

**VINYL ACETATE**  
**(CAS Reg. No. 108-05-4)**

**ACUTE EXPOSURE GUIDELINE LEVELS**  
**(AEGLs)**

**INTERIM**

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**PREFACE**

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m<sup>3</sup>]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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**EXECUTIVE SUMMARY**

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Vinyl acetate (VA) [CASRN 108-05-4] is a colorless, flammable liquid with low solubility in water (Rhum, 1970; O'Neil et al., 2001). VA is manufactured by reacting ethylene with sodium acetate (Bisesi, 2001). The U.S. production of VA in the U.S. in 1993 was reported to be 2.83 billion pounds (Chem. & Eng. News, 1994). VA is mainly used as a monomer in the production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coating and binding applications (Rhum, 1970). Poly(vinyl acetate) is also a precursor for the poly(vinyl alcohol) and poly(vinyl acetate) resins, or is copolymerized with vinyl chloride and with ethylene to form polymers or with acrylonitrile for acrylic fibers.

7

The odor of VA has been described as being immediately pleasant, but quickly becoming sharp and irritating (Rhum, 1970). The odor detection threshold is reported to be 0.12 ppm, while the recognition threshold is 0.4 ppm (U.S. EPA, 1992; AIHA, 1989; Hellman and Small, 1974).

14

The AEGL-1 is based on a human study in which inhalation exposure of humans to 4-20 ppm for 2 minutes resulted in minimal or slight throat irritation, exposure to 20 ppm for 4 hours produced persistent slight throat irritation, and exposure to 34 ppm for 2 hours resulted in persistent throat irritation (Smyth and Carpenter, 1973). The point of departure (POD) is 20 ppm, which represents a no-effect level for notable discomfort. A total uncertainty factor of 3 is applied: an interspecies uncertainty factor is not applicable, and an intraspecies uncertainty factor of 3 is applied because the irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect and therefore should not vary over time, the AEGL-1 value is not scaled across time, but rather the threshold value is adopted for all time points.

24

In the Bogdanffy et al. (1997) study, exposure of rats for 6 hours to 1000 ppm represents a NOAEL for an AEGL-2. At this concentration, histopathological olfactory effects included degeneration, necrosis, and exfoliation of the olfactory epithelial cells. Although a definitive conclusion on the reversibility of these lesions cannot be drawn due to the absence of a recovery phase, Frame (2004) concludes that the effects of acute exposure to 1000 ppm VA should be reversible based on the focal and limited nature of the olfactory lesions seen following VA exposure, as well as the known regenerative capacity of olfactory tissue. A total uncertainty factor of 10 is applied: 3 for interspecies and 3 for intraspecies variability. An interspecies uncertainty factor of 3 is applied on the basis that the mechanism of nasal toxicity appears to depend on the metabolism of VA to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of VA by the nasal cavity reported little difference among male and female mice, rats and humans in the carboxylesterase-mediated metabolism of VA, particularly by olfactory epithelium (Bogdanffy and Taylor, 1993; Bogdanffy et al., 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al., 2002). An intraspecies uncertainty factor of 10 would normally be applied based on the knowledge that considerable variability in olfactory nasal tissue occurs in humans with regard to surface area covered, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al., 2002). However, a total uncertainty factor of 30 would reduce the AEGL-2 values to concentrations that did not

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1 result in serious health effects in human volunteer studies (a UF of 30 would drive the 8-hour  
2 AEGL-2 to 25 ppm). Therefore, the intraspecies uncertainty factor was reduced to 3, and the  
3 total uncertainty factor is 10.

4 Because the reported lethality data were unreliable, the AEGL-3 values are based on the  
5 same point of departure as the AEGL-2 (Bogdanffy et al., 1997). A total uncertainty factor of 3  
6 is applied: 3 for interspecies and 1 for intraspecies variability. An interspecies uncertainty factor  
7 of 3 is applied on the same basis as for the AEGL-2: that the mechanism of nasal toxicity  
8 appears to depend on the metabolism of VA to the metabolites acetic acid and acetaldehyde via  
9 carboxylesterase and aldehyde dehydrogenase. An intraspecies uncertainty factor of 1 was  
10 applied because the endpoint of reversible nasal histopathological changes is much less severe  
11 than the toxic effects defined for an AEGL-3. Therefore, the total uncertainty factor is 3.

12 The experimentally derived AEGL-2 and AEGL-3 exposure values were scaled to AEGL  
13 time frames using the concentration-time relationship given by the equation  $C^n \times t = k$ , where  $C$   
14 = concentration,  $t$  = time,  $k$  is a constant, and  $n$  generally ranges from 1 to 3.5 (ten Berge et al.,  
15 1986). The value of  $n$  was not empirically derived because of insufficient data; therefore, the  
16 default value of  $n = 1$  was used for extrapolating from shorter to longer exposure periods and a  
17 value of  $n = 3$  was used to extrapolate from longer to shorter exposure periods. The 10-minute  
18 AEGL-2 and AEGL-3 values were set equal to the respective 30-minute values because the NAC  
19 considers it inappropriate to extrapolate from the exposure duration of 6 hours to 10 minutes.

20 A level of distinct odor awareness (LOA) for VA of 0.25 ppm was derived on the basis of the  
21 odor detection threshold from the study of Hellman and Small (1974) (see Appendix C for LOA  
22 derivation). The LOA represents the concentration above which it is predicted that more than  
23 half of the exposed population will experience at least a distinct odor intensity; about 10 % of the  
24 population will experience a strong odor intensity. The LOA should help chemical emergency  
25 responders to assess the public awareness of the exposure due to odor perception.

26 A carcinogenicity assessment was not appropriate for an acute exposure scenario on the basis  
27 that the proposed mechanism of carcinogenicity suggests a nonlinear mode of action requiring  
28 continued exposure. Therefore, a one-time exposure even to high-concentrations of VA would  
29 not be expected to result in tumor development.

30 The calculated values are listed in the tables below.

Summary of Proposed AEGL Values for Vinyl Acetate [ppm (mg/m <sup>3</sup> )]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	6.7 (24)	6.7 (24)	6.7 (24)	6.7 (24)	6.7 (24)	20 ppm for 4 hours represents no-effect level for notable discomfort in humans (Smyth and Carpenter, 1973)
AEGL-2 (Disabling)	230 (810)	230 (810)	180 (630)	110 (390)	75 (260)	Reversible histopathological nasal lesions in rats at 1000 ppm for 6 hours (Bogdanffy et al., 1997)
AEGL-3 (Lethal)	760 (2700)	760 (2700)	610 (2100)	380 (1300)	250 (880)	Reversible histopathological nasal lesions in rats at 1000 ppm for 6 hours (Bogdanffy et al., 1997)

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## 1. INTRODUCTION

Vinyl acetate (VA) is a colorless, flammable liquid with low solubility in water (Rhum, 1970; O'Neil et al., 2001). The odor of VA has been described as being immediately pleasant, but quickly becoming sharp and irritating (Rhum, 1970). The odor detection threshold is reported to be 0.12 ppm, while the recognition threshold is 0.4 ppm (U.S. EPA, 1992; AIHA, 1989; Hellman and Small, 1974). Other odor thresholds were reported but were rejected by the U.S. EPA (1992) and AIHA (1989) because they were the minimum perceptible value or the result of a passive exposure.

VA is manufactured by reacting ethylene with sodium acetate (Bisesi, 2001). The U.S. production of VA in 1993 was reported to be 2.83 billion pounds (Chem & Eng. News, 1994). VA is primarily used as a monomer in the production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coating and binding applications (Rhum, 1970). Poly(vinyl acetate) is also a precursor for the poly(vinyl alcohol) and poly(vinyl acetate) resins, or is copolymerized with vinyl chloride and with ethylene to form polymers or with acrylonitrile for acrylic fibers.

The physicochemical data of VA are presented in Table 1.

Parameter	Value	Reference
Synonyms	acetic acid ethenyl ester; acetic acid vinyl ester; 1-acetoxyethylene; ethynyl acetate; vinyl ethanoate	O'Neil et al., 2001; ACGIH, 1996
Chemical formula	C <sub>4</sub> H <sub>6</sub> O <sub>2</sub>	
Molecular weight	86.09	
CAS Reg. No.	108-05-4	
Physical state	liquid	O'Neil et al., 2001
Solubility in water	1 g/50 mL @ 20EC	O'Neil et al., 2001
Vapor pressure	115 torr @ 25EC	ACGIH, 1996
Vapor density (air =1)	3.0	Bisesi, 2001
Liquid density (water =1)	0.9317	ACGIH, 1996
Melting point	-100EC, -93EC	O'Neil et al., 2001
Boiling point	72.7EC	Rhum, 1970
Conversion factors	1 ppm = 3.52 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.284 ppm	NIOSH, 2003

## 2. HUMAN TOXICITY DATA

## 2.1. Acute Lethality

No data were found that reported lethality in humans following acute exposure.

## 2.2. Nonlethal Toxicity

Groups of three to nine volunteers were exposed to various concentrations of VA for 2 minutes up to 4 hours (Smyth and Carpenter, 1973). VA vapor was generated by feeding metered air through a spirally corrugated surface of a minimally heated Pyrex tube. 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. The only other details provided were that the concentrations were unknown to the volunteers, the concentrations were presented in random order, and the symptoms were reported privately. No description was given of the exposure chamber, if the volunteers were previously exposed or naive, or how much time lapsed between exposures. The results of the exposure are presented in Table 2.

**Table 2. Summary of Human Sensory Response to Controlled Exposures to VA<sup>a</sup>**

Exposure conc. (ppm) <sup>b</sup>	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. after exposure; eye irritation to 60 min. after exposure; subjects expressed unwillingness to work at this concentration for 8 hours

<sup>a</sup> Taken from Smyth and Carpenter, 1973.

<sup>b</sup> Corrected using calibration curve

The medical division of Union Carbide Company undertook a study to evaluate three different endpoints: the average environmental concentrations of VA that chemical workers were

1 exposed to; potential chronic health effects that may have resulted from VA exposure; and  
2 subjective human responses to short-term VA exposure (Deese and Joyner, 1969). To determine  
3 the average environmental exposure levels of VA plant workers, air samples were measured  
4 during normal operating conditions in three different production units. A total of 40 different  
5 samples (plus 2 blanks) were taken from the three production units during two separate sampling  
6 periods approximately one month apart. The total sampling time was greater than 18 hours.  
7 Samples were taken from 3-6 designated sites in each of the three production units. The location  
8 of the sampling was determined by the amount of time the operator spent in each area, the  
9 author's observation of probable exposure based on personal subjective responses, and the  
10 operator's description of duties and exposures. To measure the concentration of VA in the air,  
11 short term and long term air samples were taken. For short-term samples (10 minutes), a  
12 minimum of 15 L of air was collected by scrubbing air through a fritted glass midget impinger  
13 bubbler and a standard midget impinger in series; while long-term samples (2 hours) of 180 L  
14 were collected using standard Greenburg-Smith impingers. Calibrated rotometers metered the  
15 collection rate of 1.5 L/min, and a vacuum was provided using appropriate equipment. VA  
16 concentrations in the air samples were measured using gas chromatography. The exposure  
17 concentrations documented in this study were believed to be representative of exposure received  
18 over the previous five years on the basis that operating conditions, process methods, and physical  
19 equipment were unchanged over that time period. The measured concentrations ranged from 0-  
20 59.3 ppm, with 83% of the measured samples being less than 10 ppm. The 8-hour TWAs for the  
21 3 production facilities were 8.2, 5.2, and 7.7 ppm. Some operations, such as maintenance,  
22 resulted in brief exposures to higher concentrations. For example, concentrations measured in  
23 the breathing zone of workers as they opened the hopper door to unplug material flow were  
24 123.3, 125.6, and 326.5 ppm. The exposures lasted for 3 minutes and occurred twice daily.

25 To evaluate the potential health effects resulting from long-term exposure to VA, company  
26 medical records were evaluated and compared to a control group (Deese and Joyner, 1969).  
27 Twenty-one of 26 VA operators participated in the study. Sixteen operators had worked with  
28 VA for more than 15 years, and six for 20 years or more. Each participating VA operator was  
29 matched by taking the next operator listed alphabetically in the Medical Division Files who had  
30 an age within 5 years of the VA operator's age and who had never worked in the VA complex.  
31 The control group comprised individuals exposed to many different chemicals commonly used in  
32 the petrochemical industry, but their exposures were not categorized for this study. Medical  
33 records of the participants were evaluated for the following: all sickness-related absences  
34 between January 1 and December 31, classified according to etiology and duration; all initial  
35 visits to the Medical Division over the same interval; and all reported exposures to VA. No  
36 exposure-related differences were noted in blood chemistry results, pulmonary pathology, work  
37 days lost, or total number of initial visits for occupational injury or illness. The VA group had a  
38 higher number of total days lost due to respiratory illness and gastrointestinal conditions. Closer  
39 examination of the records revealed that these differences were due primarily to one individual  
40 in each case: one operator had a recurrent upper respiratory tract infection while another had  
41 cholecystitis. VA operators were also given a questionnaire at the time of their screening  
42 examination. The results of the questionnaire are as follows. When asked if VA bothers them  
43 under normal working conditions, 13 (61%) said no, while the remaining responses included two  
44 complaining of odor, two noting it is irritating to the throat and/or nose, three responses that it is  
45 irritating to the skin, and one that it "does bother." When asked if VA irritated their eyes, nose,

1 or throat, 15 (71%) said no, two responded “some,” three said it irritated their eyes, and one said  
2 it is noticeable but worse at times. When asked if there were any other comments, one individual  
3 commented that he liked the odor of it, while another commented that breathing in the fumes  
4 hurt his chest.

5 In the third and final part of the study by Deese and Joyner (1969), individuals were asked to  
6 provide their subjective responses to odor, eye irritation, and upper respiratory irritation during  
7 the air sampling of VA. The individuals consisted of one of the authors, a laboratory analyst  
8 assisting in sampling, and one chemical operator from each of the specific production units.  
9 Exposure concentrations ranged from 0.4 ppm to 21.6 ppm (exact concentrations reported at the  
10 three plant units were 0.4, 0.8, 2.7, 4.2, 4.2, 5.7, 6.8, 7.6, 7.6, 9.5, 9.9, or 21.6 ppm). Although  
11 there were a few notations that no odor was detected, odor was generally noted as slight at  
12 concentrations of 0.4 to 9.9 ppm. At a concentration of 21.6 ppm, the odor was noted as marked  
13 by all three individuals. Eye irritation was not noted by any of the individuals up to and  
14 including 9.9 ppm with the exception of slight eye irritation noted by the author at 5.7 and 6.8  
15 ppm. At 21.6 ppm, however, eye irritation was graded as intolerable by all three individuals.  
16 Upper respiratory irritation was present at 21.6 ppm in all three subjects as assessed by the  
17 presence of cough and/or hoarseness. Hoarseness was noted by the author at 4.2 and 5.7 ppm.  
18 Although not specifically stated by the authors in the text, it appears from looking at the table  
19 presenting the “data for atmospheric VA samples” that these exposures were of a 10-minute  
20 duration. It must be emphasized that these were not controlled exposures, and exposure could  
21 have occurred prior to the sampling period.

