NOAEL or LOAEL could not be clearly identified and substantiated in Mack et al. (1974) based on the endpoint evaluated. However, results of the Mack et al. (1974) study support findings that CS_2 can inhibit metabolic processes at low concentrations.

In the developmental study conducted by Saillenfait et al. (1989) in rats, maternal toxicity and significant reductions in fetal body weight were observed at 400 ppm but no adverse effects were observed at 200 ppm. The TD used the NOAEL of 200 ppm identified in this study as a POD to derive the POD_{HEC}. The NOAEL identified in Saillenfait et al. (1989) was selected over the free-standing NOAEL identified in Belisles et al. (1980) because the studies evaluated the same species and similar endpoints and Saillenfait et al. (1989) was able to identify a dose-response effect unlike Belisles et al. (1980).

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3.1.5.1 Freundt et al. (1976a)

Freundt et al. (1976a) is a human study; therefore, no animal-to-human adjustment is necessary. The POD from the Freundt et al. (1976a) study is based on an 8 h exposure duration, so an exposure duration adjustment to 1 h must be considered. Experimental evidence presented in this DSD clearly indicate that CS_2 induced inhibition of alcohol metabolism is both concentration (C) and duration (T) dependent. Therefore, exposure duration adjustment for the Freundt et al. (1976a) study is appropriate. Default procedures discussed in TCEQ (2012) with n = 3 are used to adjust to a 1 h exposure duration for acute studies where both C and T play a role in toxicity.

$POD_{HEC\ ADJ} = C2 = [(C1)^3 \times (T1 / T2)]^{1/3} = [(20\ ppm)^3 \times (8\ h/1\ h)]^{1/3} = 40\ ppm$

3.1.5.2 Saillenfait et al. (1989)

The POD from Saillenfait et al. (1989) is based on effects observed in animals; therefore, an animal-to-human adjustment is necessary. The critical adverse effects caused by CS_2 are systemic effects and CS_2 is treated as a Category 3 gas (TCEQ 2012). For Category 3 gases, the default dosimetric adjustment from an animal concentration to a POD_{HEC} is conducted using the following equation:

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$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

The measured blood/air partition coefficient in humans ($(H_{b/g})_H$) for CS_2 is 0.36 (Soucek 1960 as cited in IPCS 1979). No measured or predicted blood/air partition coefficient in the rat ($(H_{b/g})_A$) was available. A default value of one is used as the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A$ / $(H_{b/g})_H$) as recommended by TCEQ (2012) for a vapor producing remote effects. The resulting POD_{HEC} from the POD of 200 ppm in the Saillenfait et al. (1989) study is 200 ppm:

POD_{HEC} = POD_{ADJ} x RGDR
= 200 ppm x 1
= 200 ppm

Since the POD from the Saillenfait et al. (1989) study is based on a developmental toxicity endpoint, no exposure duration adjustment is necessary.

3.1.6 Selection of the Critical Effect

As indicated in Section 3.1.2.1.1, data suggest that increased blood acetaldehyde levels caused by inhibition of alcohol (ethanol) metabolism via the aldehyde dehydrogenase pathway is the most sensitive and relevant endpoint for short-term exposure to CS_2. The specific critical effect of CS_2 exposure in Freundt et al. (1976a) was a statistically significant increase in blood acetaldehyde levels (approximately 50%) when human subjects were exposed for 8 h to 20 ppm

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CS_2. The 20 ppm dose level from Freundt et al. (1976a) was identified as a LOAEL for mild effects and was used as the POD to derive a POD_{HEC} of 40 ppm. Since the POD_{HEC} of 40 ppm derived using the POD from the Freundt et al. (1976a) study was significantly lower than the POD_{HEC} of 200 ppm derived using the POD from the Saillenfait et al. (1989) study, it was selected as the critical effect and was used to derive the Acute ReV and ESL.

3.1.7 Adjustments of the POD_{HEC}

The MOA by which CS_2 may produce toxicity is assumed to have a threshold/nonlinear MOA. Therefore, the POD_{HEC} from Freundt et al. (1976a) was divided by relevant uncertainty factors (UFs).

The following UFs were applied to the POD_{HEC} of 40 ppm from Freundt et al. (1976a):

- A UF_H of 10 was used for intrahuman variability to account for possible sensitive individuals within the human population (e.g., individuals with mutations in the ALDH2 gene, individuals taking disulfram).

- A UF_D of 1 was used because the overall database of acute toxicological studies with CS_2 is large (ATSDR 1996; NRC 2009). The acute studies consist of both human and animal studies as well as short-term reproductive/developmental studies.

- A LOAEL-to-NOAEL uncertainty factor (UF_L) of 3 was used because the POD_{HEC} of 40 ppm from Freundt et al. (1976a) was considered a LOAEL for mild effects based on reversible biochemical changes (increased blood acetaldehyde levels) that occurred in healthy human volunteers without any noticeable functional or clinical impairment.

A total UF of 30 was applied to the POD_{HEC} of 40 ppm to derive the acute ReV of 1.3 ppm (rounded to two significant figures).

acute ReV = POD_{HEC} / (UF_H x UF_D x UF_L)
= 40 ppm / (10 x 1 x 3)
= 40 ppm / 30
= 1.3 ppm

3.1.8 Health-Based Acute ReV and ^{acute}ESL

The acute ReV of 1,300 ppb (4,100 µg/m^3) derived based on the Freundt et al. (1976a) study, was multiplied by 0.3 to calculate the ^{acute}ESL. At the target hazard quotient of 0.3, the ^{acute}ESL is 390 ppb (1,200 µg/m^3) (Table 6). Values were rounded to two significant figures at the end of all calculations.

