Development Support Document
Final, December 18, 2013
Revised Odor Value, September 1, 2015

Acetone

CAS Registry Number: 67-64-1

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on December 18, 2013.

Revised DSD September 1, 2015: the odor-based value was withdrawn because acetone does not have a pungent, disagreeable odor (TCEQ 2015).

TABLE OF CONTENTS

REVISION HISTORY ..... **I**
TABLE OF CONTENTS ..... **II**
LIST OF TABLES ..... **III**
LIST OF FIGURES ..... **III**
ACRONYMS AND ABBREVIATIONS ..... **IV**
CHAPTER 1 SUMMARY TABLES **1**
CHAPTER 2 MAJOR SOURCES, USES, AND ENDOGENOUS PRODUCTION **4**
CHAPTER 3 ACUTE EVALUATION **5**
3.1 HEALTH-BASED ACUTE REV AND ^{ACUTE}ESL 5
3.1.1 Physical/Chemical Properties *5*
3.1.2 Key and Supporting Studies *5*
3.1.2.1 Irritation 5
Stewart et al. (1975) 5
Nelson et al. (1943) 6
Matsushita et al. (1969a,b) 7
3.1.2.2 Neurobehavioral Effects 8
Key Study 8
Dick et al. (1989) 8
Supporting Studies 10
Matsushita et al. (1969a,b) 10
Seeber et al. (1991, 1992, 1993) 10
Animal Studies 11
3.1.2.3 Consideration of Developmental/Reproductive Effects 11
3.1.3 Critical Effect *12*
3.1.4 Metabolism *12*
3.1.5 Mode-of-Action (MOA) and Dose Metric *14*
3.1.6 Point of Departure (POD) for Key Study *15*
3.1.7 Dosimetric Adjustments *15*
3.1.7.1 Default Exposure Duration Adjustments 15
3.1.7.2 Adjustments of the POD_{HEC} 15
3.1.8 Health-Based Acute ReV and ^{acute}ESL *16*
3.1.9 Comparison of TCEQ's Acute ReV to ATSDR's Acute Inhalation MRL *17*
3.2. WELFARE-BASED ACUTE ESLS 17
3.2.1 Odor Perception *17*
3.2.2 Vegetation Effects *18*
3.3. SHORT-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION 18
3.4 ACUTE INHALATION OBSERVED ADVERSE EFFECT LEVELS (OAELS) 18
CHAPTER 4 CHRONIC EVALUATION **18**
4.1 NONCARCINOGENIC POTENTIAL 18
4.1.1 Physical/Chemical Properties and Key Study *19*
4.1.1.1 Physical/Chemical Properties 19

4.1.1.2 Neurological 19
Key Study 19
Satoh et al. (1996) 19
Supporting Studies 21
Stewart et al. (1975) 21
Mitran et al. (1997) 21
4.1.2 Critical Effect, MOA, and Dose Metric *22*
4.1.3 POD for the Key Study *23*
4.1.4 Dosimetric Adjustments *23*
4.1.4.1 Default Exposure Duration Adjustments 23
4.1.4.2 Adjustment of the POD_{HEC} 23
4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ *24*
4.1.6 Comparison of TCEQ's Chronic ReV to ATSDR's Chronic Inhalation MRL *25*
4.2 CARCINOGENIC POTENTIAL 26
4.3 WELFARE-BASED CHRONIC ESL 26
4.4 LONG-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION 26
4.5 CHRONIC INHALATION OAEL 26

CHAPTER 5 REFERENCES 27

5.1 REFERENCES CITED IN THE DEVELOPMENT SUPPORT DOCUMENT 27
5.2 OTHER STUDIES AND DOCUMENTS REVIEWED 30

LIST OF TABLES

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air 1
Table 2. Air Permitting Effects Screening Levels (ESLs) 2
Table 3. Chemical and Physical Data 3
Table 4. Derivation of the Acute ReV and $^{acute}ESL$ 17
Table 5. Odor Studies Conducted for Acetone 18
Table 6. Derivation of the Chronic ReV and $^{chronic}ESL$ 25

LIST OF FIGURES

Figure 1: Pathways for the Metabolism of Acetone 13

Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
A	animals
AEGL	Acute Exposure Guideline Level
AMCV	Air Monitoring Comparison Value
°C	degrees Celsius
CNS	central nervous system
DSD	Development Support Document
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
$^{chronic}ESL_{nonthreshold(c)}$	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
$^{chronic}ESL_{threshold(c)}$	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
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
F	exposure frequency, days per week
h	hour
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

Acronyms and Abbreviations	Definitions
Hg	mercury
HEC	human equivalent concentration
HQ	hazard quotient
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
n	number
N/A	not applicable
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
ReV	reference value
RGDR	regional gas dose ratio
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	intraspecies human uncertainty factor

Acronyms and Abbreviations	Definitions
UF_A	animal to human 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

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values resulting from an acute and chronic evaluation of acetone. Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on acetone's physical/chemical properties.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV	26,000 µg/m^3 (11,000 ppb) **Short-Term Health**	**Critical Effect(s):** Primarily neurobehavioral effects, secondarily sensory irritation in human volunteers
$^{acute}ESL_{odor}$	- - -	Aromatic; sweet and sharp described as neutral to unpleasant
$^{acute}ESL_{veg}$	- - -	Insufficient data
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	16,000 µg/m^3 (6,700 ppb) **Long-Term Health**	**Critical Effect(s):** Neurotoxic effects in humans
$^{chronic}ESL_{threshold(c)}$ $^{chronic}ESL_{nonhreshold(c)}$	- - -	Data are inadequate for an assessment of the human carcinogenic potential
$^{chronic}ESL_{veg}$	- - -	No data found

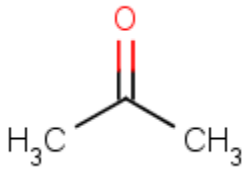
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	7,800 µg/m^3 (3,300 ppb) [a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Primarily neurobehavioral effects, secondarily sensory irritation in human volunteers
$^{acute}ESL_{odor}$	---	Aromatic; sweet and sharp described as neutral to unpleasant
$^{acute}ESL_{veg}$		Insufficient data
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	4,800 µg/m^3 (2,000 ppb) [b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Neurotoxic effects in humans
$^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data are inadequate for an assessment of the human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 26,000 µg/m^3 (11,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 16,000 µg/m^3 (6,700 ppb) multiplied by 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	CH_3COCH_3	ACGIH 2001
Chemical Structure		HSDB 2011
Molecular Weight	58.08	ACGIH 2001
Physical State at 20°C	Liquid	TRRP 2012
Color	Colorless	ACGIH 2001
Odor	aromatic	ACGIH 2001
CAS Registry Number	67-64-1	ACGIH 2001
Synonyms	2- Propanone; Dimethyl ketone; Dimethylformaldehyde; Ketone propane; Methyl ketone	ChemID Plus 2011
Solubility in water	1.00E+06 mg/L	ChemID Plus 2011
Log K_{ow}	0.24	TRRP 2012
Vapor Pressure	232 mm Hg at 25°C	ChemID Plus 2011
Relative Vapor Density (air = 1)	2	IPCS 2009
Melting Point	-95°C	ACGIH 2001
Boiling Point	56°C	ACGIH 2001
Conversion Factors	1 $\mu g/m^3$ = 0.42 ppb 1 ppb = 2.38 $\mu g/m^3$	ACGIH 2001

Chapter 2 Major Sources, Uses, and Endogenous Production

Acetone is found naturally in the environment from plants, trees, volcanic gases, and forest fires. It is also produced industrially to manufacture other chemicals that make plastics, fibers, and drugs, or used to dissolve other substances. Acetone is released into the environment during its production and use, in exhaust from automobiles, from tobacco smoke, landfills, and certain kinds of burning waste materials (ATSDR 1994). Additional information about the sources, distribution, and fate of acetone in the ambient environment can be found elsewhere (e.g., OECD 1999, ATSDR 1994, Singh et al. 1994). In regard to acetone ambient air levels in Texas, 2008-2011 TCEQ data for three sites in Region 12, for example, show the following: 24-h sample average of 0.40 ppb with a maximum of 2.4 ppb, 3-h sample average of 0.71 ppb with a maximum of 6.2 ppb, and an average of 1.8 ppb with a maximum of 4.8 ppb for available but limited 1-h data.

The following background information on endogenous production was taken from ATSDR (1994) and the American Chemistry Council Acetone Panel (2003), which should be referred to for the cited references.

