Development Support Document
Final, September 4, 2015

Vinyl Acetate

CAS Registry Number: 108-05-4

Prepared by

Jessica L. Myers, Ph.D.

Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES

Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
AEGL	Acute Exposure Guideline Level
AMCV	Air Monitoring Comparison Value
$^{\circ}$C	degrees Celsius
d	day(s)
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 effect
^{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 effects
^{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
GD	gestational day
h	hour(s)
Hg	mercury
HEC	human equivalent concentration
HQ	hazard quotient
kg	kilogram

Acronyms and Abbreviations	Definitions
LED_{10}	effective dose lower bound
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(s)
MOA	mode of action
n	number
N/A	Not applicable
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
PBPK	physiology based pharmacokinetic model
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
SD	Sprague-Dawley
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor

Acronyms and Abbreviations	Definitions
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
VA	vinyl acetate
V_E	minute volume
wk	week(s)

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 vinyl acetate (VA). Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2015a) for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on VA's physical/chemical properties.

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

Short-Term Values	Concentration	Notes
Acute ReV	2,300 µg/m^3 (670 ppb) **Short-Term Health**	**Critical Effect(s):** Persistent slight throat irritation in humans
$^{acute}ESL_{odor}$	420 µg/m^3 (120 ppb) **Odor**	50% detection threshold Sweet fruity odor or a sharp, sour odor
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	1,000 µg/m^3 (300 ppb) **Long-Term Health**	**Critical Effect(s):** Olfactory epithelial atrophy and basal cell hyperplasia in rats and olfactory epithelial atrophy and nasal submucosal gland hyperplasia in mice
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Chronic ReV based on noncarcinogenic effects is considered protective against potential carcinogenic effects (see Section 4.2)
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

[a] VA is not monitored for by the TCEQ's ambient air monitoring program, so currently no ambient air data (i.e., peaks, annual averages, trends, etc.) are available to assess VA's concentrations in Texas ambient air.

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

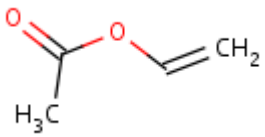
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	690 µg/m^3 (200 ppb)[a]	**Critical Effect(s):** Persistent slight throat irritation in humans
$^{acute}ESL_{odor}$	420 µg/m^3 (120 ppb) **Short-Term ESL for Air Permit Reviews**	50% detection threshold Sweet fruity odor or a sharp, sour odor
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	300 µg/m^3 (90 ppb)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Olfactory epithelial atrophy and basal cell hyperplasia in rats and olfactory epithelial atrophy and nasal submucosal gland hyperplasia in mice
$^{chronic}ESL_{threshold(c)}$	---	Chronic ESL based on noncarcinogenic effects is considered protective against potential carcinogenic effects (see Section 4.2)
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

[a] Based on the acute ReV of 2,300 µg/m^3 (670 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 1,000 µg/m^3 (300 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	$C_4H_6O_2$	NRC 2013
Chemical Structure		ChemID Plus 2009
Molecular Weight	86.09	NRC 2013
Physical State at 25°C	Liquid	NRC 2013
Color	Colorless	ATSDR 1992
Odor	Sweet, fruity, immediately pleasant but becoming sharp and irritating	ATSDR 1992; NRC 2013
CAS Registry Number	108-05-4	NRC 2013
Synonyms	VA; acetic acid, ethenyl ester; acetic acid, ethylene ester; acetic acid, vinyl ester; 1-acetoxyethylene; ethanoic acid; ethenyl ester; ethenyl acetate; ethenyl ethanoate; vinyl A monomer; vinyl ethanoate; 1-Acetoxyethylene, Ethenyl acetate, Ethenyl ethanoate, VAC, Vinyl acetate monomer, Vinyl ethanoate	ATSDR 1992; NIOSH 2005
Solubility in water	20 g/L at 20ºC	NRC 2013
Log K_{ow}	0.73	TRRP 2006
Vapor Pressure	83 mm Hg at 20°C	ATSDR 1992
Relative Vapor Density (air = 1)	3.0	HSDB 2009
Melting Point	-93.2°C	ATSDR 1992
Boiling Point	72.7°C	NRC 2013
Conversion Factors	1 $\mu g/m^3$ = 0.284 ppb 1 ppb = 3.52 $\mu g/m^3$ at 25°C	NRC 2013

Chapter 2 Major Sources and Uses

Vinyl acetate (VA) is not found naturally in the environment; it is made by reacting ethylene and sodium acetate (NRC 2013). VA is widely used in industry as a building-block for making other types of materials, such as polyvinyl acetate polymers and ethylene vinyl acetate copolymers. These products are then used in the making of glues for packaging and building products, paints, textiles, and paper (ATSDR 1992). Novel uses for VA include the production of membranes for use in medical and chemical research. Breakdown of VA in air can result in acetaldehyde and acetic acid. In 1993, production of VA in the U.S. was estimated to be 2.83 billion pounds (NRC 2013) with 3.4 million pounds produced in the US in 1996 (NTP 2001). Exposure to VA may occur from industrial facilities, due to accidental spills, contact with products that contain VA, or through exposure to hazardous waste sites (ATSDR 1992). Deese and Joyner (1969) evaluated the average environmental concentrations of VA to which chemical workers were exposed to under normal operating conditions at three different production units. They found that concentrations in the facilities ranged from 0 to 59.3 ppm, with 83% of the samples being less than 10 ppm. Exposure to the general population may occur from ambient air in communities surrounding a facility that makes or uses VA (ATSDR 1992).

Chapter 3 Acute Evaluation

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

At acute exposure durations, VA acts primarily as a respiratory irritant, causing irritation to the eyes, nose, and throat. Animal studies suggest that as concentration and duration increases, VA can cause more serious respiratory and ocular irritation, leading to cloudy red eyes and damage to the epithelium of the nasal and respiratory tract (NRC 2013).

3.1.1 Physical/Chemical Properties

VA is a flammable, colorless liquid that has been described as having a sweet fruity odor (ATSDR 1992) or a sharp, sour odor (Ruth 1986). It is very soluble in water, and is also soluble in alcohol, ether, acetone, benzene, and chloroform (ASTDR 1992). The chemical and physical properties for VA are summarized in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Study – Smyth and Carpenter (1973) – Key Study

The National Research Council (NRC 2013) reported a study done by Smyth and Carpenter (1973) where groups of three to nine human volunteers were exposed to VA concentrations ranging from 0.6 ppm to 72 ppm for exposure periods of 2 minutes (min) to 4 hours (h). VA vapor was generated by feeding metered air through a spirally corrugated surface of minimally heated Pyrex tube. The NRC stated that the calculated concentration was corrected using a curve based upon a gas chromatographic analysis of calculated concentrations ranging from 0.6 to

16,000 ppm, although dose-response information was only reported for concentrations up to 72 ppm. No details were given on the chamber conditions or the individual volunteer histories, such as prior exposures, smoking habits, age, etc. The recorded responses are detailed in Table 4.

Table 4. Summary of Human Sensory Response to Controlled Exposures to VA

Exposure conc. (ppm) [a,b]	No. of subjects	Exposure duration (min)	Response
0.6	9	2	none
1.3	9	2	9 immediate odor; 5 no odor at 2 min.
4	9	2	9 immediate odor; 3 no odor at 2 min 1 minimal eye, nose, and throat irritation
8	9	2	9 immediate odor; 1 no odor at 2 min 2 minimal eye, nose, and throat irritation
20	9	2	9 immediate odor, 1 minimal eye, nose, and throat irritation
20	3	240	3 complete olfactory fatigue in 3-116 min (avg. 63 min) 1 persistent slight throat irritation
34	3	120	1 complete, 2 partial olfactory fatigue 1 transient, 1 persistent throat irritation
72	4	30	4 strong odor, partial olfactory fatigue 4 slight throat irritation 20-60 min. following exposure; eye irritation to 60 min. after exposure; subjects expressed unwillingness to work at this concentration for 8 h

[a] Data reported in NRC (2013), originally from Smyth and Carpenter (1973).

