Development Support Document
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Propionaldehyde

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
A	animals
AEGL	Acute Exposure Guideline Level
AIC	Akaike's Information Criterion
AMCV	Air Monitoring Comparison Value
BMC	benchmark concentration
BMCL	benchmark concentration 95% lower confidence limit
BMDS	Benchmark Dose Software
^{0} C	degrees centigrade
CES_{05}	critical effect size corresponding to a 5% relative decrease in the mean when compared to controls
CES	critical effect size
CNS	central nervous system
DSD	development support document
ET	extrathoracic
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
$^{chronic}ESL_{linear(c)}$	chronic health-based Effects Screening Level for linear dose response cancer effect
$^{chronic}ESL_{linear(nc)}$	chronic health-based Effects Screening Level for linear dose response noncancer effects
$^{chronic}ESL_{nonlinear(c)}$	chronic health-based Effects Screening Level for nonlinear dose response cancer effects

$^{chronic}ESL_{nonlinear(nc)}$	chronic health-based Effects Screening Level for nonlinear dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
F	exposure frequency, days per week
GD	gestation day
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
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
MEK	methyl ethyl ketone
MOA	mode of action
n	number
N/A	not applicable
NAC	National Advisory Committee
n-BA	n-butyl acetate
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level

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
SA	surface area
SAR	structure-activity relationship
SCOB	scheduled-controlled operant behavior
SD	Sprague-Dawley
SMCs	self-reported multiple chemical sensitivity
SPGT	serum glutamic-pyruvic transaminase
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
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
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 resulting from an acute and chronic evaluation of propionaldehyde. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (2012) 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 the physical and chemical properties of propionaldehyde.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV [1 hour] (HQ = 1.0)	1800 µg/m^3 (740 ppb) **Short-Term Health**	Critical Effect: mild irritation of mucosal surfaces in human volunteers
$^{acute}ESL_{odor}$	92 µg/m^3 (40 ppb) **Odor**	Pleasant and fruity odor at low concentrations. Pungent odor at high concentrations.
$^{acute}ESL_{veg}$	- - -	Inadequate data to derive
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	130 µg/m^3 (52 ppb) **Long-Term Health**	Critical Effect: nasal atrophy in rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$,	- - -	NA
$^{chronic}ESL_{veg}$	- - -	No data found

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3,** micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; ^{acute}**ESL**, acute health-based ESL; ^{acute}**ESL$_{odor}$**, acute odor-based ESL; ^{acute}**ESL$_{veg}$,** acute vegetation-based ESL; ^{chronic}**ESL$_{threshold(nc)}$**, chronic health-based Effects Screening Level for threshold dose response noncancer effects; ^{chronic}**ESL $_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; ^{chronic}**ESL$_{threshold(c)}$**, chronic health-based ESL for threshold dose-response cancer effects; and ^{chronic}**ESL$_{veg}$,** chronic vegetation-based ESL.

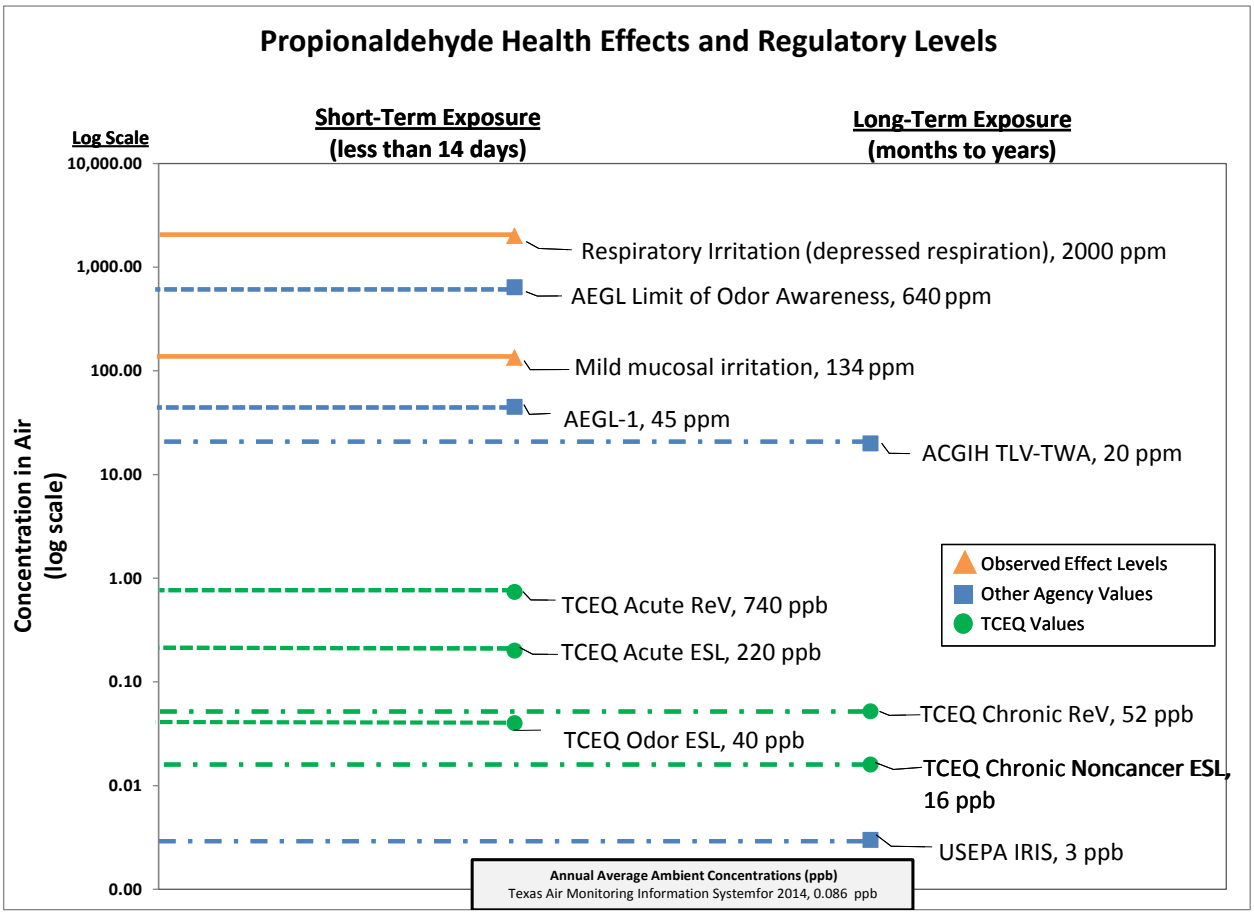
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	**Concentration**	**Notes**
Acute ESL [1 hour] (HQ = 0.3)	500 µg/m^3 (220 ppb) [a] **Short-Term Health**	Critical Effect: mild irritation of mucosal surfaces in human volunteers
$^{acute}ESL_{odor}$	92 µg/m^3 (40 ppb) **Short-term ESL for Air Permit Reviews**	Pleasant and fruity odor at low concentrations. Pungent odor at high concentrations.
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	40 µg/m^3 (16 ppb) [b] **Long-Term ESL for Air Permit Reviews**	Critical Effect(s): nasal atrophy in rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$,	- - -	NA
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Based on the acute ReV of 1800 µg/m^3 (740 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

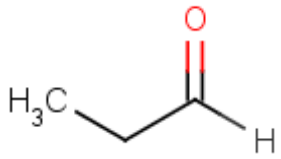
[b] Based on the chronic ReV of 130 µg/m^3 (52 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

Figure 1. Comparison of Regulatory Levels for Propionaldehyde



This figure compares acute toxicity values (acute ReV, odor-based ESL, and health-based short-term ESL) and chronic toxicity values (chronic ReV and long-term ESL) for propionaldehyde found in Tables 1 and 2 to the Acute Exposure Guideline Level-1 (AEGL-1) and AEGL Limit of Odor Awareness (LOA) (NRC 2009); American Conference of Governmental Industrial Hygienists (ACGIH) TLV-TWA (2014); and to the United States Environmental Protection Agency (USEPA) Reference Concentration (RfC) (USEPA 2008).

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C_3H_6O	AEGL 2009
Chemical Structure		USEPA 2008
Molecular Weight	58.08	AEGL 2009
Physical State at 25°C	liquid	AEGL 2009
Color	colorless	AEGL 2009
Odor	pleasant sweet and/or suffocating fruity odor	USEPA 2008
CAS Registry Number	123-38-6	AEGL 2009
Synonyms	methylacetaldehyde, propanal, propionic aldehyde, propyl aldehyde	AEGL 2009
Solubility in water	Soluble in 5 volumes water at 20°C	AEGL 2009
Log Kow	0.59	USEPA 2008
Vapor Pressure	235 mm Hg at 20°C	AEGL 2009
Relative Vapor Density (air = 1)	1.8 at 100°F	AEGL 2009
Melting Point	-81°C	AEGL 2009
Boiling Point	49°C	AEGL 2009
Conversion Factors	1 ppm = 2.38 mg/m^3 1 mg/m^3 = 0.42 ppm	USEPA 2008

Chapter 2 Major Sources and Uses

Propionaldehyde is used primarily as a reactive intermediate in the manufacture of propanol, propionic acid, polyvinyls and other plastics, fragrances, and fungicides (American Industrial Hygiene Association 2002). Exposure to propionaldehyde in ambient air may occur as a result of its release from manufacturing facilities, municipal waste incinerators, and from combustion of wood, gasoline, diesel fuel, and polyethylenes (USEPA 2008). Propionaldehyde has also been detected in tobacco smoke.

Propionaldehyde occurs naturally in coffee and apple aromas and has been identified as a volatile emission of arboreous plants. It is found in the essential oils of camphor, *Rosa centrifolia*, Clary sage, *Pinus excelsa*, and *Pinus silvestris* (American Industrial Hygiene Association 2000). Propionaldehyde has also been approved by both the U.S. Food and Drug Administration (FDA) and World Health Organization/Joint Expert Committee on Food Additives (WHO/JECFA) as a synthetic flavoring ingredient for direct addition to food (FDA 2003; WHO 1999; IPCS 1998).