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Table 6. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Values and Descriptions
Study	Freundt et al. (1976a)
Study Population	Twelve healthy male adults, ages 20 to 32 years
Study Quality	Medium to High
Exposure Methods	Inhalation Chamber
POD_{HEC}	20 ppm, LOAEL for mild effects
Critical Effects	Increase in blood acetaldehyde levels in humans with moderate intake of alcohol (0.075% blood alcohol level)
Exposure Duration	8 h
Extrapolation to 1 h	TCEQ (2012) default procedure with n = 3
$POD_{HEC\ ADJ}$ (1 h)	40 ppm
Total UFs	30
Interspecies UF	Not Applicable (N/A)
Intraspecies UF	10
LOAEL UF	3 (mild effect)
Incomplete Database UF *Database Quality*	1 High
acute ReV [1 h] (HQ = 1)	**1,300 ppb (4,100 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**390 ppb (1,200 µg/m^3)**

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3.1.9 Comparison of Acute ReV to Other Acute Regulatory Values

The acute ReV is slightly lower than the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Level (REL) of 2 ppm (6,200 µg/m^3) (OEHHA 1999) which is based on significant reductions in fetal body weight observed in Saillenfait et al. (1989). The acute ReV is lower than the 1-hour Acute Exposure Guideline Level-1 (AEGL-1) of 13 ppm (NRC 2009) based on Freundt et al. (1976a) by a factor of 10 because additional uncertainty factors were used to determine the ReV.

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Several studies have reported odor thresholds for CS_2. In Nagata (2003), the 50% odor detection threshold for CS_2 determined by the triangular odor bag method was 210 ppb. Amoore and Hautala (1983) reported a geometric mean odor threshold of 110 ppb, Leonardos et al. (1969) reported an odor recognition threshold of 210 ppb, and AIHA (1997) reported a range of all referenced odor values from 16 ppb to 420 ppb (reported in NRC 2009). The Nagata (2003) study is the only source of information for odor thresholds that meets the criteria in the TCEQ Guidelines (2012).

According to the TCEQ Guidelines (2012), odor detection values defined as the highest quality level of odor thresholds (Level 1) will be considered first in setting the $^{acute}ESL_{odor}$ values. The odor detection threshold reported by Nagata (2003) was determined by the standardized methods of measuring odor and is defined as Level 1 quality data. Therefore, the standardized odor detection threshold determined by Nagata (2003) was used to set the $^{acute}ESL_{odor}$. Accordingly, the $^{acute}ESL_{odor}$ for CS_2 is 210 ppb (650 µg/m^3).

3.2.2 Vegetation Effects

Three acute studies on the vegetation effects of CS_2 in air were located and are listed below:

- Taylor and Selvidge (1984) exposed bush beans (Phaseolus vulgaris) in a closed system to 420 to 5,600 mg/m^3 CS_2 for 6 h. No effects were observed on transpiration or photosynthesis at these concentrations. No visual injury was observed in beans exposed to 10,000 mg/m^3 CS_2 for 6 h.

- Kamel et al. (1975) exposed different species of seeds to CS_2. The most sensitive species was the seed of the wheat plant, Giza variety. Grains with a 15% moisture content suffered a 55% reduction in germination when exposed to 5.05 mg/L (5.05 x 10^8 µg/m^3) CS_2 for 24 h. Wheat seeds with a moisture content less than 15% can safely be exposed to CS_2 up to 2.53 x 10^8 µg/m^3 for 24 h.

- Verna et al. (1991) exposed seeds of multiple species to CS_2 up to 1,230 mg/L for 2 h. This exposure did not adversely affect germination.

None of the available acute studies on vegetation effects of CS_2 reported adverse effects. According to TCEQ Guidelines (2012), the vegetation-based ESL should be set at the lowest-observed–effect-level (LOEL). Since a LOEL was not reported, a vegetation-based ESL was not developed.

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3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

$^{acute}ESL_{odor}$ = 210 ppb (650 µg/m^3)
$^{acute}ESL$ = 390 ppb (1,200 µg/m^3)
acute ReV = 1,300 ppb (4,100 µg/m^3)

For the evaluation of ambient air monitoring data, the $^{acute}ESL_{odor}$ is lower than the acute ReV (Table 1), although both values may be used for the evaluation of air monitoring data. The short-term ESL for air permit evaluations is the $^{acute}ESL_{odor}$ of 210 ppb (650 µg/m^3) as it is lower than the health-based $^{acute}ESL$ (Table 2). The $^{acute}ESL$ (HQ = 0.3) is not used to evaluate ambient air monitoring data and will be used in air permitting applications.

3.4 Acute Inhalation Observed Adverse Effect Level

The acute inhalation observed adverse effect level would be the LOAEL from the key human study of 20 ppm (Freundt et al. 1976a). The $LOAEL_{HEC}$ was determined from a human study, where inhibition of alcohol metabolism and the resulting increase in blood acetaldehyde levels occurred at 20 ppm. It is probable that similar effects could occur in some individuals exposed to this level over the same (8 h) or longer durations as those used in the study. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity (e.g., individuals with a mutation in the ALDH2 gene would be expected to be more sensitive to effects of inhibition of alcohol metabolism, and effects are more likely with higher ethanol consumption). The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

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Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

A comprehensive literature search through July 2013 was conducted, and key studies were reviewed, regarding the chronic inhalation toxicity of CS_2. In addition, information presented in the ATSDR Toxicological Profile for CS_2 (1996), the ATSDR Addendum to the Toxicological Profile for CS_2 (2012), California's CS_2 RELs Document (OEHHA 1999), AEGLs (NRC 2009), American Conference of Industrial Hygienist's (ACGIH) Threshold Limit Value (TLV)-Time Weighted Average (TWA) support document (ACGIH 2006), and USEPA's IRIS Summary of CS_2 (1995) was evaluated.