22 Air emissions around Monsanto production facilities were evaluated to assess the potential  
23 for human health effects (Monsanto Company, 1989). Emission of VA was identified as a  
24 concern at the Decatur production plant on the basis of the carcinogenic action of VA. Ambient  
25 air sampling from four locations in the Texas City, Texas area revealed concentrations ranging  
26 from 0.07 to 0.57 ppm (0.25 - 2.0 mg/m<sup>3</sup>). To conduct a safety assessment, the maximum annual  
27 average concentration was obtained by computer modeling using an EPA dispersion model. The  
28 modeled annual average concentration for community exposure was estimated to be 1.8 x 10<sup>-3</sup>  
29 ppb (5.52 x 10<sup>-3</sup> F g/m<sup>3</sup>), with the highest exposure being 8.3 x 10<sup>-2</sup> ppb (0.25 F g/m<sup>3</sup>).

30 A number of studies investigating the potential health effects of workers chronically exposed  
31 to air containing chemicals including VA were published in the Russian literature. Agaronyan  
32 and Amatuni (1980) examined the prevalence of neurotoxicity and cardiovascular effects in  
33 workers exposed in a “polyvinylacetate” plant compared with workers from the mechanical  
34 department of a different factory. The exposed group was further divided into 3 groups: those  
35 that had no signs of CNS toxicity, those that had the beginning phase of neurotoxicity (as  
36 defined by neuroasthenia), and those with “asthenovegetative syndrome with pronounced  
37 autonomic-dystonia and involvement of the hypothalamic regions.” Cardiovascular findings  
38 increased in incidence with increasing neurotoxicity and included: piercing pain in the area of  
39 the heart, palpitations, muffled heart sounds, systolic murmur, hypertension, and EKG findings  
40 of tachycardia, bradycardia, decreased P wave, widened QRS complex, prolonged Q-T, and  
41 decreased T wave. Studying the same workers as Agaronyan and Amatuni (1980), Amatuni and  
42 Agaronyan (1979; 1980) also investigated potential pulmonary effects following chronic  
43 exposure to VA. They reported a progressive and significant increase in the frequency of

1 impaired lung function in proportion to increasing duration of employment history (from  $16.6 \pm$   
2  $8.7\%$  at less than a year up to  $48.4 \pm 5.1\%$  [ $p < 0.001$ ] at 15 years and longer of employment).  
3 Pulmonary effects included decreases in vital capacity, forced expired volume in one second  
4 ( $FEV_1$ ), maximal voluntary ventilation (MVV), and expiratory and inspiratory capacity ( $C_{exp}$ ;  
5  $C_{insp}$ ), with clinical manifestations of chronic bronchitis. In another study, Agaronyan and  
6 Amatuni (1982) examined workers for pulmonary ventilation function at the start of the study  
7 and again after five years of employment. They found statistically significant decreases in  
8 ventilation parameters that are primarily indicative of obstructive and mixed variant of  
9 pulmonary ventilation function impairment. Limitations of the Russian studies include:  
10 occupational exposures were to multiple chemicals, and exposure concentrations of VA were not  
11 documented.

### 12 **2.3. Developmental/Reproductive Toxicity**

13 No studies were found addressing the potential for inhaled VA to cause developmental or  
14 reproductive effects in humans.

### 15 **2.4. Genotoxicity**

16 *In vitro* incubation of VA with human lymphocytes or leukocytes has resulted in  
17 chromosome aberrations, increased sister chromatid exchanges (SCE), and DNA cross-linking.  
18 Human whole blood lymphocyte cultures incubated for 48 hours with 0.125, 0.25, 0.5, 1, or 2  
19 mM VA exhibited a peak in the frequency of micronucleated lymphocytes at 0.5 mM and 1 mM  
20 VA ( $3.2 \pm 1\%$  and  $3.1 \pm 0.7\%$ , respectively, vs.  $0.9 \pm 0.1\%$  for controls) (Mäki-Paakkanen and  
21 Norppa, 1987). The 2 mM concentration was considered a toxic concentration, resulting in a  
22 decrease in the frequency of micronucleated lymphocytes due to inhibition of mitosis. Whole  
23 blood cultures and isolated lymphocytes incubated for 48 hours with 0.25, 0.5, 1, or 2 mM VA  
24 showed a concentration-dependent increase in chromatid-type aberrations and a slight increase in  
25 chromosome-type breaks, while no effects were observed at 0.125 mM VA (Jantunen et al.,  
26 1986). Concentration-related increases in SCEs and chromosome aberrations (in first division  
27 cells) were found in human whole blood lymphocyte cultures and purified lymphocyte cultures  
28 incubated with 0.1 - 1 mM VA for 48 hours (Norppa et al., 1985; Mäki-Paakkanen et al., 1984).  
29 The most common chromosome aberration was the chromatid-type break: at 1 mM, 84% of the  
30 cells were aberrant, with 38% containing a chromatid-type exchange. Purified lymphocyte  
31 cultures exhibited a more pronounced effect on both SCEs and the number of aberrant cells  
32 (Norppa et al., 1985). Cultured human lymphocytes exposed to 0.1 - 2.4 mM VA exhibited a  
33 linear increase in SCE with increasing exposure duration up to 24 hours (He and Lambert, 1985).  
34 A 2-fold higher SCE frequency was observed in cells exposed in the late  $G_1$  phase compared to  
35 cells exposed during the early  $G_1$  phase, while cells treated during the first  $G_1$  phase had a  
36 statistically significant increase in SCE during the 3 subsequent cell cycles. Human leukocytes  
37 incubated with 10 or 20 mM VA for 4 hours at 37°C did not show evidence of direct DNA  
38 strand breaks, but did show concentration-dependent DNA cross-linking (Lambert et al., 1985).

## 2.5. Carcinogenicity

A series of epidemiological studies were conducted to investigate the potential link between employment at a Texas petrochemical plant and an increased incidence of mortality from brain cancer, specifically gliomas (Alexander et al., 1980; Austin and Schnatter, 1983a; 1983b; Waxweiler et al., 1983; Leffingwell et al., 1983). Although VA was one of the chemicals which had a greater apparent risk (Leffingwell et al., 1983), no statistically significant associations were found between exposure to specific chemicals and mortality from brain cancer (Leffingwell et al., 1983, Austin and Schnatter, 1983a). Confounding factors include, but are not limited to, concurrent exposure to other chemicals, exposure to unknown concentrations of the chemicals of concern, and the use of in-plant controls (may have obscured a significant finding).

## 2.6. Summary

Available data regarding human acute exposure to VA were limited. The odor detection and recognition threshold values for VA are 0.12 and 0.4 ppm, respectively (U.S. EPA, 1992; AIHA, 1989; Hellman and Small, 1974). A controlled human exposure study by Smyth and Carpenter (1973) reported that a 2-minute exposure to 4, 8, or 20 ppm VA resulted in minimal eye, nose, and throat irritation in 1-2 of nine exposed individuals. When exposure was increased to 34 ppm for 2 hours, one of three individuals complained of persistent throat irritation, and exposure to 72 ppm VA for 4 hours resulted in eye irritation and slight throat irritation for up to 60 minutes post exposure in all four subjects exposed. The Deese and Joyner (1969) study is of limited usefulness because it was not a controlled human exposure, but rather was simply a survey which recorded subjective symptoms of three individuals during VA air sampling of a work environment. When air concentrations measured 21.6 ppm, all three individuals reported that eye irritation was intolerable, and a slight cough and hoarseness were noted in 2 of 3 individuals. Slight eye irritation was additionally noted in 1 of 3 individuals at 5.7 or 6.8 ppm.

*In vitro* genotoxicity studies with human lymphocytes or leukocytes have reported that VA increased the number of chromosome aberrations, sister chromatid exchanges, and DNA-crosslinking. Epidemiological studies have not identified any clear relationship between VA exposure and brain cancer.

## 3. ANIMAL TOXICITY DATA

### 3.1. Acute Lethality

#### 3.1.1. Rats

Groups of 6 male and 6 female rats were exposed for 4 hours to nominal concentrations of 2000, 4000, or 8000 ppm VA (Smyth and Carpenter, 1973). The nominal concentrations were corrected using a curve based upon a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm; the corrected concentrations were 1640, 3280, and 6560 ppm. No information was provided regarding a control group, the strain or age of the rats, or the exposure chamber. VA vapor was generated by feeding liquid VA at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, it is inferred that the period of observation following

1 exposure was 14 days, based on the results of the group of studies reported by Smyth and  
 2 Carpenter (1973). Clinical signs, body weight changes, and mortality were recorded and are  
 3 presented in Table 3. Gross necropsy of the animals that died revealed pulmonary congestion  
 4 and hemorrhage, froth in the trachea, and opaque corneas. The LC<sub>50</sub> was calculated using the  
 5 moving average table of Weil and was 3680 (2660-5100) ppm.

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Table 3. Results of 4-Hour Inhalation Exposure in Rats <sup>a</sup>				
Exposure conc. (ppm)	Mortality	Days to death	Avg. weight change (g)	Clinical signs
1640	0/12	-	+60	extremities congested at 1 hr
3280	4/12	3 during exposure; 1 in 9 days	+27	gasping at 50 min.; clonic convulsions at 150 min.; death at 3 hrs
6560	12/12	all during exposure	-	Gasping at 10 min., prostrate at 25 min., clonic convulsions at 50 min., death at 90 min.

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12 <sup>a</sup> Table taken from Smyth and Carpenter, 1973; results not separated for male and female rats

13 The remaining acute lethality studies in rats lacked adequate reporting of study details; it  
 14 must be assumed that the exposure concentrations were nominal. Gage (1970) exposed 4 male  
 15 and 4 female Alderley Park specific pathogen-free rats to air saturated with VA for 5 minutes  
 16 (Gage, 1970). Exposure produced rapid anesthesia and death. Six Sherman rats (sex not  
 17 specified) were exposed to 4000 ppm VA vapor for 4 hours (no details about exposure  
 18 conditions provided) and observed for 14 days for mortality (Smyth and Carpenter, 1948). Three  
 19 of the six exposed rats died. Exposure concentration was not confirmed by analytical methods,  
 20 and no controls were used. Roumiantsev et al. (1981) reported a 4-hour LC<sub>50</sub> value of 3238 ppm  
 21 in rats. Study details were limited to the comments that animals were observed for 30 days and  
 22 that the animals died during the exposure or in the days following exposure.

### 23 3.1.2. Mice

24 Groups of 6 mice were exposed for 4 hours to nominal concentrations of 500, 1000, 2000,  
 25 4000, or 8000 ppm VA (calculated concentrations of 410, 820, 1640, 3280, and 6560 ppm as  
 26 corrected using a curve based upon a gas chromatographic analysis of calculated concentrations  
 27 ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter, 1973). No information was provided  
 28 regarding a control group; the sex, strain, or age of the mice; or the exposure chamber. VA  
 29 vapor was generated by feeding liquid VA at a constant rate through a spirally corrugated  
 30 surface of a minimally heated Pyrex tube, through which metered air was passed. Although not  
 31 specifically stated, it is inferred that the period of observation following exposure was 14 days,  
 32 based on the results of the group of studies reported by Smyth and Carpenter (1973). Clinical  
 33 signs, body weight changes, and mortality were recorded and are presented in Table 4. Gross  
 34 necropsy of the animals that died revealed pulmonary congestion and excess pleural fluid. The  
 35 LC<sub>50</sub> was calculated using the moving average table of Weil and was 1460 (925-2305) ppm.

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Exposure conc. (ppm)	Mortality	Days to death	Avg. weight change (g)	Clinical signs
410	0/6	-	+4	none
820	1/6	8 days	+3	labored breathing at 2 min.
1640	4/6	during exposure	-2.5	gasping at 5 min., clonic convulsions and death at 15 min., survivors had labored breathing
3280	5/6	during exposure	+1	gasping at 5 min., clonic convulsions and death at 30 min., one survivor had opaque eyes and poor coordination
6560	6/6	during exposure	-	Gasping at 5 min., deaths in 15, 15, 15, 20, 20, and 65 min.

<sup>a</sup> Table taken from Smyth and Carpenter, 1973.

10 Roumiantsev et al. (1981) reported a 2-hour LC<sub>50</sub> value of 3010 ppm in mice. Study details  
 11 were limited to the comments that animals were observed for 30 days and that the animals died  
 12 during the exposure or in the days following exposure.

### 14 3.1.3. Guinea Pigs

15 Groups of 6 male guinea pigs were exposed for 4 hours to nominal concentrations of 2000,  
 16 4000, 8000, or 16,000 ppm VA (calculated concentrations of 1640, 3280, 6560, and 13,120 ppm  
 17 as corrected using a curve based upon a gas chromatographic analysis of calculated  
 18 concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter, 1973). No information  
 19 was provided regarding a control group, the age of the guinea pigs, or the exposure chamber.  
 20 VA vapor was generated by feeding liquid VA at a constant rate through a spirally corrugated  
 21 surface of a minimally heated Pyrex tube, through which metered air was passed. Although not  
 22 specifically stated, it is inferred that the period of observation following exposure was 14 days,  
 23 based on the results of the group of studies reported by Smyth and Carpenter (1973). Clinical  
 24 signs, body weight changes, and mortality were recorded and are presented in Table 5. Gross  
 25 necropsy of the animals that died revealed congestion, emphysema, and scattered hemorrhages in  
 26 the lungs. The LC<sub>50</sub> was calculated using the moving average table of Weil and was 5210  
 27 (3500-7740) ppm.

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Exposure conc. (ppm)	Mortality	Days to death	Avg. weight change (g)	Clinical signs
1640	0/6	-	+57	lacrimation at 30 min., eyes and noses wet at end of exposure
3280	1/6	during exposure	+33	labored breathing and poor coordination at 55 min., lacrimation at 90 min., death at 2 hr., survivors normal
6560	4/6	3 during exposure; 1 in 3 days	-4	gasping at 10 min., clonic convulsions at 18 min., deaths at 55, 60, and 105 min., survivors weak
13,120	6/6	all during exposure	-	gasping and nose rubbing at 2 min., lacrimation at 10 min., prostrate at 22 min., and deaths at 30, 35, 45, 75, 85, and 107 min.

<sup>a</sup> Table taken from Smyth and Carpenter, 1973.

### 9 3.1.4. Rabbits

10 Groups of 4 male rabbits were exposed for 4 hours to nominal concentrations of 2000, 4000,  
 11 or 8000 ppm VA (calculated concentrations of 1640, 3280, or 6560 ppm as corrected using a  
 12 curve based upon a gas chromatographic analysis of calculated concentrations ranging from 0.6  
 13 to 16,000 ppm) (Smyth and Carpenter, 1973). No information was provided regarding a control  
 14 group, the strain or age of the rabbits, or the exposure chamber. VA vapor was generated by  
 15 feeding liquid VA at a constant rate through a spirally corrugated surface of a minimally heated  
 16 Pyrex tube, through which metered air was passed. The results of the exposure are presented in  
 17 Table 6. Gross necropsy of the animals that died revealed bloody nostrils, froth in the trachea,  
 18 excess pleural fluid and pulmonary hemorrhage. The LC<sub>50</sub> was calculated using the moving  
 19 average table of Weil and found to be 2760 (1800-4200) ppm.