The body normally contains some acetone because it is made during the breakdown of fat. The liver breaks down acetone to chemicals that are not harmful. The body uses these chemicals to make glucose (sugar) and fats that make energy for normal body functions. The breakdown of sugar for energy makes carbon dioxide that leaves your body in the air you breathe out. Acetone is one of three ketones that occur naturally in the human body. The production of ketone bodies occurs mostly inside the liver, and to a smaller extent in the lung and kidney under normal conditions (Gavin et al. 1987, Le Baron 1982, Vance 1984). Used as a source of energy, the three products are excreted into the blood and transported to all tissues and organs of the body. Depending on various factors (such as infancy, pregnancy, lactation, diabetes, physical exercise, dieting, physical trauma, and alcohol consumption), levels of endogenous acetone in breath, blood, and urine can fluctuate greatly. Endogenous levels of acetone in the human breath normally average around 560 ppb (Phillips and Greenberg 1987). In healthy men who had fasted for 12 h, the breath acetone levels ranged from 0.96 to 1.7 ppm (Jones 1987). Blood levels of acetone as high as 140 mg/L are commonly observed in post-partum infants (Peden 1964). Because endogenous acetone formation is so closely linked with the utilization of stored fats as a source of energy, background levels can fluctuate depending on an individual's health, nutrition, and level of activity (Morgott 1993). The normal plasma concentration of acetone is around 10 mg/L for adult human beings, with large fluctuations occurring in response to an individual’s energy needs (Teitz 1983). Thus, the human body is capable of rapidly producing and eliminating acetone in large amounts (2,000-3,000 mg/day) without adverse health effects. Due to their higher energy expenditure, infants and young children typically have higher acetone blood levels than adults (Peden 1964). Vigorous exercise, dieting, pregnancy, and lactation can also lead to normal fluctuations in the blood levels of acetone without any ill effect (Williamson and Whitelaw 1978, Walther and Neumann 1969).

Chapter 3 Acute Evaluation

The Development Support Document (DSD) is a summary of the key and supporting studies and procedures used by the Toxicology Division (TD) to derive inhalation toxicity values. This section is based on a review of current literature as well as background readings in AEGL (2005) and ATSDR (1994, 2011) which describe in detail the acute toxicity of acetone.

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

The acute toxicity of acetone is relatively low. Following inhalation exposure to sufficiently high concentrations of acetone, the primary effects in humans are sensory irritation and neurological effects (AEGL 2005, Satoh et al. 1996). That is, the critical effects of acetone are considered to be irritation of mucous membranes and neurobehavioral effects (EU 1997). Human data on acute inhalation exposure are available and preferred over animal data for derivation of a health-based, acute reference value (ReV) and effects screening level (ESL) (TCEQ 2012).

3.1.1 Physical/Chemical Properties

Acetone is a colorless liquid with a distinct smell and taste. Acetone evaporates readily into the air and mixes well with water. Other physical/chemical properties of acetone can be found in Table 3.

3.1.2 Key and Supporting Studies

Human volunteer studies provide short-term points of departure (PODs) for consideration in deriving the acute ReV. These human studies involve exposures to 100-1,000 parts per million (ppm) acetone for durations from approximately 5 minutes to 8 h. Although additional details are provided below, briefly, the lowest potential lowest-observed-adverse-effect-level (LOAEL) for irritation from short-term acetone exposure is around 250-300 ppm (Nelson et al. 1943, Matsushita et al. 1969a,b), with a no-observed-adverse-effect-level (NOAEL) of approximately 200 ppm (Stewart et al. 1975). The lowest potential human LOAEL identified for neurobehavioral effects is slightly lower (227 ppm based on Dick et al. 1989), and will ultimately be used as the lowest POD human equivalent concentration (POD_{HEC}) to identify the critical effect (TCEQ 2012).

3.1.2.1 Irritation

Stewart et al. (1975)

As mentioned above, this study provides the basis for the irritation NOAEL-based POD of 200 ppm. Healthy adult male and female volunteers were exposed to acetone vapor in a controlled environment chamber using exposure schemes designed to simulate exposures encountered in the industrial setting. Exposures consisted of steady, non-fluctuating vapor concentrations in addition to widely fluctuating vapor concentrations of acetone. Four male subjects (age 22-27 years) per group were exposed for either 3 or 7.5 h/day, 4 days/week, to progressively higher acetone concentrations for four weeks (i.e., 0 ppm for week 1, 200 ppm for week 2, 1,000 ppm

for week 3, 1,250 ppm for week 4). The first day of each week was an additional control exposure to 0 ppm. Female subjects (age 18-25 years) were exposed in groups of 2 to 1,000 ppm for 1 h and in groups of 3-4 to 0 or 1,000 ppm for 3 and 7.5 h/day, 4 days/week, for 1 week. As with the males, the first day of each week was an additional control exposure to 0 ppm (AEGL 2005).

A complete medical and physical examination was given to all subjects at the beginning and end of the study. Blood pressure, temperature, subjective responses, clinical signs and symptoms, and urinalysis were recorded daily. Alveolar breath analysis was performed at 0, 0.25, 0.5, 1, 2, and 3 h following exposures. Shortly before ending each weekly exposure session, cardiopulmonary testing was conducted. After four days of exposure to 1,000 ppm (7.5 h/day), 3 of 4 females reported to have regular menstrual cycles experienced an early menstrual period (≥1 week early). At various times throughout the exposures, a battery of neurophysiological and neurobehavioral tests was performed. An increase in visual evoked response (VER) was clearly exposure-related and occurred in 1 of 4 males exposed to 1,000 ppm and 3 of 4 males exposed to 1,250 ppm (7.5 h), although no such effects occurred in females exposed to 1,000 ppm (Stewart et al. 1975). Thus, after the fourth week of exposure to progressively higher acetone concentrations, 1,250 ppm serves as the clearest LOAEL for neurological effects based on results reported for this study (data not amenable to benchmark dose modeling).

Additionally, subjects were asked to report subjective responses which occurred during exposure (e.g., mild, moderate, or strong, eye, nose, throat irritation, headache, dizziness, etc.). The following number of subjects reported subjective symptoms in the groups exposed at 0, 200, 1,000, and 1,250 ppm: complaints of throat irritation 1/0/3/3; eye irritation 2/2/3/3; headache 1/1/0/0, dizziness 0/2/0/0, and tiredness 0/2/3/0. More complaints of throat and eye irritation occurred in the 1,000 and 1,250 ppm groups, but this was not the case for the 200 ppm exposure group. Irritation was not reported to increase with increasing exposure duration from 3- to 7.5-h of exposure. At 200 ppm, subjective symptoms (eye/throat irritation) were not reported more often than in controls (AEGL 2005). Thus, this study provides a 3- to 7.5-h NOAEL of 200 ppm for sensory irritation effects. While complaints of throat and eye irritation were increased at concentrations ≈5-6 times the NOAEL in this study (1,000-1,250 ppm due to dose spacing), other short-term studies provide potential LOAELs for irritation at only slightly higher acetone concentrations (≥ 250-300 ppm) and thus help put the margin between the study NOAEL and irritation LOAELs into better perspective. That is, Nelson et al. (1943) and Matsushita et al. (1969a,b) provide context for the irritation NOAEL based on the Stewart et al. (1975) study.

Nelson et al. (1943)

An average number of 10 male and female subjects were exposed in a chamber to nominal vapor concentrations of 200, 300, or 500 ppm of acetone for 3-5 minutes. The subjects rated the subjective effect of exposure on eyes, nose, and throat and rated the odor strength (if any) in a post-exposure self-classification. Additionally, each subject was asked if based on their experience they believed they could work for 8 h at the given exposure concentration. Slight irritation was noted at an irritation LOAEL for this study of 300 ppm. Exposure to 500 ppm led

to eye, nose and throat irritation in the majority of exposed (data not amenable to benchmark dose modeling). The highest concentration the majority of subjects estimated as satisfactory for an 8-h exposure based on the 3-5 minute exposure was 200 ppm (Nelson et al. 1943). The irritation LOAEL of 300 ppm and highest estimated satisfactory concentration of 200 ppm from this study support and provide additional dose-response context for the irritation NOAEL of 200 ppm from Stewart et al. (1975).

Matsushita et al. (1969a,b)

These studies provide supporting LOAELs for both irritation and neurological effects. These studies may be best suited for use as supporting studies since they were published in Japanese and TCEQ has had to rely on summaries (Matsushita 1969a) and a translated version (Matsushita 1969b) which can be difficult to clearly interpret and some details are lacking (e.g., more detailed data tables, various study design details).