[b] Corrected using calibration curve.

With the initial exposure duration of 2 min, one subject reported minimal eye, nose, and throat irritation at 4 ppm VA and one to two subjects also reported this irritation through 20 ppm. With the exposure duration increased to 240 minutes and the VA concentration increased to 20 ppm (shaded cells), irritation increased/persisted and other symptoms such as olfactory fatigue occurred. The time that irritation began was not provided. Subjects reported that they would be unwilling to work for 8 h at the highest concentration reported (72 ppm).

Although minimal irritation was reported by one out of nine volunteers after 2 min of exposure at 4 ppm VA, there was no increase in response at the same duration at 20 ppm, 5 times the concentration, suggesting there was not a dose-response at the concentrations tested for 2 min. These data also suggest that an irritation response to VA may require a longer exposure duration than 2 min, at least at the tested concentrations. Lastly, no statistical results were provided for any exposure condition tested to determine whether the response was statistically significantly increased. Therefore, as there was no dose-response, the data for the 2 min exposure duration do not demonstrate an adverse effect due to VA exposure and will not be considered further.

Study results based on the longer exposure durations are more similar to the duration of interest for derivation of the acute ReV (1 h) and are more appropriate for determining the POD. At 240 min of exposure to 20 ppm VA, one out of three volunteers reported persistent slight throat irritation. This response doubled at 34 ppm, where two out of three volunteers reported transient/persistent throat irritation in half the time (120 min), and all four volunteers reported irritation at 72 ppm (30 min). These data show a dose-response for VA-induced irritation and suggest that under these exposure conditions, and similar to other irritants, VA acts in a time and concentration dependent manner. Based on the reported results, the TCEQ identifies a minimal lowest adverse observed effect level (LOAEL) of 20 ppm for throat irritation. Since the next lowest dose of 8 ppm only had an exposure duration of 2 min, it is not comparable to the identified LOAEL and therefore cannot be used as a definitive no observed adverse effects level (NOAEL) for a longer duration (e.g., 1 h).

3.1.2.2 Animal Studies – Supporting studies

3.1.2.2.1 Bogdanffy et al. (1997)

Groups of five male Sprague-Dawley (SD) rats age 5-6 weeks (wk) were exposed to 0, 50, 200, 600, or 1,000 ppm VA (analytical concentrations) for 6 h/day (d) for 1 d, 5 d, or 5 d/wk for 4 wk. VA vapor was generated by injecting liquid VA over 6-mm glass beads contained within a glass J-tube (for 1,000 ppm) or by placing liquid VA in a three-neck flask (for 50, 200, and 600 ppm) and passing filtered compressed air over the liquid. VA-laden air was then passed into makeup air, which flowed directly to the inhalation 150 L chamber constructed from stainless steel and glass. The airflow in the chamber was maintained at 35 L/min and the chamber atmosphere was analyzed directly using gas chromatography (Bogdanffy et al. 1997). All exposures were conducted during the same 8-h period of the day to minimize physiological variations. Rats were observed for clinical signs of toxicity and weighed three times per wk. Animals were sacrificed 16 h following the last exposure, after which cell proliferation and pathological evaluations were conducted. Histopathological evaluations of the respiratory tract tissues, nasal cavities, and sections of duodenum were conducted for documentation of any gross structural or cellular changes. Cross sections of the nose, labeled levels I-V, were specifically examined for histological changes resulting from VA exposure.

Mean body weight was significantly reduced in the highest exposure group (1,000 ppm) as compared to controls; 11% following a single day exposure and 14% following 5 d of exposure. Although there were no gross abnormalities, VA exposure caused microscopic lesions in the olfactory epithelium in rats exposed to concentrations of 600 and 1000 ppm. Rats exposed to 50 and 200 ppm were histologically identical to the control animals. Lesions were observed mostly in the first three levels of the rat nasal sections, and the varying degrees of severity were characterized as minimal, mild, and moderate in nature. The data regarding these lesions can be found in Table 5. The NOAEL for this study is 200 ppm and the LOAEL for histopathology of the nasal epithelium is 600 ppm. This study was not used to identify the POD for acute ReV derivation as the NOAEL was ten times higher than the human LOAEL identified from Smyth and Carpenter (1973) for irritation, a more sensitive critical effect.

Table 5. Histopathological Lesions in the Nasal Epithelium of Rats Exposed to VA

Section of the nose [a]	Observation	Exposure Concentration (ppm)				
		0	50	200	600	1,000
Level II	Degeneration/necrosis; respiratory epithelium					
	minimal	-	-	-	-	1 [b]
	Degeneration/necrosis; olfactory epithelium					
	minimal	-	-	-	2	1
	mild	-	-	-	1	2
	moderate	-	-	-	1	2
Level III	Degeneration/necrosis; respiratory epithelium					
	minimal	-	-	-	-	1
	Degeneration/necrosis; olfactory epithelium					
	minimal	-	-	-	2	-
	mild	-	-	-	3	4
	moderate	-	-	-	-	1
Level IV	Degeneration/necrosis; olfactory epithelium					
	minimal	-	-	-	4	1
	mild	-	-	-	1	3
	moderate	-	-	-	-	-
Level V	Degeneration/necrosis; respiratory epithelium					
	minimal	-	-	-	2	3

[a] Adapted Bogdanffy et al. (1997).

[b] Incidence of lesions observed in olfactory epithelium.

3.1.2.2.2 Smyth and Carpenter (1973)

Well conducted animal studies were done with rats, mice, guinea pigs, rabbits and dogs by Smyth and Carpenter (1973, as reported in NRC 2013). The animals were exposed to VA by feeding liquid at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed (NRC 2013). Animals were exposed to nominal concentrations ranging from 0.6-16,000 ppm for a total of 4 h. Concentrations for each animal study were corrected using a curve based upon a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm (NRC 2013). Results for each species and corrected concentrations from the Smyth and Carpenter (1973) study are shown below.

Table 6. Results of Acute Inhalation Exposure in Different Species

Species	Exposure concentrations (ppm)	NOAEL (ppm)	LOAEL (ppm)	Effect at LOAEL	Effect at higher concentrations
Rats	1,640, 3,280, 6,560	--	1640	Extremities congested at 1 h	Gasping, clonic convulsions, death
Mice	410, 820, 1,640, 3,280, 6,560	410	820	Labored breathing at 2 min; 1/6 mice died	Gasping, clonic convulsions, opaque eyes, poor coordination, death
Guinea pigs	1,640, 3,280, 6,560, 13,120	--	1640	Lacrimation at 30 min, eyes and nose wet at end of exposure	Gasping, clonic convulsions, death
Rabbits	1,640, 3,280, 6,560	1640	3280	Nose red at 30 min, eyes cloudy at 90 min, normal at end of exposure, 3/4 died	Labored breathing, poor coordination, bloody nose, death
Dogs	51.25, 102.5, 205, 820, 1,640, 3,280	102.5	205	Blinking at 1 min, sclera red at 1 h	Sneezing, lacrimation, tremors

This animal study was not used to identify the POD for acute ReV derivation as even the lowest NOAEL of 102.5 ppm was over five times higher than the human LOAEL identified from Smyth and Carpenter (1973).