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Exposure conc. (ppm)	Mortality	Days to death	Avg. weight change (g)	Clinical signs
1640	0/4	-	+225	none
3280	3/4	4, 7, 13 days	-300	nose red at 30 min., eyes cloudy at 90 min., normal at end of exposure
6560	4/4	2 during exposure; 1 in 2 days; 1 in 4 days	-206	labored breathing and poor coordination at 15 min., convulsions at 17 min., noses red and lacrimation at 55 min., eyes cloudy at 70 min., deaths at 60 and 100 min., nose bloody at 2 hr

<sup>a</sup> Table taken from Smyth and Carpenter, 1973.

## 3.2. Nonlethal Toxicity

### 3.2.1. Dogs

One male beagle dog per group was exposed for 4 hours to nominal concentrations of 62.5, 125, 250, 1000, 2000, or 4000 ppm VA (Smyth and Carpenter, 1973). The nominal concentrations were corrected using a curve based upon a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm; the corrected concentrations were 51.25, 102.5, 205, 820, 1640, or 3280 ppm. VA vapor was generated by feeding metered air through a spirally corrugated surface of a minimally heated Pyrex tube. These experiments lacked a control group and no details were provided regarding the exposure chamber. All animals survived the exposures. The results of the exposure are presented in Table 7. No further details other than those listed in the table were provided.

Exposure conc. (ppm)	Clinical signs
51.25	none
102.5	none
205	blinking at 1 min., sclera red at 1 hr.
820	lacrimation at 2 min., sclera red at 4 hr.
1640	blinking and sneezing upon commencement of exposure, lacrimation at 5 min., eyelids inflamed at 30 min., nasal froth at 4 hr.
3280	rubbed eyes and nose upon commencement of exposure, tremors at 2.5 hr., froth from nostrils at 3.5 hr., eyes red

<sup>a</sup> Table taken from Smyth and Carpenter, 1973.

### 3.2.2. Rats

Gage (1970) conducted a series of experiments in which Alderley Park specific pathogen-free rats were exposed 6 hours/day for a total of 15 exposures to concentrations of 100, 250, 630, or 2000 ppm VA. Animals were exposed in a glass desiccator with wire mesh separating the animals. The purity of the chemical was not determined. The appropriate nominal concentration was produced by injecting VA at a known rate into a metered flow of air using a controlled fluid-feed atomizer, but analytical chamber concentrations were not determined during the exposures. No clinical signs or abnormal necropsy findings were observed following exposure to 100 ppm. Low body weight gain was noted in females exposed to 250 or 630 ppm, but gross necropsy and blood and urine analyses were normal. Exposure to 2000 ppm produced clinical signs of eye and nose irritation, respiratory difficulty, poor condition, and low body weight gain, and histopathological examination of the lungs revealed excess macrophages. No further details were provided.

To investigate the effect of inhaled VA on nasal epithelial cell proliferation, groups of five male Sprague-Dawley rats were exposed via whole body inhalation to target concentrations of 0,

1 50, 200, 600, or 1000 ppm VA for 6 hours/day for a total of one, five, or twenty consecutive  
2 exposures (actual exposure concentrations 0, 50.8, 199.6, 598.5, and 1007.3 ppm) (Bogdanffy et  
3 al., 1997). Rats were exposed in a 150 L stainless steel and glass dynamic inhalation chamber  
4 with an air flow of approximately 35 L/min. Chamber atmospheres were analyzed directly using  
5 gas chromatography. Rats were weighed three times a week and were observed for clinical  
6 signs. Animals were i.p. injected with 5-bromo-2'-deoxyuridine (BrdU) sixteen hours after the  
7 last exposure, and were killed 18 hours after the last exposure. The respiratory tract of the rats  
8 was examined for any gross changes, and the nasal cavities were removed and prepared for  
9 histopathological examination. Five cross-sections of the nose were made for examination, and  
10 sections of the duodenum were used as a positive control for the BrdU. No clinical signs or  
11 gross necropsy abnormalities were reported. Body weight gain in the 1000 ppm group was  
12 decreased, with the maximum decrease occurring on exposure day 5 (86% of controls).  
13 Histopathological examination revealed concentration-related olfactory epithelium changes in  
14 the 600 and 1000 ppm group animals, but the incidences and severity of the lesions were low.  
15 After one exposure, some rats developed degeneration, necrosis, and exfoliation, with the  
16 regions most affected being the dorsal one-third of the nasal septum and dorsolateral wall,  
17 Masera's organ, and the medial-most extent of the ethmoid turbinates (see Table 8 for  
18 incidences). Frame (2004) concluded that it is likely that reversibility of changes from acute  
19 exposure to 600 or 1000 ppm VA will be essentially complete both morphologically and  
20 functionally based on the focal and limited nature of the olfactory lesions seen following VA  
21 exposure, as well as the known regenerative capacity of the olfactory tissue. Following 5 or 20  
22 exposures, post necrotic repair and adaptation were seen, with changes including regenerative  
23 hyperplasia of the olfactory epithelium and attenuation and/or disorganization of the olfactory  
24 mucosa and occasional areas of squamous metaplasia (Bogdanffy et al., 1997). Additionally,  
25 olfactory nerve bundles in the olfactory lumina exhibited degeneration and atrophy. Cell  
26 labeling of rats after one 6-hour exposure revealed a concentration-related increase in cell  
27 proliferation in both the respiratory and olfactory epithelium, generally confined to the basal  
28 cells of the epithelial cell layer. The increases in the labeling index attained statistical  
29 significance in the 600 and 1000 ppm group rats. No statistically significant increases in the  
30 labeling indexes were noted in olfactory or respiratory epithelium from the groups exposed five  
31 times. However, cell proliferation of the olfactory epithelium (primarily the basal cells) was  
32 again statistically increased in the 600 and 1000 ppm groups following 20 exposures. This  
33 increase was not evident in the respiratory epithelium. The authors concluded that the cell  
34 proliferation response could be a two-phase reaction: the first is characterized as chemical insult  
35 followed by early regenerative repair (exposure days 1-5), while the second phase includes both  
36 cellular and biochemical adaptation.

1 **Table 8. Histopathological Observations in Nasal Epithelium of Rats Exposed to VA for 6 Hours** <sup>a</sup>

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Section of the Nose	Observation	Exposure Concentration (ppm)		
		0	600	1000
Level II	Degeneration/necrosis; respiratory epithelium minimal	-	-	1
	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	-	-	-
	Degeneration/necrosis; olfactory epithelium minimal	-	2	3

<sup>a</sup> From Bogdanffy et al., 1997; nasal cavities of rats exposed to 50 or 200 ppm were histologically normal.

### 3.2.3. Mice

The RD<sub>50</sub> for VA was 380 ppm in mice tested according to the ASTM E981 protocol (Dudek et al., 1996).

### 3.3. Developmental/Reproductive Toxicity

VA was administered to 24 confirmed-mated Sprague-Dawley rats/concentration by whole-body inhalation at concentrations of 0, 50, 200, or 1,000 ppm for 6 hours/day from days 6 through 15 of gestation (Hurtt et al., 1995). Observations for maternal clinical signs were made daily and body weight was recorded on gestation days (GDs) 0, 2, 4, 6, 10, 15, and 20, but food and water consumption were not measured. On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses were examined externally and viscera (half by dissection and evisceration and the remaining half by Wilson's technique). The total numbers of fetuses examined (number of litters) were 322(24), 320(22), 345(24), and 327(22) for the 0, 50, 200, and 1,000 ppm groups, respectively. Approximately half of the fetuses were examined for skeletal malformations/variations. Maternal toxicity was evident in the 1000 ppm group as indicated by statistically ( $p < 0.05$ ) decreased mean absolute body weight on GDs 10, 15, and 20 (91, 88, and 89% of controls, respectively) and body weight gain over GDs 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). High-concentration group dams had weight gain comparable to controls over GDs 15-

20 (96% of controls). Because food consumption was not measured, it is unknown if the decreased body weight was an effect of decreased food consumption. Delays in fetal growth were present in 1000 ppm group fetuses and included statistically ( $p < 0.05$ ) decreased mean fetal weight (72% of controls) and crown-to-rump length (88% of controls), and delays in ossification {[#fetuses(litters) affected for 1000 ppm group vs. controls]: incompletely ossified occipital [41(12) vs. 1(1)]; unossified No. 2 sternebra [28(10) vs. 0(0)]; unossified No. 5 sternebra [118(22) vs. 17(11)]; unossified No. 6 sternebra [126(22) vs. 16(7)]; and bipartite vertebra [52(18) vs. 24(13)]}. The delays in fetal growth correlate with maternal toxicity present in the high-concentration group. It was concluded that VA is not uniquely toxic to the fetus.

### 10 3.4. Genotoxicity and Cytotoxicity

11 VA was not mutagenic to *Salmonella typhimurium* strains TA 1535, 1537, 1538, 98, or 100  
12 with or without metabolic activation at a maximum, nontoxic VA concentration of 1000 F g/plate  
13 (Lijinski and Andrews, 1980); to *Salmonella typhimurium* strains TA 97, 98, or 100 at VA  
14 concentrations of 100-500 F g/mL (Brams et al., 1987); or to *Salmonella typhimurium* strain TA  
15 102 (VA concentrations not provided) (Jung et al., 1992; Müller et al., 1993). VA was not  
16 mutagenic towards *E. coli* strain PQ37 using the SOS chromotest (Brams et al., 1987).

17 A statistically significant and concentration-related increase in SCEs was found in both CHO  
18 cells incubated with 0.125-1 mM VA without metabolic activation and following a 4-hour pulse  
19 treatment with 0.3-5 mM VA with or without metabolic activation (Norppa et al., 1985; Mäki-  
20 Paakkanen et al., 1984). Male C57B1/6 mice exhibited a statistically significant increase in  
21 micronucleated polychromatic erythrocytes in the bone marrow 30 hours after i.p. injection of  
22 1000 or 2000 mg/kg bw of VA ( $1.33 \pm 0.29\%$  and  $1.57 \pm 0.19\%$ , respectively, vs.  $0.6 \pm 0.10\%$   
23 for olive oil-treated controls), but no increase was seen following injection of 250 or 500 mg/kg  
24 bw (Mäki-Paakkanen and Norppa, 1987). The 1000 and 2000 mg/kg concentrations were fatal  
25 to 6/14 and 8/14 mice, respectively.

26 Hepatic DNA adducts were not formed in male or female F344 rats following administration  
27 of  $^{14}\text{C}$ -labeled VA by oral gavage (1 mCi of radioactivity; rats killed 4 hours after  
28 administration) or inhalation (1200 to 1800 ppm in static exposure chamber for 4 hours) (Simon  
29 et al., 1985b). Accumulation of DNA-protein crosslinks was observed to follow S-phase kinetics  
30 when 1-100 mM VA was incubated with pUC13 plasmid DNA, calf histones, and rat liver  
31 microsomes for 3 hours at 37°C (Kuykendall and Bogdanffy, 1992a; b). DNA-protein crosslink  
32 formation was inhibited by both the addition of a carboxylesterase inhibitor (bis-(p-  
33 nitrophenyl)phosphate, or BNPP) and by the removal of the rat liver microsomes.

34 To evaluate cytotoxicity in rat nasal tissues, explants of the maxilloturbinate (lined with pure  
35 populations of respiratory epithelia) and endoturbinat-1 (lined with pure populations of  
36 olfactory epithelia) from rat nasal cavities were incubated with 0, 20, 25, 50, 100 or 200 mM,  
37 followed by assaying for acid phosphatase release (Kuykendall et al., 1993a). VA was cytotoxic  
38 both at 100 and 200 mM following incubation for 20 minutes and at 50 mM following  
39 incubation for at least 1 hour, but 25 mM VA was not cytotoxic following incubation for up to 2  
40 hours. Therefore, the 50 mM VA with incubation for 1 hour was chosen to study the effects of a

1 carboxylesterase inhibitor (BNPP) or aldehyde scavenger (semicarbazide) on VA-mediated  
2 cytotoxicity. To assess the effects of BNPP on VA induced cytotoxicity, acetaldehyde  
3 production was first measured. The study demonstrated that acetaldehyde production increased  
4 steadily up to 60 minutes for respiratory turbinates and up to 40 minutes for olfactory turbinates,  
5 reaching a plateau when acetaldehyde concentrations reached approximately 16 mM. Therefore,  
6 BNPP pretreatment was assessed using a 20 minute incubation time with 50 mM VA. BNPP  
7 pretreatment for 3 days prior to tissue collection reduced the cytotoxic effect of VA, resulting in  
8 only a 2-fold increase in acid phosphatase production compared to 3 to 4-fold increase without  
9 BNPP pretreatment. BNPP pretreatment also inhibited the metabolism of VA; acetaldehyde  
10 release into the media was reduced by 59 or 37% in respiratory and olfactory turbinates,  
11 respectively. When turbinates were incubated with semicarbazide, no effect on cytotoxicity was  
12 noted. Further evaluations demonstrated that the VA-induced cytotoxicity was the result of  
13 acetic acid production, not acetaldehyde production.

14 Kuykendall et al. (1993a; b) also assessed the formation of DNA-protein crosslinks in rat  
15 nasal epithelial tissues by VA and acetaldehyde. Isolated epithelial cells from both olfactory and  
16 respiratory turbinates incubated with 0-75 mM VA generally exhibited a concentration-related  
17 increase in DNA-protein crosslink formation. Olfactory and respiratory cells had comparable  
18 DNA-protein crosslink formation as assessed by the absolute difference in DNA accumulation in  
19 the protein-bound phases. Epithelial cells were then preincubated with increasing concentrations  
20 of BNPP for 30 minutes before the addition of 25 mM VA to assess if the carboxylesterase-  
21 dependent metabolism of VA to acetaldehyde is necessary for the DNA-protein crosslink  
22 formation. In respiratory and olfactory cells, DNA-protein crosslink formation was 3.9 and 2.9-  
23 fold higher, respectively, in cells exposed to 25 mM VA alone compared to cells from untreated  
24 turbinates, while a 76 and 78% reduction of crosslink formation, respectively, was seen in cells  
25 preincubated with 1 mM BNPP. Reduction in the crosslink formation was dependent on BNPP  
26 concentration.

