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1,2-DICHLOROETHENE
(CAS Reg. No. 540-59-0)

cis 1,2-Dichloroethene
(CAS Reg. No. 156-59-2)

trans 1,2-Dichloroethene
(CAS Reg. No. 156-60-5)

ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

FINAL

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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^3]) 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^3) 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^3) 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

1,2-Dichloroethene is a flammable, colorless liquid existing in both cis- and trans- forms and as a mixture of these two isomers. It is one of a number of two carbon chlorocarbons produced in a reaction mixture resulting from processes involved in the chlorination of ethylene to produce chlorinated monomers and solvents. The trans-isomer is commercially isolated by distillation and sold as a highly purified product that is used in precision cleaning of electronic equipment. The compound is a narcotic. Data on narcosis in humans, cats, rats, and mice, and systemic effects in cats, rats, and mice were available for development of AEGLs. The data were considered adequate for derivation of the three AEGL classifications.

The AEGL-1 was based on human exposure to 825 ppm trans-1,2-dichloroethene for 5 minutes (Lehmann and Schmidt-Kehl 1936). This concentration is a no-effect-level for eye irritation. This value was divided by an uncertainty factor of 3 to protect sensitive individuals and is considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set. (Using the full uncertainty factor of 10, yields an AEGL-1 value of 83 ppm; no effects were noted in humans exposed to 275 ppm). This uncertainty factor of 3 was applied for AEGL-1 values for both the cis- and trans-isomers. Since data suggest that the cis- isomer is approximately twice as toxic as the trans-isomer with regard to narcosis and lethality in experimental animals, a modifying factor of 2 was applied in the derivation of the cis- isomer values only. Although the AEGL-1 point-of-departure is a NOEL for eye irritation, the use of the modifying factor is justified for the cis-isomer because slight dizziness, a possible mild narcotic effect, was noted at the concentration used as starting point for the derivation of the AEGL-1. The same value was applied across the 10- and 30-minute, 1-, 4-, and 8-hour exposure time points since mild irritation is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect.

The AEGL-2 for the 4- and 8-hour time points was based on narcosis observed in pregnant rats exposed to 6000 ppm of the trans- isomer for 6 hours (Hurtt et al., 1993). Uncertainty factors of 3 each (total UF=10) were applied for both inter- and intraspecies differences. The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975). This total uncertainty factor of 10 was applied for AEGL-2 values for both the cis- and trans-isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The AEGL-2 for the 10- and 30- minute and 1-hour time points was set as a maximum exposure level for anesthetic effects in humans (Lehmann and Schmidt-Kehl, 1936). Since data suggest that the cis- isomer is approximately twice as toxic as the trans-isomer with regard to narcosis and lethality in experimental animals, a modifying factor of 2 was applied in the derivation of the cis- isomer values only.

The AEGL-3 for the 4- and 8-hour time points was based on a concentration (12,300 ppm) causing no mortality in rats exposed to trans-1,2-dichloroethene for 4-hours (Kelly, 1999). An uncertainty factor of 3 was applied for interspecies differences because rat and mouse lethality data indicate little species variability with regard to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). An intraspecies UF of 3 was also applied and is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975). The total uncertainty factor of 10 was applied for AEGL-3 values for both the cis- and trans-isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The AEGL-3 for the 10- and 30- minute and 1-hour time points was set as a maximum exposure level for intracranial pressure, nausea, and severe dizziness in humans (Lehmann and Schmidt-Kehl, 1936). Since data suggest that the cis- isomer is approximately twice as toxic as the trans-isomer with regard to narcosis and lethality in experimental animals, a modifying factor of 2 was applied in the derivation of the cis- isomer values only.

The calculated values are listed in the tables below.