In Matsushita et al. (1969a), groups of 5 healthy male university students around 22 years of age were exposed for 6 h (with a 45-minute break after 3 h) during one day to acetone concentrations of 0, 100, 250, 500, or 1,000 ppm. Very slight mucous membrane irritation (1-2 on a scale of 0-10 at 10-, 30-, and 90-minutes of exposure) and unpleasant odor were noted at exposure concentrations of 100 or 250 ppm. On the morning after exposure, the subjects of the 250 ppm group complained about neurobehavioral symptoms (e.g., feelings of tension, heavy eyes, lack of energy, weakness) while no such effects were reported for the 100 ppm group, suggesting a LOAEL of 250 ppm for neurological effects based on results from this study. All these effects (based on subjective ranking of up to seven symptoms by the subjects) were more pronounced at 500 or 1,000 ppm.

The score for unpleasant odor decreased with increasing exposure time indicating adaptation. At 3- and 7-h post-exposure to 500 and 1,000 ppm, a temporary decrease in the phagocytic activity of neutrophils and increases in eosinophil and leucocyte counts in peripheral blood were noted, possibly indicating an inflammatory reaction caused by the irritating effects of acetone vapor. All values were normal after 32-48 h. No significant difference was seen in hematological parameters in the volunteers exposed to 250 ppm compared with controls (AEGL 2005).

In Matsushita et al. (1969b), groups of 5 healthy male university students around 22 years of age were exposed 6 h per day (with a 45-minute break after 3 h), for 6 days, to acetone concentrations of 0, 250, or 500 ppm. Groups exposed to 250 ppm were either resting or exercising. Acetone blood and urine levels decreased to baseline levels each night for those exposed to 250 ppm but not to 500 ppm. Exposure to 500 ppm apparently significantly increased leucocyte and eosinophil counts in peripheral blood and decreased the phagocytic activity of neutrophils (p values not given). Slight mucous membrane irritation occurred at 250 ppm in both groups (exercising, resting) and was more severe at 500 ppm, similar to Matsushita et al. (1969a). While the odor of 250 ppm acetone was reported to disappear rapidly after entering the exposure chamber, complaints of irritation appeared to persist for the most part throughout the exposure to 250 ppm (in both groups), and to 500 ppm to a greater degree (see Figure 1 of the

study). Thus, taken together, the Matsushita et al. (1969a,b) studies suggest a possible LOAEL in the range of 100-250 ppm for irritation. The degree of irritation to the eyes and nose were similar, and greater than that to the throat. Nasal irritation was reported to lessen more with exposure time than that to the eyes or throat.

Simple reaction time showed statistically significant ($p < 0.01$) increases compared to controls during each day of 6-h exposure to 500 ppm, and during two days of exposure to 250 ppm ($p < 0.05$) in both groups (resting, exercising). Reaction time increases were less pronounced in the 250 ppm groups, and reaction time was found to increase during the first 3-h exposure and become nearly the same during the second 3-h exposure (unlike the 500 ppm group). Similar to Matsushita (1969a), on the morning after exposure, the subjects of the 250 and 500 ppm groups complained about neurobehavioral symptoms such as the lack of energy and heavy eyes (these complaints did not persist to the week following exposure). Thus, the Matsushita et al. (1969a,b) studies suggest a LOAEL of around 250 ppm for neurological effects (i.e., neurological symptoms, simple reaction time effects).

While the Matsushita et al. (1969a,b) studies suggest a LOAEL for irritation possibly in the range of 100-250 ppm, 250 ppm appears more plausible considering the irritation LOAELs from Stewart et al. (1975) and Nelson et al. (1943) along with the low irritation ratings (even in the presence of unpleasant odor). Other studies have reported higher free-standing LOAELs for irritation (e.g., 800 ppm for strong-very strong irritation in naïve subjects exposed for 20 minutes in Dalton et al. 1997; > 10,000 ppm for "objective" sensory irritation in a critical review by Arts et al. 2002; 1,000 ppm for complaints of mucosal irritation in volunteers in Seeber et al. 1992). Taken together these studies (i.e., Stewart et al. 1975, Nelson et al. 1943, Matsushita et al. 1969a,b) suggest that the lowest potential short-term threshold for irritation is perhaps around 250-300 ppm acetone, which is slightly higher than but supports the lowest potential LOAEL for neurobehavioral effects (227 ppm) from Dick et al. (1989) discussed below.

3.1.2.2 Neurobehavioral Effects

Key Study

Dick et al. (1989)

A total of 137 volunteers were recruited and tested for neurobehavioral performance before, during, and after a short duration (4 h) exposure to acetone at 237 ppm, methyl ethyl ketone at 186 ppm, acetone at 115 ppm with MEK at 88 ppm, or a placebo (analytical concentrations). Computer controlled performance testing took place in an environmental chamber containing four test stations. The total test regimen before, during, and after exposure lasted 10 h and 32 measures were collected. Double blind (subjects and experimenters) experimental sessions were conducted. A 2-h practice session took place on the day before the exposures during the three-day testing regimen. The exposure day was divided into four test periods lasting 2 h each. With the exception for a brief period for body burden sampling, the 4-h exposure (middle two periods) was continuous and contained two 2-h testing periods. Thirty-two measurements taken during

each 2-h test period were analyzed. These measurements were derived from four psychomotor tests (choice reaction time, visual vigilance, dual task, short term memory scanning), one neurophysiological test (eye blink reflex), and one sensorimotor test (postural sway). A psychological test (Profile of Mood States) was administered to subjects at the end of the post 7-8 h period and on the following day before the post 23-24 h period. The neurobehavioral performance tests and the postural sway test were presented simultaneously to the subjects and the order of test presentation remained the same in each test period. However, trial order within a test differed for each subject, and changed in each successive administration of the same test (Dick et al. 1989).

The 4-h exposure to 237 ppm acetone produced mild but statistically significant changes in performance from controls in two measures of the auditory tone discrimination task (part of the dual task test involving identifying 18 randomly-occurring critical tones among a series of 600), and on the anger hostility scale of the Profile of Mood States test in the men only (29% decrease, $p < 0.001$). In the auditory tone test, both response time ($p < 0.01$) and the false alarm rate ($p < 0.001$) significantly increased at 237 ppm acetone (≈11-12%), with the increased false alarm rate persisting to the post 7-8 h period. The placebo group significantly improved in false alarm rate over the course of the exposure and into the post 7-8 h period (i.e., the rate was cut in half), while false alarm rate in the acetone-exposed group was adversely affected (i.e., rose from 28% to 35%). False alarm rate exhibited some time dependence with the same statistically significant increases at both 3-4 and 5-6 h of exposure and a somewhat larger increase at 7-8 h post exposure when blood acetone levels continued to be significantly elevated, with a similar temporal pattern being observed for response time (see Table 5 of the study). Study authors attributed the increase in response time to mild neurological depression, and indicated that these effects generally paralleled (e.g., followed the rise of) blood acetone concentrations. There was some indication of acetone-induced changes on postural sway (i.e., standing steadiness measures by a computerized biomechanics system) based on relatively large differences from controls, though not statistically significant probably due to large standard deviations relative to the means. Neither MEK nor the combined acetone/MEK exposures produced statistically significant interpretable results. The combined exposure indicated that there was no potentiation of the acetone effects with the co-exposure to MEK or vice versa (Dick et al. 1989).

Examination of dual task performance measurements during the various testing periods indicates that the neurobehavioral effects observed were similar in tests conducted during the first 2 h of exposure compared to tests conducted in last 2 h of exposure. More specifically, the significantly increased false alarm rate measured in the auditory tone discrimination task during the first 2 h of exposure (30%) was identical to that during the second 2 h of exposure. Response time was also statistically increased during the first 2 h of exposure. As it appears these tests were given early on in each testing period, these results could have been obtained during the first hour of exposure. Thus, the average exposure of 227 ppm (analytical concentration) for the first 2 h of exposure may conservatively be considered a LOAEL for mild neurobehavioral effects, although it is not entirely clear whether this is for a 1- or 2-h exposure.

This 1-h/2-h LOAEL of 227 ppm for mild neurobehavioral effects based on results of this study is slightly lower than the 6-h LOAEL (250 ppm) for neurobehavioral effects suggested by Matsushita et al. (1969a,b) as discussed previously and below and the potential LOAEL for irritation from short-term acetone exposure (≈250 ppm). Thus, the free-standing LOAEL of 227 ppm from this study identifies the critical effect and the POD_{HEC} for derivation of the acute ReV and ESL.