### 27 **3.5. Chronic Toxicity/Carcinogenicity**

28 In a chronic toxicity and oncogenicity study, groups of male and female Crl:CD(SD)BR  
29 (Sprague-Dawley) rats and Crl:CD-1(ICR)BR mice were exposed 6 hours/day, 5 days/week for  
30 104 weeks via whole body inhalation to target concentrations of 0, 50, 200, or 600 ppm VA  
31 (Bogdanffy et al., 1994). Chamber concentrations were measured every 15 minutes using a gas  
32 chromatograph. The main group consisted of groups of 60 mice or rats of each sex that were  
33 exposed for 104 weeks, with a clinical laboratory evaluation conducted on 10 animals from each  
34 group during Week 104. In addition, there were three satellite groups of 10 male and 10 female  
35 rats or mice/group: one group had a clinical laboratory evaluations at Week 51 with euthanasia at  
36 Weeks 52-53; a second group underwent clinical laboratory evaluations at Week 81 with  
37 euthanasia at Week 82-83; a third group was exposed for 70 weeks followed by a 15-week  
38 recovery period. Clinical signs of rough coat and hunched posture were noted at all  
39 concentrations and are believed to be an effect of inhalation exposure.

40 In rats, exposure to 600 ppm resulted in statistically decreased body weight gain and  
41 decreased absolute body weight (approximately 10% less than controls at 104 week) (Bogdanffy

1 et al., 1994). Following the recovery period, male rats at 600 ppm exhibited a statistically  
2 significant increase in body weight gain compared to controls. No effects on body weight gain  
3 were observed at 50 or 200 ppm. Clinical pathology evaluation revealed a statistically  
4 significant decrease in blood glucose in females at 600 ppm at Weeks 51, 81, and 104 and a  
5 statistically significant decrease in urine volume in all rats at 600 ppm at Weeks 51 (males only),  
6 81 and 104. Corresponding increases in specific gravity and decreased pH were observed but the  
7 differences were not always statistically significant. The authors attributed the effects on blood  
8 glucose and urinary parameters to decreased food and water consumption; however, food and  
9 water consumption were not measured. Gross necropsy revealed increases in relative lung  
10 weight in both the 200 and 600 ppm groups at week 53, the 600 ppm group at week 83, and all  
11 treated groups at week 104. Following the 15-week recovery, no statistically significant  
12 differences in terminal body weight or organ weights were observed in any groups of exposed  
13 females, while body weight gain in male rats “remained slightly depressed.” Histopathological  
14 examination revealed nonneoplastic changes in the lungs and nose. Findings in the lungs were  
15 present in 600 ppm males and females and included bronchial exfoliation, intraluminal fibrous  
16 projections, macrophage accumulation, and/or peribronchiolar/perivascular lymphoid  
17 aggregates. Lesions in the nose were present in 200 and/or 600 ppm males and/or females, and  
18 included olfactory epithelial atrophy, squamous metaplasia, regeneration, inflammatory cell  
19 infiltrate, and leukocytic exudate; epithelial nest-like folds; basal cell hyperplasia; turbinate  
20 leukocyte exudate; and/or submucosal inflammatory cell infiltrate. Neoplastic changes were  
21 confined primarily to the nasal cavity in the 600 ppm exposure groups. Findings included  
22 squamous cell carcinoma (males: 0/59, 0/60, 0/59, and 2/59, respectively; females: 0/60, 0/60,  
23 0/60, and 4/59, respectively), carcinoma in situ (males: 0/59, 0/60, 0/59, and 1/59, respectively),  
24 and the benign lesion of inverted papilloma (males: 0/59, 0/60, 0/59, and 4/59, respectively).  
25 Additionally, one female at 600 ppm had a squamous cell carcinoma in the larynx.

26 In mice, body weight gain was statistically decreased in the 200 and 600 ppm groups  
27 throughout the study, and in the 50 ppm group through week 52 (Bogdanffy et al., 1994).  
28 Absolute body weight in the 600 ppm group at Week 104 was approximately 15% less than  
29 controls. Following the 15-week recovery period, 600 ppm male mice and all groups of exposed  
30 female mice exhibited a statistically significant increase in body weight gain compared to  
31 controls. No significant differences were noted in hematology or clinical chemistry parameters.  
32 Gross necropsy revealed increases in absolute and relative lung weights in 600 ppm males at  
33 weeks 53, 83, and 104, in 600 ppm females at weeks 83 and 104, and 200 ppm males only at  
34 week 83. No statistically significant differences in final body weights or organ weights were  
35 noted following a 15-week recovery. Histopathological examination revealed nonneoplastic  
36 changes in the lungs, nose, and trachea. Findings in the lungs were present primarily in males  
37 and females at 600 ppm and included accumulation of alveolar and/or brown pigmented  
38 macrophages, intra-alveolar eosinophilic material, intraluminal fibroepithelial projections,  
39 bronchial gland dilation, bronchial/bronchiolar epithelial flattening and/or exfoliation, and/or  
40 bronchial/bronchiolar epithelial disorganization. Nonneoplastic lesions in the nose were present  
41 at 200 and/or 600 ppm in males and/or females and included olfactory epithelial atrophy (mainly  
42 dorsal meatus or widespread), inflammatory exudate, mucosal inflammatory infiltrate,  
43 submucosal gland hyperplasia, squamous metaplasia at the naso/maxilloturbinate region, and  
44 replacement of olfactory by respiratory epithelium. Epithelial hyperplasia of the trachea/bronchi  
45 was evident in 600 ppm males and females. Neoplastic changes were confined to a moderately

1 invasive squamous cell carcinoma in a major bronchus of the lung of a 600 ppm male and a  
2 single adenocarcinoma in a control male.

3 IARC (1995) has concluded there is inadequate evidence in humans and limited evidence in  
4 experimental animals for the carcinogenicity of VA. Therefore, IARC states that VA is possibly  
5 carcinogenic to humans (Group 2B). The weight of evidence was: 1) VA is rapidly transformed  
6 into acetaldehyde; 2) there is sufficient evidence in experimental animals for the carcinogenicity  
7 of acetaldehyde (both VA and acetaldehyde induce nasal cancer in rats after administration by  
8 inhalation); 3) VA and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in*  
9 *vivo*.

### 10 3.6. Summary

11 Acute toxicity data for animals included: a series of studies in dogs, rats, mice, guinea pigs,  
12 and rabbits performed by Smyth and Carpenter (1973); a study in rats by Gage (1970); an RD<sub>50</sub>  
13 value reported in mice (Dudek et al., 1996); and a study investigating the histopathological  
14 lesions in the rat nasal cavity (Bogdanffy et al., 1997). Tables 9 and 10 summarize the lethal and  
15 nonlethal effects of VA.

16  
17 The Smyth and Carpenter study provided the best general toxicity data. Nonlethal  
18 concentrations produced signs of congested extremities in rats and lacrimation in guinea pigs,  
19 while no signs were noted in mice or rabbits. Dogs exhibited lacrimation, nasal froth, and  
20 tremors. Lethal concentrations produced signs of irritation (gasping, lacrimation) and central  
21 nervous system effects (poor coordination, prostration, clonic convulsions). Gross necropsy of  
22 animals that died indicated that mortality was due to lung irritation (pulmonary congestion,  
23 hemorrhages, and excess pleural fluid). Limitations of the Smyth and Carpenter studies include  
24 incomplete reporting of study details (no details provided about exposure chamber; strain and  
25 age of animals) and a lack of a control group. Chamber concentrations were not measured, but  
26 the nominal concentrations were corrected against a calibration curve.

27 The Gage (1970) study is of limited utility because the purity of the chemical is unknown,  
28 the exposure concentrations were nominal, and clinical signs were reported as a general  
29 statement, so it is not known when the clinical signs first occurred. The Dudek et al. (1996) data  
30 was published in an abstract, with the RD<sub>50</sub> being the only toxicity endpoint investigated.

31 The Bogdanffy et al. (1997) study primarily focused on histopathological lesions of rat nasal  
32 epithelium. A single, 6-hour exposure to 600 or 1000 ppm VA resulted in increased cell  
33 proliferation in respiratory and olfactory epithelium, with 200 ppm being a NOAEL for all  
34 histological effects.

35 A developmental toxicity study in rats reported maternal toxicity at 1000 ppm as evidenced  
36 by decreased maternal body weight and body weight gain, and developmental toxicity in the  
37 form of delayed fetal growth (Hurtt et al., 1995). Results of genotoxicity testing indicate that  
38 VA is clastogenic (proposed to result from the metabolite acetaldehyde) and cytotoxic (proposed  
39 to be caused by the metabolite acetic acid). A carcinogenicity bioassay reported that rats

1 exposed to 600 ppm developed nasal papillomas, squamous cell carcinomas, and carcinoma in  
 2 situ, while exposed mice did not develop the nasal tumors.

3 **TABLE 9. Summary of 4-Hour Lethal Inhalation Data in Laboratory Animals \***

Species	Conc. (ppm)	Effect	Gross Necropsy of Animals That Died
<b>General Mortality Data</b>			
rat	1640	0/12 died	-
	3280	4/12 died (3 died during exposure)	pulmonary congestion and hemorrhage, froth in trachea, and opaque corneas
	6560	12/12 died at 90 min. of exposure	
mouse	410	0/10 died	-
	820	1/6 died (by 8 days post exposure)	pulmonary congestion, excess pleural fluid
	1640	4/6 died (during exposure)	
	3280	5/6 (during exposure)	
	6560	6/6 (during exposure)	
guinea pig	1640	0/6 died	-
	3280	1/6 died (during exposure)	pulmonary congestion and emphysema, scattered hemorrhages in the lungs
	6560	4/6 died (3 during exposure)	
	13120	6/6 died (during exposure)	
rabbit	1640	0/4 died	-
	3280	3/4 died	bloody nostrils, froth in trachea, excess pleural fluid, pulmonary hemorrhages
	6560	4/4 died (2 during exposure)	
<b>Calculated 4-Hour LC<sub>50</sub> Data</b>			
rat	3680	LC <sub>50</sub>	-
mouse	1460	LC <sub>50</sub>	-
guinea pig	5210	LC <sub>50</sub>	-
rabbit	2760	LC <sub>50</sub>	-

15 \* All data from Smyth and Carpenter, 1973

TABLE 10. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure Time	Effect	Reference
dog	51.25	4	none	Smyth and Carpenter, 1973
dog	102.5	4	none	Smyth and Carpenter, 1973
dog	205	4	blinking at 1 min., sclera red at 1 hr.	Smyth and Carpenter, 1973
dog	820	4	lacrimation at 2 min., sclera red at 4 hr.	Smyth and Carpenter, 1973
dog	1640	4	blinking and sneezing at start of exposure; lacrimation at 5 min.; eyelids inflamed at 30 min.; nasal froth at 4 hr.	Smyth and Carpenter, 1973
dog	3280	4	rubbed eyes and nose at start of exposure; tremors at 2.5 hr.; froth from nostrils at 3.5 hr.; eyes red	Smyth and Carpenter, 1973
rat	1640	4	extremities congested at 1-hr of exposure; no effect level for death (0/12)	Smyth and Carpenter, 1973
rat	600	6	degeneration and necrosis in olfactory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium	Bogdanffy et al., 1997
rat	1000	6	degeneration and necrosis in olfactory and respiratory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium	Bogdanffy et al., 1997
mouse	410	4	no clinical signs reported; no effect level for death (0/6)	Smyth and Carpenter, 1973
mouse	380	-	RD <sub>50</sub>	Dudek et al., 1996
guinea pigs	1640	4	lacrimation at 30 min; eyes and nose wet at end of exposure; no effect level for death (0/6)	Smyth and Carpenter, 1973
rabbits	1640	4	no clinical signs reported; no effect level for death (0/4)	Smyth and Carpenter, 1973

#### 4. SPECIAL CONSIDERATIONS

##### 4.1. Metabolism and Disposition

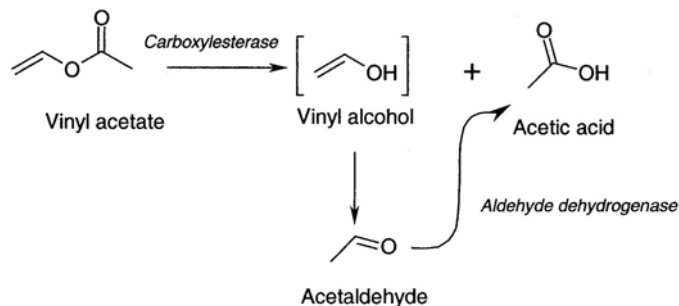
Groups of male and female Sprague-Dawley rats were exposed for 6 hours to 750 ppm <sup>14</sup>C-VA vapor by nose-only inhalation to assess excretion/metabolism and tissue distribution of VA (Strong et al., 1980). The mean proportions of radioactivity recovered over 96 hours post exposure were: 4.8% in urine, 3.6% in feces, 74.6% in expired air, and 16.4% remaining in the carcass. The amount recovered in the expired air was almost exclusively as <sup>14</sup>CO<sub>2</sub>. No radiolabeled carbonates or bicarbonates were recovered in the urine or feces. Tissue distribution

1 measurements of rats killed immediately after exposure revealed that the highest mean  
2 concentration of radioactivity (reported as F g equivalents of <sup>14</sup>C-VA/g) was found in the  
3 Harderian gland (2045), followed by the ileum (393) and submaxillary salivary gland (341).  
4 Radioactivity levels in the gastrointestinal tract contents, liver, kidneys, lung, brain, stomach,  
5 colon, and ovaries ranged from 150-300 F g equivalents/g. The pattern of distribution was  
6 essentially the same but at lower concentrations at 1, 6, or 72 hours post exposure, with the  
7 highest concentrations at 72 hours found in the Harderian gland (193 F g equivalents/g), adrenal  
8 gland (112 F g equivalents/g), and ovaries (99 F g equivalents/g). No difference in the pattern of  
9 distribution was found between sexes (except for the gonads), or following oral administration.  
10 A separate study investigating the metabolic fate of 1000 ppm <sup>14</sup>C-VA administered for 6 hours  
11 by nose-only inhalation to Sprague-Dawley rats resulted in similar results (Cresswell et al.,  
12 1980).

13 The study by Bogdanffy et al. (1997) provided information on the deposition of inhaled VA  
14 in the rat nasal cavity. The histopathology results demonstrated a strong anterior to posterior  
15 gradient, with the response moving anterior to posterior with increasing concentrations. These  
16 findings are indicative of a material in which deposition is metabolically dependent. "As VA  
17 concentration increases, fractional deposition decreases, due, in part, to saturation of the  
18 metabolism-dependent component of deposition."

19 The primary metabolic pathway of VA is hydrolysis by carboxylesterases to acetic acid and  
20 vinyl alcohol, which rearranges to form acetaldehyde (see Figure 1; Table 11) (Fedtke and  
21 Wiegand, 1990; Kuykendall et al., 1993a; Bogdanffy and Taylor, 1993; Simon et al., 1985a).  
22 Acetaldehyde can be further metabolized to acetate, which can be incorporated into the carbon  
23 pool via formation of acetyl coenzyme A and can ultimately result in the formation of CO<sub>2</sub>  
24 (Strong et al., 1980). Acetaldehyde can also be oxidized to acetic acid by aldehyde  
25 dehydrogenase, a NADH-dependent reaction (Andersen et al., 2002). Research has  
26 demonstrated that monooxygenases do not play a significant role in the metabolism of VA, and  
27 epoxide formation is not expected to be a significant metabolite (Simon et al., 1985a; Bogdanffy  
28 et al., 1999a). A gas uptake kinetic study in rats revealed a linear, concentration-dependent  
29 decay of VA up to an exposure concentration of 650 ppm, indicating the possibility of metabolic  
30 saturation (Simon et al., 1985a). At VA concentrations below saturation, the maximal clearance  
31 in rats was 30,000 mg/h/kg bw, which is similar to the maximal ventilation rate of 32,000  
32 mg/h/kg bw. Therefore, it is concluded that the metabolic rate of VA is determined by the  
33 ventilation rate when metabolic saturation has not been reached.