TABLE 1. Summary of AEGL Values for trans-1,2-Dichloroethene [ppm(mg/m^3)]

Classification	10-min.	30-min.	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	280 (1109)	280 (1109)	280 (1109)	280 (1109)	280 (1109)	Ocular irritation in humans (Lehmann & Schmidt-Kehl, 1936)
AEGL-2 (Disabling)	1000 (3960)	1000 (3960)	1000 (3960)	690 (2724)	450 (1782)	Narcosis in rats:4- & 8-h (Hurtt et al., 1993); Anesthetic effects in humans (Lehmann & Schmidt-Kehl, 1936)
AEGL-3 (Lethality)	1700 (6732)	1700 (6732)	1700 (6732)	1200 (4752)	620 (2455)	No death in rats: 4- & 8-h (Kelly, 1999); Nausea, intracranial pressure, and dizziness in humans:10-, & 30-min, &1-h (Lehmann & Schmidt-Kehl, 1936)

TABLE 2. Summary of AEGL Values for cis-1,2-Dichloroethene [ppm(mg/m^3)]

Classification	10-min.	30-min.	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)	Ocular irritation in humans (Lehmann & Schmidt-Kehl, 1936)
AEGL-2 (Disabling)	500 (1980)	500 (1980)	500 (1980)	340 (1346)	230 (911)	Narcosis in rats:4- & 8-h (Hurtt et al., 1993); Anesthetic effects in humans (Lehmann & Schmidt-Kehl, 1936)
AEGL-3 (Lethality)	850 (3366)	850 (3366)	850 (3366)	620 (2455)	310 (1228)	No death in rats: 4- & 8-h (Kelly, 1999); Nausea, intracranial pressure, and dizziness in humans:10-, & 30-min, &1-h (Lehmann & Schmidt-Kehl, 1936)

References

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1. INTRODUCTION

1,2-Dichloroethene is an extremely flammable, colorless liquid with a harsh odor, existing as both cis- and trans- forms and as a mixture (ATSDR, 1996). It is one of a number of two carbon chlorocarbons produced in a reaction mixture resulting from processes involved in the chlorination of ethylene to produce chlorinated monomers and solvents. The trans-isomer is commercially isolated by distillation and sold as a highly purified product that is used in precision cleaning of electronic equipment. The compound reacts with alkalis to form chloroacetylene gas, reacts violently with potassium hydroxide and sodium hydroxide, and can be combined with dinitrogen tetraoxide to form shock-sensitive explosives. Because of volatility, inhalation is the primary route of exposure of 1,2-dichloroethene to humans. Exposure may occur as the result of releases from production or use facilities, from contaminated wastewater and waste disposal sites, and from burning of polyvinyl and vinyl polymers (ATSDR, 1996). In 1977, production of the cis-/trans- mixture was reported by one company as 10 to 50 million pounds and by another company as 1 to 10 million pounds (NTP, 2002). The only manufacturer of the cis-isomer reported production of 0.1 to 10 million pounds; no production estimates for the trans-isomer were reported (NTP, 2002). The physicochemical data for 1,2-dichloroethene are shown in Table 3.

TABLE 3. Chemical and Physical Data for 1,2-Dichloroethene

Synonyms	1,2-Dichloroethylene, acetylene dichloride,sym-dichloroethylene, Dioform (trade name)	O'Neil et al., 2001
CAS Registry No.	540-59-0 (mixture), 156-59-2 (cis), 156-60-5 (trans)	ATSDR, 1996
Chemical formula	$C_2H_2Cl_2$	O'Neil et al., 2001
Molecular weight	96.9	O'Neil et al., 2001
Physical state	Liquid	O'Neil et al., 2001
Vapor pressure	215 (cis) or 336 (trans) mm Hg at 30EC	ATSDR, 1996
Density	1.2837 (cis) or 1.2565 (trans) g/cm^3	ATSDR, 1996
Melting/boiling/flash point	-80.5EC/60.3EC/6EC (cis); -50.0EC/48.0EC/4EC (trans)	ATSDR, 1996
Solubility in water	3.5 (cis) or 6.3 (trans) g/L at 25EC	ATSDR, 1996
LogK_{ow}	1.86 (cis), 2.06 (trans)	ATSDR, 1996
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 mg/m^3 = 0.25 ppm 1 ppm = 3.96 mg/m^3	ATSDR, 1996
Odor threshold	17 ppm; ethereal, slightly acrid odor	O'Neil et al., 2001
Henrys' Law constant	3.37 x 10^{-3} (cis) or 6.72 x 10^{-3} (trans) atm-m^3/mol	ATSDR, 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