3.1.2.2.3 Gage (1970)

Groups of 4 male and 4 female Alderley Park rats were exposed to nominal concentrations of 100, 250, 630, or 2,000 ppm for 6 h/d, 5 d/wk for 15 exposures over 3 wk. Chambers were made of a glass desiccator and were designed to house groups of four rats with wire mesh partitions to separate the animals. VA vapor concentrations were generated by injecting liquid at a known rate into a metered stream of air by means of a controlled fluid-filled atomizer. Female rats in the 250 and 630 ppm group showed low weight gain, but blood and urine tests, autopsy and organs appeared normal. Rats in the 2,000 ppm group displayed signs of eye and nose irritation, respiratory difficulty, overall poor condition, and low weight gain. Further autopsy results revealed an excess of macrophages in the lungs. No further details were provided. A lack of data and statistical significance on the actual weight gain of the female rats in this study makes it inadequate to determine a LOAEL/NOAEL.

3.1.2.3 Reproductive and Developmental Studies

No inhalation reproductive or developmental studies were available detailing exposure to VA in humans.

ATSDR (1992) notes an inhalation study (Hazleton 1980, unpublished) where developmental toxicity data were recorded for rats. Pregnant rats were exposed via inhalation to VA during gestational days (GD) 6-15 and were sacrificed on GD 20. No details were given on the duration of the exposures. A transient effect in the pregnant rats was noted following exposure to 1,000 ppm which resulted in an 18% reduction in body weight gain during the exposure, but returned to normal during the post-exposure period. It was not mentioned whether the concentration was nominal or analytical nor what other concentrations were tested, only that this was the highest concentration used. Necropsy of dams showed congestion of the lung at all exposure concentrations with highest occurrence at 1,000 ppm of VA. Reduced fetal weight thought to have been the result of the mother's marked retardation in weight gain was observed at 1,000 ppm exposure. This adverse developmental fetal effect following exposure to VA appears to be secondary to maternal toxicity. No deaths or structural defects were observed in the fetuses of the rats exposed to VA. No gross histopathological changes in reproductive organs were noted for dams, their fetuses, or female mice exposed to 1,000 ppm of VA.

Hurtt et al. (1995) conducted developmental studies where 24 confirmed-mated SD rats were exposed to nominal VA concentrations of 0, 50, 200, or 1,000 ppm (analytical concentrations of <0.21, 51.8, 197.8, and 1005 ppm, respectively) for 6 h/d from GD 6-15 and dams sacrificed on GD 20. Hurtt et al. (1995) exposed a second group of confirmed-mated SD rats to 0, 200, 1000, and 5000 ppm VA via drinking water, which the author's state gave a similar body burden of VA as the inhalation exposures (0, 25, 100, and 500 mg/kg/day respectively). No exposure-related adverse effects were noted in the drinking water study, even at the highest concentration of 5000 ppm VA. For the inhalation study, in the highest exposure group (1,000 ppm), maternal loss of mean absolute body weight was observed on days 10, 15 and 20 (91, 88, and 89% of controls, respectively). Decreased body weight gain was also noted over GD 6-10 (-10.3 vs. 17.5 g for

controls), 10-15 (64% of controls), and the entire exposure interval of GDs 6-15 (24% of controls). It was not determined whether the decrease in body weight was due to decreased food consumption since consumption was not measured. Delays in fetal growth and ossification correlated with maternal toxicity for 1,000 ppm. VA was determined not to be significantly toxic to fetuses. Consideration of these results suggests that an acute ReV based on the human LOAEL of 20 ppm from Smyth and Carpenter (1973) is expected to be protective of such effects.

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

Acute inhalation exposure to VA results in respiratory irritation at sufficiently high concentrations. Although the precise MOA for this irritation is not known, studies have shown that VA induces cytotoxicity by raising the intracellular acidity (Bogdanffy et al., 2002), which could provide some insight into the toxicity that develops following acute exposure. Once VA reaches the tissues, it is rapidly broken down into acetaldehyde and acetic acid, and kinetically this has been shown to occur more rapidly in nasal tissue than in other respiratory tissues (Bogdanffy and Taylor 1993). Acetaldehyde can be further broken down once in the cell into acetic acid by the enzyme aldehyde dehydrogenase. Both acetaldehyde and acetic acid are naturally occurring by-products within cells. VA is thought to lower inter- and intracellular pH via the production of acetic acid and acetaldehyde, and this may contribute to the irritation following VA exposure. Since the key study is based on human volunteers exposed to VA and a more appropriate dose metric is not available for the portal of entry effects observed, exposure concentration to the parent compound will be used as the default dose metric.

3.1.4 Point of Departure (POD), Critical Effect and Dosimetric Adjustments for Key Study

3.1.4.1 Key Human Study

A minimal LOAEL of 20 ppm for an exposure duration of 240 min was identified in the Smyth and Carpenter (1973) study based on persistent slight throat irritation in human volunteers and will be used as the human point-of-departure (POD_{HEC}) in further calculations of the acute ReV and $^{acute}ESL$.

3.1.4.2 Default Exposure Duration Adjustments

Since the critical effect is respiratory irritation, which is primarily concentration dependent, an exposure duration adjustment was not used to extrapolate from a 240 min (4 h) exposure to a 1 h exposure, which is consistent with TCEQ guidelines (2012). Therefore, the POD_{HEC} (POD_{ADJ}) is 20 ppm.

3.1.5 Adjustments to the POD_{HEC} and Application of Uncertainty Factors

The critical effect is persistent slight throat irritation with a minimal LOAEL of 20 ppm (Smyth and Carpenter 1973). The following uncertainty factors (UFs) were applied to the POD_{HEC} of 20

ppm: 10 for intraspecies variability (UF_H), 3 for LOAEL-to-NOAEL uncertainty (UF_L), and 1 for database uncertainty (UF_D).

- An UF_H of 10 was used to account for variation in sensitivity among the members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences, those with pre-existing medical conditions, etc.
- An UF_L of 3 was used because the exposure concentration of 20 ppm was a minimal LOAEL (one out of three volunteers reported persistent slight throat irritation).
- An UF_D of 1 was used because while the available human study only had three participants at the POD concentration, there are several animal studies available, as well as information from several animal reproductive/developmental studies. The Smyth and Carpenter (1973) study is considered a medium to high quality study and the confidence in the acute database is medium to high.

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

  = 20 ppm / (10 x 3 x 1)
  = 20 ppm / 30
  = 0.6667 ppm
  = 666.7 ppb or 670 ppb (rounded to two significant digits)

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

In deriving the acute ReV for VA, no numbers were rounded until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The resulting 1-h acute ReV is 0.67 ppm (2.3 mg/m^3) or 670 ppb (2,300 µg/m^3) based on the Smyth and Carpenter (1973) 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 200 ppb (690 µg/m^3) (Table 7).

Table 7. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Values and Descriptions
Study	Smyth and Carpenter 1973
Study population	3-9 human volunteers
Study quality	Medium
Exposure Concentrations	Inhalation at 0.6, 1.3, 4, 8, 20, 34, and 72 ppm
Exposure Durations	2 min – 240 min
Critical Effects	Persistent slight throat irritation
POD_{HEC} (minimal LOAEL)	20 ppm (three volunteers at this exposure concentration)
Exposure Duration	240 min
POD_{ADJ}	20 ppm
Total UFs	30
Interspecies UF	10
LOAEL-NOAEL	3
Incomplete Database UF *Database Quality*	1 Medium-high
Acute ReV [1 hr] (HQ = 1)	**2,300 µg/m^3 (670 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**690 µg/m^3 (200 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

VA is a flammable, colorless liquid that has been described as having a sweet fruity odor (ASTDR 1992) or a sharp, sour odor (Ruth 1986). An odor detection threshold value of 120 ppb (420 µg/m^3) VA was reported by Hellman (1974). The Hellman reference is the only available and acceptable information source for VA that meets AIHA and USEPA evaluation criteria. Following TCEQ (2015b), the Hellman (1974) value of 420 µg/m^3 (120 ppb) was selected as the $^{acute}ESL_{odor}$.