Supporting Studies

Some additional human studies (Matsushita et al. 1969a,b, Seeber et al. 1991, 1992, 1993) and limited animal studies serve as supporting studies on the potential neurobehavioral effects of acetone, although human data are emphasized below as they are preferred for derivation of the acute ReV (TCEQ 2012).

Matsushita et al. (1969a,b)

As indicated above in the discussion of acetone-induced irritation, these studies provide a supporting LOAEL for neurological effects as well, and may be best suited for use as supporting studies since they were published in Japanese and TCEQ has had to rely on summaries (Matsushita et al. 1969a) and a translated version (Matsushita et al. 1969b) which can be difficult to clearly interpret and some details are lacking (e.g., more detailed data tables, various study design details). Again, in one study (Matsushita et al. 1969a) groups of 5 healthy male university students around 22 years of age were exposed for 6 h (with a 45-min break after 3 h) to acetone concentrations of 100, 250, 500, or 1,000 ppm, and in the other (Matsushita et al. 1969b) exposures were for the same duration to 250 and 500 ppm. To briefly summarize neurological effects specifically: on the morning after exposure, the subjects of the 250 ppm group complained about neurobehavioral symptoms (e.g., heavy eyes, lack of energy) in both studies, while no such effects were reported for the 100 ppm group in the first study (Matsushita et al. 1969a); and in the second study (Matsushita et al. 1969b) simple reaction time showed statistically significant ($p < 0.05$) increases during the first two days of exposure to 250 ppm, during the first 3-h exposure in particular. All reported effects were more pronounced at higher exposure levels (e.g., 500 or 1,000 ppm). These results suggest a supporting LOAEL of 250 ppm for neurological effects (i.e., neurobehavioral symptoms, increased reaction time) in these studies.

As discussed above, the 6-h LOAEL (250 ppm) for neurobehavioral effects based on results from the Matsushita et al. (1969a,b) studies support that based on the key study of Dick et al. (LOAEL of 227 ppm), which provides the POD_{HEC} for derivation of the acute ReV and ESL.

Seeber et al. (1991, 1992, 1993)

Documentation of the German occupational value (MAK) for acetone (DFG 1993) and a European Commission acetone document (EC 1997) were relied upon for summaries of these German studies. The Seeber et al. (1991, 1992, 1993) studies involved groups of 16 men exposed to 980-1,000 ppm for 4- or 8-h (or during the workday) to evaluate potential effects on various

neurobehavioral endpoints (i.e., simple and choice reaction time, short-term memory, color vigilance test). Increases in the number of complaints of mucosal irritation (summed values for eyes, mouth, throat and nose) were reported in the studies. Although no significant neurobehavioral performance effects were found to have a clear relationship with exposure, it is noted that ratings of well-being (feelings of unpleasantness) were adversely affected and clearly exposure related (along with irritation) in all three studies. For example, ratings of annoyance, tension, and tiredness were significantly affected. The feelings of unpleasantness correlated significantly with the amount of acetone per mg creatinine in the urine. Thus, although no reduction in neurobehavioral performance parameters was found (unlike in Dick et al. 1989), adverse effects on mood, a neurological outcome (Chou and Williams 1998), were reported (e.g., annoyance, tension) and are interpreted to lend some support for the effect on mood observed in the Profile of Mood States test in Dick et al. at a lower concentration (i.e., changes in the anger hostility scale at 227 ppm).

Animal Studies

Although the focus of this document is on relevant human data, the neurotoxicity of acetone has been documented in some supporting experimental animal studies. An increase in response time was seen for a complex operant discrimination task in juvenile baboons exposed to 500 ppm (1,210 mg/m^3) acetone for 7 days (Geller et al. 1979 as cited by EU 1997). This concentration is similar to that associated with significantly increased response time and false alarm rate in Dick et al. (227 ppm) and that associated with neurobehavioral symptoms in the Matsushita et al. studies (250 ppm). A more recent study examining place conditioning in rats exposed to 0, 5,000, 10,000, or 20,000 ppm acetone for 1 h observed a dose-response in a markedly decreased locomotor activity profile indicative of central nervous system depression (i.e., neurotoxicity) at concentrations as low as 5,000 ppm (Lee et al. 2010). Lastly, in mice exposed to a continuous series of 30-minute acetone exposure sessions at six levels increasing from 100 to 56,000 ppm (242 to 135,520 mg/m^3), decreased response rates were observed at 1,000 ppm (2,420 mg/m^3) and above (Glowa and Dews 1987 as cited by EU 1997).

3.1.2.3 Consideration of Developmental/Reproductive Effects

Human data on the potential developmental and reproductive effects of acetone are very limited and are largely not very useful due to study limitations (e.g., confounders, small numbers). For example, Stewart et al. (1975) indicated that after four days of exposure to 1,000 ppm (7.5 h/day), 3 of 4 females reported to have regular menstrual cycles experienced an early menstrual period (≥1 week early). However, useful animal data are available. NTP (1988) conducted inhalation developmental studies in rats and mice, and ATSDR (1994) provides the following summary.

> In a development study in rats exposed intermittently to acetone during gestation, the only effect was a slight, but significant ($p < 0.05$), decreased mean male and female fetal body weight at 11,000 ppm (NTP 1988). The dams exposed at this level had significantly ($p < 0.05$) reduced body weight during gestation, reduced uterine

> weight, and reduced extragestational weight on gestational day 20. No effects were seen on sex ratio, incidence of fetal variations, reduced ossification sites, or mean fetal variations. The percent of litters with at least one fetal malformation was higher in the 11,000 ppm group than in the control group, but no statistically significant increased incidences of fetal malformations were observed. In mice similarly exposed during gestation, however, there was a slight, but significant ($p < 0.05$) increase in percent late resorptions, decrease in mean male and female fetal weights, and increase in the incidence of reduced sternebral ossification in the 6,600 ppm group. The only evidence of maternal toxicity at this exposure level was statistically significant increased absolute and relative liver weight.

No effects were found on sex ratio or the incidence of malformations or skeletal variations combined, and no reproductive effects (i.e., no effects on number of implants/litter, percent live pups/litter, or mean percent resorptions/litter) were observed in rats or mice in this inhalation developmental study. The NOAEL was 2,200 ppm for maternal and developmental toxicity in both species. Because the developmental LOAELs (6,600 in mice and 11,000 ppm in rats) are so much higher and no reproductive effects were observed, an acute ReV based on neurobehavioral effects in humans (LOAEL of 227 ppm) is expected to be protective of any potential developmental/reproductive effects. The same is true for the chronic ReV.

3.1.3 Critical Effect

Following exposure to acetone, the primary effects in humans are neurobehavioral and irritation, with neurobehavioral effects having the slightly lower POD_{HEC} and serving as the critical effect.

3.1.4 Metabolism

The following information and figure on acetone metabolism was taken from USEPA (2003), which should be referred to for the cited references.

> In brief, based on human and animal studies and *in vitro* studies, the metabolism of acetone may occur via at least two routes (see Figure 1 below). The principal metabolic pathways are dependent on the site of metabolism and on the concentration of acetone. The metabolites are incorporated into glucose and other substrates of intermediary metabolism that ultimately produce carbon dioxide. In the first metabolic step, common to all potential pathways, acetone is oxidized to acetol by acetone monooxygenase, an activity associated with CYP2E1. This step requires O_2 and NADPH (Casazza et al. 1984). In the first pathway, acetol is converted to methylglyoxal, which in turn is metabolized to glucose through a lactate intermediate. The conversion of acetone via the methylglyoxal pathway is mediated by acetone monooxygenase (CYP2E1) and acetol monooxygenase (CYP2E1) to form methylglyoxal. The conversion of methylglyoxal to lactate is mediated by glyoxylase I and II and glutathione-S-transferase. This pathway is primarily a hepatic

pathway. In the second pathway, the acetol intermediate is converted to L-1,2-propanediol by an extrahepatic mechanism that has not been fully characterized. The metabolism of acetone via the 1,2-propanediol pathway to lactate is mediated by alcohol dehydrogenase and aldehyde dehydrogenase (Dietz et al. 1991). Gluconeogenesis may proceed through the formation of an active form of acetate. 1,2-Propanediol may be converted to glucose through a series of intermediates including lactate. Sakami (1950) proposed a pathway by which acetone is converted to formate and acetate.