An accidental fatality from occupational exposure to 1,2-dichloroethene occurred when a

male rubber factory worker entered a vat containing rubber dissolved in 1,2-dichloroethene (Hamilton, 1934). Symptoms of toxicity, exposure concentration and duration, and isomeric composition of the vapor were not reported. No other data concerning human lethality from 1,2-dichloroethene exposure were located in the available literature.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Short-term inhalation experiments were conducted with "relatively" low concentrations of trans-dichloroethene (Lehmann and Schmidt-Kehl, 1936). Two doctoral candidates self-administered the chemical (as a vapor) in a well insulated 10 m^3 room. Using a manual sprayer and later a vaporizer (with attached oxygen tank), the chemical was uniformly distributed through the exposure chamber by means of fan and a ventilator. The concentration of trans-dichloroethene in the exposure chamber was determined analytically by determining the chlorine content in the gas mixture employing the “lime method” from which the dichloroethene content was then calculated. Both individuals were exposed simultaneously in the same room. They appeared to react very similarly. Experiments lasted for 5 to 30 minutes. Based on concentrations of trans-dichloroethene in inspired and expired air, the authors estimated that approximately 73% of the chemical was absorbed. Exposure parameters and effects are presented in Table 4.

TABLE 4. Inhalation Exposure of trans-1,2-Dichloroethene to Two Human Subjects

Concentration (ppm)	Time (min)	Effect
275	5	No effect
825	10	Slight dizziness after 5 min.
950	5	Slight burning of eyes
1000	30	Dizziness after 10 min.; slight burning of eyes
1200	10	Dizziness after 5 min.; drowsiness; initially, slight burning of eyes
1700	5	Dizziness after 3 min.; slight burning of eyes; intracranial pressure; nausea (symptoms persist for ½ h after exposure)
2200	5	Severe dizziness after 5 min; intracranial pressure; nausea (symptoms persist for ½ h after exposure)

[a]Lehmann and Schmidt-Kehl, 1936

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding human exposure to 1,2-dichloroethene were not available.

2.3. Developmental/Reproductive Toxicity

No developmental/reproductive toxicity data concerning 1,2-dichloroethene were identified in the available literature.

2.4. Genotoxicity

No data concerning the genotoxicity of 1,2-dichloroethene in humans were identified in the available literature.

2.5. Carcinogenicity

No data concerning the carcinogenicity of 1,2-dichloroethene in humans were identified in the available literature.

2.6. Summary

Only anecdotal data regarding human lethality from exposure to 1,2-dichloroethene were available, and exposure concentration, time and isomeric composition were not reported. Nonlethal exposure-response data suggest that 1,2-dichloroethene induces reversible neurological symptoms in humans. Exposures involved two human subjects exposed to concentrations of 275 to 2200 ppm trans-1,2-dichloroethene/m^3 for 5 to 30 minutes.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

Gradiski et al. (1978) reported a 6-hour LC_{50} of 21,723 ppm trans-1,2-dichloroethene for female OF1SPF mice; the cause of death was not reported.

Lehmann and Schmidt-Kehl (1936) exposed groups of three mice (sex and strain not specified) to cis-1,2-dichloroethene as follows: 65,000 mg/m^3 (16,250 ppm) for 140 min., 70,000 mg/m^3 (17,500 ppm) for 77 min., or 90,000 mg/m^3 (22,500 ppm) for 66 min. All of these mice died. In the same study, groups of three mice were also exposed to the trans- isomer as follows: 75,000 mg/m^3 (18,750 ppm) for 102 min., 80,000 mg/m^3 (20,000 ppm) for 95 min., 105,000 mg/m^3 (26,250 ppm) for 32 min., or 129,000 (32,250 ppm) mg/m^3 for 30 minutes (Table 10). All of these mice also died.

