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Carbon Disulfide

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List of Acronyms and Abbreviations	Definitions
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
$^{\circ}$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	Definitions
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	Definitions
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
$\mu g/m^3$	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
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
POD_{OC}	occupational point of departure

List of Acronyms and Abbreviations	Definitions
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 nerve conduction velocity
SD	Sprague-Dawley
SMCs	self-reported multiple chemical sensitivity
SNAP	sensory 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
USEPA	United States Environmental Protection Agency

List of Acronyms and Abbreviations	Definitions
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 2015a) 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	**25,000 µg/m^3 (8,000 ppb) Short-Term Health**	**Critical Effect(s):** Free-standing NOAEL for significant increase in blood acetaldehyde levels in humans with moderate intake of alcohol in the absence of clinical or functional impairment.
$^{acute}ESL_{odor}$	- - -	Sweet, pleasant, ethereal odor for technical grade (pure) CS_2
$^{acute}ESL_{veg}$	- - -	Concentrations producing effects were significantly above other short-term values. Therefore, an $^{acute}ESL_{veg}$ was not derived.
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	**110 µg/m^3 (34 ppb) 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)

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
^{acute}ESL [1 h] (HQ = 0.3)	7,500 µg/m^3 (2,400 ppb) [a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Free-standing NOAEL for significant increase in blood acetaldehyde levels in humans with moderate intake of alcohol in the absence of clinical or functional impairment.
^{acute}ESL$_{odor}$	---	Sweet, pleasant, ethereal odor for technical grade (pure) CS_2
^{acute}ESL$_{veg}$	---	Concentrations producing no observed effects were significantly above other short-term values. Therefore, an ^{acute}ESL$_{veg}$ was not derived.
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	**32 µg/m^3 (10 ppb) [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 25,000 µg/m^3 (8,000 ppb) 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 110 µg/m^3 (34 ppb) 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	ACGIH 2006
Odor	Sweet, pleasant, ethereal odor for pure CS_2	ACGIH 2006
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 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 µg/m^3 (0.19 ppb and 28 ppb), respectively at an upwind location, and 1.40 and 156 µg/m^3 (0.44 and 49.9 ppb), respectively, at a downwind location (Legge et al. 1990a, b cited in Health Canada 2000). TCEQ 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 µg/m^3, similar to the mean concentration detected in six outdoor air samples (0.3 µg/m^3) (Phillips 1992 in Health Canada 2000).

Chapter 3 Acute Evaluation

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

TCEQ conducted a comprehensive literature search 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). In general, acute animal inhalation studies support the findings of human studies.

Acute exposure to >240 ppm CS_2 causes central nervous system (CNS) effects and respiratory tract irritation in humans. A German study conducted by Lehman (1894) (as discussed in NRC 2009) covered a wide range of exposure concentrations in two healthy male volunteers.

- Exposure to 180 to 240 ppm for up to 4 ¾ hours caused "moderate odor annoyance, (but) no other subjective symptoms."
- Exposure to 260 - 420 ppm for up to 4 hours caused "tension in the eyes, slight dizziness, headache, slight cough, feeling of exhaustion, slight lacrimation, and burning eyes."
- Concentrations of 435 - 820 ppm for up to 4 hours exposure caused "tickle in the throat, burning eyes, tingling; slight headaches, temporary impairment of reading ability, feeling of heat in the forehead, cough, and slight dizziness. After the end of exposure: strong, persistent headaches, irritation of the larynx, cough attacks, palpitations, dizziness,

anxiety, reddened face, increased pulse, paleness and cold sweat, unmotivated laugh ("mirth")."