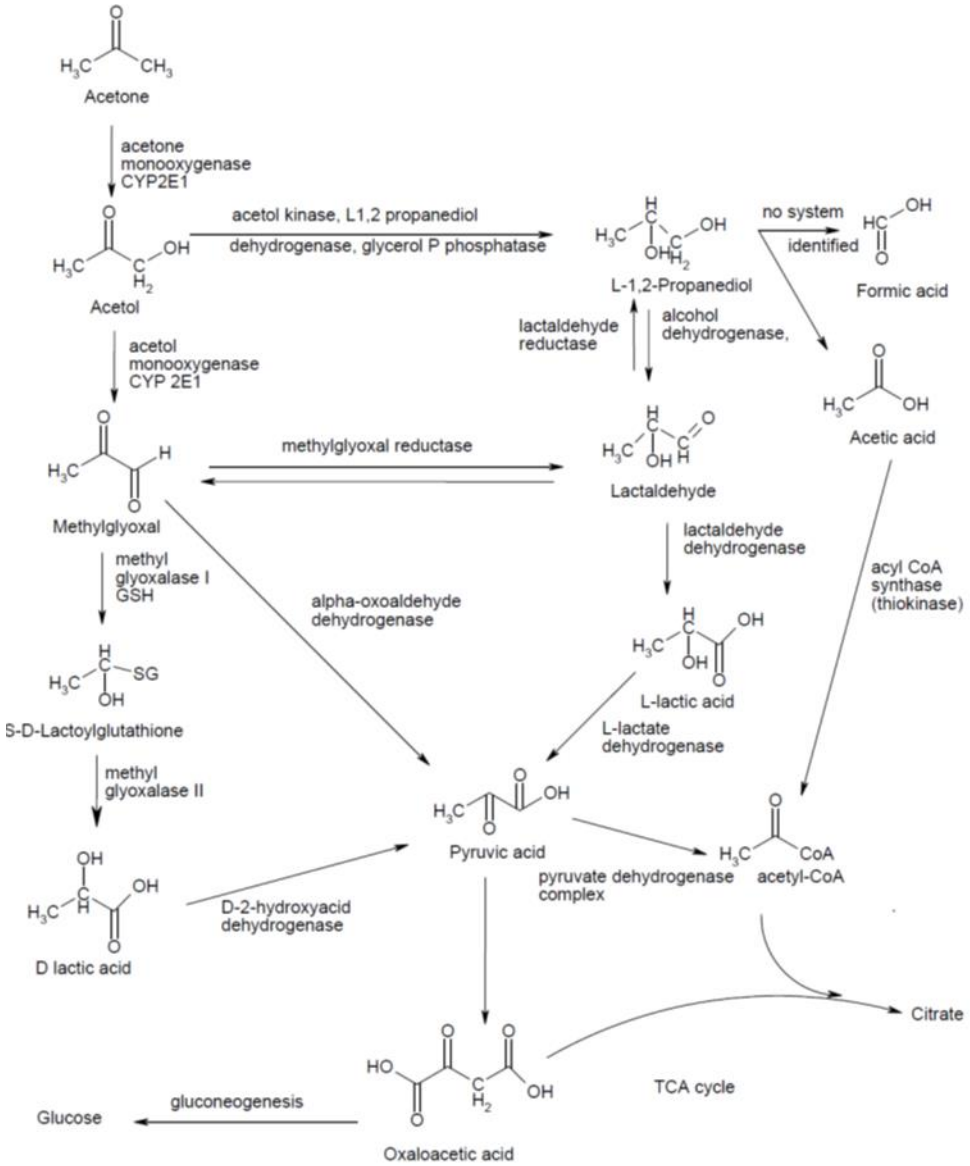


Figure 1: Pathways for the Metabolism of Acetone

> The data also demonstrates that the pathways for acetone metabolism are concentration-dependent. At lower concentrations, acetone is metabolized in the liver through the methylglyoxal pathway similar to biological conditions of fasting or exertion where the acetone is formed from fatty acids to produce glucose. Thus, at low plasma concentrations acetone serves as a gluconeogenic substrate. At higher concentrations an alternate pathway predominates and mediates the conversion of acetone to 1,2-propanediol. Although some studies indicate that 1,2-propanediol serves as an intermediate in the production of glucose, it is conceivable that the conversion from acetone to the diol diverts acetone from gluconeogenesis and facilitates the loss of acetone via urine.
>
> Enzymes involved in the metabolism of acetone are inducible. The metabolism of acetone through the methylglyoxal route is mediated largely by CYP2E1, which can be induced by fasting, experimental diabetes, or exposure to ethanol or acetone; therefore, acetone induces its own metabolism (ATSDR 1994, Mandl et al. 1995, WHO 1998).

Thus, the metabolic pathways of acetone are relatively well understood. Most of its intermediate or final metabolites are not considered toxic, with the possible exception of formate. Acetone appears to be the active compound. The fate of acetone in the body appears to be concentration-dependent. At low levels (e.g., endogenous), human data indicate that acetone is mostly lost through metabolism to other cellular constituents (e.g., acetone is largely retained and serves as an intermediate in gluconeogenesis). At higher levels, excess acetone is eliminated. For example, levels of acetone lost through expiration (acetone and acetone-derived carbon dioxide) increase disproportionately at higher concentrations. Additionally, although exposure to acetone at concentrations below 15 ppm produces no detectable acetone in the urine, above that level acetone appears in the urine at about 1% of the blood plasma concentration. Overall, data suggest excess acetone may be readily lost from the body (USEPA 2003). Following inhalation or oral exposure, acetone is eliminated within about 1-3 days in humans (ATSDR 1994).

3.1.5 Mode-of-Action (MOA) and Dose Metric

Generally, acetone does not accumulate in any tissue and its metabolites do not appear to be toxic or retained. While all the details of the mechanism of the neurological/neurobehavioral effects of acetone are yet to be fully elucidated, as a solvent, acetone may interfere with the composition of the membranes and alter their permeability to ions (ATSDR 1994). The relatively nonpolar, lipophilic properties of acetone enhance its ability to cross the blood-brain barrier (USEPA 2003). In regard to irritation, which potentially has only a slightly higher LOAEL, acetone's mucous membrane irritation is possibly due to its lipid solvent properties (ATSDR 1994, USEPA 2003).

Neurobehavioral effects (and sensory irritation) from short-term exposure to solvents such as acetone are threshold effects. For effects with a threshold MOA, a POD_{HEC} is determined and

appropriate uncertainty factors are applied to derive a ReV (TCEQ 2012). Air concentration is the dose metric available from the key study.

3.1.6 Point of Departure (POD) for Key Study

A POD_{HEC} equal to the LOAEL of 227 ppm was selected for the key study (Dick et al. 1989) based on mild neurobehavioral effects in humans.

3.1.7 Dosimetric Adjustments

3.1.7.1 Default Exposure Duration Adjustments

An exposure duration adjustment was not conducted as the neurobehavioral effects of acetone observed in the key study were similar in tests conducted during the first 2 h of exposure relative to tests conducted in last 2 h of exposure. As discussed above, the significantly increased ($p < 0.001$) false alarm rate measured in the auditory tone discrimination task during the first 2 h of exposure (30%) was identical to that during the second 2 h of exposure. Response time was also statistically increased ($p < 0.01$) during the first 2 h of exposure. As it appears these tests were given early on in each testing period, these results could have been obtained during the first hour of exposure so adjusting the POD for exposure duration (e.g., from 2 h to 1 h) would be inappropriate. Therefore, the exposure concentration at the 1-h duration of interest for derivation of an acute ReV was conservatively assumed to be equal to this LOAEL (227 ppm) based on results from the key study. Thus, the POD_{HEC} remains 227 ppm.

3.1.7.2 Adjustments of the POD_{HEC}

The POD_{HEC} is based on mild neurobehavioral effects; the MOA is assumed to produce a threshold response. The default for noncarcinogenic effects is to determine a POD_{HEC} and apply uncertainty factors (UFs) to derive an acute ReV (i.e., assume a threshold MOA) (TCEQ 2012).

The following UFs were applied to the POD_{HEC} of 227 ppm for neurobehavioral effects in humans from the key study of Dick et al. (1989): 10 for intraspecies human variability (UF_H), 2 for use of LOAEL (UF_L), and 1 for database uncertainly (UF_D); the total UF = 20.