3.1.2. Rats

Groups of 5 male and 5 female Crl:CD (SD)BR rats were exposed to 12,300, 22,500, 28,100, or 34,100 ppm trans-1,2-dichloroethene or 12,100, 13,500, 15,700, or 23,200 ppm cis-1,2-dichloroethene for 4 hours in a 300 L stainless steel and glass chamber (Kelly, 1999). The test atmospheres were generated by metering liquid dichloroethene into a heated glass Instatherm flask with either a Fluid Metering pump or a Hamilton Syringe Drive. Nitrogen introduced into the flask swept the dichloroethene vapor into the air supply duct to the exposure chamber. The chamber concentration of dichloroethene was controlled by varying the amount of the metered liquid delivered to the evaporation flask. The chamber concentration of test substance was determined by gas chromatography at 15-minute intervals during each exposure. Chamber air-flow, temperature, and relative humidity were monitored continually. Liver, kidney, lung, and heart were examined histologically. The 4-hour LC_{50} value was 24,100 ppm for trans-1,2 dichloroethene and 13,700 ppm for cis-1,2-dichloroethene. Data are summarized in Table 5.

TABLE 5. Four-h Exposure of Rats to cis- and trans-1,2-Dichloroethene*			
Concentration (ppm)	**Mortality**	**Observations**	
trans-1,2-Dichloroethene			
		During Exposure**	**After Exposure**
12,300	0/10	Prostrate, decreased response followed by no response to alerting stimulus, normal response 30 min. after exposure	Normal weight gain
22,500	4/10	Prostrate, no response to alerting stimulus (recovery time not noted)	Lethargy, irregular respiration, slight weight loss one day followed by normal weight gain
28,100	7/10	Prostrate, no response to alerting stimulus (recovery time not noted)	Weakness, slight to severe weight loss one day followed by normal weight gain
34,100	10/10	Prostrate, no response to alerting stimulus	-
cis-1,2-Dichloroethene			
12,100	0/10	Prostrate, no response to alerting stimulus (recovery in 1 h post-exposure)	Normal weight gain rate
13,500	6/10	Prostrate, no response to alerting stimulus (recovery time not noted)	Weakness, irregular respiration, immediately after exposure, slight to severe weight loss one day followed by normal weight gain; centrilobular fatty liver changes (2/10)
15,700	10/10	Prostrate, no response to alerting stimulus	Centrilobular fatty liver changes (4/10)
23,200	10/10	Prostrate, no response to alerting stimulus	-

*Kelly, 1999. **Deaths occurred during exposure.

3.1.3. Cats

Cats (2/concentration) were exposed to cis-1,2-dichloroethene at concentrations ranging from 20,000 to 114,000 mg/m^3 (5000 to 28,500 ppm) for 9 to 360 minutes (Lehmann and Schmidt-Kehl, 1936). "Pure" chemical was obtained from I.G. Farben and was further purified by multiple fractionated distillations followed by boiling point measurements. Ambient air was suctioned from a 360 L exposure chamber utilizing a large gas valve which was rotated by means of a bucket wheel located in a water container on the same level as the valve. The experimental aerosol was produced by one of two methods: 1) either by passing a small stream of air through a Woulfsche flask containing a measured amount of chemical for a given time period and adding chemical by opening a burette or 2) by forcing a side air stream through a bulb tube containing the liquid dichloroethene and mixing with the main air stream. The concentration of dichloroethene in the exposure chambers was determined in one of two ways: (1) by dividing the evaporated portion of the chemical by the air volume over a specific time period or (2) analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Actual concentrations achieved ranged from 98.2% to 100.7% of the nominal concentrations, suggesting reliability and accuracy in the exposure concentrations. The mean experimental ventilation rate was 1050 L/hr. The exposures resulted in death at various times, ranging from 3 minutes to 7 days, after exposure. Details are presented in Table 9.