- Concentrations of 640 - 960 ppm for up to 3 hours 30 minutes caused "unmotivated laughing ("mirth"), intermittent stinging headaches, and dizziness. After exposure: severe, persisting headaches, congestion at night, and feeling dazed next day."
- Concentrations of 1,100 - 1,190 ppm for up to 2 hours caused "immediate feeling of pressure in the head, dizziness, nausea, vertigo, increased pulse, intense headaches, skin of face feeling hot; increased pulse rate, tingling and paresthesia in arms."
- Concentrations of 1,850 - 2,140 ppm for 1 hour caused persistent headaches after end of exposure, "rapidly developing headache, pressure in the head, feeling of heat in the face, irritation of pharynx progressing to cough, nausea; persistent hiccups; anxiety, increased pulse, increasing dizziness, beginning central paralysis, mental capabilities highly impaired, difficulty performing tasks. After end of exposure: persistent headaches, staggered gait, strong dazed feeling, sudden salivation with increased pulse, vomiting, headaches persisting until next morning, disturbed sleep, and two days of feeling ill."
- Concentrations of 2,180 ppm to above 3,000 ppm for more than 30 minutes caused "strong dizziness, nausea, semi-narcotic state, tingling, shallow, irregular respiration with deep gasping. After exposure: leg muscle aches, feeling nervous and upset, intermittent headaches for 12 days."

In humans, acute exposure to lower concentrations of CS_2 that do not cause notable CNS effects ($\leq$ 80 ppm) cause 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). Section 3.1.2.1 provides a review of available human studies on these effects. 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, and concomitant exposure to other chemicals) prevent their use in the development of ReVs. CS_2 has been identified as a reproductive and developmental toxicant in animals. The lowest LOAEL identified in an animal reproductive/developmental toxicity study was 400 ppm and occurred in the presence of maternal toxicity. Section 3.1.2.2 provides a review of available reproductive and developmental toxicity studies in humans and animals.

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. A summary of chemical and physical properties of CS_2 are presented in Table 3.

3.1.2 Key and Supporting Studies

Well-conducted human studies demonstrate the acute effect of CS_2 inhalation on alcohol (ethanol) metabolism and xenobiotic biotransformation reactions. Since these studies demonstrate effects at concentrations below those that cause other adverse effects, they are used as key and supporting studies from which a human equivalent point of departure was derived. A human equivalent point of departure was also derived based on information obtained from animal developmental/reproductive studies. TCEQ developed acute ReV and ESL values based on the lowest, most protective human equivalent point of departure.

3.1.2.1 Human Studies

TCEQ identified three human experimental studies conducted by Mack et al. (1974), Freundt and Lieberwirth (1974), and Freundt et al. (1976a) as key and supporting studies for the acute evaluation of CS_2 that are summarized in Table 4. TCEQ identified additional human studies but they were not used due to poor study quality or the inability to verify study details, as in the case of Lehman (1894).

3.1.2.1.1 Key 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 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 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 dose-response effect was observed after 1 h of exposure. One hour 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 estimates from 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.

The observed increase in acetaldehyde levels in Freundt et al. (1976a) (up to slightly more than twice control levels) occurred without any noticeable alcohol intolerance effect in alcoholized participants (i.e., flushing, hypotension, nausea, and tachycardia). Available literature on the medication disulfram, a drug sometimes given as treatment for alcoholism, suggests that a blood acetaldehyde level of 5 to 10 times the normal level causes an alcohol intolerance effect in individuals. The resulting irritating flushing reaction along with accelerated heart rate, shortness of breath, throbbing headache, mental confusion and blurred vision is intended to discourage alcoholics from drinking. Assuming that a 5-10 fold increase in acetaldehyde levels can cause an "adverse" reaction, concentrations higher than 80 ppm would be expected to elicit this type of response in alcoholized individuals. In fact, alcohol intolerance has been reported to occur in German workers exposed to CS_2 (most likely higher concentrations than used in Freundt et al. 1976a) and 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). CS_2 is a metabolite of disulfram and may be responsible for some of the effects elicited by disulfram (Peachey et al. 1981). 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, TCEQ believes it is appropriate to consider increased blood acetaldehyde levels and potential alcohol intolerance induced by CS_2 exposure to be a relevant endpoint for toxicity factor development.