3.2.2 Vegetation Effects

After a literature review, no data were found on any adverse effects of VA on vegetation.

3.3 Short-Term ESLs

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

- acute ReV = 2,300 µg/m^3 (670 ppb)
- ^{acute}ESL = 690 µg/m^3 (200 ppb)
- ^{acute}ESL$_{odor}$ = 420 µg/m^3 (120 ppb)

The acute ReV for VA is 2,300 µg/m^3 (670 ppb). The short-term ESL used for air permit reviews is the ^{acute}ESL$_{odor}$ of 420 µg/m^3 (120 ppb) as it is lower than the health-based ^{acute}ESL of 690 µg/m^3 (200 ppb) (Table 2).

3.4 Acute Inhalation Observed Adverse Effect Level

Risk assessors, and the general public, often ask to have information on the levels in air where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in DSDs (TCEQ 2015a). The minimal LOAEL value of 20 ppm determined in the Smyth and Carpenter (1973) study was a concentration at which at least one person observed persistent slight throat irritation from a 240 min exposure to 20 ppm VA exposure. Therefore, this study was used in the derivation of the acute inhalation observed adverse effect level. The acute inhalation observed adverse effect level represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study (240 min) or longer. However effects are not a certainty as there may be differences in sensitivity. No adjustments were made to the POD because the selected study was a human study and described respiratory irritation. The acute inhalation observed adverse effect level of 20 ppm is provided for informational purposes only. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies may identify a lower POD.

The margin of exposure between the observed adverse effect level (20 ppm) and the ReV (0.67 ppm) is a factor of 30.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Animal studies using low concentrations of VA report respiratory irritation effects resulting from point-of-entry (POE) tissue damage, while the use of higher concentrations leads to tumor formation and carcinogenesis. In animal models, VA acts as a threshold carcinogen at the POE, with an early event being tissue damage, which then leads to tumor formation. For the chronic evaluation, the initial nasal tissue damage will be used as the critical effect to derive a chronic ReV, and this would also be protective of carcinogenic effects (as discussed in Section 4.2). No

chronic human studies were suitable for deriving a chronic ReV, so animal studies were used to conduct the chronic evaluation.

4.1.1 Physical/Chemical Properties

The primary physical and chemical properties of VA are discussed in Chapter 3 and summarized in Table 3.

4.1.2 Key and Supporting Studies

4.1.2.1 Human Study - Deese and Joyner (1969)

Deese and Joyner (1969) measured VA concentrations in three production units of a Gulf Coast chemical plant and surveyed workers to assess possible exposure-related health effects. Concentrations in the plants ranged from not detected to 49.3 ppm, and time weighted 8-h averages were calculated to be between 5.2 and 8.2 ppm depending on the location of the worker. These averages did not take into account periodic peaks in VA concentrations from certain activities, where VA concentrations could be between 50 and 300 ppm. A health effects review was conducted on the VA workers and matched controls from other areas in the plant. Some differences were observed in blood chemistry parameters; however they fell within the range of normal, so this was not deemed significant. No exposure-related differences were observed in medical history screens or in time lost due to sickness. The authors concluded that at these concentrations, VA appeared to not have any detrimental effects on health. It was assumed that the measured concentrations were the same over the last 5 years at the plant, although no conclusive evidence was presented. No information was given on the possible co-exposures, making this study difficult to use in the development of a chronic ReV.

4.1.2.2 Animal Studies

4.1.2.2.1 Key Study – Bogdanffy et al. (1994)

Bogdanffy et al. (1994) conducted a 2-year chronic inhalation study that looked at both the toxicity and oncogenicity of VA in mice and rats. Although tumor formation was observed, data indicate that the initial tissue damage at the POE is the primary step in VA's MOA leading to carcinogenicity. Equal numbers of male and female Crl:CD(SD)BR rats (SD-derived outbred strain) and Crl:CD(1CR)BR (Swiss mouse-derived outbred strain) were placed into four treatment groups with the following per group: 60 in the main 104-wk study, 10 for clinical evaluation at wk 51 and euthanasia between wk 52-53, 10 for clinical evaluation at wk 81 and euthanasia between wk 85-86, and 10 were exposed for 70 wk followed by a 15 wk recovery period. Each treatment group was then randomly assigned a VA exposure concentration: 0, 50, 200, or 600 ppm, with mean chamber concentrations measured at 49.4 ± 2.4, 200.5 ± 9.7, and 594.7 ± 16.8 ppm. Air concentrations within the chambers were measured every 15 min using gas chromatography, and the animals were exposed to VA for 6 h/d, 5 d/wk for 104 wks (unless otherwise stated in treatment group, minus 2 days for holidays).

The researchers collected and examined an exhaustive number of samples, tissues and pathological endpoints, including:

- Blood samples – red and white blood cell counts, hemoglobin concentrations, cell volume, sodium, chloride, calcium, glucose, and blood urea nitrogen.
- Urine samples – volume, pH, glucose, protein, ketone, and blood.
- Body and organ weights – adrenals, gonads, kidneys, lungs, spleen, brain, heart, liver, pituitary, and thyroids.
- Tissue samples – histopathological analysis of fixed samples from 45 different tissues and organs including, muscle, bone, brain, eyes, glands, individual sections of the respiratory and digestive tract, reproductive organs, and any lesions or masses, etc.
- A second histopathological analysis of the respiratory tract was conducted by an independent group.

All of the noted exposure-related effects were confined to the respiratory region in both species; no signs of systemic toxicity were observed. No increases in mortality were noted, and no significant exposure-related changes in the hematological and clinical parameters across both species were observed. Details of the gross pathological findings are listed below.

Results from the rat study:

- At 200 ppm, relative lung weights were increased at the 53 wk interim euthanasia, but this difference was not observed at 83 wk. Body weights were similar to those of controls.
- At 600 ppm, a statistically significant reduction in body weight gain (10% lower compared to controls at 104 wk) was observed. Relative lung weights were increased in both the 53 wk and 83 wk interim euthanasia groups. Female rats showed a decrease in blood glucose levels, but no other hematological changes were observed in either sex. Decreased urine production was noted in both sexes. The authors attributed these changes to decreased food and water intake, although these parameters were not measured.

Results from the mouse study:

- At 50 ppm, mice showed a decrease in body weight gain throughout the initial 53 wk study, but had recovered by the end of the full study at 104 wks.
- At 200 ppm, body weights in the mice were significantly decreased at the end of the 104 wks. Absolute and relative lung weights were increased in the male mice after 53 wks.

Several non-neoplastic endpoints were examined and characterized in both the rat and mice studies and are detailed below:

Results from the rat study:

Non-neoplastic changes were not observed in the respiratory epithelium in the nasal cavity of the rats. Olfactory epithelial atrophy and basal cell hyperplasia showed the highest level of significant difference in both the 200 and 600 ppm exposure groups and had the most highly correlated dose-response relationship. These lesions were also specifically mentioned by the authors as being the most prominent and consistent compound-related non-neoplastic treatment-related changes. A summary of the most significant non-neoplastic changes in the rat study is shown in Tables 8-11.