3.2. Nonlethal Toxicity

3.2.1. Cats

Fasted cats (2/experiment) were exposed to cis- or trans-1,2-dichloroethene vapors in a series of experiments (Lehmann and Schmidt-Kehl, 1936). "Pure" chemical was obtained from I.G. Farben and was further purified by multiple fractionated distillations followed by boiling point measurements. Ambient air was suctioned from a 360 L exposure chamber utilizing a large gas valve which was rotated by means of a bucket wheel located in a water container on the same level as the valve. The experimental aerosol was produced by one of two methods: 1) either by passing a small stream of air through a Woulfsche flask containing a measured amount of chemical for a given time period and adding chemical by opening a burette or 2) by forcing a side air stream through a bulb tube containing the liquid dichloroethene and mixing with the main air stream. The concentration of dichloroethene in the exposure chambers was determined in one of two ways: 1) by dividing the evaporated portion of the chemical by the air volume over a specific time period or 2) analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Actual concentrations achieved ranged from 98.2% to 100.7% of the nominal concentrations. The mean experimental ventilation rate was 1050 L/hr. Due to the variability in researchers, there were some inconsistencies in observations. Endpoints measured included equilibrium effects, lethargy, light narcosis, and deep narcosis. Effects on equilibrium were defined as swaying and difficulty in getting up and moving around. Lethargy was defined as the complete inability to move and was tested by gently lifting the head with a wooden rod. If the head fell back following removal of the rod, the cat was considered lethargic. Light narcosis was defined as the absence of extremity reflexes, and deep narcosis was defined as the absence of corneal and extremity reflexes. Also observed were irritating effects on mucous membranes (eyes, nose, mouth, salivary glands) and respiratory rate. The animals were observed for at least 8 days after exposure. Respiratory rates corresponding to lethargy, light narcosis, and deep narcosis were 61, 75, and 72 breaths/min, respectively, for the trans isomer; and 85, 99, and 92 breaths/min, respectively, for the cis isomer. Study design and observations are presented in Tables 6-9.

TABLE 6. Sublethal Effects in Cats Exposed to trans-1,2-Dichloroethene for 22-248 Min[a]

Concentration [mg/m^3 (ppm)]	Time (min)	Effects on Equilibrium (min[b])	Lethargy (min[b])	Light Narcosis (min[b])	Deep Narcosis (min[b])
72,000 (18,000)	348	7-8	37-43	320-340	330-345
86,400 (21,600)	213	4	22-23	152-157	206-210
110,000 (27,500)	75	3-5	8-9	20-21	69-70
147,000 (36,750)	23	1-3	5	7-9	14-18
189,200 (47,300)	22	1	3	5	12-13

[a]Lehmann and Schmidt-Kehl, 1936 Two animals/exposure (1 male and 1 female; or 2 males); body weight 2.05-4.05 kg

Symptoms of irritation (salivation, licking, sneezing, and eye blinking) occurred immediately and after several min.

Following deep narcosis, corneal reflexes returned after a few min to ½ h. One animal died (exposure not given).

[b]Time in min after initiation of exposure when effect was observed.

TABLE 7. Sublethal Effects in Cats Exposed to trans-1,2-Dichloroethene For 10-390 Min[a]

Concentration (mg/m^3 (ppm)	Time (min)	Effects on Equilibrium (min[b])	Lethargy (min[b])	Light Narcosis (min[b])	Deep Narcosis (min[b])
43,000 (10,750)	390	57-60	325-390	Absent	Absent
52,000 (13,000)	360	18-21	100-115(spasms)	Absent	Absent
97,000 (24,250)	163	19	18-19 (spasms)	Absent	No data
101,500 (26,250)	268	2-3	16-18 (spasms)	172-192 (spasms in 1 male)	238-268
117,000 (29,250)	188	Instantly-2 min.	3-10 (cough spasms)	27-83	178-188
129,000 (32,250)	129	3-4 (spasms)	6-14 (spasms)	40-100	87-158
136,000 (34,000)	136	No data	4-5	21-42	127-132
138,000 (34,500)	50	Immediately (1 male)	6-9	19-21 (spasms in 1 female)	49-50
158,500 (39,500)	15	No data	4-6	11-12	14-15 (spasms)
191,000 (47,750)	10	5	3-9 (spasms in 1 male)	7-10	9-12

[a]Lehmann and Schmidt-Kehl, 1936

Two cats/exposure (1 male and 1 female, or 2 males); body weight 2.1-4.5 kg.

Symptoms of irritation (salivation, licking, coughing, biting) occurred immediately and after several min. Vomiting occurred in 2 animals. Following deep narcosis, corneal and leg reflexes returned after a few min. Three animals died (exposure not given). Spasms (convulsions) affected extremities, chewing muscles, and diaphragm, but were not severe.