Based on information obtained in the literature and guidance in ATSDR (2007), the TCEQ determined that the increase in blood acetaldehyde levels seen after acute exposure to 80 ppm CS_2 for 1 hour was not an adverse effect in this study and was therefore selected as the no-observed-adverse-effect-level (NOAEL). 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 NOAEL of 80 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 Study (Freundt and Lieberwirth 1974)

Because the study was only available in German, details were obtained directly from NRC (2009). Eleven healthy male volunteers, 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). No details on participant alcohol consumption were 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 levels of subjects were 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 in 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 exposed to 20 ppm CS_2 for 8 h without alcohol intake showed a non-significant 30% decrease in blood glucose after exposure. When this group received alcohol, 16-24 h after CS_2 exposure, a 108% increase in serum total bilirubin and slight but not statistically significant increases in serum albumin, total protein, uric acid, and alkaline phosphatase were observed.

A NOAEL of 80 ppm for an 8 hour exposure was identified in this study due to lack of clear adverse effects at the exposure concentrations tested, although information from this study adds to the weight of evidence that CS_2 exposure significantly affects blood chemistry and liver function in a dose-dependent manner at concentrations as low as 20 ppm.

3.1.2.1.3 Supporting Study (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, 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 3 h 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 3 h 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), there are uncertainties in actual percent changes in free AAP levels observed at each exposure concentration and time interval. There were also no data showing any morphologic or clinical changes associated with the inhibition of Phase I biotransformation of amidopyrine, all of which prevented TCEQ from determining whether the observed effect was truly adverse. Therefore, 80 ppm for a 3 h exposure was identified as a NOAEL in the Mack et al. (1974) study because a LOAEL could not be clearly identified and substantiated. Results of the Mack et al. (1974) study add to the weight of evidence that CS_2 can significantly inhibit enzyme activity at all concentrations tested (10 ppm to 80 ppm).

Table 4. Key and Supporting Human Acute Inhalation Studies Used to Derive the POD_{HEC}

Exposure Group	Concentration (ppm) and Duration (h)	NOAEL	LOAEL	Observed Effects	Reference
12 healthy male volunteers, ages 20-32 years	0, 20, 40, or 80 ppm; 8 h total; blood samples collected at 1 h intervals	80 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 total	80 ppm	---	Statistically significant decrease in blood glucose and significant rise of serum total bilirubin in alcoholized subjects	Freundt and Lieberwirth (1974)
19 healthy male volunteers, ages 21-40 years	0, 10, 20, 40, or 80 ppm; 6 h total; urine samples collected at 3 h intervals	80 ppm	---	Inhibition of Phase I microsomal drug biotransformation	Mack et al. (1974)

[a] The NOAEL of 80 ppm identified in Freundt et al. (1976a) for a 1 h exposure duration was used as the point-of-departure (POD) to derive a POD_{HEC}. Supporting studies were Freundt and Lieberwirth (1974) and Mack et al. (1974), both with a NOAEL of 80 ppm, but for durations longer than 1 h.

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, and 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). Table 5 summarizes some of the available, more reliable animal studies that evaluate the developmental and reproductive toxicity of CS_2.

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 postnatal day 21. The study did not give details on any changes (if any) in food consumption. Maternal toxicity (reduced maternal weight gain) and reduced fetal

body weight were observed at 400 and 800 ppm. No effects were observed on implantation, resorption, fetus survival/number, 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 clubfoot 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 (19% reduction in maternal weight gain) and 5%-6% 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 days 0-21 or 7-21 (rabbits). Unexposed control animals were included for both pregestational and gestational 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 reduction 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 gestational 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, a decrease in the 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 gestational day 19. The mothers were allowed to deliver and

both mothers and pups were observed through postnatal day 21. 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 and a LOAEL of 500 ppm for maternal toxicity, reproductive, and developmental effects were 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 a decrease in ejaculation latency, a decrease in ejaculated sperm count, and a decrease in mount latency were observed 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). This study identidied a LOAEL of 600 ppm 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. See Section 3.1.2.2.2.1 for more details.	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. See Section 3.1.2.2.2.1 for more details.	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)
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	500	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)

Animal Strain	Concentration (ppm) and Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Critical Effect	Reference
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 also been shown to be absorbed by the skin in humans (NRC 2009). In both humans and animals, the lungs mainly excrete unmetabolized CS2 while most of the absorbed CS_2 is metabolized and eliminated in the form of different metabolites through the kidneys (NRC 2009).