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1 Figure 1. Metabolic Scheme of VA (taken from Bogdanffy et al., 2001)

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TABLE 11. Degradation of VA and Production of Acetaldehyde with Time					
Source (Incubate)	VA conc. (ppm)	Time (sec)	Conc. in incubate (F mol/mL)		Reference
			VA	Acetaldehyde	
human plasma	29	0	0.307	0.025	Strong et al., 1980
		550	0.024	0.292	
	129	0	1.380	0.000	
		720	0.031	1.177	
human whole blood	129	0	1.380	0.000	Strong et al., 1980
		900	0.074	1.187	
rat plasma	25	0	0.280	ND	Cresswell et al., 1980
		270	0.011	0.263	
	100	0	1.11	0.052	
		270	0.079	1.05	
rat whole blood	100	0	1.10	0.014	Cresswell et al., 1980
		565	ND	1.06	
homogenized rat liver	100	0	0.924	0.064	Cresswell et al., 1980
		260	0.041	0.969	
homogenized mouse liver		0	0.570	0.050	Cresswell et al., 1980
		320	0.020	0.533	

10 Information on the kinetics of VA hydrolysis is available for whole blood, plasma, red blood  
 11 cells, liver microsomes, and nasal tissue. The half-life of VA in whole blood and liver  
 12 homogenates was comparable in rats (60-125 and 50-167 seconds, respectively) and mice (114  
 13 and 66 seconds, respectively), with the most active compartment being the plasma compartment

(57-72 and 36 seconds for rats and mice, respectively) (Creswell et al., 1980; Fedtke and Wiegand, 1990). Hydrolysis of VA in humans was generally slower than in rats and mice, with a half-life for VA in human whole blood of 210-246 seconds and in the human plasma of 150 or 3720 seconds. However, the half-life of VA in red blood cells was similar in humans (330 seconds) and rats (336 seconds) (Fedtke and Wiegand, 1990). The kinetic parameters of enzyme-mediated hydrolysis by rat liver and lung microsomes, rat and human plasma, and purified carboxylesterase were determined and are presented in Table 12.

**TABLE 12. Summary of Kinetics of Vinyl Acetate from Various Sources**

Source of enzyme	pH	Km (mM)	Vmax (F mol/min/mg protein)	Reference
Rat liver microsomes	8.0	0.73	23	Simon et al., 1985a
Rat lung microsomes	8.0	6.1	6.2	Simon et al., 1985a
Rat plasma	8.0	4.0	0.56	Simon et al., 1985a
Human plasma	8.0	7.1	0.69	Simon et al., 1985a
Respiratory nasal mucosa (mice and rats)	7.4	0.3-0.43	22-46	Bogdanffy and Taylor, 1993
Olfactory nasal mucosa (rats and mice)	7.4	0.20-0.52	89-165	Bogdanffy and Taylor, 1993
Purified carboxyl esterase	8.0	0.65	238	Simon et al., 1985a

Because the nasal cavity was the target organ of toxicity following chronic exposure to VA, metabolism of VA by nasal tissue was examined. Through the use of a carboxylesterase inhibitor [bis-(p-nitrophenyl)phosphate (BNPP)] and monooxygenase inhibitors (such as diallyl sulfide (DAS)), it was determined that metabolism of VA by the nose is carboxylesterase dependent (Bogdanffy et al., 1999a; Plowchalk et al., 1997). Histochemical staining of the rat nasal cavity revealed that a high-affinity carboxylesterase was bound to the luminal plasma membrane (Bogdanffy et al., 1999a). To examine the kinetics of nasal carboxylesterase-mediated metabolism of VA, homogenized samples of nasal respiratory and olfactory mucosa from male and female rats and mice were incubated with VA (Bogdanffy and Taylor, 1993). Few differences in kinetics were observed between male or female rats or mice; however, the olfactory mucosa had higher activity than the respiratory mucosa (see Table 12), a result also seen following histochemical staining of the nasal passages of Fischer 344 rats and B6C3F1 mice (Bogdanffy et al., 1987). To investigate the differences in metabolism of rat versus human nasal tissues, an *in vitro* gas technique which used whole-tissue samples and PBPK modeling were employed (Bogdanffy et al., 1998). Rat respiratory carboxylesterase and aldehyde dehydrogenase activities were approximately three and two times higher than those of humans, respectively, while the rat olfactory enzyme activities were equivalent to humans (see Table 13). Km values did not differ between species.

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TABLE 13. Summary of Kinetics of Vinyl Acetate Using Whole-Tissue Samples and PBPK Modeling Techniques <sup>a</sup>				
Enzyme	Tissue	Km (mg/mL)	Vmax	
			Activity/ specimen (mg/h)	Activity/ epithelial cell volume (mg/h/mm <sup>3</sup> )
Carboxylesterase	Maxilloturbinate <sup>b</sup>	0.04	2.10	1.89
	3EV <sup>b</sup>	0.05	1.68	1.82
Aldehyde dehydrogenase	Maxilloturbinate	0.80	0.05	0.15
	3EV	0.80	0.10	0.07
Carboxylesterase	Middle turbinate <sup>b</sup>	0.05	1.50	0.57
	Dorsal meatus <sup>b</sup>	0.05	0.90	1.94
Aldehyde dehydrogenase	Middle turbinate	1.10	0.30	0.08
	Dorsal meatus	1.10	0.05	0.08

10 a Table reproduced from Bogdanffy et al., 1998

11 b Maxilloturbinate (rat) and middle turbinate (human) are lined with respiratory epithelium. 3EV (rat) and dorsal  
12 meatus(human) are lined with olfactory epithelium. 3EV = ventral scroll of the third ethnoturbinate

13 As in the whole body gas uptake study (Simon et al., 1985a), substrate inhibition of rat nasal  
14 carboxylesterase *in vitro* was noted at high concentrations (Bogdanffy and Taylor, 1993). This is  
15 also evident when considering the studies of the rat nose that demonstrated that *in vivo*  
16 deposition of VA in the upper respiratory tract is concentration dependent (Plowchalk et al.,  
17 1997). At low concentrations, removal of VA from the airstream is highly efficient: greater than  
18 93% of VA was extracted by the rat nose at a VA concentration of 76 ppm or less. At VA  
19 concentrations of 76-550 ppm, extraction of VA progressively decreased to about 40%,  
20 remaining at this level until a VA concentration of approximately 2000 ppm. Acetaldehyde in  
21 expired air increased to an apparent maximum of 227 ppm, which corresponded to a VA  
22 exposure concentration of 1000 ppm.

## 23 4.2. Mechanism of Toxicity

24 Several papers have been written regarding the mode of action of VA (Bogdanffy et al.,  
25 2001; 1999b; Hengstler et al., 2003; Bogdanffy, 2002; Bolt, 2003; Bogdanffy and Valentine,  
26 2003; Andersen et al., 2002). Metabolism studies have demonstrated that VA is metabolized to  
27 acetic acid and vinyl alcohol, which rearranges to form acetaldehyde (Bogdanffy and Taylor,  
28 1993; Simon et al., 1985a). The acetaldehyde can be further metabolized to acetic acid.  
29 Genotoxicity and cytotoxicity tests demonstrated that clastogenicity and cytotoxicity required  
30 the presence of carboxylesterases (Kuykendall and Bogdanffy, 1992a; 1992b; Kuykendall et al.,  
31 1993a). It was further determined that the production of acetic acid was responsible for the  
32 observed cytotoxicity, while acetaldehyde was responsible for the DNA-protein crosslinking  
33 observed in test systems (Kuykendall et al., 1993a). The proposed mechanism of cytotoxicity is  
34 that of a lowering of inter- and intra-cellular pH by the production of acetic acid (Plowchalk et

1 al., 1997; Bogdanffy et al., 2001; Kuykendall et al., 1993a). An *in vitro* study measuring the pH  
 2 of individual rat respiratory and olfactory nasal epithelial cells before and during exposure to VA  
 3 confirmed a concentration-related decrease in pH with increasing VA concentration, with a  
 4 maximum decrease in pH of 0.3 pH units (Lantz et al., 2003). The cytotoxic response leads to  
 5 cellular degeneration followed by cellular proliferation (Plowchalk et al., 1997; Bogdanffy et al.,  
 6 2001; Kuykendall et al., 1993a). Clastogenic effects include chromosomal aberrations, SCE,  
 7 and/or DNA crosslinking in human lymphocytes (Mäki-Paakkanen and Norppa, 1987; Jantunen  
 8 et al., 1986; Norppa et al., 1985; Mäki-Paakkanen et al., 1984; He and Lambert, 1985; Lambert  
 9 et al., 1985); CHO cells (Norppa et al., 1985; Mäki-Paakkanen et al., 1984); rat liver microsomes  
 10 (Kuykendall and Bogdanffy, 1992a; 1992b); and rat nasal epithelial tissues (Kuyendall et al.,  
 11 1993a; 1993b). The clastogenic effects appear to be due to the production of acetaldehyde, a  
 12 weak DNA protein crosslinking agent (Kuykendall et al., 1993a) in combination with a lowering  
 13 of pH (Morita, 1995). Acetaldehyde-induced DNA protein crosslinks are more stable at a pH  
 14 lower than the physiological pH (Kuyendall and Bogdanffy, 1992a). Therefore, the following  
 15 continuum of response has been proposed (Bogdanffy et al., 2001):

16	VA metabolism
17	9
18	reduction of pH
19	9
20	cytotoxic response - olfactory degeneration
21	9
22	cellular proliferation
23	9
24	tumorigenic response

25 Studies have indicated that metabolic saturation of VA occurs. Simon et al. (1985a) reported  
 26 that metabolic saturation is reached around 650 ppm in rats. In the rat nose, removal of VA from  
 27 the airstream is highly efficient at low concentrations (greater than 93% of VA was extracted by  
 28 the rat nose at a VA concentration 76 ppm or less), while increasing concentrations resulted in  
 29 decreasing extraction efficiency (at VA concentrations of 76-550 ppm, extraction of VA  
 30 progressively decreased to about 40%, remaining at this level until a VA concentration of  
 31 approximately 2000 ppm) (Plowchalk et al., 1997). Therefore, it appears that olfactory  
 32 degeneration would be the primary endpoint until metabolic saturation in the nasal cavity is  
 33 reached. Once metabolic saturation has occurred, VA would be able to make it further down  
 34 into the respiratory tract. This is evidenced by the strong anterior to posterior gradient seen  
 35 during histopathological examination of the rat nasal cavity following acute exposure to inhaled  
 36 VA (Bogdanffy et al., 1997), by the histopathological changes noted in the lungs of rats and mice  
 37 exposed to 600 ppm in the 2-year bioassay (Bogdanffy et al., 1994), and by the pulmonary  
 38 changes seen in rats, mice, guinea pigs, and rabbits exposed to acute, lethal concentrations  
 39 (Smyth and Carpenter, 1973).

#### 40 4.3. Structure Activity Relationships

41 Structure activity relationships were not used for derivations of AEGLs for VA.

#### 1 **4.4. Other Relevant Information**

##### 2 **4.4.1. Species Variability**

3 Four-hour LC<sub>50</sub> data varied by a factor of 3.6, with sensitivity from greatest to least being  
4 mice > rabbits > rats > guinea pigs (Smyth and Carpenter, 1973). Regardless of species, the  
5 cause of death was attributed to pulmonary distress.

6 It has been proposed that olfactory degeneration would be the primary endpoint of inhaled  
7 VA toxicity until metabolic saturation in the nasal cavity is reached (Bogdanffy et al., 1997).  
8 Therefore, much research is available regarding the metabolism of VA by the nasal cavity. In  
9 general, little difference was observed between male and female mice and rats and humans in the  
10 carboxylesterase-mediated metabolism of VA, particularly by olfactory epithelium (Bogdanffy  
11 and Taylor, 1993; Bogdanffy et al., 1998). Esterase distribution in the nasal respiratory tissue of  
12 humans is believed to be similar to that of rats (Andersen et al., 2002). However, considerable  
13 variability in olfactory nasal tissue occurs in humans with regard to surface area covered,  
14 composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more  
15 characteristic olfactory tissue), and age-related changes (Andersen et al., 2002). Children appear  
16 to have a histological organization similar to rodents, in that the olfactory epithelium is well-  
17 developed and delineated. Aging humans develop a very heterogenous mucosa with respiratory-  
18 like epithelial cells populating the olfactory region. The glandular structures become sparse and  
19 non-esterase-containing tissues fill the submucosa. However, esterase histochemistry of adult  
20 olfactory mucosa revealed that sustentacular cells and Bowman's glands do contain significant  
21 quantities of carboxylesterase.

##### 22 **4.4.2. Susceptible Populations**

23 Data regarding susceptible populations were not available. While older populations may not  
24 be as susceptible to olfactory degeneration in the nose, this group may have increased  
25 susceptibility of the respiratory epithelium or even greater pulmonary susceptibility due to  
26 decreased removal of VA in the nose.

##### 27 **4.4.3. Concentration-Exposure Duration Relationship**

28 The relationship between concentration and duration of exposure as related to lethality was  
29 examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors  
30 and gases. The authors subjected the individual animal data sets to probit analysis with exposure  
31 duration and exposure concentration as independent variables. An exponential function  $C^n \times t =$   
32  $k$ , where the value of  $n$  ranged from 0.8 to 3.5 for different chemicals was found to be an  
33 accurate quantitative descriptor for the chemicals evaluated. Approximately 90 percent of the  
34 values of  $n$  range between  $n=1$  and  $n=3$ . Consequently, these values were selected as the  
35 reasonable lower and upper bounds of  $n$ . A value of  $n=1$  is used when extrapolating from shorter  
36 to longer time periods because the extrapolated values represent the most conservative approach  
37 in the absence of other data. Conversely, a value of  $n=3$  is used when extrapolating from longer  
38 to shorter time periods because the extrapolated values are more conservative in the absence of  
39 other data.

#### 4.4.4. Repeated Exposure Data

A 4-week range finding study and 3-month subchronic study in rats and mice were performed by the same laboratory and are reported below. Although the repeated-exposure studies are not relevant for an acute exposure derivation, they do support the premise that exposure to “lower” concentrations is compensated for by nasal scrubbing, while exposure to concentrations exceeding the scrubbing capacity of the nasal cavity result in lower respiratory tract effects.