The primary target of CS_2 is the nervous system. Numerous human epidemiological studies have been conducted using workers exposed to CS_2, and adverse health effects have been well characterized. Chronic exposure can cause neurophysiological and neuropathological changes (decreased peripheral nerve conduction velocity in motor and sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes). All other adverse effects caused by chronic CS_2 exposure including cardiovascular, reproductive, ophthalmologic, and renal, occur at higher concentrations than nervous system effects; therefore the key and supporting studies used

to derive the chronic ReV are based on nervous system effects. Animal studies support the findings of human studies and are described in detail elsewhere (USEPA 1995; ATSDR 1996 and 2012; OEHHA 2001).

4.1.1 Physical/Chemical Properties and Key Study

4.1.1.1 Physical/Chemical Properties

For physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.1.2 Human Studies

4.1.1.2.1 Key Human Study (Godderis et al. 2006)

Godderis et al. (2006) evaluated the neurobehavioral and clinical effects of CS_2 inhalation exposure on viscose rayon workers. The goal of the Godderis et al. (2006) study was to determine whether adverse effects occurred below the then-current occupational TLV of 31 mg/m^3 (10 ppm) set by the ACGIH (1994), using the same health outcomes evaluated in a study conducted by Vanhoorne et al. (1995). Workers were initially divided into two exposure groups: Exposure Group (EG)1, n=60 < 31 mg/m^3 (10 ppm) and EG2, n=25 > 31 mg/m^3 (10 ppm). The average yearly exposure to CS_2 for the exposure groups were: EG1= 8.9 mg/m^3 ± 1.1 (2.84 ppm) and EG2= 59.2 mg/m^3 ± 5.2 (18.9 ppm). Exposure groups were based on a cumulative exposure index calculated for each worker as the cumulative product of the number of years in a job and the exposure concentration. Also the cumulative exposure index was reported as: EG1–59.5 years x mg/m^3 and EG2–746 years x mg/m^3. The estimated exposure levels for the jobs were based upon recent and historic monitoring for homogeneous exposure groups (spinners, bleach, stable, and post-preparation). The control group (n=66) consisted of workers from a plastic-processing factory, an assembly factory, and a starch-processing factory, and were not exposed to CS_2 or any other toxic compound in their work environment. Neurobehavioral and clinical effects were assessed using various approaches including standardized and validated questionnaires, clinical neurological examination, computer-assisted neurobehavioral tests, and neurophysiological examinations (nerve conduction and electromyography [EMG]). There was no mention of blinding the evaluators in any of these evaluations or tests. Confounding variables included age, race, educational level, personality score, smoking, alcohol use, motivation, shift work, and body mass index (BMI). Individuals who abused alcohol were excluded from the study.

Disequilibrium complaints and sensory-motor complaints were statistically significantly higher for the total exposure group for the Q16 questionnaire results compared to controls. Multiple logistic regressions showed borderline significant differences between controls, EG1 and EG2 alone for sensory-motor complaints after correction for different confounding variables ($p \leq 0.07$). The proportion of workers with absent sensation in one of five sensory functions (temperature, vibration, touch, pinprick or position) and the presence of positional tremor were higher in the total exposure group compared to controls. After correction for co-variables using multiple

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--exposure estimates were based on job categories (not personal measurements)
--based on time in each job category, cumulative exposure was estimated for each worker
--average yearly exposure was calculated as cumulative/years worked
--based on the average exposure, works were divided into groups with average exposure greater than or less than the TLV.

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logistic regression, a significantly higher proportion of EG1 had positional tremor compared to controls and significantly more individuals with abnormal sensation were in EG1 and EG2 compared to controls.

With respect to neurobehavioral examination system results, digital span backwards, finger-tapping dominant hand, and finger-tapping non-dominant hand were significantly worse in the total exposure group compared to controls. After correcting for confounding variables, only differences in finger tapping dominant and non-dominant hand were significant when comparing EG1, EG2, and controls. Four out of ten nerve conduction velocity tests were statistically significantly different from controls (Table 7). Analysis of variance (ANOVA) with Duncan's multiple range test showed significantly slower sural nerve sensible conduction velocity (SCV), longer sural sensible nerve response amplitude (SNAP) duration, and lower SNAP amplitude and sympathetic skin response (SSR) amplitude in EG1 and EG2 compared to controls ($p<0.05$). The same results were found after controlling for confounding variables using univariate analysis of co-variance (ANCOVA) (all $p<0.03$) (Table 8).

Results clearly indicate an effect of CS_2 on various neurotoxicity endpoints. Because results showed that subclinincal and clinical effects occurred in individuals exposed to less than the TLV, Godderis et al. (2006) attempted to better predict the no–observed-effects-level (NOEL) by re-doing the ANCOVA and multiple logistic regression analyses using three subgroups of exposure: N1 group (n=34) exposed to ≤ 10 mg/m^3 (3.2 ppm), N2 group (n=25) exposed to 10.01 to 30.00 mg/m^3 (3.2 to 9.6 ppm), and N3 group (n=26) exposed to > 30 mg/m^3 (9.6 ppm).