Propionaldehyde has been detected in ambient and indoor air in several studies. Baez et al. (2003) measured the concentrations of propionaldehyde in outdoor air in Mexico to be 0.08-6.7 ppb (0.0002–0.016 mg/m^3) over a 2-hour period. Propionaldehyde was detected at concentrations ≤14 parts per billion (ppb) (0.033 mg/m^3) in Los Angeles air when measured over 1-hour during severe photochemical pollution episodes (Grosjean 1982) and at concentrations ranging from 7–25 ppb (0.017–0.06 mg/m^3) in the exhaust from an idling jet airplane, measured for approximately 30 minutes at 50 meters behind the engine (Miyamoto 1986). Propionaldehyde has also been measured in cigarette smoke at concentrations of 6.9 µg per 40 mL puff (72.8 ppm) (Newsome et al. 1965 as cited in Egle 1972). Using air monitoring data from the Texas Air Monitoring Information System (TAMIS), the annual mean concentration for propionaldehyde in 2014 for the six 24-hour canister sites across Texas that reported data for propionaldehyde was 0.086 ppb.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

This section is based on a review of current literature as well as background readings in AEGL 2009 which describe in detail the acute toxicity of propionaldehyde. The TCEQ used key studies from AEGL (2009) as well as data from the most recent publications, if available, to derive acute toxicity factors for propionaldehyde. The Development Support Document (DSD) is a summary of the key and supporting studies used by the TD to derive toxicity values.

There is extremely limited information on the acute effects of propionaldehyde in humans, and no information is available on the chronic, reproductive, developmental or carcinogenic effects of propionaldehyde in humans. No studies were available on possible childhood or other age group susceptibility to propionaldehyde. Likewise, no studies investigating possible gender

differences in susceptibility specific to propionaldehyde were found. No studies investigating other sensitive populations, such as asthmatics, were available.

As with other aldehydes, propionaldehyde is an irritant to the eyes, skin and upper respiratory tract. Toxicological data indicate that adverse acute and chronic effects occur only at fairly high doses, and overall toxicity is mild. Propionaldehyde is not a reproductive or developmental toxicant and does not produce systemic toxicity in subchronic inhalation studies in animals. Animal studies have reported that high levels (see below) of inhaled propionaldehyde results in respiratory and cardiovascular effects, anesthesia and liver damage.

3.1.1 Physical/Chemical Properties

Propionaldehyde is an aldehyde, also known as propanal, propionic aldehyde, methylacetaldehyde, propyl aldehyde, propaldehyde, and propylic aldehyde. Propionaldehyde is a colorless liquid with a pleasant and fruity odor at low concentrations and a pungent odor at high concentrations (USEPA 2008). Propionaldehyde is soluble in water. It has a relatively high vapor pressure and is present as vapor in air. Relevant physical and chemical properties of propionaldehyde can be found in Table 3.

3.1.2 Key Human Study (Sim and Pattle 1957)

The evidence from human inhalation studies of propionaldehyde is extremely limited. The single available study by Sim and Pattle (1957) reported exposure of 12 healthy males, ages 18 to 45, to a single concentration of propionaldehyde of 134 ppm (measured concentration) for 30 minutes. The authors note mild irritation to mucosal surfaces and occasional comment regarding the odor of the substance. There is some uncertainty associated with using this study to derive toxicity factors because the subjects were allowed to smoke during exposure and certain methodological details (e.g. incidence of smoking in control versus exposed volunteers) were lacking. However this study can be utilized to estimate levels of exposure at which mild mucosal irritation may be observed (see Figure 2). It should be emphasized that this is a conservative approach due to the uncertainty regarding the actual exposure level of these volunteers who were allowed to smoke. That is, actual exposure may have been higher than 134 ppm because propionaldehyde is found in cigarette smoke. The level of 134 ppm was considered a free-standing lowest-observed-adverse-effect-level (LOAEL) for irritation and used as a point of departure (POD) to derive acute ReV and ESL.

3.1.3 Supporting Animal Studies

3.1.3.1 Acute Lethality

Rabbits, guinea pigs, and mice

Rabbits, guinea pigs, and mice were exposed to 1,200 ppm (2,856 mg/m^3) propionaldehyde for up to 10 hours in a study by Salem and Cullumbine (1960). The method of exposure was not

described and the results were only briefly reported. The animals showed blinking, closing of the eyes, and rubbing of their faces with their paws. After this initial phase, respiration became slow and deep with convulsions observed just prior to death. All rabbits (n=5) died after a mean exposure of 4 hours. All mice (n=50) died during exposure after a mean exposure of 5 hours. All guinea pigs survived the exposure period and 3 out of 20 exposed animals died on subsequent days after the exposure period. Autopsy revealed edematous and hemorrhagic lungs with fluid observed in the pleural cavity.

Rats

Gage (1970) exposed Alderley Park rats (2 male and 2 female) to an estimated 333,000 ppm of propionaldehyde. Mortality was observed after 30 minutes. Rats exposed to 16,000 ppm died within 2.25 hours, and 5 out of 6 exposed rats succumbed within 4 hours when exposed to 8,000 ppm. There was no mortality among rats exposed to 4,000 ppm for 4 hours. Propionaldehyde was administered by inhalation to male and female Alderley Park SPF rats 6 hours/day for 6 consecutive days at 1,300 ppm. There were no deaths during the exposure interval. In the same study, male and female Alderley Park SPF rats were exposed to 90 ppm for 6 hours/day, 5 days/week for 4 weeks. There were no deaths and no signs of toxicity during the exposure interval.

In a study by the Union Carbide Corporation (1951), reported by Smyth et al. (1951), six rats that were exposed to 333,000 ppm propionaldehyde died within 10 minutes. Mortality was observed in six rats exposed to 16,000 ppm for 2.5 hours and also in 5 out of 6 rats exposed to 8,000 ppm for 4 hours. No mortality was observed in 6 rats exposed to 4,000 ppm for 4 hours. Gross examination of the lungs revealed edema, congestion, and hemorrhage.

Groups of 8 rats were exposed for 30 minutes to concentrations of propionaldehyde ranging from 13,120 to 34,030 ppm. The lethal concentration required to observe 50% mortality (LC_{50}) determined from this study was 25,420 ppm. Rats died during or shortly after the exposure period or recovered after about one hour and appeared to be unaffected on the day after the experiment (Skog 1950).

Five male and five female Sprague-Dawley rats were exposed for 4 hours to 2,190 ppm propionaldehyde. No rats died during the exposure or subsequent 14-day observation period (Eschbach 1981 as cited in AEGL 2009).

3.1.3.2 Acute Non-lethal Toxicity

Union Carbide (1993) exposed male rats to 0, 150, 750, and 1,500 ppm (measured: 0, 151, 745, and 1,453 ppm) propionaldehyde for 6-hours per day for approximately 40 days and noted increased hemoglobin levels, hematocrit and monocyte concentrations. The mean thymic weight and relative kidney weights were increased in males of the high exposure group but not in females. Exposure-related effects in the olfactory epithelium of the anterior two sections of the

nasal cavities were noted as well as vacuolization of nasal epithelium. At 150, 750, and 1,500 ppm, vacuolization of the nasal epithelium was noted as well as atrophy in females exposed to 750 ppm and males exposed to 150 ppm propionaldehyde. A dose-response was observed at a higher incidence and increasing severity at the 1,500 ppm dose and included marked atrophy in 9 out of 15 females and 6 out of 15 males. One male exposed to 750 ppm and two exposed to 1,500 ppm showed evidence of squamous metaplasia. Rhinitis was observed in males exposed to 750 ppm and 1,500 ppm and females exposed to 750 ppm propionaldehyde.

Groups of 8 rats were exposed for 30 minutes to concentrations of propionaldehyde ranging from 13,120 to 34,030 ppm. Inhalation was reported to produce anesthetic effects in most rats. Histology was conducted three weeks after exposure, and evidence of bronchitis and bronchopneumonia of the lungs and hyperemia of the liver and kidneys (Skog 1950) was observed.

Male and female rats (5 of each) were exposed to 1,930 ppm propionaldehyde. Lacrimation was seen in a few animals beginning 15 minutes after the start of exposure and lasted up to 2 days. Upon necropsy, no exposure related pathological changes were observed (Eschbach 1981 as cited in AEGL 2009).

Male Wistar rats were exposed to propionaldehyde concentrations ranging from 1,260-84,000 ppm via inhalation for 1-minute intervals (Egle et al. 1972). Propionaldehyde induced changes in blood pressure and heart rate compared to controls exposed to clean air. While 1,266 ppm appears to be a No Observed Effect Level (NOEL) for rat cardiac responses, the biological significance of these changes is uncertain for a number of reasons: (1) because of the high concentrations of propionaldehyde required to produce effects, (2) due to the transient nature of the effect which returned to control levels within 5 seconds after ending exposure, and (3) because of the mild nature of the effect.

RD50

Male Fischer-344 rats were exposed for 10 minutes to various concentrations (up to 10,000 ppm) of propionaldehyde. The RD50 value (the concentration at which respiration rate was depressed by 50%) was 6,789 ppm and the NOEL for respiratory rate changes was 72 ppm (Babiuk et al. 1985).

Steinhagen and Barrow (1984) determined the RD50 for sensory irritation in B6C3F1 and Swiss-Webster mice. Groups of three to four mice per strain were exposed via inhalation for 10 minutes to varying concentrations of propionaldehyde. The RD50 was calculated to be 2,078 ppm in B6C3F1 mice and 2,052 ppm in Swiss-Webster mice. The vapor concentration of propionaldehyde capable of causing 50% reduction in respiratory rate (RD50) during a 10-minute whole body exposure was 2,070 ppm in B6C3F1 male mice and 2,052 ppm in male Swiss-Webster mice (Steinhagen and Barrow 1984). The RD50 in Fischer F344 rats was 6,789 ppm (Babiuk et al. 1985).

Additional supporting studies are summarized in Table 4 as well as in Appendix C.