Table 8. Incidence of Olfactory Epithelial Atrophy in Male Rats

VA (ppm)	N in group	Very Slight	Slight	Moderate	Severe	Total
0	59	0	0	0	0	0
50	60	1	2	0	0	3
200	59	4	47***	2	0	53
600	59	0	7*	33***	10***	50

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Table 9. Incidence of Olfactory Epithelial Atrophy in Female Rats

VA (ppm)	N in group	Very Slight	Slight	Moderate	Severe	Total
0	60	0	0	0	0	0
50	60	1	0	0	0	1
200	60	4	23***	0	0	27
600	59	0	18***	30***	3	51

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Table 10. Incidence of Basal Cell Hyperplasia in Male Rats

VA (ppm)	N in group	Very Slight	Slight	Moderate	Severe	Total
0	59	2	0	0	0	2
50	60	5	0	0	0	5
200	59	3	40***	11***	0	54
600	59	1	21***	22***	2	46

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Table 11. Incidence of Basal Cell Hyperplasia in Female Rats

VA (ppm)	N in group	Very Slight	Slight	Moderate	Severe	Total
0	60	0	0	0	0	0
50	60	0	0	0	0	0
200	60	7*	24***	3	0	34
600	59	0	35***	16***	0	51

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Results from the mouse study:

> The non-neoplastic changes present in the nasal cavity were, in general, morphologically very similar to those found in the rat study, with a few key differences. Unlike the rat study, where lesions were only present in the olfactory epithelium in the nasal cavity, the mouse study found lesions present in both the olfactory epithelium and in the respiratory epithelium. Respiratory epithelium metaplasia was also present in the mouse in areas of olfactory epithelial atrophy, suggesting replacement of damaged olfactory epithelium with regenerating respiratory epithelium. In the rats, regeneration of olfactory epithelium was often accompanied by a keratinizing squamous epithelium. The non-neoplastic changes that showed the highest level of significant difference in both the 200 and 600 ppm exposure groups and had the most highly correlated dose-response relationship in the mouse were olfactory epithelial atrophy and nasal submucosal gland hyperplasia (Tables 12-15), though there were several other noted changes.

Table 12. Incidence of Olfactory Epithelial Atrophy in Male Mice

VA (ppm)	N in group	Slight	Moderate	Severe	Total
0	52	0	1	0	1
50	48	0	0	0	0
200	53	1	8*	4	13
600	50	0	5	39***	44

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Table 13. Incidence of Olfactory Epithelial Atrophy in Female Mice

VA (ppm)	N in group	Slight	Moderate	Severe	Total
0	56	0	0	0	0
50	57	0	0	0	0
200	55	0	12***	2	14
600	51	0	5*	45***	50

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Table 14. Incidence of Nasal Submucosal Gland Hyperplasia in Male Mice

VA (ppm)	N in group	Slight	Moderate	Total
0	52	3	0	3
50	48	3	0	3
200	53	28***	8**	36
600	50	25***	15***	40

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Table 15. Incidence of Nasal Submucosal Gland Hyperplasia in Female Mice

VA (ppm)	N in group	Slight	Moderate	Total
0	56	2	0	2
50	57	5	0	5
200	55	42***	7**	49
600	51	35***	13***	48

*p<0.05;***p<0.001 by Fisher's pair-wise test compared to control group. Table adapted from Bogdanffy et al. (1994). Incidence totals were added for this analysis, so no statistics were conducted on the total incidence of these lesions.

Olfactory epithelial atrophy and basal cell hyperplasia in rats and olfactory epithelial atrophy and nasal submucosal gland hyperplasia in mice are the most consistent compound-related changes, and therefore they will be considered the critical effect for this chronic study. At 50 ppm there were no statistically significant differences in these endpoints from controls, therefore the NOAEL for olfactory epithelial atrophy (both species), basal cell hyperplasia (rats), and nasal submucosal gland hyperplasia (mice) is considered to be 50 ppm with a corresponding LOAEL of 200 ppm.

4.1.2.2.2 Supporting Study - Owen (1980a,b) (as cited in NRC 2013)

Groups of 20 male and female CD 1 mice (Owen 1980a) and CD rats (Owen 1980b) were exposed to VA via inhalation to analytical concentrations of 0, 50, 200, or 1,000 ppm for 6 h/d, 5 d/wk for 13 wk. Nothing was noted in the rats in the 50 or 200 ppm exposure groups, but rats exposed to1,000 ppm displayed signs of physical stress, including ruffled fur, respiratory distress, and hunched posture. They also had several gross and histological changes, including decreased overall body weight gain (62% and 56% of controls for males and females, respectively), smaller volume and more concentrated urine, and increased lung weight relative to body weight (126% and 130% of controls for males and females, respectively). No other changes were noted. The mice appeared to be more sensitive than the rats, as the physical signs of stress were also apparent in the 200 ppm exposure group, and several more effects were noted in the 1,000 ppm group than were seen in the rats. These effects included decreased overall body weight gain (40% and 50% of controls for males and females, respectively), increased lung weight relative to body weight (148% and 580% of controls for males and females, respectively), microscopic lesions in the upper and lower respiratory tissues, focal to diffuse rhinitis in the nasal cavity with occasional mucosal metaplasia, chronic inflammation associated with epithelial goblet cells, multifocal bronchitis to bronchiolitis, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar or bronchial exudation. No other changes at any other doses were noted. The critical effect of decreased body weight and increased relative lung weight in mice had a NOAEL that was the same as that identified in the Bogdanffy et al. (1994) study

(50 ppm). However the study quality, exposure duration, and in depth histopathological analysis makes the Bogdanffy et al. study better suited for use in identifying a POD.

4.1.2.3 Reproductive and Developmental Studies

No developmental or reproductive studies following human exposure to VA via inhalation were identified. The only available inhalation developmental or reproductive studies are detailed in Section 3.1.2.3. Maternal toxicity, along with the correlated fetal effects, were only present at the highest concentration tested (1000 ppm); therefore, protecting against the POE effects observed at 200 ppm in the Bogdanffy et al. (1994) study will also protect against any possible reproductive or developmental effects.

4.1.3 MOA and Dose Metric

Chronic exposure to VA via inhalation induces olfactory epithelial atrophy, basal cell and nasal submucosal gland hyperplasia in rats and mice. Once VA reaches the tissues, it is rapidly broken down into acetaldehyde and acetic acid, and kinetically this has been shown to occur more rapidly in nasal tissue than in other respiratory tissues (Bogdanffy and Taylor 1993). Acetaldehyde can be further broken down once in the cell into acetic acid by the enzyme aldehyde dehydrogenase. Both acetaldehyde and acetic acid are naturally occurring by-products within cells, and these naturally low levels are thought to result in VA's threshold MOA. At the cellular level, VA is thought to lower inter- and intracellular pH via the production of acetic acid. Acetaldehyde may also contribute to this increased cytotoxicity when tissue levels significantly exceed physiological levels. Bogdanffy (2002) states that intracellular acidification is proposed as the first pharmacodynamic step in a series of events that ultimately lead to tumorigenesis in nasal epithelial cells exposed to VA. Because acetaldehyde and acetic acid both induce intracellular acidification, the tissue concentrations of these metabolites would be the most appropriate dose metric for VA toxicity. However, since the key study is based on animals exposed to VA and a more appropriate dose metric is not available, exposure concentration to the parent compound will be used as the default dose metric.

4.1.4 POD, Critical Effect, and Dosimetric Adjustments

Using Bogdanffy et al. (1994) as the key study, the NOAEL for olfactory epithelial atrophy and basal cell hyperplasia in rats and olfactory epithelial atrophy and nasal submucosal gland hyperplasia in mice is 50 ppm. Using this exposure concentration as the POD should protect against the most consistent treatment-related non-neoplastic changes identified by Bogdanffy et al. (1994).