Regarding the statistically significant nerve conduction findings in the three subgroups, Godderis et al. (2006) stated "Of the nerve conduction results, sural (SNAP) amplitude and duration and sural SCV were (borderline) significantly worse in all three subgroups…" (Table 9). SSR amplitude was significantly diminished only in N1 and N3, with no clear dose-response relationship. Based on the limited data presented for the three exposure subgroups, and the lack of a consistent dose-response relationship for the nerve conduction velocity results, the TD did not use data from the three subgroups to determine the POD. However, the information supports using the exposure estimate for EG1 (average yearly exposure [geometric mean] of 8.9 mg/m^3 [2.84 ppm]) as the POD.

A LOAEL of 8.9 mg/m^3 (2.84 ppm) for mild effects was identified in this study based on statistically significant reduced nerve conduction velocity in workers exposed for an average of 8.5 years (standard deviation 8.0). As noted above, 8.9 mg/m^3 (2.84 ppm) was the average yearly exposure concentration calculated for EG1. Nerve conduction velocity, while reduced compared to controls, was still within a range of clinically normal values, so the effect is considered indicative of mild neurotoxicity and the LOAEL was considered a LOAEL for mild effects (ACGIH 2006). Godderis et al. (2006) was selected as the key study used to derive the chronic ReV because of the high quality of the study and the fact that adverse effects on nerve conduction were reported at lower concentrations than in other studies of similar quality (Johnson et al. 1983; Vanhoorne et al. 1995).

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Table 7. Statistically Significant Peripheral Nerve Conduction Velocity Results (Godderis et al. 2006)

Nerve Conduction Velocity	Geometrical Mean (Standard Error)				Unit	P (t-test)
	Control Group	EG1 (n=60) < 10 ppm[a]	EG2 (n=25) > 10 ppm[b]	Total Exposed		
Log (sural SNAP amplitude)	10.50 (1.05)	5.58 (1.18)	2.86 (1.38)	4.57 (1.16)	µV	<0.001
Log (sural SCV)	55.58 (1.02)	41.39 (1.09)	27.6 (1.24)	36.81 (1.09)	m/s	<0.001
Log (sural SNAP duration)	1.93 (1.06)	3.43 (1.15)	5.29 (1.31)	3.90 (1.13)	ms	<0.001
Log (SSR amplitude)	768.60 (1.07)	379.75 (1.26)	418.60 (1.37)	390.84 (1.20)	µV	0.002

SNAP, sensible nerve response amplitude; **SCV**, conventional sensible nerve conduction velocity; **SSR**, sympathetic skin response

[a] EG1 had an average yearly exposure (geometric mean ±SE) of 8.9 mg/m^3 ± 1.1 and a cumulative exposure index of 746.6 years* mg/m^3 ± 17.1

[b] EG2 had an average yearly exposure of 59.2 mg/m^3 ± 5.2 and a cumulative exposure index of 746.6 years* mg/m^3 ± 116.1

Table 8. Statistically Significant Results of ANCOVA (p≤0.03) on Nerve Conduction Velocity Studies Comparing Exposure Groups to Control Group (Godderis et al. 2006)

Nerve Conduction Velocity	Contrast Estimate (Standard Error)		
	EG1 (n=60) < 10 ppm	EG2 (n=25) > 10 ppm	Adjusting Covariates p≤0.05
Log (sural nerve SNAP amplitude)	–0.36 (0.09)	–0.41(0.13)	Race[a] (β = 0.04)
Log (sural nerve SCV)	–0.13 (0.05)	–0.18 (0.07)	None
Log (sural SNAP duration)	0.29 (0.08)	–0.29 (0.12)	None
Log (SSR amplitude)	–0.42 (0.13)	–0.481 (0.19)	None

SNAP, sensible nerve response amplitude; **SCV**, conventional sensible nerve conduction velocity; **SSR**, sympathetic skin response

[a] Dependent variable is increasing with confounding variable

Table 9. Statistically Significant Results of ANCOVA on Nerve Conduction Velocity Results in Three Exposure Subgroups (Godderis et al. 2006)

Nerve Conduction Velocity	Contrast Estimate		
	N1 (n=34) ≤ 10 mg/m^3 (3.2 ppm)	**N2 (n=25) 10.01 - 30.00 mg/m^3 (3.2 - 9.6 ppm)**	**N3 (n=26) > 30 mg/m^3 (9.6 ppm)**
sural nerve SNAP amplitude	–0.37, p=0.001	–0.26, p=0.041	–0.552, p<0.001
sural SNAP duration	0.23, p=0.019	0.35, p=0.002	0.423, p<0.001
sural nerve SCV	–0.118, p=0.043	–0.114, p=0.083	–0.226, p=0.001

4.1.1.2.2 Supporting Human Studies

4.1.1.2.2.1 Johnson et al. (1983)

Johnson et al. (1983) studied the effects of CS_2 exposure on a cohort of male viscose rayon workers (n=145) compared to a group of non-exposed artificial fiber plant workers (n=212) located on the same premises. The mean exposure period was 12.1 ± 6.9 years. Exposed workers were divided into three groups based on previous exposure histories, job descriptions, and current carbon disulfide levels established on the basis of 8-hour personal monitors. The median CS_2 levels of these three groups were 1.4, 4.1, and 7.6 ppm. Workers were excluded on the basis of alcohol consumption, diabetes, or elevated blood lead levels to control for potential confounding factors. Maximum motor conduction velocity (MCV) was measured in the ulnar and peroneal nerves and SCV was measured in the sural nerve. Surface electrodes were used to measure nerve conduction velocity and both latency and amplitude ratios were calculated. Participants were also asked to answer a questionnaire with questions about central and peripheral nervous system symptoms. Neurophysiological results were compared among the three exposure groups plus an overall exposure group, and the non-exposed control group.