Table 4. Summary of Acute Animal Inhalation Studies

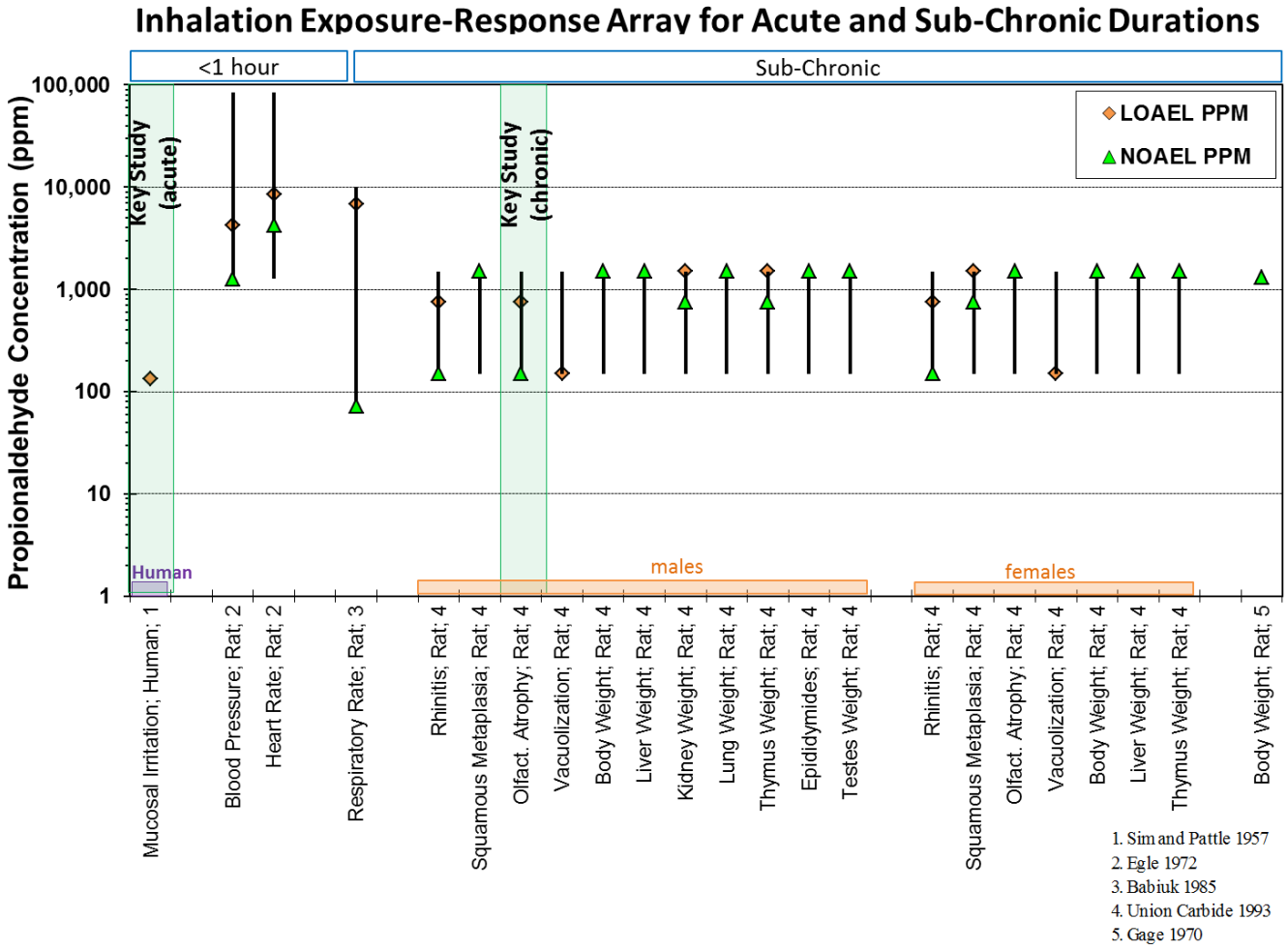
Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	1,266ppm	1 minute	No effect on blood pressure or heart rate	Egle 1972
Rat	1,300 ppm	6 hours/day for 6 days	No body weight gain Liver cell vacuolation	Gage 1970
Rat	1,930 ppm	4 hours	Lacrimation	Eschbach 1981[a]
Mouse Swiss-Webster	2,052 ppm	10 minutes	RD50	Steinhagen and Barrow 1984
Mouse B6C3F1	2,078 ppm	10 minutes	RD50	Steinhagen and Barrow 1984
Mouse Swiss-Webster	2,681 ppm	Unknown	RD50	Luo et al. 1993[a]
Mouse NIH	3,703 ppm	Unknown	RD50	Luo et al. 1993[a]
Rat	4,220 ppm	1 minute	Increase in blood pressure	Egle 1972a
Mouse	5,230 ppm	5 minutes	Anesthesia	Axelsson et al. 1953
Rat	6,789 ppm	10 minutes	RD50	Babiuk et al 1985

Note that some of these studies provided only limited information and are therefore not summarized in this section (3.1.3.2). Available details are described in Appendix C.

[a] This study is described in the 2009 AEGL document.

Figure 2 summarizes key human and animal studies used to generate an exposure-response array. The key study for acute effects (Sim and Pattle 1957, mucosal irritation) and chronic effects (Union Carbide 1993, olfactory atrophy) are highlighted and discussed further below.

Figure 2. Exposure Response Array for Propionaldehyde



3.1.4 Mode-of-Action (MOA) Analysis and Dose Metric

Similar to the MOA for other aldehydes (e.g., see TCEQ 2008 DSD for formaldehyde), the MOA for minor eye or nasal irritation after exposure to propionaldehyde may involve interaction with local nerve endings or trigeminal stimulation. Arts et al. (2006) state the free nerve endings of the trigeminal system innervate the walls of the nasal passages and eyes and respond with nasal pungency or watery/prickly eyes to a large variety of volatile chemicals.

As the concentration of propionaldehyde increases, it first causes a perception of odor, then minor eye irritation followed by irritation to the respiratory tract. Chemical stimulation of the vagal or glossopharyngeal nerves may be involved as well as trigeminal stimulation for irritation. Eye and respiratory irritation are threshold effects which may occur in tissues at sites where propionaldehyde is deposited and absorbed [i.e., portal-of-entry (POE)]. Because the precise MOA of the toxic response is not fully elucidated and data on other more specific dose metrics are not available, the exposure concentration of the parent chemical was used as the default dose metric.

3.1.4.1 Metabolism and Pharmacokinetics

Propionaldehyde is reactive and readily oxidizes to propionic acid via aldehyde dehydrogenase (ALDH), and propionaldehyde has been demonstrated to be a substrate for ALDH. Propionaldehyde dehydrogenase expression is ubiquitous and activity has been identified in mice, rats, and humans (AIHA 2002). No evidence was found to suggest that the effects reported for propionaldehyde are mediated by propionic acid.

Propionaldehyde is not expected to accumulate in humans. The low acute lethality potential and lack of systemic effects (except at high doses) suggest that ocular and upper respiratory irritation are the key effects. It should be noted that obligate nose breathing in rodents results in a higher delivery to the nasal epithelium than in humans, making it likely that rats and mice exhibit a greater susceptibility to nasal lesions than humans. Like acetaldehyde, metabolism of propionaldehyde to propionic acid is substantially decreased in liver preparations from individuals who are genetically heterozygous for the mutant form of aldehyde dehydrogenase-2 (Wang et al. 2002).

3.1.4.2 Toxicodynamics and Toxicokinetics

Like other aldehydes, most inhaled propionaldehyde is deposited and absorbed in regions of the upper respiratory tract with which it first comes into contact. The only detailed information for propionaldehyde was reported by Egle (1972), who reported that the retention of propionaldehyde vapor in the respiratory tract of dogs was approximately 75 to 80% of the inhaled dose at air concentrations between 100 and 400 ppm (250 mg/m^3 to 1,000 mg/m^3). Retentions of 75% to 80% were also measured in the dog at tidal volumes ranging from approximately 110 to 200 ml (Egle 1972).

3.1.5 Point of Departure (POD) for Key Study

The 30-minute LOAEL of 134 ppm for mild irritation of the mucosal surfaces was identified in Sim and Pattle (1957) and used as the POD to derive an acute ReV for propionaldehyde. Eye and respiratory irritation was also observed in several acute animal studies. The irritation observed in animals is assumed to be similar to humans. Additionally, irritation of mucosal surfaces was reported in healthy male volunteers exposed to other aldehydes, i.e., formaldehyde, acetaldehyde, crotonaldehyde, and n-butyraldehyde (Sim and Pattle, 1957). Therefore, eye and upper respiratory tract irritation is considered to be the critical effect for acute exposure to propionaldehyde.

3.1.6 Dosimetric Adjustments and Adjustments of the POD_{HEC}

3.1.6.1 Exposure Duration Adjustments

The POD from the Sim and Pattle (1957) human inhalation study is based on a free-standing LOAEL of 134 ppm for irritation. Because eye or respiratory irritation is a concentration-dependent effect, a duration adjustment from 30 minutes to 1 hour was not applied. Therefore, the POD_{HEC} for 1-hour exposure is 134 ppm.

3.1.6.2 Adjustments of the POD_{HEC}

The MOA by which propionaldehyde produces irritation in humans is assumed to have a threshold for the response, so a POD was determined and uncertainty factors (UFs) were applied to derive an acute ReV. The following UFs were applied to the adjusted POD_{HEC} of 134 ppm:

- UF_H = A full UF_H of 10 was used to account for human variation because the key study did not include sensitive subpopulations.

- UF_L = 3 because a LOAEL was utilized in the absence of an available NOAEL. However, a 3 was used as the effect of mild irritation is of low severity.

- UF_D = 6 because the acute database includes a number of animal studies reporting portal-of-entry (POE) effects and one study reporting mild POE effects in human volunteers (Sim and Pattle 1957). The quality of the key study is considered moderate to low; and, the confidence in the database is moderate.

- The total UF = 180

  acute ReV= POD_{HEC} / (UF_H x UF_L x UF_D)

  acute ReV= 134 ppm / (10 x 3 x 6)

  acute ReV= 0.744 ppm or 740 ppb (1,800 µg/m^3) (rounded to two significant figures)

3.1.7 Acute ReV and ^{acute} ESL

In deriving the acute ReV, no numbers were rounded until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded ReV of 740 ppb was then used to calculate the ESL. The ^{acute} ESL of 220 ppb (500 µg/m^3) is based on the acute ReV multiplied by a hazard quotient of 0.3, then rounded to two significant figures at the end of all calculations (Table 5). Refer to Appendix B for an Uncertainty Analysis for the acute ReV.