[b]Time after initiation of exposure when effect was observed.

TABLE 8. Sublethal Effects in Cats Exposed to cis-1,2-Dichloroethene for 17-288 Min

Concentration (mg/m^3 (ppm))	Time (min)	Effects on Equilibrium (min[b])	Lethargy (min[b])	Light Narcosis (min[b])	Deep Narcosis (min[b])
38,200 (9550)	288	60	121-165	238-265	246-285
39,600 (9900)	225	18-61	40-27	140-142	155-224
42,200 (10,500)	162	1 (1 male)	22-46	56-57	153-161
42,500 (10,625)	210	absent	43-65	55-65	141-210
50,600 (12,650)	117	2-6	13-22	32-35	72-114
56,300 (14,075)	66	5	14-17	25-26	64-66
61,400 (15,350)	26	3-5	12-15	16-19	24-25
76,000 (19,000)	24	5	10-11	13	16-19
100,000 (25,000)	17	2.5-5	7-8	9-10	12-13

[a]Lehmann and Schmidt-Kehl, 1936

Two cats/exposure (1 male and 1 female, or 2 males); body weight 2-3.2 kg.

Symptoms of irritation (salivation, licking, sneezing) occurred immediately and after several min. Vomiting occurred in 2 animals.

Following deep narcosis, corneal and leg reflexes returned after a few min, and ability to walk after a few min to ½ h. Three animals died (exposure not given).

[b]Time after initiation of exposure when effect was observed.

TABLE 9. Cats Exposed to cis-1,2-Dichloroethene for 9-360 Min[a]

Concentration [mg/m^3 (ppm)]	Time (min)	Effects on Equilibrium (min[b])	Lethargy (min[b])	Light Narcosis (min[b])	Deep Narcosis (min[b])
20,000 (5000)	360	120-180, head and leg spasms	Absent after 360 min	Absent after 360 min	Absent after 360 min, 1 died after 2 d
35,000 (8750)	234	120, Leg spasms	122-126	125-171, scratching	230-232,1 died
42,000 (10,500)	48	7	17	20	48, 1 died after 3 min
48,000 (12,000)	105	No data	12-44	15-68	27-104, 1 died after 1 d
49,000 (12,500)	122	7	37-69	72-88	90-121, 1 died after 5 d
53,000 (13,250)	118	8	17-30, spasms	21-60, restless, nystagmus	118-124,1 died after 2 d
62,000 (15,500)	49	6	10-17	4-20	12-48, both died on first d
64,000 (16,000)	37	No data	17-21	26	36-31
68,000 (17,000)	25	5, restless, scratching and biting	7-12, Leg spasms	17-22	21-23
77,000 (19,250)	25	Restless	6, spasms	8-9	13-24, 1 died after 7 d
98,000 (24,500)	20	3-5	8-10	11-18	12-20
114,000 (28,500)	9	No data	3-4	5	7-9, 1 died

[a]Lehmann and Schmidt-Kehl, 1936
Two cats/exposure (1 male and 1 female, or 2 males); only one male cat was exposed to 42 mg/L for 48 min; body weight 2.2-4.6 kg.
[b]Time after initiation of exposure when effect was observed

3.2.2. Rats

Groups of 6 female SPF Wistar rats (180-200 g) were given single 8-hour exposures to 0, 200, 1000, or 3000 ppm trans-1,2-dichloroethene vapors (Freundt et al., 1977). Experimental concentrations were monitored by gas chromatography, and were within 3% of the nominal concentrations. Animals were sacrificed immediately after the exposure period. The incidence of slight to severe fatty degeneration of hepatic lobules and Kupffer cells and pulmonary capillary hyperaemia and alveolar septum distention was increased in all treatment groups when compared to controls. Pneumonic infiltration and fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation were observed in animals in the 3000 ppm group. Decreased serum albumin, urea nitrogen, and alkaline phosphatase activity were observed in the 1000 ppm group after 8 hours of exposure; however, these effects are of questionable biological significance because none were outside the normal range for rats. Leukocyte counts were decreased after exposure to 200 ppm 1,2-dichloroethene for 8 hours, and a decreased erythrocyte count was observed in the 1000 ppm group after 8 hours. It should be noted that the results of this study are inconsistent with the total database for 1,2-dichloroethylene and results, especially the reported pathological changes, are of questionable toxicological significance.