A small but significant (p<0.05) reduction in sural SCV and peroneal MCV was observed in the total exposed group compared to the control group. CS_2 exposure caused a dose-dependent decrease in peroneal nerve MCV, with a statistically significant difference (p<0.05) between the highest exposure group (7.6 ppm) and the control group. A reduction in the ratio of the amplitudes of muscle action potentials obtained from peroneal nerves stimulation was significant in the highest exposure group. A significant association was made between the cumulative exposure index for MCV and the decreased MCV in the total exposed group compared to the control group. No other endpoints evaluated in exposed individuals, including self-reported symptoms related to the peripheral nervous system, were found to be significantly different from controls. The LOAEL identified in this study was 7.6 ppm, based on significantly decreased peroneal nerve MCV.

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Commented [h32]: This sentence needs some editing – and perhaps should be broken into multiple sentences. I'm not following what is being compared with what.

USEPA (1995) used this study to derive the Inhalation Reference Concentration (RfC). This study was also used to derive the ATSDR (1996) chronic Minimal Risk Level (MRL), OEHHA (2001) chronic REL, and the Health Canada Tolerable Concentration (TC) (2000). The Godderis et al. (2006) study was published after these agencies derived chronic inhalation CS_2 regulatory values.

4.1.1.2.2.2 Vanhoorne et al. (1995)

Vanhoorne et al. (1995) studied the effects of CS_2 exposure on a cohort of male workers in a Belgian viscose rayon factory (n=111) compared to a group of non-exposed individuals from other plants (n=74). CS_2 exposure concentrations associated with different jobs in the viscose rayon factory ranged from 4 to 112 mg/m^3 (time-weighted average for eight hours). Many of the jobs involved levels of exposure in excess of the TLV at that time of 31 mg/m^3 (10 ppm). Participants were evaluated using a self-administered questionnaire, a clinical neurological examination, and electroneuromyography. Data were analyzed with multiple regression methods and adjusted for a number of confounders.

Commented [h33]: How were exposure levels evaluated?

With respect to the self-administered questionnaire, after adjusting for confounders, cumulative CS_2 exposure was significantly associated with symptoms consistent with polyneuropathy in the legs (i.e., increased leg pain ($p<0.01$), tingling ($p<0.007$), insensitive spots ($p<0.001$), and fatigue in legs ($p<0.003$)). Increased symptoms occurred with increasing cumulative CS_2 exposure.

No relationship was found between cumulative CS_2 exposure and the prevalence of abnormal neurologic findings from the physical examinations.

With respect to electroneuromyographic findings, exposed individuals had a significantly more prevalent abnormal recruitment pattern, and the prevalence of this finding increased with increasing CS_2 exposure. After adjusting for confounders in regression analysis, abnormal recruitment pattern was significantly associated with cumulative CS_2 exposure ($p<0.02$). All motor conduction velocities were significantly lower in the exposed than in the non-exposed subjects ($p<0.001$). A gradation of the effects of exposure was apparent, with a significant decrease in conduction velocities of those exposed to < 31 mg/m^3 ($p<0.01$). Regression analysis gave similar results, showing a negative association between cumulative CS_2 exposure and conduction velocities. The LOAEL identified in this study was 10 ppm (31 mg/m^3).

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4.1.1.2.2.3 Other Supporting Human Studies

Hirata et al. (1984 as cited in ACGIH 2006) conducted a study of Chinese workers exposed to daily average CS_2 concentrations of 1.45 ppm. Exposed workers were found to have reduced ulnar nerve motor conduction velocities and slower motor fibers. Hirata et al. (1996) conducted a study of Japanese workers exposed to CS_2. Workers in the 1996 study were exposed to CS_2 at a mathematical average of 4.76 ppm and experienced statistically significantly reduced nerve conduction velocities in peroneal and sural nerves compared to controls. Reduced conduction velocities in the ulnar nerve were not found to be statistically significantly different from

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controls in the 1996 study, contrary to findings in the 1984 study. Differences in reported effects were possibly due to uncertainties in exposure histories.

Vasilescu and Florescu (1980 as cited in ACGIH 2006) conducted a study on 30 male workers exposed to an average of 4.8 ppm CS_2 over a period of 10 to 16 years. Some workers were exposed to CS_2 concentrations as high as 224 ppm for short time intervals. Exposed individuals experienced decreased amplitude of sensory evoked potentials on stimulation of digital fibers, mild slowing of sensory conduction velocity, and decreased amplitude of sensory evoked potentials in distal muscles.

4.1.2 Mode of Action and Dose Metric

With respect to long-term toxicity, the formation of reactive thiocarbamates seems to play a role in the development of lesions in the nervous system. It has been postulated that the axonal degeneration that underlies the neuropathy caused by CS_2 is the result of the reaction of CS_2 with protein amino groups to yield initial adducts (dithiocarbamate derivatives). Covalent binding of CS_2 with the formation of thiocarbamates and subsequent cross-linking of neurofilaments was demonstrated in rats after subacute to subchronic exposure (Erve et al. 1998a, b; Harry et al. 1998). Progressive crosslinking of the neurofilament is postulated to occur during its transport along the axon, and covalently crosslinked masses of neurofilaments may occlude axonal transport at the nodes of Ranvier, ultimately resulting in axonal swelling and degeneration (Health Canada 2000).

Commented [h36]: Reference?

Exposure concentration of the parent chemical will be used as the default dose metric since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available.

Commented [h37]: This is not needed in order to use other dose metrics, although I agree with the ultimate conclusion, because of the latter reason (data on other dose metrics are lacking).