Table 5. Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Values and Descriptions**
Study	Sim and Pattle 1957
Study Population	Male volunteers (age 18-45)
Study Quality	Moderate to low
Exposure Methods	Inhalation of 134 ppm (measured concentration)
POD_{HEC}	134 ppm
Critical Effects	Mild irritation of mucosal surfaces
LOAEL	134 ppm
POD	134 ppm
Exposure Duration	30 minutes
Extrapolation to 1 h (POD_{ADJ})	134 ppm (no adjustment – effects were concentration dependent)
POD_{HEC}	134 ppm
Total UFs	180
Interspecies UF (UF_A)	NA
Intraspecies UF (UF_H)	10
LOAEL-to-NOAEL UF (UF_L)	3
Incomplete Database UF (UF_D) Database Quality	6 Medium
^{acute} ReV [1 h] (HQ = 1)	**1,800 µg/m^3 (740 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**500 µg/m^3 (220 ppb)**

3.1.8 Comparison of TCEQ's Acute ReV to Other Available Values

TCEQ's acute ReV of 740 ppb is lower than the AEGL-1 value of 45,000 ppb. It should be noted that AEGL values are designed to be used in emergency response planning and may be set at or near effect levels, whereas TCEQ values are designed to protect the general population including sensitive individuals.

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

Propionaldehyde has a sweet and ester-like odor that has been described as pleasant and fruity at low concentrations and pungent at high concentrations. The $^{acute}ESL_{odor}$ for propionaldehyde, using an evidence-integration approach and historical information as described in the Approaches to Derive Odor-Based Values (TCEQ 2015) is 92 µg/m^3 (40 ppb).

3.2.2 Vegetation Effects

A limited amount of information on environmental effects of propionaldehyde is available. Based upon the physical and chemical properties, propionaldehyde is not predicted to be a persistent environmental contaminant. Primarily, this is because propionaldehyde is highly water soluble and has an octanol/water partition coefficient of less than 1. Similar to other aldehydes, it is a reactive molecule and readily oxidizes to propionic acid, which can be metabolized in biological organisms (AEGL 2009). Given these considerations, propionaldehyde does not pose the threat of persistent environmental contamination.

A single study demonstrates that propionaldehyde can inhibit the germination of seeds, but only at relatively high concentrations (Union Carbide 1977). Therefore, the health-based values described elsewhere in this document would be expected to provide adequate protection against such effects and a specific vegetation-based value will not be derived.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

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

- Acute ReV = 740 ppb (1,800 µg/m^3)
- $^{acute}ESL$ = 220 ppb (500 µg/m^3)
- $^{acute}ESL_{odor}$ = 40 ppb (92 µg/m^3)

For the evaluation of ambient air monitoring data, both the acute ReV of 740 ppb (1,800 µg/m^3) and the $^{acute}ESL_{odor}$ of 40 ppb (92 µg/m^3) are used (Table 1). The short-term ESL for air permit reviews is the odor-based $^{acute}ESL_{odor}$ of 40 ppb as it is lower than the health-based ^{acute} ESL of 220 ppb (500 µg/m^3) (Table 2).

3.4 Acute Inhalation Observed Adverse Effect Level

As described in section 3.1.2, Sim and Pattle (1957) reported mild irritation to mucosal surfaces in volunteers exposed to a single concentration of propionaldehyde of 134,000 ppb for 30 minutes. The $LOAEL_{HEC}$ of 134,000 ppb can be considered an acute inhalation observed effect level. There is some uncertainty associated with using this study to derive toxicity factors because the subjects were allowed to smoke during exposure and certain methodological details (e.g. incidence of smoking in control versus exposed volunteers) were lacking. However this study can be utilized to estimate levels of exposure at which mild mucosal irritation may be observed. The $LOAEL_{HEC}$ determined from human studies (where effects occurred in some individuals) represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same duration used in the Sim and Pattle (1957) study (or longer durations). However, it is not certain that all individuals will experience mild mucosal irritation at the same concentration of propionaldehyde. Nevertheless, this effect is considered relevant, and is consistent with the observation of nasal effects in rats exposed subchronically to similar concentrations of propionaldehyde (150,000 ppb). This effect is also consistent with the irritant properties of propionaldehyde and POE effects observed in studies for other aldehydes. The acute inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012). The margin of exposure between the inhalation observed effect level of 134,000 ppb to the ReV of 740 ppb is a factor of 181.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

The major effect noted upon repeated exposure to high concentrations of propionaldehyde in a study conducted by Union Carbide (1993) appeared to be associated with tissues that come in direct contact with the vapor, particularly the tissues of the nasal septum. In addition to the nasal lesions, evidence of hematological changes in male rats, predominantly associated with erythrocytes, and a slight effect on male relative kidney weight was noted at the 1,500 ppm exposure concentration without histopathological confirmation of tissue damage. Decreased food consumption was noted in females exposed to vapor concentrations of 750 and 1,500 ppm. The NOAEL for systemic toxicity was 150 ppm. While this is an industry-funded study and does not appear in the peer-reviewed literature, this study has been used by USEPA as the basis for a noncancer RfC. Given the quality of the study, the TCEQ is confident that the Union Carbide (1993) study is suitable for use as the basis of a chronic noncancer ReV.

4.1.1 Physical/Chemical Properties

Physical and chemical properties of propionaldehyde have been previously discussed in Section 3.1.1 and are summarized in Table 3.

4.1.2 Key and Supporting Studies

4.1.2.1 Human Studies

No studies addressing chronic exposure to propionaldehyde were identified.

4.1.2.2 Key Animal Study (Union Carbide 1993)

In a developmental study conducted by Union Carbide (1993)[a] groups of male and female CD rats were exposed to propionaldehyde by inhalation of 0, 150, 750, and 1,500 ppm (measured: 0, 151, 745, and 1,453 ppm) for 6 hours/day for 7 days/week. Males were exposed for 52 days and females were exposed for 48 days, then held for 6-day recovery interval before sacrifice. Animals did not display overt signs of toxicity at any time during the study. Body weight gains and food consumption, however, were decreased in females in the 750 and 1,500 ppm groups during the first week of exposure. Microscopic examination revealed statistically significant treatment-related effects on nasal epithelium in the anterior two sections of the nasal cavity in both sexes in all propionaldehyde-exposed groups. A LOAEL of 150 ppm for nasal effects was identified. Vacuolization of nasal epithelium was primarily evident in low and intermediate exposure groups, while atrophy was observed in intermediate and high exposure groups. A NOAEL of 150 ppm for vacuolization of nasal epithelium was identified. The injury appeared to be diminished in females, possibly as a result of the 6-day recovery interval. The results of this study showed a dose-response increase in the incidence of atrophy of the olfactory epithelium.

A benchmark concentration (BMC) analysis was conducted on the incidence of atrophy of the olfactory epithelium in male rats as observed in the Union Carbide (1993) study. Although nasal effects were seen in both males and females, there was a clear decrease in incidence and severity in females that was likely due to differing exposure periods than utilized for males (cessation of exposure after gestational day 20 and sacrifice on postnatal day 4 in females versus continuous exposure in males). Thus, nasal lesion in male rats was the most biologically and toxicologically relevant response identified, and the available concentration-response information supports the use of this analytical approach. The results from the BMC analysis and the model outputs are shown in Appendix A.

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[a] This study met the requirements of the following Good Laboratory Practice Standards: Toxic Substances Control Act (TSCA), 40 CFR Part 792; Organization for Economic Co-operation and Development (OECD), C(81) 30 (Final).

Table Summary of Chronic Animal Inhalation Studies

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	90 ppm	6 hours/day for 20 days	No Effect	Gage 1970
Rat	151 ppm	52 days	Vacuolization and atrophy of olfactory epithelium	Union Carbide 1993
Rat	745 ppm	52 days	Vacuolization and atrophy of olfactory epithelium	Union Carbide 1993
Rat	750 ppm	6 hours/day for 28 days	Rhinitis Squamous metaplasia Olfactory atrophy	Union Carbide 1993
Rat	1,453 ppm	52 days	Marked atrophy and squamous metaplasia of olfactory epithelium	Union Carbide 1993
Rat	1,500 ppm	6 hours/day for 28 days	Organ weight changes	Union Carbide 1993
Rat	2,592 ppm	52 days	No lethality or clinical signs, effects on body weight, increase in hemoglobin, hematocrit, and monocytes	Union Carbide 1993

4.1.2.3 Supporting Animal Studies

Male and female Alderley Park rats (4 of each) were exposed 6 hours/day for 6 days to 1,300 ppm propionaldehyde or 6 hours/day for 20 days to 90 ppm (Gage 1970). A number of endpoints were evaluated in the study, including hematology, urinalysis, macroscopic and microscopic examination of various organs including the lungs, but not nasal epithelium. Upon necropsy, organs appeared normal, and microscopic examination of tissues identified vacuolization of hepatocytes in rats exposed to 1,300 ppb. The description of the results in this study is very limited.

4.1.2.4 Reproductive/Developmental Toxicity

One-generation inhalation study in rat

Male and female rats were exposed to propionaldehyde by inhalation for 6 hours per day, 7 days per week, at concentrations of 0, 150, 750, or 1500 ppm. Males received 53 consecutive daily exposures; females were exposed through gestation day 20, for a maximum of 48 days. Females were allowed to litter and pups were evaluated for body weight, viability, and survival until post-natal day 4 at which time both dams and pups were sacrificed and necropsied. No significant effects of exposure were noted on any reproductive parameter assessed. Mating index and fertility index for males and females were similar among all groups. Pup body weights were not

affected by exposure, although body weight gain of pups from the highest exposure group was slightly depressed (Union Carbide 1993). Litter size and viability were similar among exposure groups (150, 750 and 1,500 ppm) and the control. Information on the effects of propionaldehyde on the developing embryo and fetus was obtained in the same study. There was no evidence of external malformations in pups from dams exposed to vapor at concentrations up to 1,500 ppm over the entire gestation. Thus the NOAEL for reproductive toxicity was greater than 1,500 ppm.