Bogdanffy et al. (1999) conducted a biology-based risk assessment of the inhalation toxicity data presented in the Bogdanffy et al. (1994) paper that included benchmark dose (BMD) modeling of the data and the use of a physiologically based pharmacokinetic (PBPK) model. Although this was a well conducted study that used the same animal data that was used in the development of a chronic ReV, there were aspects of this study that resulted in this PBPK model not being used.

First, for the initial BMD, Bogdanffy et al. (1999) combined the non-neoplastic and the neoplastic histological results and carried forward this "olfactory precursor lesion' data through the PBPK model. Since the goal is to protect against a precursor event, combining tumor incidence data with the non-neoplastic incidence data, although conservative, would not be consistent with the TCEQ guidelines. Second, the BMD models that were produced by Bogdanffy et al. (1999) did not fit the data well as determined by the EPA and TCEQ guidelines. For determination of a good fit model, the p value should be above 0.1, but Bogdanffy et al. (1999) stated that "the p values for the non-neoplastic changes were generally less than 0.01." So although this was a well-developed PBPK model that used the same critical effect data presented here, it was not used further in this analysis. However, using their combined incidence data and BMD modeling along with the PBPK model, the effective dose lower bound (LED_{10}) was calculated to be 47.1 ppm. This value is very close to the NOAEL of 50 ppm, so although this model will not be used in this analysis, it does support the POD that was selected.

4.1.4.1 Default Exposure Duration Adjustments

Animals were exposed for 6 h/day, 5 d/wk, for up to 104 wks. An adjustment from a discontinuous to a continuous exposure duration was conducted (TCEQ 2015a) as follows:

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

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week:

$POD_{ADJ} = 50\ ppm \times (6/24) \times (5/7) = 8.9286\ ppm$

4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

VA is very water soluble and causes POE effects mainly in the nasal region (Category 1 gas). This would suggest using a pharmacokinetic dosimetric animal-to-human adjustment factor (DAF) of 1 given that the USEPA (2012) suggests a regional gas dose ratio (RGDR) of 1 for the extrathoracic (ET) region (i.e., external nares to the beginning of the trachea), which includes the nose. Thus, the POD_{HEC} is equal to the POD_{ADJ} of 8.9286 ppm.

Bogdanffy et al. (1999) calculated several model-based values for rat and human cellular VA concentrations and pH levels. Using the biologically derived data, the DAF for steady-state VA tissue concentrations and for intracellular pH would also be 1, given that the rat and human parameters are very similar. These data would support the use of the USEPA default DAF = 1. For steady-state acetaldehyde tissue concentrations, the biologically derived data would suggest the use of a DAF = 0.2 due to the higher acetaldehyde concentrations found in humans than in rats. Because cytotoxicity appears to rely on both acetic acid and acetaldehyde, and since intracellular acidification is proposed as the first pharmacodynamic step in a series of events that ultimately lead to tumorigenesis in nasal epithelial cells exposed to VA Bogdanffy (2002), a

DAF based on intracellular pH would be the most appropriate adjustment factor to use, and in this case is equal to the default DAF of 1.

4.1.5 Adjustments to the POD_{HEC} and Application of UFs

A POD_{HEC} based on a NOAEL was used as the POD and UFs were applied to derive a ReV (i.e., a threshold MOA for a noncarcinogenic endpoint). The following UFs were applied to the POD_{HEC} of 8.9286 ppm: 10 for UF_H, 3 for UF_A, and1 for UF_D, for a total UF of 30.

- A UF_H of 10 was used to account for variation in sensitivity among the members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences, those with pre-existing medical conditions, etc.
- A UF_A of 3 was used because a dosimetric adjustment from animal-to-human exposure was conducted which accounts for toxicokinetic differences but not toxicodynamic differences.
- A UF_D of 1 was used because there are several chronic studies available for VA, including an acute reproductive/developmental study, and similar NOAELs are identified in the different studies. The quality of the study used as the POD is considered high, and the confidence in the chronic database is medium to high.

chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 8.9286 ppm / (10 x 3 x 1)
= 8.9286 ppm / 30
= 0.2976 ppm
= 297.6 ppb
= 300 ppb (rounded to 2 significant figures)

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

The chronic ReV of 297.6 ppb was rounded to two significant figures at the end of all calculations resulting in a value of 300 ppb (1,000 μg/m^3). The rounded chronic ReV was then multiplied by 0.3 to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 90 ppb (300 μg/m^3). (Table 16).

Table 16. Derivation of the Chronic Noncarcinogenic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	Values and Descriptions
Study	Bogdanffy et al., 1994
Study Population	Male and female Crl:CD(SD)BR rats and Crl:CD(1CR)BR mice, 60 of each in main study, 10 of each in three interim euthanasia groups
Study Quality	High
Exposure Method	Exposure via inhalation at 0, 50, 200 and 600 ppm
Critical Effects	Olfactory epithelial atrophy and basal cell hyperplasia in rats and olfactory epithelial atrophy and nasal submucosal gland hyperplasia in mice
POD (NOAEL)	50 ppm
Exposure Duration	6 h/d, 5 d/wk for 104 wks
Extrapolation to continuous exposure (POD_{ADJ})	8.9286 ppm
POD_{HEC}	8.9286 ppm
Total UFs	30
Intraspecies UF	10
Interspecies UF	3
LOAEL UF	1
Subchronic to chronic UF	1
Incomplete Database UF	1
Database Quality	Medium to high
Chronic ReV (HQ = 1)	**300 ppb (1,000 µg/m^3)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**90 ppb (300 µg/m^3)**

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

The USEPA determined a Reference Concentration for Chronic Inhalation Exposure (RfC) of 200 µg/m^3 (57 ppb). According to the USEPA, "the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population

(including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime". The TCEQ-derived Chronic ReV of 1,000 μg/m^3 is comparable in nature to the USEPA's RfC of 200 μg/m^3, although the USEPA's RfC is lower than the TCEQ's Chronic ReV. The USEPA used the same POD as was used to derive the Chronic ReV, although the original Hazleton Report by Owen et al. (1988) was cited instead of the published paper by Bogdanffy et al. (1994). The same duration adjustment was made, however the USEPA used a RGDR of 0.15 to perform the animal-to-human dosimetric adjustment, while the TCEQ used a RGDR of 1 (TCEQ 2015a). The USEPA conducted their inhalation RfC assessment in 1990, but updated guidance on inhalation gas dosimetry has since been published (USEPA 2012). For the UFs, the USEPA used a total UF of 30 (10 for intraspecies variability and 3 for interspecies variability), the same that was used by the TCEQ.

4.2 Carcinogenic Potential

There has been some debate on the carcinogenic potential of VA due to the varying results from experimental tests and epidemiological studies. VA is considered to have a threshold MOA by the TCEQ and the USEPA, which derived an RfC rather than a URF. Due to this threshold MOA, protecting against the precursor noncarcinogenic effects would also be protective of any carcinogenic effects. Therefore, a carcinogenic ReV was not calculated. Available data on the carcinogenicity of VA are detailed below.

4.2.1 Carcinogenic Weight of Evidence

VA has been evaluated for carcinogenic potential by IARC, NIOSH, and ACGIH (Table 17). According to USEPA's Cancer Guidelines (2005), VA shows suggestive evidence of carcinogenic potential in animals via the inhalation route. Generally, the TCEQ only performs carcinogenic dose-response assessments for chemicals considered by the TCEQ to be "Carcinogenic to Humans" and "Likely to Be Carcinogenic to Humans" and for which available data adequately characterize the dose-response curve.