4.1.3 POD for Key Study and Dosimetric Adjustments

In the key study by Godderis et al. (2006), workers exposed to 2.84 ppm CS_2 for an average of 8 years (± 8.0) had statistically significant reductions in nerve conduction velocity compared to controls. While exposed individuals had significantly lower nerve conduction velocities than controls, the reductions in nerve conduction velocities were found to be within a clinically normal range of values (ACGIH 2006; Johnson et al. 1983). However, nerve conduction velocity can vary widely, so a decreased value may still be indicative of an adverse effect; therefore, the occupational point of departure (POD_{OC}) of 2.84 ppm is considered a LOAEL for mild neurotoxic effects.

Commented [h38]: This is the first time that the average duration of exposure is noted. The duration should be noted also in the initial presentation of the study.

4.1.3.1 Default Exposure Duration Adjustments

The POD_{OC} of 2.84 ppm was obtained from a human occupational study. Since workers are assumed to be exposed for 8 h/d, 5 d/week, it was necessary to adjust the POD_{OC} to a continuous exposure concentration using the following dosimetric adjustments:

$$\mathrm{POD_{HEC}} = \mathrm{POD_{OC}} \times \left(\frac{\mathrm{VE_{ho}}}{\mathrm{VE_{h}}}\right) \times \left(\frac{\mathrm{days/week_{oc}}}{\mathrm{days/week_{res}}}\right)$$

Where:

POD_{HEC} = human equivalent concentration POD applicable to the general public
POD_{OC} = occupational time-weighted average POD
VE_{ho} = default occupational ventilation rate for an eight-hour day (10 m^3/day)
VE_h = default non-occupational ventilation rate for a 24-hour day (20 m^3/day)
$days/week_{oc}$ = occupational exposure frequency, usually 5 days/week
$days/week_{res}$ = residential exposure frequency; usually 7 days/week

Therefore:

POD_{HEC} = 2.84 ppm x 10/20 x 5/7
POD_{HEC} = 1.014 ppm

4.1.4 Adjustments of the POD_{HEC}

The critical effect identified in Godderis et al. (2006) is reduced nerve conduction velocity and is considered a mild neurotoxic effect. This effect is assumed to have a threshold; therefore, UFs were applied to the POD_{HEC} to derive the chronic ReV (i.e., assume a threshold/nonlinear MOA).

- A UF_H of 10 was applied to account for human variability and sensitive subpopulations (e.g., children, the elderly, individuals with pre-existing conditions) to the effects of CS_2.
- A UF_D of 1 was used because the database for CS_2 was considered complete and of high quality.
- A UF_L of 3 was used because the POD was considered a LOAEL for mild effects. The nerve conduction velocity observed at the POD, although reduced compared to controls, was still within range of clinically normal values; therefore, these effects are indicative of mild neurotoxicity.
- A UF_{sub} was not used because workers exposed to the POD were employed for an average of 8.5 (±8.0) years which is considered a chronic exposure duration.
- A UF_A was not used because a human occupational study was used as the key study.

A total UF of 30 was applied to the POD_{HEC} of 1.014 ppm to derive the chronic ReV of 34 ppb (rounded to two significant figures):

Chronic ReV = $POD_{HEC}/(UF_H \times UF_D \times UF_L)$
= 1.014 ppm /(10 x 1 x 3)
= 1.014 ppm/30

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= 0.0338 ppm
= 34 ppb (rounded to two significant figures)

4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

The chronic ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 34 ppb (110 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 10 ppb (32 µg/m^3) (Table 10).

Table 10. Derivation of the Chronic ReV and $^{chronic}ESL$

Parameter	Values and Descriptions
Study	Godderis et al. (2006)
Study Population	85 exposed male workers (EG1: < 10 ppm , n = 60 and EG2: >10 ppm, n = 25); further divided into three subgroups of average exposure, N1: ≤ 10 mg/m^3 (n = 34), N2: 10.01 to 30.00 mg/m^3 (n = 25), and N3: > 30 mg/m^3 (n = 26)
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Statistically significant reductions in nerve conduction velocity
POD_{OC}	2.84 ppm
Exposure Duration	8 h/d, 5 d/week, for an average of 8.5 (±8.0) years
Extrapolation to continuous exposure (POD_{ADJ})	1.014 ppm
POD_{HEC}	1.014 ppm
Total UFs	30
Interspecies UF	Not Applicable
Intraspecies UF	10
LOAEL UF	3
Subchronic to chronic UF	Not Applicable

Commented [h39]: The number of controls is an important part of the description of the study population – and an important determinant of study power.

Incomplete Database UF *Database Quality*	1 High
Chronic ReV (HQ = 1)	**34 ppb (110 µg/m^3)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**10 ppb (32 µg/m^3)**

4.1.6 Comparison of TCEQ's Chronic ReV to other Long-Term, Health Protective Comparison Levels from Other Agencies

Table 11 presents a comparison of the TCEQ chronic ReV to long-term, health protective comparison values developed by other agencies. Note that all agencies besides TCEQ developed chronic inhalation toxicity factors before Godderis et al. (2006) was published, although a recent addendum to the ATSDR Toxicological Profile for CS_2 (ATSDR 2012) reviews the Godderis et al. (2006) study. The TCEQ chronic ReV is similar to the TC developed by Health Canada (2000) and is an order of magnitude or more lower than values developed by ATSDR, USEPA, and OEHHA.