Intraamniotic injection developmental study in rat

Timed-pregnant female Sprague-Dawley rats were injected under anesthesia on gestation day 13. Embryos in one uterine horn received intraamniotic injection of propionaldehyde at doses of 10, 100, or 1,000 µg/embryo. Females were sacrificed on gestation day 20. Uterine horns were removed and number of dead or resorbed fetuses was determined. Live fetuses were examined for external malformations. Propionaldehyde treatment resulted in a dose-dependent increase in embryo mortality. The increase in embryolethality was significant at the highest dose when compared to saline-injected controls. There was no increase in fetal malformations up to the highest concentration tested (Slott and Hales 1985).

4.1.3 Mode of Action and Dose Metric

The MOA for chronic nasal lesions is similar to the MOA for acute effects discussed in Section 3.1.4 Because the precise MOA of the toxic response is not fully elucidated and data on other more specific dose metrics are not available, the exposure concentration of the parent chemical was used as the default dose metric.

4.1.4 PODs for Key Study and Critical Effect

The critical effect identified from the key study (Union Carbide 1993) was atrophy of olfactory epithelium in male rats. This effect is considered biologically relevant, exhibited a concentration-response relationship, and was observed at the lowest exposure concentration tested (150 ppm). The atrophy at this dose was of minimal severity and not noted in females, possibly due to the longer duration of exposure of male compared to female rats. This effect is consistent with the irritant properties of propionaldehyde and POE effects observed in studies for other aldehydes. Along with atrophy, vacuolization of olfactory epithelium was also noted. However this effect is considered homeostatic and adaptive and characteristic of and often accompanying cells undergoing atrophy (EPA 2008).

Taken together, the nasal lesion data for propionaldehyde over the range of exposures tested showed progression in both severity and incidence and was noted in both male and female rats. In addition, this pattern of nasal lesion progression (atrophy with vacuolization, necrosis, and squamous metaplasia) was also noted with exposure to acetaldehyde (EPA 2008). Given that liver and cardiac effects described earlier required exposure to much higher concentrations, it is appropriate to select atrophy of olfactory epithelium as the critical endpoint for derivation of toxicity factors.

Benchmark Dose Modeling was conducted for atrophy of olfactory epithelium in male rats exposed to 150-1,500 ppm propionaldehyde utilizing data from Union Carbide 1993. Results are presented in Appendix A. A $BMCL_{10}$ of 55.9915 ppm was derived from this modeling and utilized as the POD.

4.1.5 Dosimetric Adjustments

4.1.5.1 Exposure Duration Adjustments

The key study utilized exposure durations of 6 h/day, 7 days/week for 7 weeks. Based on this, the following duration adjustment was derived:

$$POD_{ADJ} = POD \times (D/24\ h) \times (F/7\ days)$$

where:
POD_{ADJ} = POD from animal studies, adjusted to a continuous exposure scenario
POD = POD from animal studies, based on discontinuous exposure regimen
D = exposure duration (hours per day)
F = exposure frequency (days per week)

$$POD_{ADJ} = 55.9915\ ppm \times (6/24\ h) \times (7/7\ days) = 13.9979\ ppm$$

Based on dosimetric adjustment described above, the POD_{ADJ} is 13.9979 ppm.

4.1.5.2 POD Human Equivalent Concentration (POD_{HEC})

In accordance with TCEQ guidance[b] for deriving inhalation ReVs, propionaldehyde is categorized as a Category 1 gas with extrathoracic (ET) respiratory effects. A default dosimetric adjustment factor (DAF) of 1 will be applied when the critical effect is in the extrathoracic respiratory tract region (includes the nasal and oral passages, pharynx, and larynx). Internal dose equivalency in the ET region for rats (and other laboratory animals) and humans is achieved through similar external air exposure concentrations, not one adjusted by the ratio of ventilation (VE) to surface area (SA). Therefore, the POD_{HEC} is 13.9979 ppm.

For Category 1 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$$
$$= 13.9979\ ppm \times 1$$

[b] White paper on revisions to animal-to-human inhalation dosimetric adjustments. TCEQ (2013)

=13.9979 ppm

4.1.6 Adjustments of the POD_{HEC}

The MOA by which propionaldehyde produces nasal atrophy in rats is assumed to have a threshold for the response, so a POD was determined and uncertainty factors (UFs) were applied to derive a chronic ReV. The following UFs were applied to the adjusted POD_{HEC} of 13.9979 ppm:

- UF_H = 10 to account for human variation.
- UF_A = 3 for the uncertainty of interspecies toxicodynamic variability, because the animal-human differences in toxicokinetics were largely accounted for through the use of the default dosimetric adjustment from animal-to-human exposure.
- UF_{sub} = 3 because the rat exposure durations in the Union Carbide study were 7 weeks, which is considered a subchronic exposure duration for rats (USEPA 1994). Additionally, because propionaldehyde has a low K_{ow} it is expected to be rapidly oxidized and not expected to accumulate in humans. Therefore, a UF_S of 3 is considered to be sufficient.
- UF_D = 3 because the chronic noncancer database includes one subchronic inhalation key study in the rat (Union Carbide), and one reproductive toxicity study in the rat (Union Carbide). The quality of the key study is considered high; and, the confidence in the database is low to moderate.
- The total UF = 270[c]

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

The chronic ReV value was calculated by the following equation:

$$\text{Chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_S \times UF_D)$$
$$= 13.9979 \text{ ppm} / (10 \times 3 \times 3 \times 3)$$
$$= 0.052 \text{ ppm or } 52 \text{ ppb } (130 \text{ µg/m}^3)$$

Values were rounded to two significant figures at the end of all calculations. The derived chronic ReV of 52 ppb (130 µg/m^3) was used to calculate the $^{chronic}ESL_{threshold(nc)}$. The $^{chronic}ESL_{threshold(nc)}$

[c] In addition to the considerations listed for each UF, the critical effect occurs at the portal-of-entry and is considered minimally adverse, and the use of nasal lesions observed in rats as the critical effects for humans is very conservative.

of 16 ppb (40 µg/m^3) is based on the chronic ReV multiplied by a HQ of 0.3, then rounded to two significant figures at the end of all calculations (Table 6 below). Refer to Appendix B for an Uncertainty Analysis for the chronic ReV. The resulting ReV and $^{chronic}ESL_{threshold(nc)}$ are used for the evaluation of ambient air monitoring data and air permits.

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

Parameter	**Values and Descriptions**
Study	Union Carbide 1993
Study Population	Male rats
Study Quality	High
Exposure Methods	Whole body
Critical Effects	Atrophy of olfactory epithelium
LOAEL	150 ppm
NOAEL	NA
POD	55.9915 ppm
Exposure Duration	6h/day, 7days/week for 7 weeks
Extrapolation to continuous exposure (POD_{ADJ})	13.9979 ppm
POD_{HEC}	13.9979 ppm
Total UFs	270
Interspecies UF (UF_A)	3
Intraspecies UF (UF_H)	10
Subchronic-to-Chronic UF (UF_S)	3
Incomplete Database UF (UF_D) Database Quality	3 Medium
Chronic ReV (HQ = 1)	**130 µg/m^3 (52 ppb)**
$^{chronic}ESL_{threshold\ (nc)}$ (HQ = 0.3)	**40 µg/m^3 (16 ppb)**

4.1.8 Comparison of TCEQ's Chronic ReV to USEPA's Chronic Reference Concentration

TCEQ's chronic ReV of 52 ppb (130 µg/m^3) is higher than the chronic value (RfC) derived by USEPA's IRIS program (3 ppb). Although both agencies chose the same critical effect from the

same study (Union Carbide), TCEQ utilized newer BMD software and an updated approach to dosimetric adjustment[d] that was published since release of the EPA draft document for propionaldehyde (EPA 2008). In addition, while EPA chose to use a UF_{sub} of 10, as described in TCEQ Guidelines (TCEQ 2012) ECETOC[e] recommends that no adjustment for exposure duration is needed (i.e., $UF_{sub} = 1$) for chemicals that have: (1) local effects (i.e., irritation); or (2) a relatively short toxicokinetic half-life, no toxic metabolite, no potential for bioaccumulation and/or cumulative toxicity, and no reactivity to tissue components. However, in order to be conservative, the TD chose a UF_{sub} of 3 in this instance.

4.2 Carcinogenic Potential

4.2.1 Summary

The USEPA evaluated the oral carcinogenicity data for propionaldehyde, and determined that there is "inadequate information to assess the carcinogenic potential" for propionaldehyde. No human health effects data or chronic animal bioassay studies are available that assess the carcinogenic effects of propionaldehyde, but there is some limited data regarding the potential genotoxicity of propionaldehyde in bacteria and mammalian cells *in vitro* (Section 4.2.2.1*)* Propionaldehyde was found to be mutagenic in *S. typhimurium* strain TA1534 (Sampson and Bobik 2008) and nonmutagenic in all other strains tested (Dillon et al. 1998, Aeschbacher et al. 1989, Mortelmans et al. 1986). Propionaldehyde produced a concentration-related increase in chromosome aberrations in Chinese hamster embryonic cells (Furnus et al. 1990) and chromosome breaks in CHO cells (Seoane and Dulout 1994). In addition, propionaldehyde induced a concentration-related increase in unscheduled DNA synthesis in rat, but not human, hepatocytes (Martelli 1997, Martelli et al. 1994) and a weak, concentration-related increase in DNA-Protein crosslinks in cultured human lymphoma cells (Costa et al. 1997).

In the 1993 Union Carbide study, a low incidence of squamous metaplasia was observed in male rats after inhalation of propionaldehyde (Section 4.2.2.2 below). This may be viewed as an adaptive response typical of nasal epithelial tissues in response to continued irritation. Alternatively, the lesion could contribute to tumorigenesis if the initial injury progressed to atypia, hyperplasia, and altered cell proliferation. However, because these specific alterations were not observed after exposure to propionaldehyde, it appears the presence of squamous metaplasia alone constitutes a nonneoplastic lesion in nasal tissue and is not a suitable endpoint for assessing cancer risk.