In another study, Freundt and Macholz (1978) exposed groups of 10 female Wistar rats to 0, 200, 600, 1000, or 3000 ppm cis- or trans-1,2-dichloroethene for 8 hours. A statistically significant ($p<0.05$), dose-dependent increase in hexobarbital sleeping time and zoxazolamine paralysis time was observed in all treated groups, indicating decreased activity of the P-450 enzymes that normally metabolize these compounds. The effect was observed in animals exposed to both isomers; however, the effect was more severe in rats exposed to the cis- isomer.

Hurtt et al. (1993) exposed groups of 24 pregnant Crl:CD BR rats to 0, 2000, 6000, or 12,000 ppm trans-1,2-dichloroethene in 150 L square, pyramidal, stainless steel and glass exposure chambers 6 hours/day on days 7-16 of gestation. The test atmosphere was generated by vaporization of the dichloroethene from glass, gas-washing bottles placed in temperature-regulated water baths and the vaporized test material was swept into 3-neck glass mixing flasks. Filtered, conditioned dilution air was added to the mixing flasks at 30 L/min to sweep vapors into the exposure chamber. The chamber concentration of test substance was determined by gas chromatography at 30-minute intervals during each exposure. Chamber airflow, temperature, and relative humidity were monitored continually. Decreased body weight gain was observed in dams exposed to 12,000 ppm, and decreased maternal food consumption was observed in dams exposed to 6000 and 12,000 ppm. Narcotizing effects were observed in dams exposed to 6000 and 12,000 ppm. Signs of eye irritation were observed immediately following exposure(s). At 2000 ppm, 13/24 animals exhibited a clear ocular discharge and 3/24 exhibited periocular wetness. At 6000 ppm, 22/24 had ocular discharge and 17/24 had periocular wetness, and at 12,000 ppm all 24 dams showed both ocular discharge and periocular wetness. Alopecia, lethargy and salivation were observed in dams exposed to 12,000 ppm. An increase in the mean number of resorptions per litter was observed at 6000 and 12,000 ppm; however, the values were within historical control ranges. A decrease in mean combined female fetal weight was observed at 12,000 ppm. No other fetal effects were observed.

In a subchronic study, groups of 15 male and 15 female Crl:CD (SD)BR rats were exposed to 0, 200, 1000, or 4000 ppm trans-1,2-dichloroethene (99.9% pure) 6 hours/day, 5 days/week for 90 days in a 1400 L stainless steel and glass chamber (Kelly, 1998). The test atmospheres were generated by metering liquid dichloroethene into a heated glass Instatherm flask with either a Fluid Metering pump or a Hamilton Syringe Drive. Nitrogen introduced into the flask swept the dichloroethene vapor into the air supply duct to the exposure chamber. The chamber concentration of dichloroethene was controlled by varying the amount of the metered liquid delivered to the evaporation flask. The chamber concentration of test substance was determined by gas chromatography at 15-minute intervals during each exposure. Chamber airflow, temperature, and relative humidity were monitored continually. No treatment-related effects on body weight, body weight gain, food consumption, clinical signs, clinical chemistry, hematology, gross or microscopic pathology or liver cell proliferation were observed.

In a 14-week feeding study, groups of 10 male and 10 female F344/N rats were fed diets with microcapsules containing trans-1,2-dichloroethene (NTP, 2002). Dietary concentrations of 3125, 6250, 12,500, 25,000 and 50,000 ppm microencapsulated trans-1,2-dichloroethene resulted in average daily doses of 190, 380, 770, 1540, and 3210 mg/kg for male rats and 190, 395, 780, 1580, and 3245 for female rats. Groups of 10 rats/sex served as untreated and vehicle controls. There was no treatment-related mortality. Mean body weights of males in the 50,000 ppm group were decreased approximately 6% (p#0.01) compared to vehicle controls. On day 21 and at

week 14, there were slight decreases (p#0.05 or 0.01) in hematocrit values, hemoglobin concentrations, and erythrocyte counts in males and females in the 25,000 and 50,000 ppm groups. At week 14, these effects were also noted in males in the 6250 and 12,500 ppm groups. Liver weights were increased up to 10% (p#0.05 or 0.01) in females in the 6250 ppm group and higher compared to vehicle controls, and kidney weights were decreased approximately 22% (p#0.05) in males in the 25,000 and 50,000 ppm groups. No treatment-related gross or microscopic lesions were noted.