Table 11. Long-Term, Health Protective Comparison Levels Developed by TCEQ and Other Agencies

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value (ppb)	POD_{HEC}	Total Uncertainty Factor	Key Study and Critical Effect
TCEQ (2013)	Reference Value (ReV)	34	1,014 ppb LOAEL	30	Godderis et al. (2006); minimal decrease in nerve conduction velocity
USEPA (1995)	Reference Concentration (RfC)	224	6,304 ppb BMC_{10} [NOAEL (mean) of 5,100 ppb]	30	Johnson et al. (1983); minimal decrease in nerve conduction velocity
ATSDR (1996)	Minimal Risk Level (MRL)	300	7,600 ppb LOAEL [NOAEL (median) of 4,100 ppb]	30	Johnson et al. (1983); minimal decrease in nerve conduction

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value (ppb)	POD_{HEC}	Total Uncertainty Factor	Key Study and Critical Effect
					velocity
Health Canada (2000)	Tolerable Concentration (TC)	32	1,600 ppb $BMCL_{05}$ [NOEL of 4,160 ppb]	50	Johnson et al. (1983); minimal decrease in nerve conduction velocity
OEHHA (2001)	Reference Exposure Level (REL)	300	2,540 ppb $BMCL_{05}$	10	Johnson et al. (1983); minimal decrease in nerve conduction velocity

4.2 Carcinogenic Potential

There is no definitive evidence that CS_2 has carcinogenic potential so a chronic carcinogenic value was not developed.

Commented [h40]: "No definitive evidence" suggests that there is some evidence for carcinogenicity. This needs more information – are there any relevant data? Has carcinogenicity been evaluated in humans and/or animals? I understand not going into detailed study summaries, but at least some additional information on the type of data set would be useful.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects of CS_2.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values:

- Chronic ReV 34 ppb (110 µg/m^3)
- $^{chronic}ESL_{threshold(nc)}$ 10 ppb (32 µg/m^3)

The chronic ReV of 34 ppb (110 µg/m^3) will be used for the evaluation of ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ of 10 ppb (32 µg/m^3) is the long-term ESL used for air permit reviews (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is not used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Level

The chronic inhalation observed adverse effect level would be the LOAEL from the key human study (TCEQ 2012). In Godderis et al. (2006), workers exposed to 2.84 ppm CS_2 for an average of 8.5 years (± 8.0) had statistically significant reductions in nerve conduction velocity. The relevant POD_{OC} was 2.84 ppm and is considered a LOAEL for mild neurotoxic effects. The POD_{HEC} of 1.014 ppm calculated from the human study (Godderis et al. 2006) was associated with a reduction in nerve conduction velocity and represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same or longer durations as those reported in the study. Importantly, effects are not a certainty due to intraspecies differences in sensitivity. The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

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Appendix A

Appendix A and Table 12 contains a summary of acute animal inhalation studies that support the acute human inhalation studies described in section 3.1.2.1.

Freundt and Dreher (1969) examined the effect of CS_2 on metabolism of various drugs (hexobarbital-Na, aminophenazone, and procaine-HCl) by the liver. Female Wistar rats were exposed by inhalation to 0, 20, 50, 100, 200, or 400 ppm CS_2 for 8 h. Rats were injected with 100 mg/kg hexobarbital-Na immediately after exposure. Rats exposed to 20 ppm CS_2 for 8 h had twice the sleep duration as controls (indicating inhibition of hexobarbital metabolism) while exposure to 400 ppm for 8 h caused an increase in sleep duration by a factor of 5.5. Exposure to 100 ppm for 1 h doubled sleep duration. Inhibition of hexobarbital metabolism continually increased during the 100 ppm/8 h exposure, and then decreased exponentially after exposure ended. Inhibition was no longer present 24 h after exposure. Inhibition of metabolism of aminophenazone was determined by measuring urinary excretion of total 4-aminoantipyrine for 24 h. The excretion of 4-aminoantipyrine was inhibited by 70% during the first 6 h after exposure to 50 ppm CS_2. Metabolism of procaine-HCl was only slightly inhibited. Ordinary liver function tests (BSP clearance measured in the bile, SLDH, SGDT, and SGOT) remained normal even at the highest exposure concentration (400 ppm/8 h). Experimental methods and results were only briefly described in this study.

Commented [h42]: SLDH and SGOT measure damage to liver cells, no liver function. (BSP clearance is a measure of function.) I'm not sure what SGDT is – is that the same as SGPT? (all abbreviations should be spelled at first use, and some of these abbreviations were not in the abbreviations list. Also,the modern terms are now ALAT, ASAT, not SGPT/SGOT. I do see that many of the abbreviations are addressed in the next study writeup.

Freundt and Kurzinger (1975) exposed female Wistar rats by inhalation to 0, 20, 100, 200, or 400 ppm CS_2 for 8 h. A significant, dose-related decrease in liver glycogen content was observed in all exposed groups. The decrease developed slowly and steadily and was rapidly reversible after exposure ended. The decrease in liver glycogen content was associated with an increase of hepatic lactate and a decrease of serum potassium and calcium concentrations. A dose-dependent and rapidly reversible rise in inorganic phosphate concentration was also observed. Body temperature fell significantly at 100 ppm and above. Oxygen consumption of the liver tissue *ex vivo* was elevated after exposure to 400 ppm/8 h. Significant decreases in relative liver weight occurred at all concentrations although liver weight decreases were similar between 20 ppm and 100 ppm groups with greater (and dose-dependent) decreases observed in 200 ppm and 400 ppm groups. The maximum relative liver weight decrease occurred at 400 ppm and was approximately 20%. Body weights (less than 1%), intake of food and water, and fecal excretion were decreased after 8 h exposure to both 100 ppm and 400 ppm. No significant change was noted in liver function tests (Bromsulphalein (BSP) clearance measured in the bile, serum lactate dehydrogenase (SLDH), serum glutamic-pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT)) at any of the exposure concentrations up to the highest concentration tested (400 ppm/8 h).