Table 17. Carcinogenic Weight of Evidence

Group	Classification
International Agency for Research on Cancer (IARC 1995)	Group 2B, possibly carcinogenic to humans
National Institute for Occupational Safety (NIOSH 1998)	"Suspect carcinogen"
ACGIH 2004	A3, confirmed animal carcinogen with unknown relevance to humans
USEPA 1992 (revised in 2000)	"EPA has not classified VA as to its possible human carcinogenicity"

4.2.2 Relevant Data

4.2.2.1 Epidemiological Studies

Two studies have looked at excess risk for cancer for industrial workers exposed to a number of chemicals including VA, although causality and significance were difficult to tease apart due to confounding factors. Hengstler et al. (2003) discussed the details and limitations of both studies in their review:

> "A cohort study including 4806 individuals employed at a plant for the manufacture of synthetic chemicals in the United States was performed between 1942 and 1973 by Waxweiler et al. The cohort had an excess risk for cancer of the respiratory system [resulting in a standardized mortality ratio of 1.5 (95% confidence interval: 1.1-2.0)]. Thus, exposure of these cancer patients to 19 chemicals, including VA, was examined. Exposure of the patients with cancer of the respiratory system to VA was below the mean exposure expected for the members of the cohort with the same year of birth and age at commencement of work in the plant. A subgroup of employees with undifferentiated non-small-cell lung cancer had a slight, but statistically nonsignificant, cumulative exposure to VA. Thus, these results do not provide evidence for a carcinogenic effect of VA in humans.
>
> A case-control study was performed in a cohort of 29,139 men employed in a chemical manufacturing environment (Ott et al., 1989). Nested case-control studies of non-Hodgkin's lymphoma, multiple myeloma, nonlymphocytic leukemia, and lymphocytic leukemia were conducted in men from two chemical facilities and a research center, Exposure ratios were examined in relation to 21 specific chemicals. The results are difficult to interpret because exposure to VA was associated with a decreased risk for nonlymphocytic leukemia (odds ratio: 0.5), but slightly increased odds ratios for non-Hodgkin's lymphoma (odd ratio: 1.2) or multiple myeloma (odds ratio: 1.6).
>
> In conclusion, evaluation of epidemiologic data on a possible carcinogenic effect of VA is difficult because most individuals in the existing epidemiological studies were exposed to several chemicals. Nevertheless, the existing data do not support a carcinogenic effect of VA in humans."

4.2.2.2 Animal Study - Bogdanffy et al., 1994

Details on the Bogdanffy et al. (1994) study are provided in Section 4.1.2. This study was used to develop the noncarcinogenic ReV based on the critical effects in the nasal epithelium. Briefly, groups of 60 male and female mice and rats were exposed via inhalation to 0, 50, 200, and 600 ppm VA for 6 h/d, 5 d/wk, for 104 wks. Chemical lots were tested for purity (>99%) and air concentrations inside the chambers were measured every 15 min, making this a very thorough and well conducted study. Following the exposure regime, all of the animals were sacrificed and an extensive full-body pathological workup was done, including a nasal and respiratory

histological examination for signs of tumor formation. The noted non-neoplastic changes are listed in Section 4.1.2. No signs of neoplasia or tumor-related changes were observed in the mice at any exposure level. In the rats, however, 12 nasal tumors (8 in males and 4 in females) were identified, mainly in the highest 600 ppm exposure group, while one was found in the 200 ppm group. Similar to the patterns of tissue damage described previously, the oncogenic responses to VA exposure were also mainly confined to the nasal cavity in rats and included endophytic and exophytic papillomas, squamous cell carcinoma, carcinoma *in situ* in olfactory regions, and endophytic papilloma in respiratory regions. Squamous cell carcinomas were also found either in areas normally covered by cuboidal epithelium or areas of unknown origin. One squamous cell carcinoma was found in the larynx of a rat of the 600 ppm groups. One squamous cell carcinoma was found in the lung of a mouse of the 600 ppm group. The NOAEL for all effects was 50 ppm in both species. The tumorigenic response appears to be nonlinear. The nonlinear dose response and the unique nature of the rodent nasal cavity suggest that specific risk extrapolation models should be developed for VA.

Table 18. Frequency of Nasal Tumor Formation in Rats Following VA Exposure

Incidence of nasal tumors [a]	**Control**	**50 ppm**	**200 ppm**	**600 ppm**
Males	(59)	(60)	(59)	(59)
Benign inverted papilloma	0	0	0	4
Malignant squamous cell carcinoma	0	0	0	2
Benign papilloma	0	0	1	0
Malignant carcinoma *in situ*	0	0	0	1
Total nasal tumors in males	0	0	1	7**
Females	(60)	(60)	(60)	(59)
Benign inverted papilloma	0	0	0	0
Malignant squamous cell carcinoma	0	0	0	4
Benign papilloma	0	0	0	0
Malignant carcinoma *in situ*	0	0	0	0
Total nasal tumors in females	0	0	0	4
Total nasal tumors for both sexes [b]	0	0	1	11

**p<0.01 by Fisher's pair-wise test compared to control group

[a] Numbers in parentheses represent the number of animals in each group that were histologically examined

[b] Adapted from Bogdanffy et al. (1994), totals for combined sexes added for this analysis; no statistics were conducted.

4.2.3 Carcinogenic MOA

Chronic exposure to sufficiently high VA concentrations via inhalation induces nasal epithelial tumors in rats, but not in mice. Once VA reaches the tissues, it is rapidly broken down into acetaldehyde and acetic acid, and kinetically this has been shown to occur more rapidly in nasal tissue than in other respiratory tissues (Bogdanffy and Taylor 1993). Acetaldehyde can be further broken down once in the cell into acetic acid by the enzyme aldehyde dehydrogenase. Both acetaldehyde and acetic acid are naturally occurring by-products within cells, and these naturally low levels are thought to result in VA's threshold MOA. Acetaldehyde is the mutagenic metabolite of VA, while acetic acid induces cytotoxic and proliferative effects (Albertini 2013). At high concentrations, acetaldehyde is able to interact with DNA directly forming DNA adducts. For more detailed information on the role of acetaldehyde, Albertini (2013) recently published a thorough review on the genotoxicity of VA. VA is also thought to lower inter- and intracellular pH via the production of acetic acid and acetaldehyde. Intracellular acidification is proposed as one of the first pharmacodynamic step in a series of events that culminate in tumorigenesis of nasal and upper gastrointestinal tract epithelial cells exposed to VA (Bogdanffy 2002). This acidification of nasal epithelial cells in rats leads to an increase in H^+ ions causing Ca^{2+} to be displaced from binding sites and blocking intracellular signaling that can promote differentiation. Blocking this signaling can lead to extended proliferation, expansion of the undifferentiated cell population, and clonal expansion of spontaneous or chemical-induced mutants (Bogdanffy 2002). Eventually the steady accumulation of genetic damage results in malignant conversion, although at a very late stage in the life span of the animal (Bogdanffy 2001). VA tumorigenesis occurs at higher exposure concentrations where acetaldehyde becomes saturated and acetic acid formation is maximal causing nasal tissue to respond to the cytotoxic events through a compensatory increase in cell proliferation. This compromises the cell's ability to repair acetaldehyde-induced genetic damage and decrease the time available for spontaneous dissociation and repair of DNA protein crosslinks. Carboxylesterases metabolize VA to acetic acid and acetaldehyde. VA loses its genotoxic activity in the absence of carboxylesterase. Both acetaldehyde, through DNA-protein crosslinks, and acetic acid, through decreases in pH, contribute to the overall genotoxicity (Bogdanffy et al. 1999).