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[d] White paper on revisions to animal-to-human inhalation dosimetric adjustments. TCEQ (2013):

[e] European Center for Ecotoxicology and Toxicology of Chemicals

4.2.2 Genotoxicity/mutagenicity

4.2.2.1 *In vitro studies*

Propionaldehyde was negative in seven strains of *Salmonella typhimurim* at concentrations up to 10,000 ug/plate, in the presence and absence of rat, mouse, or hamster S-9 (Mortelmans et al. 1986, Dillon et al. 1998, Pool and Wiessler 1981, Aeschbacher et al. 1989). Propionaldehyde induced a dose-dependent increase in mutation frequency in Chinese hamster V79cells in the absence of metabolic activation (Brambilla et al. 1989). Chinese Hamster Ovary (CHO) cells exposed to propionaldehyde displayed increases in chromosomal aberrations (Furnus et al. 1990) and weak increases in the incidence of lagging chromosomes when compared to untreated controls. However, there was no difference in chromatin bridges or lagging fragments between control and treatment groups (Seoane and Dulout 1994). Smith et al. 1990 reported that propionaldehyde was not mutagenic in CHO cells exposed to noncytotoxic concentrations.

4.2.2.2 *In vivo studies*

Propionaldehyde was administered to groups of male and female Swiss-Webster mice as a single IP injection at doses of 240, 480, or 768 mg/kg (25%, 50% or 80% of the LD50, respectively). Animals were sacrificed at 12, 24, and 48 hours after treatment and bone marrow was collected. Polychromatic erythrocytes were examined for micronuclei. Although the males in the high dose group had higher incidence of micronuclei than vehicle controls, the overall incidences of micronuclei and the distribution were within normal regions. Therefore, propionaldehyde was not considered to be an inducer of micronuclei under the conditions tested (Vergnes and Morabit 1993).

In 1993, Union Carbide exposed male and female CD rats (15/sex/group) to 0, 150, 750, or 1,500 ppm propionaldehyde for 6 hours/day, 7 days/week, during a 2-week premating period and a 14-day mating phase. The mated females were exposed daily through GD 20 for a minimum of 35 days and a maximum of 48 days depending upon when they mated (average exposure period was 38 days). The females were then allowed to deliver their litters naturally and raise pups until day 4, when they were sacrificed. The males continued to be exposed until sacrifice in week 7, for a total of 52 exposures.

In males, body weights, weight gains, clinical observations, and food consumption were similar across all exposure groups and controls. At necropsy, no gross lesions were found. However, similar to females, microscopic examination identified exposure-related effects in the olfactory epithelium of the nasal cavity that consisted of vacuolization in the low and intermediate exposure groups and atrophy in the intermediate and high exposure groups. These effects were localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 2/15, 10/15, and 15/15 at 0, 150, 750, and 1,500, respectively. The severity of the nasal lesions increased with exposure concentration being minimal at 150 ppm, minimal to moderate at 750 ppm, and mild to marked at 1,500 ppm. Squamous metaplasia of the respiratory epithelium was reported in one male exposed to 750 ppm and two males exposed to 1,500 ppm. Increased

incidence of minimal to moderate rhinitis was noted at the 750 and 1,500 ppm exposures. The decrease in incidence and severity of the nasal lesions in females relative to males may be attributed to the differences in exposure durations and approximate 6-day period between cessation of exposures after GD 20 and sacrifice on day 4 of lactation in females. This observation may also indicate that these effects are reversible and that repair and regeneration of the olfactory epithelium has been initiated. This may be viewed as an adaptive response resulting from irritation, especially as atypia, disorganization, hyperplasia, changes in cell proliferation, and tumor formation were not observed in this study.

4.3 Welfare-Based Chronic ESL

No information was found to indicate that chronic vegetation effects result from exposure to propionaldehyde

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV = 52 ppb (130 µg/m^3)
- $^{chronic}ESL_{threshold(nc)}$ = 16 ppb (40 µg/m^3)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{threshold(nc)}$ of 16 ppb as no $^{chronic}ESL_{nonthreshold(c)}$ was derived (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is set to protect noncancer nasal lesions from chronic exposure. For evaluation of air monitoring data, the chronic ReV of 52 ppb is used (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Level

There is no long term data available to assess the concentration at which exposure to propionaldehyde would be expected to result in chronic effects in humans. However, the LOAEL of 150 ppm (150,000 ppb) was identified for nasal effects (atrophy) in rats exposed subchronically to propionaldehyde (Union Carbide 1993). Given that this is a POE, similar effects could be anticipated in humans exposed to this concentration. In addition, this concentration is similar to the acute inhalation observed effect level in humans described above. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 150,000 ppb is provided for informational purposes only (TCEQ 2012). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. The margin of exposure between the chronic inhalation observed adverse effect level of 150,000 ppb to the chronic ReV of 52 ppb is a factor of 2,884.

Chapter 5 References

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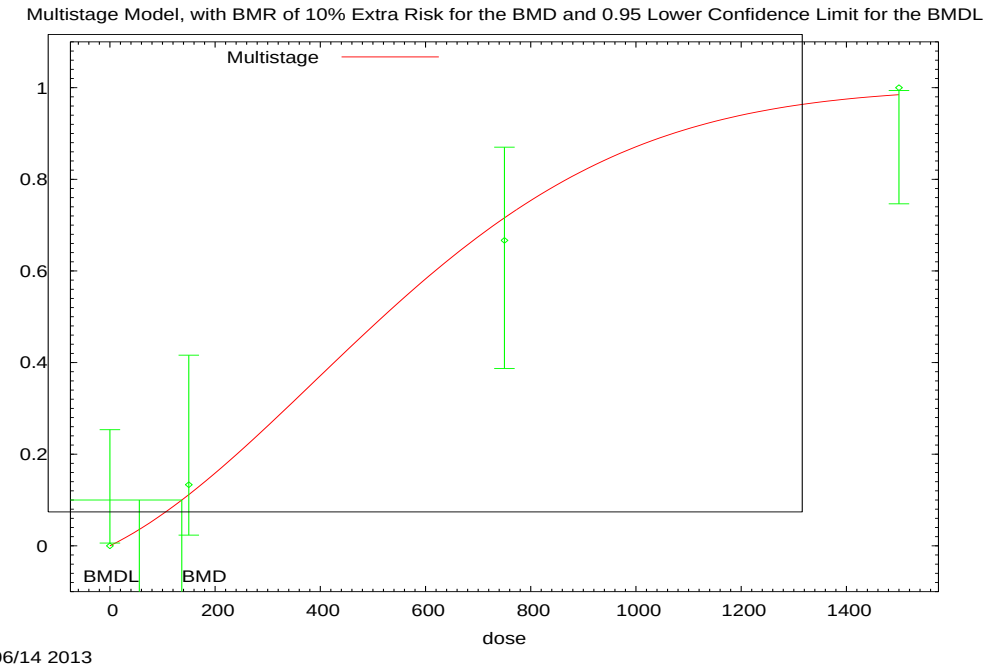
Appendix A Benchmark Dose Modeling

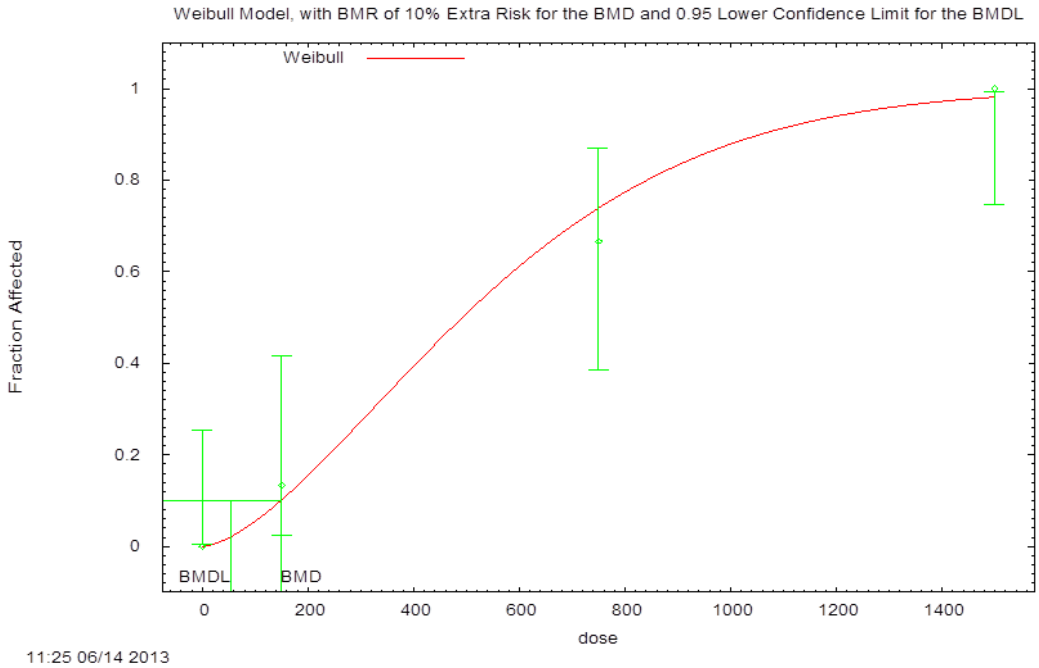
Incidence of critical effect (atrophy of olfactory epithelium) in male rats exposed to propionaldehyde (Union Carbide 1993).