3.1.3.3 MOA for Inhibition of Ethanol Metabolism and Phase I Xenobiotic Biotransformation

The reactive sulfur generated by CYP450 metabolism of CS_2 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). Ethanol is oxidatively metabolized by two pathways in the liver, 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 the 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 that results in the synthesis of ALDH2(2), 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 (about 5 - 7 times the level of acetaldehyde produced in those with normal ALDH2 genes after moderate alcohol consumption (Enomoto et al. 1991)). 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.

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 xenobiotics (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. TCEQ 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, inhibition of xenobiotic transformation, statistically significant decrease in blood glucose and significant rise of serum total bilirubin in alcoholized subjects, 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.

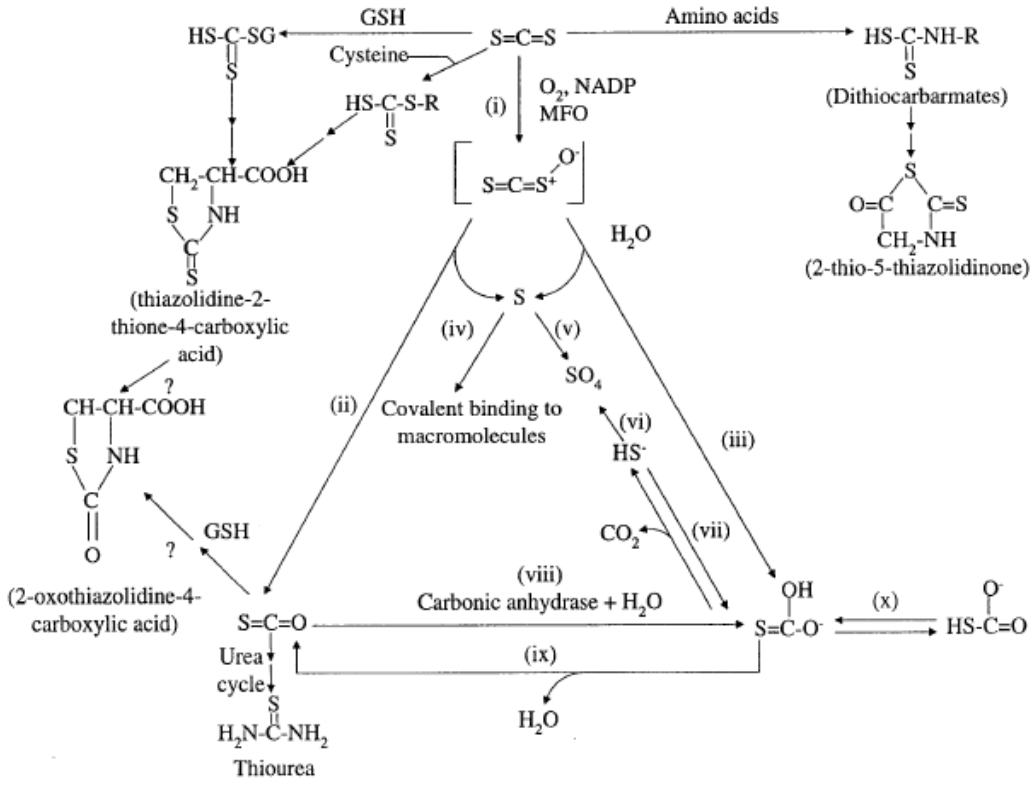

Figure 1. Proposed Metabolic Pathways for Carbon Disulfide (Figure 2-3 from ATSDR 1996)

3.1.5 PODs for Key Studies and Dosimetric Adjustments

The POD identified in Freundt et al. (1976a) was 80 ppm for a 1 h exposure duration, supported by Mack et al. (1974) and Freundt and Lieberwirth (1974), and was used to derive a POD_{HEC} based on significantly increased blood acetaldehyde levels resulting from inhibition of ethanol metabolism in the absence of adverse clinical or functional impairment.