Groups of 5 male and 5 female Sprague-Dawley rats or CD 1 mice were exposed 6 hours/day, 5 days/ week for 4 weeks to 0, 50, 150, 500, or 1000 ppm VA (Owen, 1979a; b). The 50 ppm exposure was increased to 1500 ppm on day 10 (rats) or day 8 (mouse) due to a lack of marked clinical effects in the 1000 ppm groups. Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, with chamber concentrations measured every 15 minutes by gas chromatography. Mean measured concentrations (ppm; v/v) for the rat and mouse exposures were 51.3, 150.5, 497.6, 1000.2, and 1488.5 (rats) or 1488.7 (mouse). All animals survived treatment. While similar effects were noted in both rats and mice, mice were more sensitive. A concentration-related increase in incidence and severity of respiratory distress and hunched posture was noted in groups of rats exposed to 500 ppm or greater and in groups of mice exposed to 150 ppm or greater (actual incidences not provided, so data for exposure Day 1 not available). A concentration-related decrease in overall body weight gain was noted, with body weight gains for the 150, 500, 1000, and 50/1500 ppm groups as follows: male rats: 104, 102, 81 and 79% of controls, respectively; female rats: 95, 92, 80, and 78% of controls, respectively; male mice: 67, 44, 33, and 33% of controls, respectively; female mice: 80, 80, 40, and 0% of controls, respectively. No gross necropsy findings were noted, and no hematopoietic abnormalities were present during the analysis of bone marrow samples. Spleen weight relative to body weight was decreased at exposure concentrations of 1000 or 50/1500 ppm in male rats (85 and 82% of controls, respectively), male mice (80 and 74% of controls, respectively) and female mice (74 and 72% of controls, respectively). The biological relevance of this finding is unknown. The histopathology report of a 28-day study was included in the study by Owen (1980a), and appears to be from this Owen (1979a) study. Findings in the nasal turbinates, trachea, and bronchi of mice exposed to 50/1500 ppm were similar to those reported in the 3-month study described below.

In a subchronic study, groups of 10 male and 10 female CD rats or CD-1 mice were exposed 6 hours/day, 5 days/week for 13 weeks to 0, 50, 200, or 1000 ppm VA (Owen, 1980a; b). Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, with chamber concentrations measured every 15 minutes by gas chromatography. Mean measured concentrations were 0.5, 51, 200, and 999 ppm. A number of effects were noted in rats exposed to 1000 ppm, including: intermittent respiratory distress, hunched posture, and ruffled fur (actual incidences not provided, so data for Day 1 exposure are not available); decreased overall body weight gain (62 and 56% of controls for males and females, respectively;  $p < 0.01$ ); smaller volume and more concentrated urine compared to controls; and increased lung weight relative to body weight (126 and 130% of controls for males and females, respectively;  $p < 0.01$ ) (Owen, 1980b). No effects were noted during ophthalmoscopic examination, hematology or blood

1 chemistry analysis, or gross or microscopic examination of exposed rats (the nasal turbinate was  
2 included in the microscopic examination).

3 Mice again appeared to be more sensitive to VA exposure (Owen, 1980a). Intermittent  
4 respiratory distress, hunched posture, and ruffled fur were noted in the 200 ppm group over the  
5 first nine days of exposure, while 1000 ppm mice exhibited respiratory distress throughout the  
6 exposure and hunched posture and ruffled fur intermittently (actual incidences not provided, so  
7 data for exposure Day 1 not available). Other effects were limited to the 1000 ppm exposure  
8 group. Nine animals from the 1000 ppm group died as a consequence of routine blood sampling.  
9 It was postulated that VA exposure made the mice more susceptible to the anesthesia used  
10 during the sampling period. High-concentration group males and females had decreased overall  
11 body weight gain (40 and 50% of controls, respectively;  $p < 0.01$ ) and increased lung weight  
12 relative to body weight (148 and 155% of controls, respectively;  $p < 0.01$ ). Microscopic  
13 examination revealed exposure-related lesions in the upper and lower respiratory tissues of mice  
14 exposed to 1000 ppm. The upper respiratory tract lesions were confined to the nasal cavity and  
15 included focal to diffuse rhinitis with associated exudation and transudation into the nasal  
16 passages and occasional mucosal metaplasia. The inflammation was chronic in nature and  
17 associated with hyperplasia of epithelial goblet cells. Findings in the laryngeal sections were  
18 difficult to assess because of variation in the section (in this section, mucosal epithelium  
19 undergoes changes from an oral to respiratory epithelium). Non-inflammatory changes were  
20 noted in the trachea as well as several areas of suspected metaplasia or hyperplasia. The  
21 metaplasia was characterized by a loss of ciliated epithelium and reduction in epithelial size from  
22 a columnar to a cuboidal cell. Changes in the pulmonary parenchyma were confined to the  
23 bronchial system and manifested as multi focal bronchitis to bronchiolitis, multi focal  
24 bronchiectasis, bronchial epithelial metaplasia and hyperplasia and occasional bronchiolar or  
25 bronchial exudation. The author commented that these lesions were consistent with changes  
26 often observed in mice experimentally, or infected with respiratory pathogens. However, the  
27 absence of similar changes in the control mice precludes an interpretation of infectious  
28 pathogenesis. It is possible that exposure to VA may be synergistic with the induction of  
29 microbial pathogens.

## 30 **5. DATA ANALYSIS AND PROPOSED AEGL-1 VALUES**

### 31 **5.1. Summary of Human Data Relevant to AEGL-1**

32 A controlled human exposure study by Smyth and Carpenter (1973) reported that a 2-minute  
33 exposure to 4, 8, or 20 ppm VA resulted in minimal eye, nose, and throat irritation in one-to-two  
34 of nine exposed individuals. Exposure to 20 ppm for 4 hours resulted in one in three individuals  
35 reporting persistent slight throat irritation, and when exposure was increased to 34 ppm for 2  
36 hours, one of three individuals complained of persistent throat irritation. Exposure to 72 ppm  
37 VA for 4 hours resulted in eye irritation and slight throat irritation for up to 60 minutes post  
38 exposure in all four subjects exposed. The irritation was such at exposure to 72 ppm for 4 hours  
39 that subjects expressed an unwillingness to work at this concentration for 8 hours. Deese and  
40 Joyner (1969) reported intolerable eye irritation and a slight cough and hoarseness during a 10-  
41 minute exposure to 21.6 ppm VA, and slight eye irritation in 1 of 3 individuals at 5.7 or 6.8  
42 ppm. However, this study is of limited usefulness because it was not a controlled human

1 exposure, but rather was simply a survey which recorded subjective symptoms of 3 individuals  
 2 during VA air sampling of a work environment. Therefore, the reported concentration of 21.6  
 3 ppm may not reflect the full exposure the individuals received.

#### 4 **5.2. Summary of Animal Data Relevant to AEGL-1**

5 Irritation was noted in a dog exposed for 4 hours to 205 ppm (blinking was noted 1 minute  
 6 into the exposure, and the sclera were red at 1 hour of exposure) (Smyth and Carpenter, 1973).  
 7 In the Bogdanffy et al. (1997) study, no histopathology was noted at 0, 50 or 200 ppm for any of  
 8 the exposures (1, 5, or 20 days for 6 hours/day excluding weekends) in the olfactory or  
 9 respiratory epithelium of rats. Thus, 200 ppm is a NOEL for these endpoints.

#### 10 **5.3. Derivation of AEGL-1**

11 The AEGL-1 is based upon the no-effect level for notable discomfort. Human exposure to  
 12 20 ppm resulted in one of three individuals reporting persistent slight throat irritation, while  
 13 exposure to 34 ppm for 2 hours resulted in one of three individuals complaining of persistent  
 14 throat irritation. Exposure to 72 ppm for 4 hours resulted in irritation severe enough that the  
 15 exposed subjects expressed an unwillingness to work at this concentration for 8 hours (Smyth  
 16 and Carpenter, 1973). Therefore, exposure to 20 ppm represents a no-effect level for notable  
 17 discomfort. A total uncertainty factor of 3 is applied: an interspecies uncertainty factor is not  
 18 applicable, and an intraspecies uncertainty factor of 3 is applied because the irritation is caused  
 19 by a local effect of the chemical and the response is not expected to vary greatly among  
 20 individuals. Because irritation is considered a threshold effect and therefore should not vary  
 21 over time, the AEGL-1 value is not scaled across time, but rather the threshold value is adopted  
 22 for all time points.

23 AEGL-1 values are presented in Table 14.

24 **TABLE 14. AEGL-1 Values for Vinyl Acetate [ppm (mg/m<sup>3</sup>)]**

25 <b>10-minute</b>	<b>30-minute</b>	<b>1-hour</b>	<b>4-hour</b>	<b>8-hour</b>
26 6.7 (24)	6.7 (24)	6.7 (24)	6.7 (24)	6.7 (24)

27 A level of distinct odor awareness (LOA) for VA of 0.25 ppm was derived on the basis of the  
 28 odor detection threshold from the study of Hellman and Small (1974) (see Appendix C for LOA  
 29 derivation). The LOA represents the concentration above which it is predicted that more than  
 30 half of the exposed population will experience at least a distinct odor intensity; about 10 % of the  
 31 population will experience a strong odor intensity. The LOA should help chemical emergency  
 32 responders in assessing the public awareness of the exposure due to odor perception.

### 33 **6. DATA ANALYSIS AND PROPOSED AEGL-2 VALUES**

#### 34 **6.1. Summary of Human Data Relevant to AEGL-2**

35 As discussed in Section 5.1., a controlled human study by Smyth and Carpenter (1973)  
 36 reported exposure to 34 ppm for 2 hours resulted in one of three individuals complaining of

1 persistent throat irritation, while exposure to 72 ppm VA for 4 hours resulted in eye irritation and  
2 slight throat irritation for up to 60 minutes post exposure in all four subjects exposed. The  
3 irritation was such at exposure to 72 ppm for 4 hours that subjects expressed an unwillingness to  
4 work at this concentration for 8 hours.

## 5 **6.2. Summary of Animal Data Relevant to AEGL-2**

6 No histopathology or cell proliferation were noted in the olfactory or respiratory epithelium  
7 of rats exposed for 6 hours to 0, 50 or 200 ppm VA, while concentration-related olfactory  
8 epithelium changes (degeneration, necrosis, and exfoliation) and a concentration-related increase  
9 in cell proliferation in both the respiratory and olfactory epithelium were present in the 600 and  
10 1000 ppm group animals (Bogdanffy et al., 1997). Although a definitive conclusion on the  
11 reversibility of these lesions cannot be drawn due to the absence of a recovery phase,  
12 reversibility of these changes from acute exposure to 600 or 1000 ppm VA should be essentially  
13 complete both morphologically and functionally based on the focal and limited nature of the  
14 olfactory lesions seen following VA exposure, as well as the known regenerative capacity of the  
15 olfactory tissue (Frame, 2004).

## 16 **6.3. Derivation of AEGL-2**

17  
18 The first choice of data for an AEGL derivation are human data. Smyth and Carpenter  
19 (1973) reported that exposure to 72 ppm for 4 hours resulted in irritation such that subjects  
20 expressed an unwillingness to work at this concentration for 8 hours. While this concentration  
21 represents an effect level for notable discomfort, it does not represent a concentration  
22 corresponding to definition of an AEGL-2 endpoint. Therefore, the rat histopathology data  
23 reported by Bogdanffy et al. (1997) are the basis for the AEGL-2.

24 In the Bogdanffy et al. (1997) study, exposure of rats for 6 hours to 1000 ppm VA represents  
25 a NOAEL for an AEGL-2 on the basis that the histopathological olfactory effects (degeneration,  
26 necrosis, and exfoliation of the olfactory epithelial cells) are predicted to be reversible (Frame,  
27 2004). A total uncertainty factor of 10 is applied: 3 for interspecies and 3 for intraspecies  
28 variability. An interspecies uncertainty factor of 3 is applied on the basis that the mechanism of  
29 nasal toxicity appears to depend on the metabolism of VA to the metabolites acetic acid and  
30 acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the  
31 metabolism of VA by the nasal cavity reported little difference among male and female mice and  
32 rats and humans in the carboxylesterase-mediated metabolism of VA, particularly by olfactory  
33 epithelium (Bogdanffy and Taylor, 1993; Bogdanffy et al., 1998). Esterase distribution in the  
34 nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al., 2002).  
35 An intraspecies uncertainty factor of 10 would normally be applied based on the knowledge that  
36 considerable variability in olfactory nasal tissue occurs in humans with regard to surface area  
37 covered, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with  
38 more characteristic olfactory tissue), and age-related changes (Andersen et al., 2002). However,  
39 a total uncertainty factor of 30 would reduce the AEGL-2 values to concentrations that did not  
40 result in serious health effects in human volunteer studies (a UF of 30 would drive the 8-hour  
41 AEGL-2 to 25 ppm). Therefore, the intraspecies uncertainty factor was reduced to 3, and the  
42 total uncertainty factor is 10.

The experimentally derived exposure values were scaled to AEGL time frames using the concentration-time relationship in the equation  $C^n \times t = k$ , where  $C$  = concentration,  $t$  = time,  $k$  is a constant, and  $n$  generally ranges from 1 to 3.5 (ten Berge et al., 1986). The value of  $n$  was not empirically derived because of insufficient data; therefore, the default value of  $n = 1$  was used for extrapolating from shorter to longer exposure periods and a value of  $n = 3$  was used to extrapolate from longer to shorter exposure periods. The 10-minute AEGL-2 was set equal to the 30-minute value of 230 ppm because the NAC considers it inappropriate to extrapolate from the exposure duration of 6 hours to 10 minutes.

AEGL-2 values are presented in Table 15.

10-minute	30-minute	1-hour	4-hour	8-hour
230 (810)	230 (810)	180 (630)	110 (390)	75 (260)

## 7. DATA ANALYSIS AND PROPOSED AEGL-3 VALUES

### 7.1. Summary of Human Data Relevant to AEGL-3

No human data were available for derivation of an AEGL-3.

### 7.2. Summary of Animal Data Relevant to AEGL-3

Mortality data were available for rats, mice, guinea pigs, and rabbits (Smyth and Carpenter, 1973; see Table 16). Chamber concentrations were not measured, but nominal concentrations were corrected against a calibration curve. Lethal concentrations produced signs of irritation (gasping, lacrimation) and central nervous system effects (poor coordination, prostration, clonic convulsions), and death was attributed to lung irritation (pulmonary congestion, hemorrhages, and excess pleural fluid).

Species	LC <sub>50</sub> <sup>b</sup>	BMCL <sub>05</sub> <sup>c</sup>	BMC <sub>01</sub> <sup>c</sup>
Rat	3680	1791	2651
Mouse	1460	226	355
Guinea pig	5210	1303	1953
Rabbit	2760	933	2364

<sup>a</sup> Data from Smyth and Carpenter, 1973

<sup>b</sup> Values reported in Smyth and Carpenter, 1973

<sup>c</sup> Calculated using US EPA Benchmark Dose Software version 1.3.2.