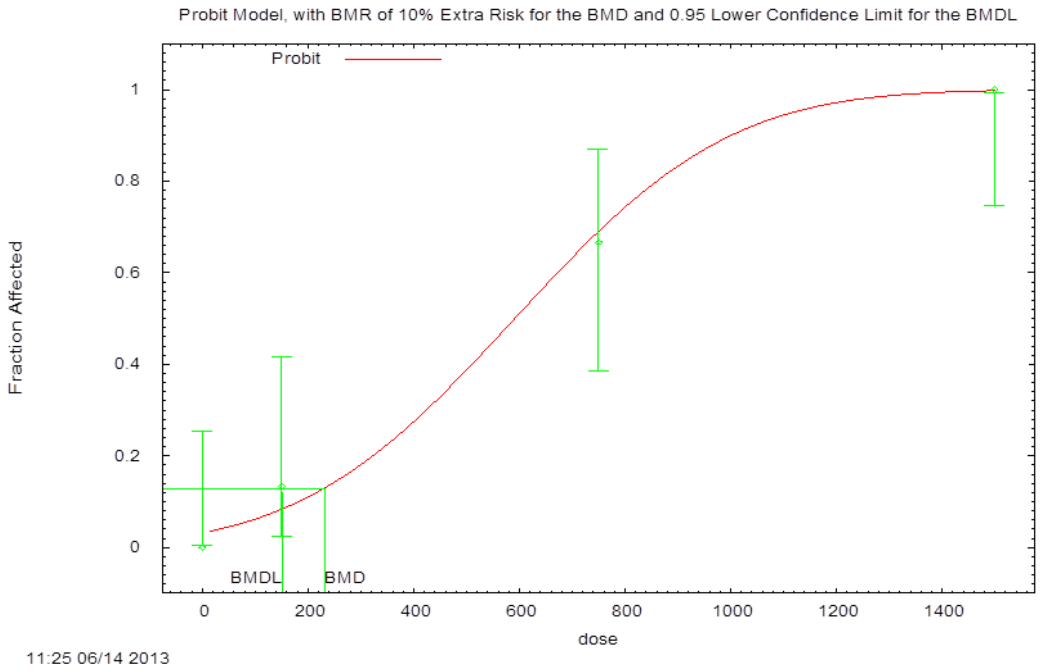
Dose	Observed	Size
0	0	15
150	2	15
750	10	15
1500	15	15

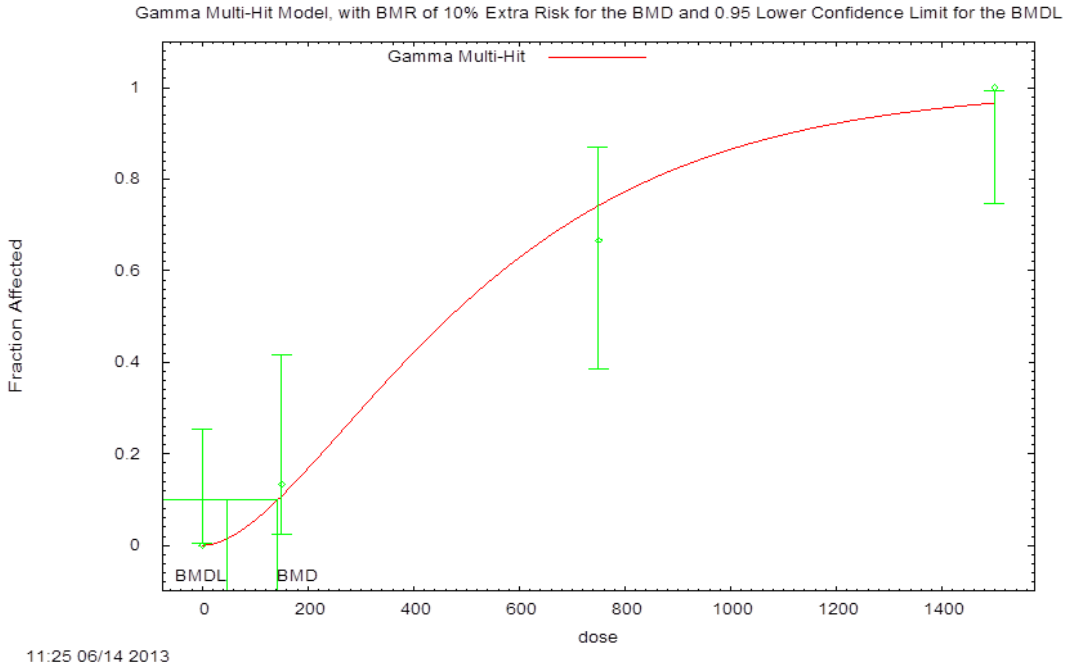
Summary of BMC modeling results based on incidence of olfactory epithelium atrophy in male rats.

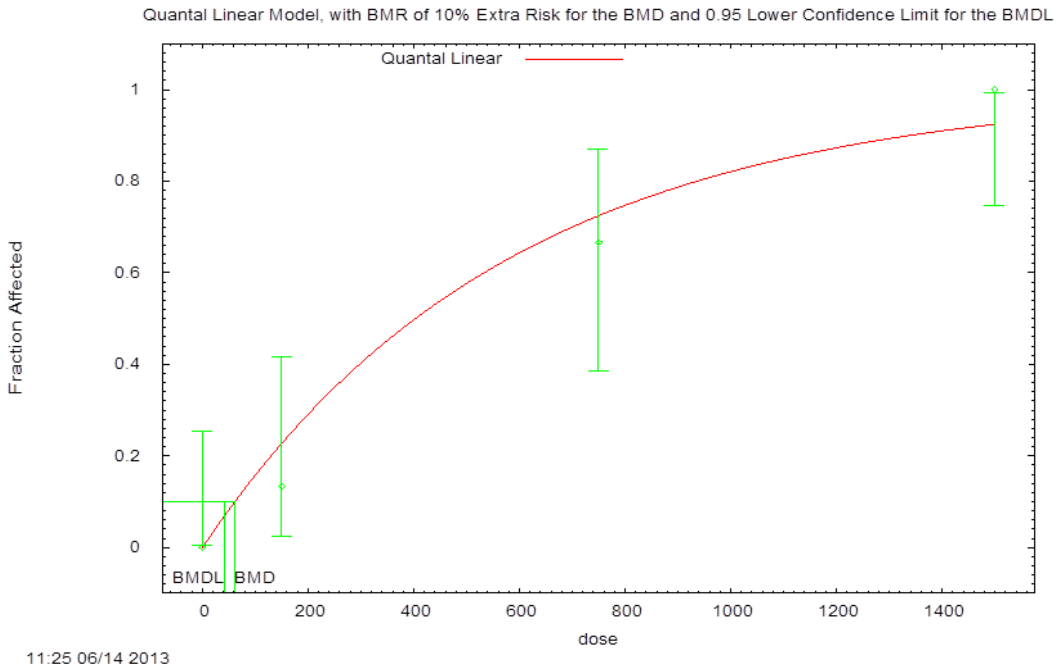
Model Name	AIC	P-value	Specified Effect	Scaled residual for dose group near BMD	BMD	BMDL
Multistage	35.5773	0.7853	0.1	0.265	136.713	55.9915
Weibull	35.9657	0.6659	0.1	0.427	149.805	53.4178
Probit	36.3759	0.5885	0.1	0.708	230.939	151.51
Gamma	36.4169	0.5852	0.1	0.31	142.573	45.6226
Quantal-Linear	36.3352	0.5238	0.1	0	61.1881	42.5618
Logistic	36.7737	0.5113	0.1	0.786	256.914	162.918
LogProbit	37.5236	0.3916	0.1	0.339	145.727	68.2822
LogLogistic	37.8641	0.3612	0.1	0.374	146.948	62.8689

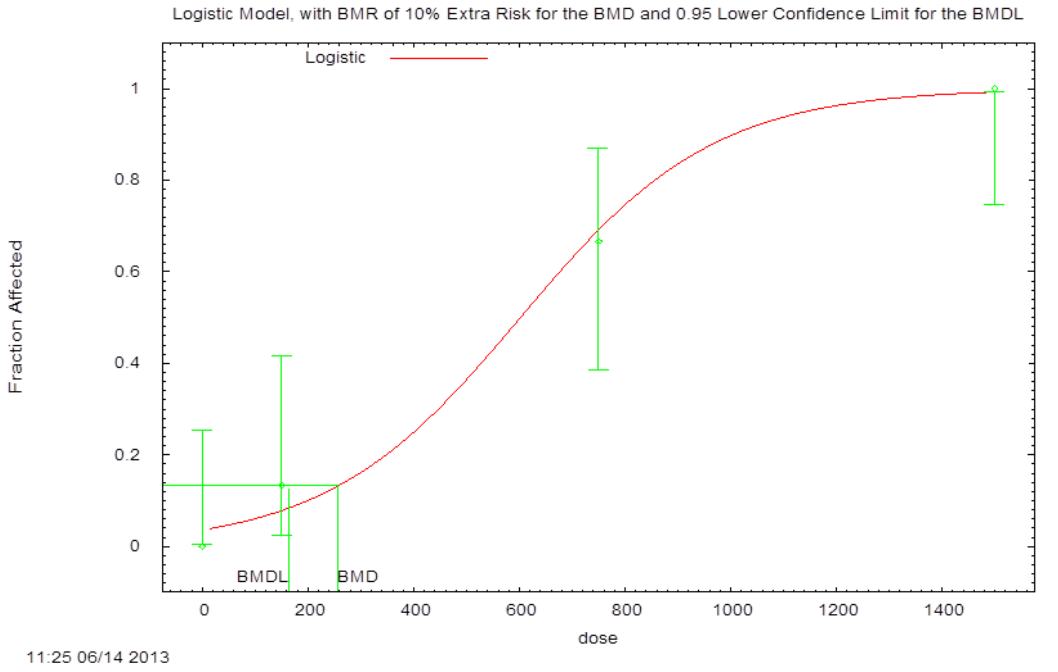

Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Multistage
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013

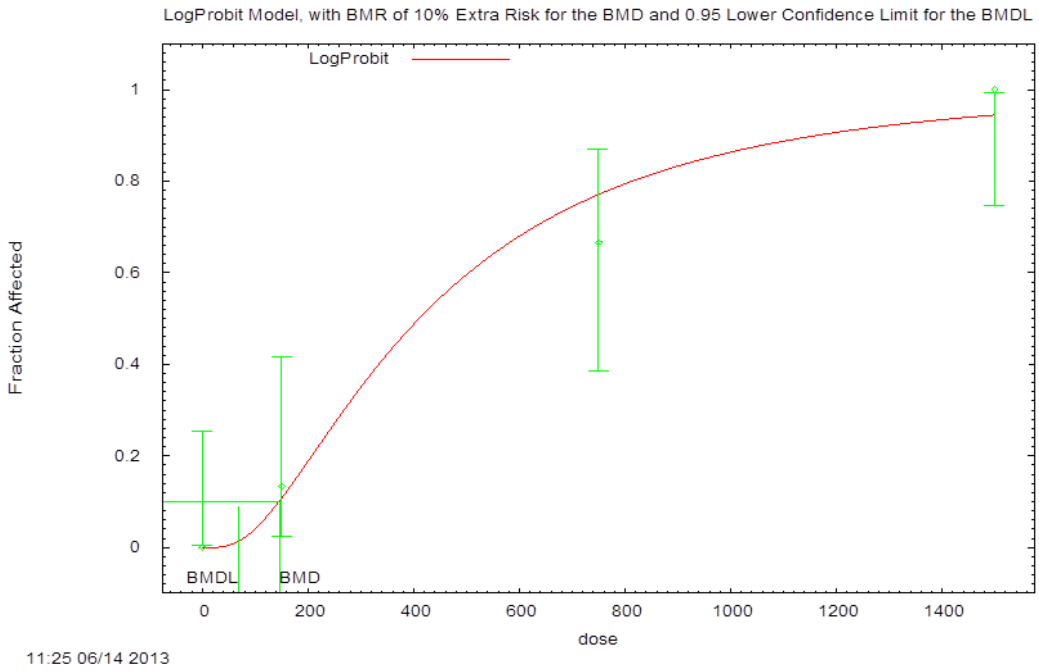

Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Weibull
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013