In the developmental study conducted by Saillenfait et al. (1989) in rats, significant reductions in maternal body weight gain (19%) and fetal body weight (5% to 6%) were observed at 400 ppm but no adverse effects were observed at 200 ppm. TCEQ 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). A higher NOAEL of 250 ppm was identified in studies conducted by WIL Research Laboratories, Inc. (1992) and Nemec et al. (1993); however, the studies identified a higher LOAEL and were conducted in a different strain of rat than the Saillenfait et al. (1989) study.

3.1.5.1 Freundt et al. (1976a)

Freundt et al. (1976a) was a human study; therefore, no animal-to-human adjustment was necessary. The POD from the Freundt et al. (1976a) study was based on a 1 h exposure duration; therefore, adjustment to a 1 hour duration was not necessary and the POD_{HEC} was 80 ppm.

POD_{HEC} = 80 ppm

3.1.5.2 Saillenfait et al. (1989)

The POD from Saillenfait et al. (1989) was based on effects observed in animals; therefore, an animal-to-human adjustment was necessary. The critical adverse effects caused by CS_2 are systemic effects and CS_2 was treated as a Category 3 gas (TCEQ 2012). For Category 3 gases, the default dosimetric adjustment from an animal concentration to a POD_{HEC} was 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 was 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 was 200 ppm:

$$POD_{HEC} = POD_{ADJ} \times RGDR$$
$$= 200 \text{ ppm} \times 1$$
$$= 200 \text{ ppm}$$

The POD from the Saillenfait et al. (1989) study was based on a NOAEL (absence of maternal toxicity and reduced fetal body weight) from a developmental study; therefore, no exposure duration adjustment was necessary according to TCEQ Guidelines (2012) due to potential sensitive windows of exposure.

3.1.6 Selection of the Critical Effect

The TCEQ identifies the relevant, adverse health effect observed at the lowest POD_{HEC} in appropriate sensitive (i.e., human relevant) species as the critical adverse effect (TCEQ 2012). Thus, POD_{HEC}s corresponding to effect levels (e.g., LOAELs, BMCs) are needed to make direct comparisons in order to identify the critical effect. Comparing NOAEL-type PODs or PODs that are incomparable in regard to the occurrence of effects (e.g., NOAEL-based versus LOAEL-

based POD_{HEC} values) cannot generally be relied upon to be informative regarding the first effect that may be expected to occur as concentrations rise (i.e., the critical effect).

The POD_{HEC} corresponding to an effect level could not be determined from the Fruendt et al. (1976a) study. The 80 ppm dose level from Freundt et al. (1976a) was identified as a NOAEL and was used as the POD to derive a POD_{HEC} of 80 ppm. The POD_{HEC} corresponding to an effect level from the Saillenfait et al. (1989) study was 400 ppm for a 6 h exposure duration.

Since the POD_{HEC} of 80 ppm derived using the POD from the Freundt et al. (1976a) study was lower than the POD_{HEC} of 200 ppm derived using the POD from the Saillenfait et al. (1989) study, the Freundt et al. (1976a) study 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 because the endpoint used for the POD was based on a NOAEL. 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 80 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, women).

- 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 available 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) was not used because the POD_{HEC} of 80 ppm from Freundt et al. (1976a) was considered a NOAEL 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 10 was applied to the POD_{HEC} of 80 ppm to derive the acute ReV of 8.0 ppm (rounded to two significant figures).