- A full UF_H of 10 was used to account for potential intraspecies human variability in the absence of relevant data. There are no human data in potentially sensitive subpopulations (e.g., those with some level of diabetic ketoacidosis) or animal data particularly relevant to potential age-dependent sensitivity (e.g., children, the elderly), although newborn rats have a 1.5- to 4.2-fold lower LD_{50} (USEPA 2003, AEGL 2005). For example, increased susceptibility could be conferred to those with elevated endogenous levels (i.e., higher body burden) of acetone due to uncontrolled diabetes, a high-fat/low-carbohydrate diet, or fasting conditions where fat is metabolized to form acetoacetate, which in turn is converted to acetone. Under these conditions, a high level of acetyl CoA generated from the beta-oxidation of fatty acids coupled with a limited supply of oxaloacetate and a lack of dietary carbohydrate can lead to ketosis (USEPA 2003). In regard to acetone-induced

irritation, which potentially has only a slightly higher LOAEL, ATSDR (1994) indicates that individual sensitivity appears to be highly variable (ATSDR 2011 further indicates that the general population may be more sensitive than workers with repeated exposure which may exhibit some degree of sensory adaptation).

- A LOAEL-to-NOAEL UF_L of 2 was used because the neurobehavioral key study LOAEL (227 ppm) is relatively close (within a factor of 2.3) to the neurobehavioral NOAEL (100 ppm) from a supporting study (Matsushita et al. 1969a) and well below other potential acute neurological NOAELs (e.g., NOAEL of 1,000 ppm from Stewart et al. 1975 for an increase in VER), and effects were mild in only 2 of 32 neurobehavioral performance parameters measured.
- A database UF_D of 1 was used because the overall acute toxicological database for acetone is high based on data from numerous controlled human and laboratory animal studies which provide a robust database for the evaluation of many relevant endpoints and the identification of critical effects. For the acute inhalation exposure of humans, data are available for systemic, immunological, and neurological effects. The systemic effects include respiratory irritation, cardiovascular effects, gastrointestinal effects, and hematological effects, with no indications of hepatic or renal effects. For animals acutely exposed via inhalation, data exist for death, systemic effects, and neurological, developmental, and reproductive effects. Systemic effects, for example, consist of respiratory irritation, hepatic effects, renal effects, and body weight changes (ATSDR 1994).

acute ReV= POD_{HEC} / (UF_H x UF_L x UF_D)
= 227 ppm / (10 x 2 x 1)
= 227 ppm / 20
= 11.35 ppm
= 11,350 ppb

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

Rounded to two significant figures, the resulting 1-h acute ReV is 11 ppm (26 mg/m^3) or 11,000 ppb (26,000 µg/m^3) based on the Dick et al. (1989) key study. The rounded ^{acute}ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 3,300 ppb (7,800 µg/m^3) (Table 2).

Table 4. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Values and Descriptions
Study	Dick et al. (1989)
Study Population	137 human volunteers
Study Quality	High
Exposure Methods	Inhalation Chamber, exposure to 227 ppm
POD_{HEC}	227 ppm (free-standing LOAEL)
Critical Effects	Mild effects on neurobehavioral performance
Exposure Duration	1-2 h
Extrapolation to 1 h	Conservatively, no adjustment made
POD_{ADJ} (1 h)	227 ppm
Total UFs	20
Interspecies UF	Not Applicable (N/A)
Intraspecies UF	10
LOAEL UF	2
Incomplete Database UF *Database Quality*	1 High
acute ReV [1 h] (HQ = 1)	**26,000 µg/m^3 (11,000 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**7,800 µg/m^3 (3,300 ppb)**

3.1.9 Comparison of TCEQ's Acute ReV to ATSDR's Acute Inhalation MRL

TCEQ's acute (1-h) ReV of 11 ppm (11,000 ppb) is similar to the acute (1-14 day) inhalation minimal risk level (MRL) of 26 ppm listed on ATSDR's website as derived in 1994 based on neurotoxicity (available at ATSDR), although not documented in ATSDR (1994).

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Acetone's odor has been described as aromatic or sweet and sharp with the hedonic tone described as neutral to unpleasant (Leonardos et al. 1969, Hellman and Small 1974). Published odor detection threshold values are summarized in Table 5. Since the odor for acetone is not pungent or disagreeable and the odor detection thresholds for acetone are significantly above health-based values, an $^{acute}ESL_{odor}$ was not derived (TCEQ 2015).

Table 5. Odor Studies Conducted for Acetone

Investigator	Odor Detection Threshold Value	Quality Level
May (1966)	1,832,600 µg/m^3 (770,000 ppb)	3
Dravnieks (1974)	3,689,000 µg/m^3 (1,550,000 ppb)	3
Hellman & Small (1974)	114,240 µg/m^3 (48,000 ppb)	3
van Doorn et al. (2002)	380,000 µg/m^3 (160,000 ppb)	2
Nagata (2003)	100,000 µg/m^3 (42,000 ppb)	1

3.2.2 Vegetation Effects

No studies sufficient to derive an $^{acute}ESL_{veg}$ were located.

3.3. Short-Term ESL and Values for Air Monitoring Evaluation

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

$^{acute}ESL$ = 7,800 µg/m^3 (3,300 ppb)
acute ReV = 26,000 µg/m^3 (11,000 ppb)

For the evaluation of short-term ambient air monitoring data (typically ≤ 1 h), the acute ReV of 26,000 µg/m^3 (11,000 ppb) is used (Table 1). The short-term ESL for air permit evaluations is the $^{acute}ESL$ of 7,800 µg/m^3 (3,300 ppb) (Table 2). The $^{acute}ESL$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.4 Acute Inhalation Observed Adverse Effect Levels (OAELs)

In regard to acute inhalation OAELs under Section 3.13 of TCEQ (2012), as the lowest human LOAELs for mild neurobehavioral effects and irritation are in the range of 227-250 ppm, these levels are considered the lowest concentrations where such effects in the human population could be expected to occur in some members of the population exposed for a sufficient duration (e.g., similar to that in the critical studies). Adverse effects are not a certainty at these concentrations and durations, although depending upon the sensitivities of the study populations relative to those exposed environmentally, other subpopulations could be more sensitive. This is provided for informational purposes only.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

This section is based on a review of current literature, USEPA (2003), and ATSDR (2011). Chronic inhalation data for humans are limited, and some of that identified is of limited utility due to a lack of detailed study information, lack of dose-response, confounding exposures, etc.

No chronic inhalation animal studies were identified. However, human data are preferred and one chronic inhalation human study (Satoh et al. 1996) will serve as the key study. While the inhalation human study of Stewart et al. (1975) was used by ATSDR (1994) to derive the chronic inhalation MRL, here this 4-week study is only used as a supporting study along with a supporting chronic study (Mitran et al. 1997).

4.1.1 Physical/Chemical Properties and Key Study

4.1.1.1 Physical/Chemical Properties

Physical/chemical properties of acetone have been previously discussed in Chapter 3, Section 3.1.1. Also, the main chemical and physical properties of acetone are summarized in Table 3.

4.1.1.2 Neurological

Neurological symptoms and neurobehavioral examinations appear to be among the most sensitive means to detect health effects in occupationally-exposed acetone workers (Satoh et al. 1996).

Key Study

Satoh et al. (1996)

This study examined the neurotoxic effects of acetone in 110 male workers at three acetate fiber plants. A total of 67 nonexposed male plant workers served as controls. The acetone-exposed workers were exposed only to acetone and they did not use any protective devices. No other solvents or toxic substances were used in the plants. Mean worker length of acetone exposure was 14.9 years. Acetone exposure levels were assessed by personal passive monitors and biological monitoring indices measured at the end of the work shift. Results were 19.6-1,018 ppm in the breathing zone (mean 364 ppm), 2.5-422 ppm in alveolar air (mean 97.3 ppm), 4-220 mg/L in blood (mean 66.0 mg/L), and 0.75-170 mg/L in urine (mean 37.8 mg/L). Exposed workers were classified into three categories based on breathing zone air concentrations: highly exposed (> 500 ppm), moderately exposed (250-500 ppm), and less exposed (< 250 ppm) (USEPA 2003, Satoh et al. 1996).

Neurobehavioral tests used to assess narcosis included finger tapping, simple reaction time, and choice reaction time. The Benton visual retention test and forward and backward digit span tests were used to assess memory. A series of five questionnaires was used to assess subjective symptoms. The first questionnaire appraised 54 subjective symptoms during the previous six months that were selected as symptoms induced by long-term exposure to organic solvents, with eight additional symptoms probably related to acetone exposure. The second questionnaire was the Manifest Anxiety Scale (MAS) to evaluate anxiety, and the third was the Self-rating Depression Scale (SDS) to assess depression. The fourth questionnaire series appraised 11 subjective symptoms before starting work on the day in question, contained a blank space for any other symptoms, and was designed to supply information on alcohol drinking, smoking, and

medical drug use on the previous day. The fifth questionnaire consisted of 17 subjective symptoms experienced during or after finishing work on a particular day and contained a blank space for any other symptoms (Satoh et al. 1996).