4.2.4 Approaches for Evaluating Carcinogenic Potential

Typically, carcinogens are evaluated based on a nonthreshold MOA and a linear low-dose extrapolation is done in order to determine an air concentration at an excess risk level of 1 in 100,000 (TCEQ 2015a). This does not apply, however, to chemicals that have a threshold MOA, as is the case for VA, which is recognized as a classic threshold carcinogen by the USEPA (2005). For threshold chemicals, protecting against the early noncarcinogenic effects that are key events in carcinogenicity, such as cytotoxicity in this case, will also protect against the later, more severe tumorigenic effects. Therefore, a carcinogenic ReV was not determined as the noncarcinogenic ReV is considered protective against both endpoints.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetation 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 = 1,000 μg/m^3 (300 ppb)
- $^{chronic}ESL_{threshold\ (nc)}$ = 300 μg/m^3 (90 ppb)

The chronic ReV is 1,000 μg/m^3 (300 ppb) (Table 1). The $^{chronic}ESL_{threshold\ (nc)}$ of 300 μg/m^3 (90 ppb) is the long-term ESL used for air permit reviews (Table 2).

4.5 Chronic Inhalation Observed Adverse Effect Level

Observed inhalation adverse effect levels are described in more detail in Section 3.4 and in TCEQ (2015a). The chronic POD determined from the Bogdanffy et al. (1994) study was based on non-neoplastic changes (olfactory epithelial atrophy and basal cell hyperplasia in rats and olfactory epithelial atrophy and nasal submucosal gland hyperplasia in mice) following 200 ppm VA inhalation exposure. The LOAEL of 200 ppm, where effects occurred in some animals, represents a concentration at which similar effects could possibly occur in some individuals exposed over the same duration or longer. Based on the TCEQ guidelines (2012), no duration adjustment is needed; however an animal-to-human dosimetric adjustment is used to calculate the $LOAEL_{HEC}$. Since the RGDR is 1, based on updated guidelines from the USEPA (2012), the $LOAEL_{HEC}$ is equal to the LOAEL of 200 ppm. Effects are not a certainty as there may be inter- and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 200 ppm is provided for informational purposes only (TCEQ 2015a). 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. Note that mild sensory irritation may occur at lower concentrations than tissue damage. (i.e., the acute inhalation observed adverse effect level of 20 ppm is a concentration at which at least one person observed persistent slight throat irritation from a 240 min exposure).

The margin of exposure between the observed adverse effect level (200 ppm) and the chronic ReV (0.3 ppm) is a factor of approximately 670.

Chapter 5 References

5.1 References Cited in the Development Support Document

Albertini, R.J. 2013. Vinyl acetate monomer (VAM) genotoxicity profile: Relevance for carcinogenicity. Critical Reviews in Toxicology. 43(8): 671-706.

American Conference of Industrial Hygienists (ACGIH). 2001. Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH.

Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for vinyl acetate.

American Industrial Hygiene Association (AIHA). 1989. Odor Thresholds for Chemical with Established Occupational Health Standards. Akron, Ohio.

Bogdanffy, M.S. and Tayler, M.L. 1993. Kinetics of carboxylesterase-mediate hydrolysis of the nasal carcinogen vinyl acetate. Drug Metabolism and Disposition. 21:1107-1111.

Bogdanffy, M.S., Dreef-Van Der Meulen, H.C., Beems., R.B., Feron, V.J., Casciere., T.C., Tyler, T.R., Vinegar, M.B., and Rickard, R.W. 1994. Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. Fundamental and Applied Toxicology. 23:215-229.

Bogdanffy, M.S., Gladnick, N.L., Kegelman, T., and Frame S.R. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 1 9: 331-350.

Bogdanffy, M.S., Sarangapani, R., Plowchalk, D.R., Jarabek, A. and Andersen, M.E. 1999. A biologically based risk assessment for vinyl acetate-induced cancer and noncancer inhalation toxicity. Toxicological Sciences. 51: 19-35.

Bogdanffy, M.S., Plowchalk, D.R., Sarangapani, R., Starr, T.B., and Andersen, M.E. 2001. Mode-of-action-based dosimeters for interspecies extrapolation of vinyl acetate inhalation risk. Inhal. Toxicol. 13: 377-396.

Bogdanffy, M.S. 2002. Vinyl Acetate-Induced Intracellular Acidification: Implications for Risk Assessment. Toxicological Sciences. 66: 320-326.

Canada Office of Environmental Health Hazard Assessment (CA OEHHA) Determination of Noncancer Chronic Reference Exposure Levels Batch 2B December 2001. Chronic Toxicity Summary. Vinyl Acetate. Accessed January 2011 http://oehha.ca.gov/air/chronic_rels/pdf/vinylace.pdf

Chem ID Plus. Names & Synonyms: VA RN: 108-95-2 2009. Available from: http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp.

Deese, D.E. and Joyner, R.E. 1969. Vinyl Acetate: A study of Chronic Human Exposure. American Industrial Hygiene Association Journal. 30:5:449-457.

Gage JC. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br J Ind Med 27:1-18.

Hazardous Substances Data Bank (HSDB). 2009 update. United States National Library of Medicine, http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~4s7Qns:1 , accessed August 10, 2010.

Hazleton. 1980d. Vinyl acetate: oral and inhalation teratology studies in the rat. U.S. EPA/OTS public files. Hazleton Labs Europe Ltd. Document no. FYI-OTS-0184-0278.

Hellman T.M. and Small, F. H. 1974. Characterization for the Odor Properties of 101 Petrochemicals Using Sensory Methods. J. Air Pollut. Control Assoc. 24:979-982.

Hurtt, M.E., Vinegar, M.B., Rickard, R.W., Cascieri, T.C., and Tyler, T.R. 1995. Developmental toxicity of oral and inhaled vinyl acetate in the rat. Fund. Appl. Toxicol. 24: 198-205.

National Institute of Occupational Safety and Health (NIOSH). 2005. NIOSH Pocket guide to chemical hazards. Available from: http://www.cdc.gov/niosh-rtecs/AKD59F8.html#AIHAAP

National Research Council (NRC). 2013. Vinyl Acetate. Acute Exposure Guideline Level (Final) in Acute Exposure Guideline Levels (AEGLs) for Selected Airborne Chemicals. Volume 14.

Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: A review. American Industrial Hygiene Association Journal. 47:142-151.

Smyth HF Jr, Carpenter CP. 1973; Vinyl acetate: Single animal inhalation and human sensory response. Carnegie Mellon University, Division of Sponsored Research, Chemical Hygiene Fellowship, Pittsburgh, PA. Special report f/36-72.

Texas Commission on Environmental Quality (TCEQ). 2015a. TCEQ Guidelines to develop toxicity factors. Revised RG-442. Office of the Executive Director, Austin, TX.

Texas Commission on Environmental Quality (TCEQ). 2015b. Approaches to Derive Odor-Based Values. Proposed April 2015. Office Office of the Executive Director, Austin, TX. http://www.tceq.texas.gov/toxicology/dsd/dsds_about.html

Texas Risk Reduction Program (TRRP). 2006. Chemical/Physical Properties Table. Texas Commission on Environmental Quality. accessed June 25, 2009. available from www.tceq.state.tx.us/assets/public/remediation/trrp/trrptoxchph_2006.xls.

United States Environmental Protection Agency (USEPA). 1990. Vinyl acetate. Integrated Risk Information System (IRIS) on-line database.

United States Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development. Washington, D.C. EPA/600/8-90/066F.

United States Environmental Protection Agency (USEPA). 2005. Guidelines for carcinogen risk assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B.

United States Environmental Protection Agency (USEPA). 2012 Advances in inhalation gas dosimetry for derivation of a reference concentration (RfC) and use in risk assessment. Washington, D.C. EPA/600/R-12/044.

5.2 Other Studies and Documents Reviewed by the TD

Hazardous Substances Data Bank (HSDB). online database. National Toxicology Information Program, National Library of Medicine 2009 [cited. Available from: http://www.toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~MZMe0B:1.