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D \times UF_L)$$
$$= 80 \text{ ppm} / (10 \times 1 \times 1)$$
$$= 80 \text{ ppm} / 10$$
$$= 8.0 \text{ ppm}$$

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

The acute ReV of 8,000 ppb (25,000 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

2,400 ppb (7,500 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}	80 ppm, free-standing NOAEL
Critical Effects	POD based on a free-standing NOAEL. Effects observed were an increase in blood acetaldehyde levels in humans with moderate intake of alcohol (0.075% blood alcohol level) without adverse functional or clinical impairment.
Exposure Duration	1 h
POD_{HEC}	80 ppm
Total UFs	10
Interspecies UF	Not Applicable
Intraspecies UF	10
LOAEL UF	1
Incomplete Database UF *Database Quality*	1 High
acute ReV [1 h] (HQ = 1)	**8,000 ppb (25,000 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**2,400 ppb (7,500 µg/m^3)**

3.1.9 Comparison of Acute ReV to Other Acute Regulatory Values

The acute ReV is slightly higher 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). Had the TCEQ chosen the POD_{HEC} of 200 ppm from the Saillenfait et al. (1989) study to derive the acute ReV, the acute ReV would have been 6.7 ppm for a 6 h exposure duration (using a total of 30 for UFs), which is similar to the acute ReV of 8 ppm for a 1 hour exposure duration.

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Pure CS_2 has a sweet, pleasant, ethereal odor. According to TCEQ (2015b), an odor-based ESL was not developed.

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. Seed germination of wheat seeds of the Giza variety with a 9% moisture content was slightly impaired at all concentrations tested. The reduction of germinated seeds was about 9% at the 12% moisture content, with further reductions in germination rate with increasing CS_2 concentrations. At the 15% moisture content level, the reduction in seed germination was much more severe. Wheat seeds with a moisture content of 15% suffered a 28% reduction in germination when exposed to CS_2 at 200 cc/m^3 for 24 h, a 41% reduction at 300 cc/m^3, and a 65% reduction at 400 cc/m^3.

- 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.

Of the available acute studies on vegetation effects of CS_2, only Kamel et al. (1975) reported adverse effects. According to TCEQ Guidelines (2012), the vegetation-based ESL should be set at the lowest-observed-effect-level (LOEL). The LOEL reported in Kamel et al. (1975) was 200 cc/m^3 (2.52E5 mg/m^3) for reduction in germination of wheat seeds with a 9-15% moisture content. Since the concentration that produced adverse effects on seed germination (2.52E5 mg/m^3) is hundreds of times higher than concentrations known to cause adverse effects in humans, a vegetation-based ESL was not derived.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

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

- acute ReV = 8,000 ppb (25,000 µg/m^3)
- ^{acute}ESL = 2,400 ppb (7,500 µg/m^3)

For the evaluation of ambient air monitoring data, the acute ReV of 8,000 ppb (25,000 µg/m^3) is used. The short-term ESL for air permit evaluations is the ^{acute}ESL = 2,400 ppb (7,500 µg/m^3) (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data but will be used in air permitting applications.

3.4 Acute Inhalation Observed Adverse Effect Level

Details from a human study cited in NRC (2009) suggest acute exposure to concentrations of CS_2 above 240 ppm can cause CNS effects as well as respiratory tract irritation; however, these data were not considered reliable and were not used for toxicity factor development. Reliable data were not available to determine the $LOAEL_{HEC}$ for increased blood acetaldehyde levels in humans with moderate intake of alcohol; therefore, an acute inhalation observed adverse effect level was not developed.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

A comprehensive literature search 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) were 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 the resulting adverse health effects have been well characterized. Chronic exposure can cause neurophysiological and neuropathological changes (e.g., decreased peripheral nerve conduction velocity in motor and sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes).

In some studies, chronic exposure to CS_2 in workers has also been associated with cardiovascular effects, including electrocardiographic (ECG) abnormalities (Bortkiewicz et al. 2001, Chang et al. 2006), increased serum low-density lipoprotein (LDL) cholesterol, and decreased serum high-density lipoprotein (HDL) cholesterol concentrations (Stanosz et al. 1994, Kotseva et al. 2001a), albeit at high exposure concentrations and with potential confounders. Other observed

associations include increased triglyceride plasma levels (Luo et al. 2003), development of atherosclerosis, increased risk of coronary heart disease (CHD) (Wronska-Nofer et al. 2002), and increased risk of mortality from ischemic heart disease (IHD) (Peplonska et al. 1996). Other recent studies on cardiovascular effects have shown weak associations or inconclusive results (Sulsky et al. 2002, Tan et al. 2002, Braeckman et al. 2001, Kotseva et al. 2001b, Korinth et al. 2003, Omae et al. 1998, and Price et al. 1997). Given the conflicting evidence in the literature, the TCEQ chose not to consider cardiovascular effects as a potential critical effect for derivation of the chronic ReV.