The study reports that acetone levels in alveolar air, urine, and blood were directly correlated with exposure levels, indicating that equilibrium is reached under continuous exposure resulting in absorption of acetone into the cardiovascular system. No differences between exposed workers and controls were observed on the MAS and SDS or for electrocardiogram, phagocytic activity, hematology, and clinical chemistry. While a statistically significant decrease in simple reaction time and digit span activity was observed among exposed workers aged 30-44 years, no dose-response was clear and this effect did not occur in workers aged <30 or ≥45 years. During or after work, symptoms of eye irritation, tearing, acetone odor, and nausea were reported by 13.7-45.1% of exposed workers vs. 3.9-23.5% of unexposed controls, each of which were statistically significant. Over the previous six months, neurological symptoms such as heavy feelings in the head, faint feelings, and nausea were reported by 23.6-25.8% of exposed workers vs. 2.9-9.8% of controls, each of which were statistically significant. These symptoms showed clear dose-response relationships. Thus, this study showed higher frequencies of subjective symptoms related to neurological and irritation effects in workers chronically exposed to acetone (Satoh et al. 1996, USEPA 2003).

Although the study authors noted that information on the relationship between potential short-term peaks and symptomology would have been desirable, this study may nevertheless be used to determine a LOAEL for development of a chronic ReV. Neurological effects and irritation were statistically elevated in acetone-exposed workers. The range of these daily breathing zone exposures was wide (5-1,212 ppm), with an overall mean of 361.4 ppm. Figure 1 of the Satoh et al. (1996) study, which shows the prevalence of heavy feelings in the head by exposure group, was examined to ascertain more specific information concerning the lowest exposure levels producing this statistically elevated effect. While the lowest exposure group (< 250 ppm) had a similar prevalence of this symptom compared to controls (just over 10%), the prevalence was over twice as high (> 25%) in the moderately-exposed group (250-500 ppm), and over three times as high (≈ 45%) in the high exposure group (> 500 ppm). Based on these findings, the TCEQ tentatively identifies the midpoint of the moderately-exposed group (375 ppm) as the LOAEL for neurological effects (e.g., heavy feelings in the head, faint feelings, nausea) from this study for purposes of deriving the chronic ReV (data are not amenable to benchmark dose modeling). The LOAEL of 375 ppm happens to be not appreciably different from the overall mean (361.4 ppm) associated with neurological and irritation effects in this study. However, the overall mean is considered more uncertain for use as a POD_{HEC} given the wide range of exposures (5-1,212 ppm), including those that did not produce effects. An accurate value representative of the NOAEL in the less exposed worker group cannot be reliably determined for use as a POD. Thus, the LOAEL will be used and a minimal UF_L applied to calculate a value within the range of the less exposed group for derivation of the chronic noncarcinogenic ReV and the $^{chronic}ESL_{threshold(nc)}$.

Supporting Studies

Stewart et al. (1975)

ATSDR (1994) used this study to derive the chronic inhalation MRL, although this 4-week study with progressively higher exposures each week is only used here as a supporting study. In this study, healthy adult male and female volunteers were exposed to acetone vapor in a controlled environment chamber using exposure schemes designed to simulate exposures encountered in the industrial setting. Exposures consisted of steady, non-fluctuating vapor concentrations in addition to widely fluctuating vapor concentrations of acetone. Four male subjects (age 22-27 years) per group were exposed for either 3 or 7.5 h/day, 4 days/week, to progressively higher acetone concentrations for four weeks (i.e., 0 ppm for week 1, 200 ppm for week 2, 1,000 ppm for week 3, 1,250 ppm for week 4). The first day of each week was an additional control exposure to 0 ppm. Female subjects (age 18-25 years) were exposed in groups of 2 to 1,000 ppm for 1 h and in groups of 3-4 to 0 or 1,000 ppm for 3 and 7.5 h/day, 4 days/week, for 1 week. As with the males, the first day of each week was an additional control exposure to 0 ppm (AEGL 2005).

A complete medical and physical examination was given to all subjects at the beginning and end of the study. Blood pressure, temperature, subjective responses, clinical signs and symptoms, and urinalysis were recorded daily. Alveolar breath analysis was performed at 0, 0.25, 0.5, 1, 2, and 3 h following exposures. Shortly before ending each weekly exposure session, cardiopulmonary testing was conducted. After four days of exposure to 1,000 ppm (7.5 h/day), 3 of 4 females reported to have regular menstrual cycles experienced an early menstrual period (≥1 week early). At various times throughout the exposures, a battery of neurophysiological and neurobehavioral tests was performed. An increase in visual evoked response (VER) was clearly exposure-related and occurred in 1 of 4 males exposed to 1,000 ppm and 3 of 4 males exposed to 1,250 ppm (7.5 h), although no such effects occurred in females exposed to 1,000 ppm (Stewart et al. 1975). Thus, after the fourth week of exposure to progressively higher acetone concentrations, 1,250 ppm serves as the clearest LOAEL for neurological effects based on results reported for this study (data not amenable to benchmark dose modeling).

Although ATSDR (1994) used this study to derive the chronic inhalation MRL, it is not an ideal exposure regimen for identification of a subchronic LOAEL since exposures were only for 4 weeks and were not to 1,250 ppm each day but to progressively increasing concentrations. Thus, the higher LOAEL for neurological effects from this study (1,250 ppm) compared to that from Satoh et al. (375 ppm) is only used as supportive information.

Mitran et al. (1997)

In this study, 71 coin-printing factory workers with a mean length of exposure of 14 years were evaluated for both central and peripheral nervous system effects by comparison to matched controls (n=86). Mood disorders, irritability, memory difficulties, sleep disturbances, headache, numbness of the hands or feet, eye and upper respiratory tract irritation, cutaneous symptoms (e.g., rashes), bone, joint and/or muscle pain, nausea, abdominal pain and other digestive

symptoms were reported more frequently in exposed workers as compared with controls. Although the results of motor nerve conduction tests on the median, ulnar, and peroneal nerves indicated statistically significant reductions in latency, amplitude and/or duration of both proximal and distal responses, no consistent pattern of effect was observed. Statistically significant reductions in nerve conduction velocity in all nerves studied was reported in exposed workers as compared with controls. For the exposed workers, statistically significant delays in reaction time were observed for the visual test and a lower mean distributive attention score when compared with the controls. Eight-hour acetone exposure levels in the workplace air of the exposed workers ranged from 416 to 890 ppm (988 to 2,114 mg/m^3) (USEPA 2003, ATSDR 2011, Mitran et al. 1997).

The increased signs of neurotoxicity (mood disorders, irritability, memory difficulty, sleep disturbances, and headache) reported among these workers chronically exposed to acetone at concentrations of 416-890 ppm appear to provide some support for the neurological chronic LOAEL of 375 ppm based on Satoh et al. (1996), falling between that value and the LOAEL of 1,250 ppm based on the supporting 4-week Stewart et al. (1975) study. However, USEPA (2003) notes that the Mitran et al. (1997) study presents minimal information. This confounds a meaningful appraisal of the study design and includes a lack of information regarding the selection of controls, parameters used for age-matching and other variables, experimental procedures (e.g., blind versus non-blind determinations), and temperature control (i.e., age-matching and consistent temperature control are known critical parameters in nerve conduction velocity measurements). Other important potential confounding issues cited include no establishment of a dose-response relationship and an inability to rule out likely coexposure to other toxins at the coin and metal plant. For these reasons, USEPA (2003) considers the study inappropriate for the establishment of an inhalation reference concentration. Similarly, while this study provides limited support to the chronic neurological LOAEL from Satoh et al. (1996), further assessment/analysis of the results is not justified and it will not be used as a key study here.

4.1.2 Critical Effect, MOA, and Dose Metric

Neurotoxicity (e.g., heavy feelings in the head, faint feelings, nausea) is the critical effect which serves as the basis for the POD_{HEC}.