1 Nonlethal concentrations in the Smyth and Carpenter (1973) study produced signs of  
2 congested extremities in rats, lacrimation in guinea pigs, and no signs in mice or rabbits. In a  
3 nonlethal study in dogs, a dog exhibited lacrimation, nasal froth, and tremors at the highest  
4 exposure concentration of 3280 ppm for 4 hours, while exposure to 1640 ppm produced irritation  
5 but no CNS effects (Smyth and Carpenter, 1973). Exposure to 1000 ppm VA for 6 hours/day, 5  
6 days/week for 4 weeks was not lethal to groups of 5 male and 5 female rats or mice (Owen,  
7 1979a; b).

8 As discussed in the AEGL-2 derivation section, no histopathology or cell proliferation were  
9 noted in the olfactory or respiratory epithelium of rats exposed for 6 hours to 0, 50 or 200 ppm  
10 VA, while concentration-related olfactory epithelium changes (degeneration, necrosis, and  
11 exfoliation) and a concentration-related increase in cell proliferation in both the respiratory and  
12 olfactory epithelium were present in the 600 and 1000 ppm group animals (Bogdanffy et al.,  
13 1997). Although a definitive conclusion on the reversibility of these lesions cannot be drawn  
14 due to the absence of a recovery phase, effects of acute exposure to 600 or 1000 ppm VA should  
15 be reversible based on the focal and limited nature of the olfactory lesions seen following VA  
16 exposure, as well as the known regenerative capacity of olfactory tissue (Frame, 2004).

17 A carcinogenicity assessment was not appropriate for an acute exposure scenario on the basis  
18 that the proposed mechanism of carcinogenicity suggests a nonlinear mode of action requiring  
19 continued exposure. Therefore, a one-time exposure even to high-concentrations of VA would  
20 not be expected to result in tumor development.

### 21 **7.3. Derivation of AEGL-3**

22 When available, a  $BMCL_{05}$  calculated using benchmark dosing is often used as a basis for the  
23 AEGL-3. The 4-hour mortality data provided by Smyth and Carpenter (1973), however, produce  
24  $BMCL_{05}$  values ranging from 226 ppm in mice to 1791 ppm in rats. The 226 ppm value appears  
25 unreasonable in context of other available data. For example, a group of 10 mice survived  
26 exposure to VA for 6 hours/day, 5/days/week, for 4 weeks (Owen, 1979a). Because the  
27 exposure concentrations in the Smyth and Carpenter (1973) study were not measured, but  
28 corrected using a curve based on gas chromatographic analysis of calculated concentrations, it is  
29 possible that the exposure concentrations reported are not accurate. Therefore, these data were  
30 not used for derivation of the AEGL-3.

31 No other lethality data were available for derivation of an AEGL-3. Therefore, the AEGL-3  
32 is based on the same endpoint as the AEGL-2: exposure of rats for 6 hours to 1000 ppm VA  
33 produced reversible histopathological changes in the nasal cavity (Bogdanffy et al., 1997). A  
34 total uncertainty factor of 3 is applied: 3 for interspecies and 1 for intraspecies variability. An  
35 interspecies uncertainty factor of 3 is applied on the basis that the mechanism of nasal toxicity  
36 appears to depend on the metabolism of VA to the metabolites acetic acid and acetaldehyde via  
37 carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of VA by  
38 the nasal cavity reported little difference among male and female mice, rats and humans in the  
39 carboxylesterase-mediated metabolism of VA, particularly by olfactory epithelium (Bogdanffy  
40 and Taylor, 1993; Bogdanffy et al., 1998). Esterase distribution in the nasal respiratory tissue of  
41 humans is believed to be similar to that of rats (Andersen et al., 2002). An intraspecies  
42 uncertainty factor of 1 was applied because the endpoint of reversible nasal histopathological

1 changes is much less severe than the toxic effects defined for an AEGL-3. Therefore, the total  
2 uncertainty factor is 3.

3 The experimentally derived exposure values were scaled to AEGL time frames using the  
4 concentration-time relationship in the equation  $C^n \times t = k$ , where  $C$  = concentration,  $t$  = time,  $k$  is  
5 a constant, and  $n$  generally ranges from 1 to 3.5 (ten Berge et al., 1986). The value of  $n$  was not  
6 empirically derived because of insufficient data; therefore, the default value of  $n = 1$  was used  
7 for extrapolating from shorter to longer exposure periods and a value of  $n = 3$  was used to  
8 extrapolate from longer to shorter exposure periods. The 10-minute AEGL-3 was set equal to  
9 the 30-minute value of 230 ppm because the NAC considers it inappropriate to extrapolate from  
10 the exposure duration of 6 hours to 10 minutes.

11 AEGL-3 values are presented in Table 17.

13 <b>10-minute</b>	<b>30-minute</b>	<b>1-hour</b>	<b>4-hour</b>	<b>8-hour</b>
14 760 (2700)	760 (2700)	610 (2100)	380 (1300)	250 (880)

## 15 **8. SUMMARY OF PROPOSED AEGL VALUES**

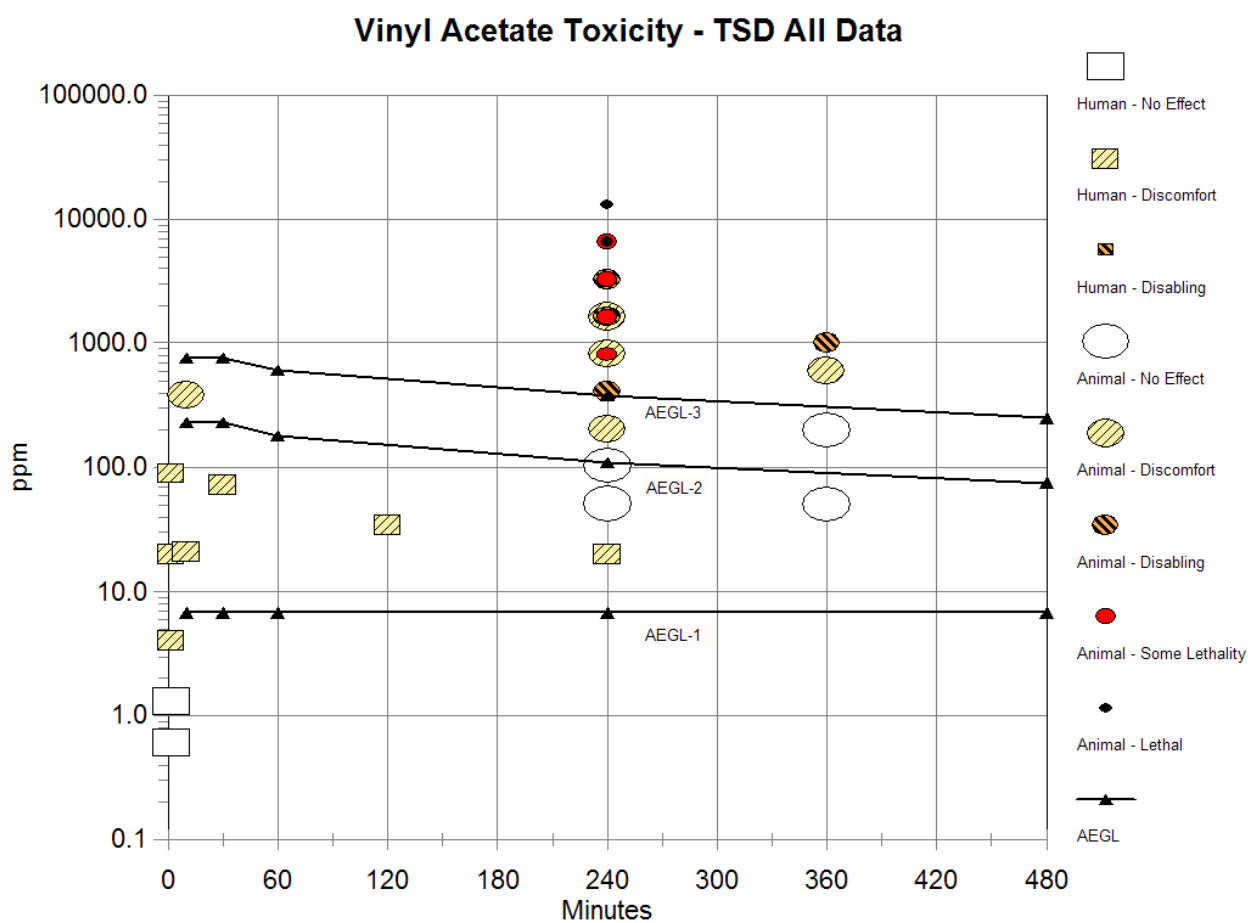
### 16 **8.1. AEGL Values and Toxicity Endpoints**

17 The Smyth and Carpenter (1973) study was used for the AEGL-1 derivations on the basis of  
18 irritation in humans, but the human data from this study could not be compared with other  
19 human data to verify consistency due to an overall limited database for AEGL-1 effects. The  
20 AEGL-2 derivation is based on reversible nasal histopathological changes because other AEGL-  
21 2-type effects were not available. The AEGL-3 was also based on the same nasal  
22 histopathological changes. The proposed AEGL values for VA are summarized in Table 18.

24 <b>Classification</b>	<b>Exposure Duration</b>				
	<b>10-minute</b>	<b>30-minute</b>	<b>1-hour</b>	<b>4-hour</b>	<b>8-hour</b>
25 AEGL-1 26 (Nondisabling)	6.7 (24)	6.7 (24)	6.7 (24)	6.7 (24)	6.7 (24)
27 AEGL-2 28 (Disabling)	230 (810)	230 (810)	180 (630)	110 (390)	75 (260)
29 AEGL-3 30 (Lethal)	760 (2700)	760 (2700)	610 (2100)	380 (1300)	250 (880)

31 A useful way to evaluate the AEGL values in context of existing empirical data is presented  
32 in Figure 2. For this plot, the toxic response was placed into severity categories. The severity  
33 categories fit into definitions of the AEGL health effects: 0 = no effects; 1=discomfort; 2 =

1 disabling; 3 = lethal, and PL = partially lethal (an experimental concentration at which some of  
 2 the animals died and some did not). The effects that place an experimental result into a  
 3 particular category vary according to the spectrum of data available on a specific chemical and  
 4 the effects from exposure to that chemical. The doses often span a number of orders of  
 5 magnitude, especially when human data exist. Therefore, the concentration is placed on a log  
 6 scale. The graph in Figure 2 plots the VA AEGL values along with the existing acute animal  
 7 toxicity data for VA in terms of the categories assigned to them. From this plot, one sees that the  
 8 AEGL values are below any exposure concentration in animals resulting in any effects, and  
 9 should therefore be protective of human health.



10 Fi  
 11 g  
 12 ur  
 13 e 2. Category Plot of Human and Animal Toxicity Data Compared to AEGL Values

14 **8.2. Comparison with Other Standards and Guidelines**

15 Standards and guidance levels for workplace and community exposures are listed in  
 16 Table 19.

TABLE 19. Extant Standards and Guidelines for Vinyl Acetate (ppm [ $\text{mg}/\text{m}^3$ ])						
Guideline	Exposure Duration					
	10 min.	15 min.	30 min.	1 hour	4 hour	8 hour
AEGL-1	6.7		6.7	6.7	6.7	6.7
AEGL-2	230		230	180	110	75
AEGL-3	760		760	610	380	250
ERPG-1 (AIHA) <sup>a</sup>				5		
ERPG-2 (AIHA)				75		
ERPG-3 (AIHA)				500		
PEL-TWA (OSHA) <sup>b</sup>						not established
IDLH (NIOSH) <sup>c</sup>			not established			
REL-TWA (NIOSH) <sup>d</sup>		4 [15] (ceiling)				
TLV-TWA (ACGIH) <sup>e</sup>						10 [35] 3A
TLV-STEL (ACGIH) <sup>f</sup>						15 [53]
MAK (Germany) <sup>g</sup>						not established at the present - 3A
MAC (The Netherlands) <sup>h</sup>						5 [18]

<sup>a</sup>**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 1991)**

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for VA is based on an odor threshold of 0.5-1 ppm in human volunteers (Smyth and Carpenter, 1973) and on the lack of irritation reported in workers exposed long-term to VA at concentrations of 5-10 ppm (Deese and Joyner, 1969).

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for VA is based upon evidence that healthy humans can tolerate the irritant effects at concentrations of approximately 75 ppm for 60 min (Smyth and Carpenter, 1973) and on the subchronic exposures in animals, where no effects were observed at 50-200 ppm (Owen, 1980a; b). Thus, air concentrations of 75 ppm or lower should not cause severe respiratory tract irritation in almost all individuals when exposed for no more than a 1-hour period.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for VA is based upon the assumption that nearly all individuals could be exposed to 500 ppm VA for up to 1 hour without experiencing or developing life-threatening health effects. In the most sensitive species, mice, concentrations of 1000 ppm were lethal to 1 of 6 animals (Smyth and Carpenter, 1973). In chronic studies at

1 600 ppm, no effect on rat survival and only a slight effect on mice survival was observed. Although other  
2 species demonstrated greater resistance to the lethal effects, all species exhibited signs consistent with  
3 respiratory tract irritation.

4 <sup>b</sup>**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time**  
5 **Weighted Average)** (OSHA 1996) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no  
6 more than 10 hours/day, 40 hours/week.

7 <sup>c</sup>**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)**  
8 (NIOSH 2003) represents the maximum concentration from which one could escape within 30 minutes without  
9 any escape-impairing symptoms, or any irreversible health effects.

10 <sup>d</sup>**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits -**  
11 **Time Weighted Average)** (NIOSH 2003)  
12 is defined analogous to the ACGIH-TLV-TWA.

13 <sup>e</sup>**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value -**  
14 **Time Weighted Average)** (ACGIH 1996; 2003)  
15 is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which  
16 nearly all workers may be repeatedly exposed, day after day, without adverse effect. The notation of 3A  
17 designates that VA is a confirmed animal carcinogen with unknown relevance to humans.

18 <sup>f</sup>**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche  
19 Forschungsgemeinschaft [German Research Association] 2002)  
20 is defined analogous to the ACGIH-TLV-TWA. The notation 3A are substances for which the criteria for  
21 classification in Category 4 or 5 are fulfilled but for which the database is insufficient for the establishment of a  
22 MAK value.

23 <sup>g</sup>**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the  
24 auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000)  
25 is defined analogous to the ACGIH-TLV-TWA.

### 26 **8.3. Data Adequacy and Research Needs**

27 All three AEGL levels were derived, but the overall database was limited. The Smyth and  
28 Carpenter (1973) study was used for the AEGL-1 derivations on the basis of irritation in humans,  
29 but the human data from this study could not be compared with other human data to verify  
30 consistency due to an overall limited database for AEGL-1 effects. The AEGL-2 derivation is  
31 based on reversible nasal histopathological changes because other AEGL-2-type effects were not  
32 available. The AEGL-3 was also based on the same nasal histopathological changes. If the  
33 mouse mortality data reported by Smyth and Carpenter (1973) are used to derive AEGL-3  
34 values, the values are unreasonable in context of available data. Because the exposure  
35 concentrations in the Smyth and Carpenter (1973) study were not measured, but corrected using  
36 a curve based on gas chromatographic analysis of calculated concentrations, it is possible that  
37 the exposure concentrations reported are not accurate. Therefore, it was decided not use any of  
38 the mortality data from the Smyth and Carpenter (1973) for derivation of the AEGL-3, and the  
39 conservative endpoint of reversible nasal histopathological changes was used.