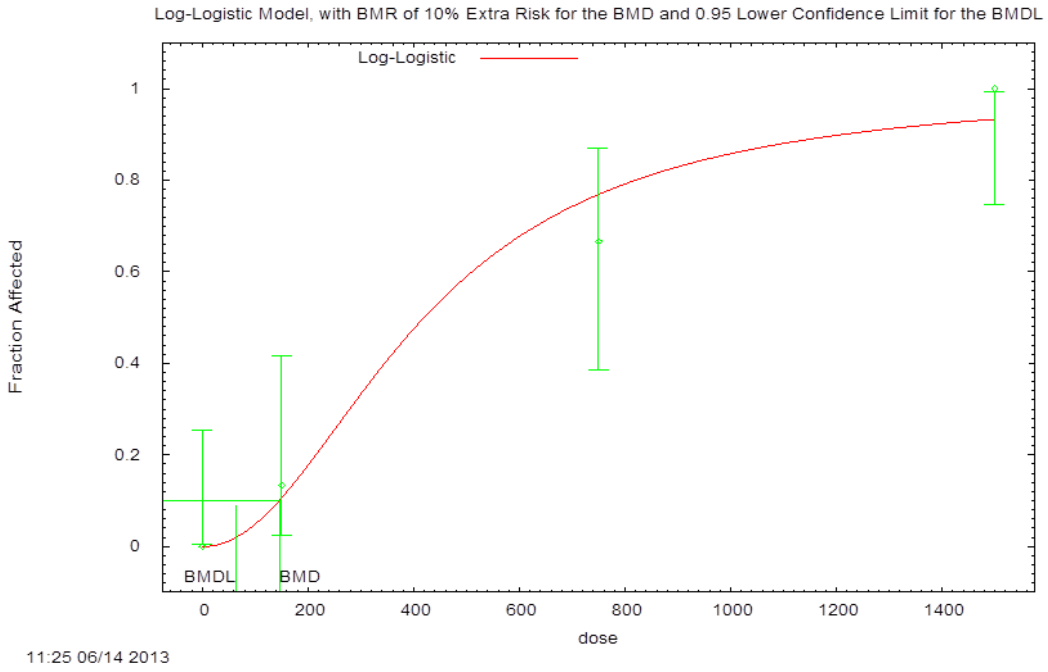

Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Probit
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013


Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Gamma Multi-Hit
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013


Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Quantal Linear
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013


Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Logistic
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013


LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
LogProbit
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013


Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Log-Logistic
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
200
400
600
800
1000
1200
1400
dose
11:25 06/14 2013

Appendix B Uncertainty Analysis

Issue	Potential Impact	Decision	Justification
Acute ReV			
Choice of key study	Potentially significant	Sim and Pattle 1957 study chosen	Only study available reporting acute exposure in humans.
Choice of endpoint	Potentially significant	Mild mucosal irritation was the only effect reported in human volunteers	Mild mucosal surface irritation in volunteers is consistent with eye and respiratory irritation observed in experimental animals.
Chronic ReV			
Choice of key study	Potentially significant	Union Carbide 1993 study chosen	No adequate alternatives available
Choice of noncancer endpoint	Use of cardiac response versus olfactory epithelium atrophy could increase ReV	ReV is based on the most biologically relevant, sensitive endpoint in accordance with TCEQ Guidelines	The selected endpoint is consistent with the expected properties of propionaldehyde (irritation) and is reasonably anticipated to be relevant to human exposure. Cardiac effects were observed in acute studies conducted at concentrations at least eight-fold higher than those that induced nasal irritation.
Human relevance of selected endpoint	If not relevant, ReV may be unnecessarily conservative	Assumed human relevance	Given mode of action (reactivity of aldehyde functional group) with tissue regardless of location within respiratory tract, there is relatively little uncertainty concerning the applicability of relevance to humans.

Comparison of propionaldehyde effects with other aldehydes

Acute

The critical effect of mild irritation of the mucosal surfaces was identified in Sim and Pattle (1957) and used to derive an acute ReV for propionaldehyde. Eye and respiratory irritation was

also observed in several acute animal studies. The irritation observed in animals is assumed to be similar to humans. Additionally, irritation of mucosal surfaces was reported in healthy male volunteers exposed to other aldehydes, i.e., formaldehyde, acetaldehyde, crotonaldehyde, and n-butyraldehyde (Sim and Pattle, 1957). Therefore, eye and upper respiratory tract irritation is considered to a relevant critical effect for acute exposure to propionaldehyde.

Chronic

The severity and incidence of these nasal effects noted in the key study (Union Carbide 1993) were dependent on exposure concentration and duration. A similar pattern and progression of nasal olfactory lesions were observed in rats exposed to acetaldehyde for up to 65 exposure days (Dorman et al., 2008). Olfactory epithelial degeneration increased in incidence and severity with both exposure concentration and duration. The presence of vacuolization was also noted. Olfactory degeneration was observed prior to vacuolization upon interim sacrifice at each exposure concentration tested, and vacuolization was not observed at exposure concentrations that did not induce degeneration. In rats exposed chronically to isobutyraldehyde, nonneoplastic lesions (squamous metaplasia) of the respiratory epithelium was observed at concentrations ≥500 ppm, degeneration of the olfactory epithelium at 2,000 ppm, and inflammation at 2,000 ppm (NTP, 1999). No increases in neoplastic nasal lesions were observed in this study. Exposure to formaldehyde for 13 weeks also produced similar effects in the nasal respiratory epithelium, consisting of epithelial hyperplasia, squamous metaplasia, and increases in cell proliferation at concentrations as low as 3 ppm (Zwart et al., 1988).

Appendix C Other Studies and Documents Reviewed by the TD

The 2009 AEGL document lists a study by Eschbach (1981) in Table 3 reporting lacrimation in rats exposed to 1,930 ppm for 4 hours. This study could not be located.

In an abstract from the 32nd Annual meeting of the Society of Toxicology, Luo et al. (1993) (as cited in AEGL 2009) provide RD50 values for propionaldehyde of 3,703 and 2,681 ppm in two strains of mice (NIH and Swiss-Webster). The authors suggest a TLV of 80 ppm for propionaldehyde. Additional details were not available.

Axelsson et al. (1953) exposed mice to 12.6 mg/L (5,230 ppm) propionaldehyde and tested for anesthetic effect. Effects ranging from uncoordinated movement to complete anesthesia were observed over the course of treatment, which appears to be approximately 6 minutes or less, although methodological details are lacking for this report. From this study, an RD50 of 5,230 ppm was identified for anesthetic effects.

Limited information on estimated LC50 values is available in the AEGL document. In rats exposed to 333,000 ppm, 1 out of 12 rats died after 3 minutes and 5 out of 6 rats died after 10 minutes (BASF 1975 as cited in AEGL 2009). An LC50 of 8,938 ppm in mice is predicted based on 2 hour exposure by Izmerov et al. (1982) (as cited in AEGL 2009) and an LC50 of 8,200 ppm in mice after an unknown exposure apparently based on a study by Wang (1957). No further information on these studies is available.

A 1983 study by Melnikova and Tokanova, originally in Russian, was described in the AEGL 2009 document. According to a short translation by the Russian Research Institute of Hygiene, Toxicology and Occupational Pathology, this study exposed male Wistar rats to continuous inhalation of propionaldehyde at 4.3 ppm for 3 weeks. This exposure did not cause any observable effects, but at autopsy, changes in parenchymal organs, desquamative bronchitis and interstitial pneumonia were noted. The same study also reported continuous exposure to 1.6-533 ppm propionaldehyde for up to 75 days. Though various effects were reported (tachypnea, irritation of the ocular mucosa and upper respiratory tract, and parenchymal changes in liver and kidney), no clear conclusions can be drawn due to the limited reporting in the translation of this study.

Wang et al. (2002) performed a genotype analysis of the ALDH2 gene in the livers of human volunteers in order to investigate the metabolism of a variety of aldehydes. Of a total of 39 subjects, 8 were heterozygotes of the wild-type (ALDH2*1) and mutant (ALDH2*2) alleles, and the others were homozygotes of the wild-type allele. The ability of mitochondria isolated from these livers to metabolize propionaldehyde, acetaldehyde, formaldehyde, *n*-butyraldehyde, capronaldehyde, and heptaldehyde was significantly ($p < 0.05$) lower (between 37 and 93%, depending on the aldehyde; 80% for propionaldehyde) in the heterozygotes (ALDH2*1/*2) compared to the homozygotes (ALDH2*1/*1), showing differences in metabolism between the

two genotypes. However, the mitochondrial activity was not lower for octylaldehyde, decylaldehyde, retinaldehyde, benzaldehyde, 3-hydroxybenzaldehyde, 2,5-dihydroxybenzaldehyde, phenylacetaldehyde, and 3-phenylpropionaldehyde, showing similar metabolism between the two genotypes. Based on these results, the authors hypothesized that polymorphisms of the ALDH2 gene appear to exist in the human population, which may alter the metabolism of the short aliphatic chain aldehydes. It is not clear, however, if the potential increase to parent aldehyde exposure exists *in vivo* for heterozygotes.