The MOA for neurological effects caused by acetone is not fully known. While all the details of the mechanism of acetone-induced neurotoxicity are yet to be fully elucidated, as a solvent, acetone may interfere with the composition of the membranes and alter their permeability to ions (ATSDR 1994). The relatively nonpolar, lipophilic properties of acetone enhance its ability to cross the blood-brain barrier (USEPA 2003). Neurotoxic effects from exposure to solvents such as acetone are threshold effects. For effects with a threshold MOA, a POD_{HEC} is determined and appropriate UFs are applied to derive a ReV (TCEQ 2012).

Exposure concentration of the parent chemical will be used as the default dose metric since data on other more specific dose metrics are not available.

4.1.3 POD for the Key Study

A LOAEL of 375 ppm based on neurotoxic effects in the key chronic human study (Satoh et al. 1996) was used as the occupational POD (POD_{OC}) value.

4.1.4 Dosimetric Adjustments

4.1.4.1 Default Exposure Duration Adjustments

Because Satoh et al. (1996) is an occupational study, the occupational exposure level (LOAEL-based POD_{OC}) must be adjusted to an environmental exposure level applicable to the general public. Thus, the POD_{OC} value of 375 ppm (LOAEL) was used to calculate a POD adjusted for exposure duration for use as the POD_{HEC}.

$POD_{HEC} = POD_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$

where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)
VE_h = nonoccupational ventilation rate for a 24-h day (20 m^3/day)
$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)
$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

$POD_{HEC} = 375 \text{ ppm} \times (10/20) \times (5/7) = 133.9 \text{ ppm}$

4.1.4.2 Adjustment of the POD_{HEC}

The POD_{HEC} is based on neurological effects, which are noncarcinogenic in nature. The default for noncarcinogenic effects is to determine a POD_{HEC} and apply UFs to derive a ReV (i.e., assume a threshold MOA) (TCEQ 2012).

The following UFs were applied to the POD_{HEC} of 133.9 ppm (duration-adjusted LOAEL) for neurotoxic effects in humans from the key study of Satoh et al. (1996): 10 for UF_H, 2 for UF_L, and 1 for UF_D; the total UF = 20.

- A full UF_H of 10 was used to account for potential intraspecies human variability in the absence of relevant data. There are no human data in potentially sensitive subpopulations (e.g., those with some level of diabetic ketoacidosis) or animal data particularly relevant to potential age-dependent sensitivity (e.g., children, the elderly), although newborn rats have a 1.5- to 4.2-fold lower LD_{50} (USEPA 2003, AEGL 2005). For example, increased susceptibility could be conferred to those with elevated endogenous levels (i.e., higher body burden) of acetone due to uncontrolled diabetes, a high-fat/low-carbohydrate diet, or fasting conditions where fat is metabolized to form acetoacetate, which in turn is converted to acetone. Under these conditions, a high level of acetyl CoA generated from the beta-oxidation of fatty acids coupled with a limited supply of oxaloacetate and a lack of dietary carbohydrate can lead to ketosis (USEPA 2003).
- A minimal UF_L of 2 was used since application of this value to the LOAEL (375 ppm) to estimate a NOAEL would result in a concentration (187.5 ppm) well within the range of

exposures (< 250 ppm) not associated with the increased symptomology [the duration-adjusted POD_{HEC} of 133.9 ppm is already within this range].

- A UF_D of 1 was used because while there are few chronic and/or subchronic studies, the overall toxicological database for acetone is high (evaluating many relevant endpoints in humans and animals) and existing shorter-term studies are considered adequate to identify and characterize the critical health hazards of acetone (e.g., neurotoxicity/narcosis, irritation), which likely explains why longer-term studies of this common chemical are sparse. Acetone is not particularly toxic or bioaccumulative, and because it is produced endogenously, the human body has a significant capacity to effectively eliminate it. Additionally, several subchronic inhalation animal studies evaluating various endpoints (e.g., neurotoxicity, hematological parameters, histological examinations) are available for isopropanol, which is mainly metabolized to acetone (USEPA 2003), and do not support a different endpoint than that utilized for the chronic assessment as more sensitive. Based on a balanced view of these chemical-specific considerations, there is minimal concern about the lack of more long-term studies, and the overall confidence in the database for derivation of a chronic ReV for acetone is considered medium.

chronic ReV = POD_{HEC} / (UF_H x UF_L x UF_D)
= 133.9 ppm / (10 x 2 x 1)
= 133.9 ppm / 20
=6.69 ppm
=6,690 ppb

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

Rounding to two significant figures, the chronic ReV is 6,700 ppb or 16,000 µg/m^3. This chronic ReV is expected to be protective of not only the potential chronic neurotoxic effects of acetone, but also potential effects associated with shorter-term exposure (e.g., irritation, potential irregular menstrual cycles at 1,000 ppm for one week, potential developmental and reproductive effects as discussed in Section 3.1.2.3). The rounded chronic ReV is then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target hazard quotient of 0.3, the rounded $^{chronic}ESL_{threshold\ (nc)}$ is 2,000 ppb or 4,800 µg/m^3.

Table 6. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	Values and Descriptions
Study	Satoh et al. (1996)
Study Population	110 exposed and 67 unexposed male workers
Study Quality	High
Exposure Method	Breathing zone daily concentrations
Critical Effects	Neurotoxicity (heavy feelings in the head, faint feelings, nausea)
POD_{OC}	375 ppm (LOAEL)
Exposure Duration	14.9 years (mean)
Extrapolation to continuous exposure	375 ppm x 10 m^3/20 m^3 day x 5d/7d
POD_{HEC}	133.9 ppm
Total UFs	20
Interspecies UF	N/A
Intraspecies UF	10
LOAEL UF	2
Subchronic to chronic UF	N/A
Incomplete Database UF *Database Quality*	1 Medium
Chronic ReV (HQ = 1)	**16,000 µg/m^3 (6,700 ppb)**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	**4,800 µg/m^3 (2,000 ppb)**

4.1.6 Comparison of TCEQ's Chronic ReV to ATSDR's Chronic Inhalation MRL

TCEQ's chronic ReV of 6.7 ppm (6,700 ppb) is similar to the chronic inhalation MRL of 13 ppm in ATSDR (1994). The $^{chronic}ESL_{threshold(nc)}$ of 2.0 ppm (2,000 ppb) is somewhat lower and is similar to the USEPA (2003) reference dose (RfD of 0.9 mg/kg-day) converted to an air concentration (1.3 ppm) using the simple route-to-route equation (Equation 3-8) in TCEQ (2012) (calculations not shown).

4.2 Carcinogenic Potential

USEPA (2003) provides the following information in Section 4.6 (Weight-Of-Evidence Evaluation and Cancer Characterization):

"In accordance with the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999) data are *inadequate for an assessment of the human carcinogenic potential* of acetone. This weight-of-evidence determination is based on the availability of one human study of limited utility, no chronic animal studies, and no additional information on structural analogues with known carcinogenic potential. Acetone has tested negative in almost all genotoxicity studies."

Since there are no human or animal studies or other data indicating that acetone has carcinogenic potential, a chronic carcinogenic ESL (e.g., $^{chronic}ESLnon_{threshold(c)}$) is not applicable and cannot be developed.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV = 16,000 µg/m^3 (6,700 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 4,800 µg/m^3 (2,000 ppb)

The chronic ReV of 16,000 µg/m^3 (6,700 ppb) will be used for the evaluation of ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ of 4,800 µg/m^3 (2,000 ppb) 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 OAEL

In regard to the lowest chronic concentrations producing neurological symptoms in humans, the LOAEL selected was 375 ppm (midpoint of the exposure group), although the associated worker group was exposed to a range of 250-500 ppm. Therefore, in regard to chronic inhalation OAELs for neurological symptoms based on chronic data (as well as the irritation generally reported in chronically-exposed acetone workers in Satoh et al. 1996), concentrations in this range should be considered. This is supported by relevant acute data where the lowest human LOAELs for mild neurobehavioral effects and irritation are in the range of 227-250 ppm. The difference between the inhalation OAEL concentrations identified for the acute and chronic scenarios may simply be the result of the concentrations selected for testing in the acute volunteer chamber studies versus the chronic occupational exposure group cutoffs selected by study authors for analysis.

Thus, based on both chronic and acute data collectively, concentrations in the range of 227-500 ppm should be considered as the lowest levels where neurological and irritation symptoms in the

human population could be expected to occur in some members of the population. Adverse effects are not a certainty within this concentration range for a given duration although they would be more likely towards the upper end of the range. Depending upon the sensitivity of the study population relative to those exposed environmentally, other subpopulations could be more sensitive. This is provided for informational purposes only.

Chapter 5 References

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