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**APPENDIX A: Derivation of AEGL Values**

1

**Derivation of AEGL-1**

2

Key Study: Smyth and Carpenter, 1973

3

Toxicity endpoint: Human exposure to 20 ppm for 4 hours resulted in one of three individuals complaining of persistent slight throat irritation, and exposure to 34 ppm for 2 hours resulted in one of three individuals complaining of persistent throat irritation (no longer slight). Therefore, exposure to 20 ppm represents a no-effect level for notable discomfort.

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Time scaling: None; because irritation is considered a threshold effect and therefore should not vary over time, the AEGL-1 value is not scaled across time, but rather the threshold is used at the point of departure for all time points.

10

11

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Uncertainty factors: Total of 3:  
Interspecies: 1  
Intraspecies: 3

14

15

16

Modifying factor: NA

17

10-minute, 30-minute, 1-hour, 4-hour, 8-hour AEGL-1: Concentration producing effect is used at the point of departure for all time points:  $20 \text{ ppm}/3 = 6.7 \text{ ppm}$

18

1 **Derivation of AEGL-2**

2 Key Studies: Bogdanffy et al., 1997

3 Toxicity endpoints: exposure of rats to 1000 ppm for 6 hours is considered a NOAEL for an  
4 AEGL-2 based on reversible nasal histopathological changes5 Time scaling  $C^n \times t = k$  (this document; default of  $n = 1$  for shorter to longer exposure  
6 periods and  $n=3$  for longer to shorter exposure periods)  
7  $[(1000 \text{ ppm})/10]^1 \times 6 \text{ hr} = 600 \text{ ppm}\text{Ⓐr}$   
8  $[(1000 \text{ ppm})/10]^3 \times 6 \text{ hr} = 6.0 \times 10^6 \text{ ppm}\text{Ⓐr}$ 

9 Total uncertainty factors: 10

10 Interspecies: 3

11 Intraspecies: 3

12 Modifying factor: NA

13 Calculations:

14 10-minute AEGL-2 10-min AEGL-2 value was set equal to the 30-min AEGL-2 value of 230  
15 ppm because it is considered inappropriate to extrapolate from a 6-hr  
16 exposure to an exposure duration of 10 min.17 30-minute AEGL-2  $C^3 \times 0.5 \text{ hr} = 6.0 \times 10^6 \text{ ppm}\text{Ⓐr}$   
18  $C^3 = 1.2 \times 10^7 \text{ ppm}$   
19  $C = 229 \text{ ppm} = 230 \text{ ppm}$ 20 1-hour AEGL-2  $C^3 \times 1 \text{ hr} = 6.0 \times 10^6 \text{ ppm}\text{Ⓐr}$   
21  $C^3 = 6.0 \times 10^6 \text{ ppm}$   
22  $C = 182 \text{ ppm} = 180 \text{ ppm}$ 23 4-hour AEGL-2  $C^3 \times 4 \text{ hr} = 6.0 \times 10^6 \text{ ppm}\text{Ⓐr}$   
24  $C^3 = 1.5 \times 10^5 \text{ ppm}$   
25  $C = 114 \text{ ppm} = 110 \text{ ppm}$ 26 8-hour AEGL-2  $C^1 \times 8 \text{ hr} = 600 \text{ ppm}\text{Ⓐr}$   
27  $C^1 = 75 \text{ ppm}$   
28  $C = 75 \text{ ppm}$

1 **Derivation of AEGL-3**

2 Key Studies: Bogdanffy et al., 1997

3 Toxicity endpoints: exposure to 1000 ppm for 6 hours produced reversible nasal  
4 histopathological changes5 Time scaling:  $C^n \times t = k$  (this document; default of  $n = 1$  for shorter to longer exposure  
6 periods and  $n=3$  for longer to shorter exposure periods)7  $[(1000 \text{ ppm})/3]^1 \times 6 \text{ hr} = 2000 \text{ ppm}\text{Ⓐr}$ 8  $[(1000 \text{ ppm})/3]^3 \times 6 \text{ hr} = 2.22 \times 10^8 \text{ ppm}\text{Ⓐr}$ 

9 Total uncertainty factors: 3

10 Interspecies: 3

11 Intraspecies: 1

12 Modifying factor: NA

13 10-minute AEGL-3 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value of 760  
14 ppm because it is considered inappropriate to extrapolate from a 6-hr  
15 exposure to an exposure duration of 10 min.16 30-minute AEGL-3  $C^3 \times 0.5 \text{ hr} = 2.22 \times 10^8 \text{ ppm}\text{Ⓐr}$ 17  $C^3 = 4.44 \times 10^8 \text{ ppm}$ 18  $C = 763 \text{ ppm} = 760 \text{ ppm}$ 19 1-hour AEGL-3  $C^3 \times 1 \text{ hr} = 2.22 \times 10^8 \text{ ppm}\text{Ⓐr}$ 20  $C^3 = 2.22 \times 10^8 \text{ ppm}$ 21  $C = 605 \text{ ppm} = 610 \text{ ppm}$ 22 4-hour AEGL-3  $C^3 \times 4 \text{ hr} = 2.22 \times 10^8 \text{ ppm}\text{Ⓐr}$ 23  $C^3 = 5.55 \times 10^7 \text{ ppm}$ 24  $C = 381 \text{ ppm} = 380 \text{ ppm}$ 

25

26 8-hour AEGL-3  $C^1 \times 8 \text{ hr} = 2000 \text{ ppm}\text{Ⓐr}$ 27  $C^1 = 250 \text{ ppm}$ 28  $C = 250 \text{ ppm}$ 

29

1      **APPENDIX B: Calculation of Level of Distinct Odor Awareness for VA**

**1 Derivation of the Level of Distinct Odor Awareness (LOA)**

2 The level of distinct odor awareness (LOA) represents the concentration above which it  
3 is predicted that more than half of the exposed population will experience at least a distinct odor  
4 intensity, about 10% of the population will experience a strong odor intensity. The LOA should  
5 help chemical emergency responders to assess the public awareness of the exposure due to odor  
6 perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

7 For derivation of the odor detection threshold ( $OT_{50}$ ), a study is available in which the  
8 odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm) has also  
9 been determined:

10 Hellman and Small (1974):  
11 odor detection threshold for VA: 0.12  
12 odor detection threshold for n-butanol: 0.3 ppm  
13 corrected odor detection threshold ( $OT_{50}$ ) for VA:  $0.12 \text{ ppm} * 0.04 / 0.3 = 0.016 \text{ ppm}$

14 The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived  
15 using the Fechner function:

$$16 \quad I = k_w * \log (C / OT_{50}) + 0.5$$

17 For the Fechner coefficient, the default of  $k_w = 2.33$  will be used due to the lack of chemical-  
18 specific data:

$$19 \quad 3 = 2.33 * \log (C / 0.016) + 0.5$$

20 which can be rearranged to:

$$21 \quad \log (C / 0.016) = (3 - 0.5) / 2.33 = 1.07$$

22 and results in:

$$23 \quad C = (10^{1.07}) * 0.016 = 11.8 * 0.016 = 0.1888 \text{ ppm}$$

24 The resulting concentration is multiplied by an empirical field correction factor. It takes  
25 into account that in every day life factors, such as sex, age, sleep, smoking, upper airway  
26 infections and allergy as well as distraction, increase the odor detection threshold by a factor of  
27 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which  
28 leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3  
29 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a  
30 correction factor of  $4 / 3 = 1.33$ ;

$$31 \quad \text{LOA} = C * 1.33 = 0.189 \text{ ppm} * 1.33 = 0.25 \text{ ppm}$$

32 The LOA for VA is 0.25 ppm.

1 **APPENDIX C: Derivation Summary for Vinyl Acetate AEGL Values**

**ACUTE EXPOSURE GUIDELINE LEVELS FOR  
VA (CAS Reg. No. 108-05-4)  
DERIVATION SUMMARY**

<b>AEGL-1 VALUES</b>				
<b>10-minute</b>	<b>30-minute</b>	<b>1-hour</b>	<b>4-hour</b>	<b>8-hour</b>
<b>6.7 ppm</b>	<b>6.7 ppm</b>	<b>6.7 ppm</b>	<b>6.7 ppm</b>	<b>6.7 ppm</b>
Key Reference: Smyth, H.F., and Carpenter, C.P. 1973. Initial submission: Vinyl acetate: Single animal inhalation and human sensory response with cover letter dated 082792. Carnegie-Mellon Institute. Submitted by Union Carbide Corporation. Doc. # 88-920010328.				
Test Species/Strain/Number: 3-9 human volunteers (3 volunteers for concentration chosen for derivation)				
Exposure Route/Concentrations/Durations: 0.6, 1.3, 4, 8, or 20 ppm for 2 minutes; 20 ppm for 4 hours; 34 ppm for 2 hours; 72 ppm for 30 minutes				
Effects:				
Exposure Conc. (ppm)	No. 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. 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. after exp; eye irritation to 60 min. after exposure; subjects expressed unwillingness to work at this concentration for 8 hours	
Endpoint/Concentration/Rationale: Exposure to 4-20 ppm for 2 minutes and 20 ppm for 240 minutes produced slight throat irritation; exposure to 34 ppm for 2 hours resulted in one of three individuals complaining of persistent throat irritation; and exposure to 72 ppm for 4 hours resulted in irritation severe enough that the exposed subjects expressed an unwillingness to work at this concentration for 8 hours (Smyth and Carpenter, 1973). Therefore, exposure to 20 ppm for 4 hours represents a no-effect level for notable discomfort.				

1	Uncertainty Factors/Rationale:
2	Total uncertainty factor: 3
3	Interspecies: 1
4	Intraspecies: 3 because the irritation is caused by a local effect of the chemical and the response is not
5	expected to vary greatly among individuals.
6	Modifying Factor: NA
7	Animal to Human Dosimetric Adjustment: NA
8	Time Scaling: Because irritation is considered a threshold effect and therefore should not vary over time, the
9	AEGL-1 value is not scaled across time, but rather the threshold value is applied to all times.
10	Data Adequacy: This was an acceptable study. Due to the nature of the database, it was not possible to compare
11	these data with other human data to verify consistency.

AEGL-2 VALUES				
10-minute	30-minute	1-hour	4-hour	8-hour
230 ppm	230 ppm	180 ppm	110 ppm	75 ppm
Key Reference: 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. <i>Inhal. Toxicol.</i> 9: 331-350.				
Test Species/Strain/Number: 5 male, Sprague-Dawley rats/group				
Exposure Route/Concentrations/Durations: 0, 50, 200, 600, or 1000 ppm for 6 hours/day				
Effects: 0, 50, 200 ppm - no effects 600 ppm - degenerative lesions and increased cell proliferation in olfactory epithelium; effects are reversible 1000 ppm - increased incidence/severity in olfactory epithelium lesions; some minimal lesions noted in respiratory epithelium; increased cell proliferation in olfactory epithelium; effects are reversible.				
Endpoint/Concentration/Rationale: exposure to 1000 ppm for 6 hours is considered a NOAEL for an AEGL-2 based on reversible nasal (olfactory) histopathological lesions				
Uncertainty Factors/Rationale: Total uncertainty factor: 10: Interspecies: 3 - The mechanism of nasal toxicity appears to depend on the metabolism of VA to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of VA by the nasal cavity reported little difference among male and female mice and rats and humans in the carboxylesterase-mediated metabolism of VA, particularly by olfactory epithelium. Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats. Intraspecies: 3; a higher factor is unjustified because that would reduce the AEGL-2 values to concentrations that did not result in serious health effects in human studies (for example, an UF of 30 would drive the 8-hour AEGL-2 to 25 ppm).				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: The experimentally derived exposure values were then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$ , where $C$ = concentration, $t$ = time, $k$ is a constant, and $n$ generally ranges from 1 to 3.5 (ten Berge et al, 1986). The value of $n$ was not empirically derived because of insufficient data; therefore, the default value of $n = 1$ was used for extrapolating from shorter to longer exposure periods and a value of $n = 3$ was used to extrapolate from longer to shorter exposure periods. The 10-minute AEGL-2 was set equal to the 30-minute value of 230 ppm because the NAC considers it inappropriate to extrapolate from the exposure duration of 6 hours to 10 minutes.				
Data Adequacy: Histopathology represents a sensitive endpoint for an AEGL-2-type effect, and should be protective of human health.				

**AEGL-3 VALUES**

10-minute	30-minute	1-hour	4-hour	8-hour
760 ppm	760 ppm	610 ppm	380 ppm	250 ppm
Key Reference: Bogdanffy, M.S., Gladnick, N.L., Kegelmann, T., and Frame S.R. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. <i>Inhal. Toxicol.</i> 9: 331-350.				
Test Species/Strain/Number: 5 male, Sprague-Dawley rats/group				
Exposure Route/Concentrations/Durations: 0, 50, 200, 600, or 1000 ppm for 6 hours/day				
Effects: 0, 50, 200 ppm - no effects 600 ppm - degenerative lesions and increased cell proliferation in olfactory epithelium; effects are reversible 1000 ppm - increased incidence/severity in olfactory epithelium lesions; some minimal lesions noted in respiratory epithelium; increased cell proliferation in olfactory epithelium; effects are reversible.				
Endpoint/Concentration/Rationale: exposure to 1000 ppm for 6 hours is considered a NOAEL for an AEGL-2 based on reversible nasal (olfactory) histopathological lesions				
Uncertainty Factors/Rationale: Total uncertainty factor: 3: Interspecies: 3 - The mechanism of nasal toxicity appears to depend on the metabolism of VA to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of VA by the nasal cavity reported little difference among male and female mice and rats and humans in the carboxylesterase-mediated metabolism of VA, particularly by olfactory epithelium. Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats. Intraspecies: 1 because the POD is far below the a lethal concentration				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: The experimentally derived exposure values were then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$ , where $C$ = concentration, $t$ = time, $k$ is a constant, and $n$ generally ranges from 1 to 3.5 (ten Berge et al, 1986). The value of $n$ was not empirically derived because of insufficient data; therefore, the default value of $n = 1$ was used for extrapolating from shorter to longer exposure periods and a value of $n = 3$ was used to extrapolate from longer to shorter exposure periods. The 10-minute AEGL-3 was set equal to the 30-minute value of 760 ppm because the NAC considers it inappropriate to extrapolate from the exposure duration of 6 hours to 10 minutes.				
Data Adequacy: Histopathology represents a sensitive endpoint for an AEGL-2-type effect and is below the AEGL-3-type effect, and should be protective of human health.				