Other adverse effects caused by chronic CS_2 exposure including reproductive, ophthalmologic, and renal effects, 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 and EG2.

- Participants in EG1 (n=60) were exposed to < 31 mg/m^3 (10 ppm). The average yearly exposure was 8.9 $mg/m^3 \pm 1.1$ (2.84 ppm).

- Participants in EG2 (n=25) were exposed to > 31 mg/m^3 (10 ppm). The average yearly exposure was 59.2 $mg/m^3 \pm 5.2$ (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. In addition, 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 (details of how alcohol abuse was defined were not reported in 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. 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 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 and, EG2 to 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 sensory nerve 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).

Results indicate an effect of CS_2 on various neurotoxicity endpoints. Because results showed that subclinical and clinical effects occurred in individuals exposed to less than the TLV, Godderis et al. (2006) attempted a better prediction of the no-observed-effects-level (NOEL) by re-doing the ANOVA and 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…" 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 TCEQ 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 of 2.84 ppm (8.9 mg/m^3)) as the POD.

A LOAEL of 2.84 ppm (8.9 mg/m^3) 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, 2.84 ppm (8.9 mg/m^3) 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). Benchmark dose modeling was not conducted because only two exposure groups were evaluated (EG1 and EG2).

Table 7. Statistically Significant Peripheral Nerve Conduction Velocity Results[a]

Nerve Conduction Velocity	Geometrical Mean (Standard Error)				Unit	P (t-test) for Total Exposed Compared to Controls
	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**, 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 (2.84 ppm) and a cumulative exposure index of 59.5 years* mg/m^3 ± 17.1

[b] EG2 had an average yearly exposure of 59.2 mg/m^3 ± 5.2 (18.9 ppm) and a cumulative exposure index of 746.6 years* mg/m^3 ± 116.1

Table 8. Results of ANCOVA (p≤0.03) on Nerve Conduction Velocity Studies[b]

Nerve Conduction Velocity	Contrast Estimate (Standard Error)	
	EG1 (n=60) < 10 ppm	EG2 (n=25) > 10 ppm
Log (sural nerve SNAP amplitude)[a]	–0.36 (0.09)	–0.41(0.13)
Log (sural nerve SCV)	–0.13 (0.05)	–0.18 (0.07)
Log (sural SNAP duration)	0.29 (0.08)	0.29 (0.12)
Log (SSR amplitude)	–0.42 (0.13)	–0.481 (0.19)

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

[a] Contrast estimates were adjusted for race and were significant at the p≤0.05 level.

[a] Adapted from Table 5 in Godderis et al. (2006)
[b] Adapted from Table 6 in Godderis et al. (2006)

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.

The following agencies used the Johnson et al. (1983) study to develop risk levels:

- USEPA (1995) for the Inhalation Reference Concentration (RfC)
- ATSDR (1996) for the chronic Minimal Risk Level (MRL)
- OEHHA (2001) for the chronic REL
- Health Canada (2000) for Tolerable Concentration (TC)

The Godderis et al. (2006) study used by the TCEQ 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) and compared them 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 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. Axonal degeneration that underlies the neuropathy caused by CS_2 has been postulated to be 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 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 to be a LOAEL for mild neurotoxic effects.

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 (default 10 m^3/day)
VE_h = default non-occupational ventilation rate for a 24-hour day (default 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 (minimal LOAEL?). This effect is assumed to have a threshold effect. 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 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 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 9).

Table 9 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 Levels from Other Agencies

Table 10 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 10. 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 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_{OC} of 2.84 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 similar effects could probably 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 inter-individual differences in sensitivity. The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

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