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Commented [h43]: Was there any discussion of the significance or cause of the decreased liver weight?
Increased liver weight may reflect enzyme induction – increased protein synthesis. But here the enzyme inhibition seems to be at the protein level, rather than the gene expression level. But I wondered if there is also some possible effect on enzyme levels.

Freundt et al. (1976a) exposed female Wistar rats by inhalation to 0, 20, or 400 ppm CS_2 for 8 hours or to 400 ppm CS_2 for 8 hours, every other night, for a total of 12 exposures. Rats were given 2 g/kg ethanol by intraperitoneal injection (i.p.) and then exposed to CS_2 again until blood collection. Blood ethanol concentrations decreased linearly in a similar fashion in both CS_2 exposed animals and controls. At the time of onset of ethanol elimination from the blood,

Commented [h44]: This is linearly with time after exposure?

acetaldehyde levels rose to reach a plateau after 30 minutes to an hour. Blood acetaldehyde levels were significantly elevated in CS_2 exposed animals, but the increase was not related to the CS2 concentration (difference between 20 and 400 ppm was not significant). Blood acetaldehyde was also increased in CS2-exposed humans that also received ethanol, as discussed in Section 3.1.2.1.1 (Freundt et al. 1976a). After rats were exposed to control air or 400 ppm CS_2 for 8 hours, 1.25 g/kg of acetaldehyde was administered by i.p. injection. Acetaldehyde was eliminated rapidly in both exposed and control animals although CS_2 exposed animals had a significantly lower rate of elimination and a prolonged excretion half-life.

Freundt et al. (1976b) exposed female Wistar rats and female NMRI mice to 0, 20, 50, 100, 200, or 400 ppm CS_2 for 8 h. Immediately after termination of exposure, animals were treated with various xeniobiotics and subsequently tested for the excretion of metabolites of the xenobiotics. At all experimental concentrations of CS_2, the excretion of the following metabolites was significantly delayed indicating inhibition of Phase I metabolism: 4-OH-antipyrine from antipyrine, acetaminophenol from acetanalid and phenacetin, 4-aminoantipyrine from aminopyrine, and trichloroethanol and trichloroacetic acid from trichloroethene. Phase II N-acetylation and glucuronidation pathways were not significantly affected up to 400 ppm CS_2. Phase I inhibitory effects were reversible from 6 to 36 hours post-exposure. In addition, CS_2 exposure significantly increased hexobarbital-induced sleep duration in rats in a dose-dependent manner.

McKenna and DiStefano (1977) exposed Male Sprague-Dawley rats to 0.1 – 2.0 mg/L (32 – 640 ppm) CS_2 for 4, 6, and 8 h. Exposure to a minimum concentration of 64 ppm for 8 h caused a decrease of dopamine in the brain. Neither signs of toxicity, nor the absence of toxic effects were reported in the study. Increasing exposure led to decreased activity of dopamine β-carboxylase. The effect of CS_2 was attributed to the formation of dithiocarbamates, which complex with copper, since in vitro inhibition of purified dopamine-β-hydroxylase by carbon disulfide was dependent on preincubation with amines capable of dithiocarbamate formation. The inhibition of dopamine-β-hydroxylase decreased progressively with increasing Cu^{2+} concentration, and equimolar concentrations of Cu^{2+} and inhibitor were without effect, suggesting that the inhibition occurred through the binding of enzymic copper.

Acute exposure to higher concentrations of CS_2 (> 100 ppm) has resulted in more severe adverse effects in animals including developmental/reproductive toxicity (see Section 3.1.2.3), CNS effects (reduced activity and hyperexcitability, stupor, ataxia, tremor, convulsions, narcosis, respiratory arrest), decreased body weight, and death (ATSDR 1996; NRC 2009).

Table 12. Summary of Acute Animal Inhalation Studies Noting Adverse Effects Below 100 ppm (POD_{HEC} = 20 ppm).

Animal Strain	Concentration (ppm) and Duration (h)	Critical Effect	Reference[a]

Commented [h45]: This sentence is unclear. I understand the second phrase, but it's not clear how (or if) this relates to the time of onset of ethanol elimination. Ethanol elimination presumably started immediately after the injection, so can you just include the second phrase in the sentence?

Deleted: A similar effect was observed in humans

Commented [h46]: Yes? You introduce control animals in the next sentence.

Deleted: xenobiotics

Commented [h47]: This is awkward wording. I assume you're just saying that no information was provided on whether there were any signs of toxicity.

Commented [h48]: Please explain how 100 ppm corresponds to an HEC of 20 ppm

Animal Strain	Concentration (ppm) and Duration (h)	Critical Effect	Reference[a]
female Wistar rats	0, 20, 50, 100, 200, or 400; 8 h	Inhibition of microsomal drug biotransformation; ≥ 20 ppm	Freundt and Dreher (1969)
female Wistar rats	0, 20, 100, 200, or 400; 8 h	Liver effects, increase in whole-body oxygen uptake, fall in body temperature, decrease of body weight; ≥ 20 ppm	Freundt and Kurzinger (1975)
female Wistar rats and female NMRI mice	0, 20, 50, 100, 200, or 400; 8 h	Inhibition of Phase I microsomal biotransformation of drugs; ≥ 20 ppm	Freundt et al. (1976b)
male Sprague-Dawley rats	32 - 640; 8 h	Decrease of brain dopamine in adrenal glands of heart; ≥ 64 ppm	McKenna and DiStefano (1977)

Deleted: biotransformation

Commented [h49]: Or change text to noradrenaline – but text and table should use same terms.

Deleted: noradrenaline