In another oral study, McCauley et al. (1995) administered cis-1,2-dichloroethene by gavage in corn oil to groups of 10 male and 10 female Sprague-Dawley rats. Doses were 1.0, 3.0, 10.0, and 22.0 mmol/kg/day for 14-days or 0.33, 1.00, 3.00, or 9.00 mmol/kg/day for 90-days. There were no treatment-related deaths or histopathlogical lesions noted. Increased relative liver weights (p#0.05) were noted in both sexes and all doses tested in the 14-day study (up to 19% increase) and at 1.0 mmol/kg and above in the 90-day study (up to 26% increase).

3.2.3. Mice

Three mice (sex not given)/experiment were exposed to either cis- or trans 1,2-dichloro-ethene vapors (Lehmann and Schmidt-Kehl, 1936). "Pure" chemical was obtained from I.G. Farben and was further purified by multiple fractionated distillations followed by boiling point measurements. Ambient air was suctioned from a 136 L exposure chamber utilizing a large gas valve which was rotated by means of a bucket wheel located in a water container on the same level as the valve. The experimental aerosol was produced by one of two methods: 1) either by passing a small stream of air through a Woulfsche flask containing a measured amount of chemical for a given time period and adding chemical by opening a burette or 2) by forcing a side air stream through a bulb tube containing the liquid dichloroethene and mixing with the main air stream. The concentration of dichloroethene in the exposure chambers was determined in one of two ways: 1) by dividing the evaporated portion of the chemical by the air volume over a specific time period or 2) analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Actual concentrations achieved ranged from 98.2% to 100.7% of the nominal concentrations. The mean experimental ventilation rate was 1050 L/hr. Observations included effects on equilibrium (described as swaying), lethargy (described as the inability to move), and loss of foot reflexes. Also observed were irritating effects on mucous membranes (eyes, nose, mouth, salivary glands) and respiratory rate. Data are summarized in Tables 10 and 11.

TABLE 10. Effects in Mice Exposed to cis-1,2-Dichloroethene for 66-150 Min[a]

Concentration [mg/m^3(ppm)]	Time (min)	Effects on Equilibrium (min[b])	Lethargy (min[b])	Loss of Reflex (min[b])	Death/Recovery
27,000 (6750)	150	13	91	86 (2 mice)	Recovery in 3-19 min
40,000 (10,000)	150	7	11	24	Recovery in 10 min
50,000 (12,500)	149	5	9	19	Recovery in 10 min
65,000 (16,250)	140	3	6	9	All died in 75-140 min
70,000 (17,500)	77	1	3	5	All died in 55-77 min
90,000 (22,500)	66	1	3	4	All died in 24-66 min

[a]Lehmann and Schmidt-Kehl, 1936
3 animals/exposure; sex not given; body weight 17-25 g; time at which effect occurred is average for 3 mice. At the beginning of exposure, the animals became restless and excited. After a few min, they assumed a side position which occurred almost simultaneously with a loss of reflexes at the higher concentrations. The respiratory rate was usually in the range of 150-180 breaths/minute, but occasionally reached as high as 300. Fewer spasms were seen in animals exposed to the cis isomer compared to the trans isomer. None of the animals that survived the exposure period, died later. Recovery occurred rapidly.
[b]Time after initiation of exposure when effect was observed

TABLE 11. Mice Exposed to trans-1,2-Dichloroethene for 30-155 Min[a]

Concentration (mg/m^3(ppm))	Time (min)	Effects on Equilibrium (min[b])	Decreased Activity, Lethargy (min[b])	Loss of Reflex (min[b])	Death/Recovery
45,000 (11,250)	155	19	115	155	Recovery in 5-10 min
50,000 (12,500)	135	15	110	119	Recovery in 5 min
58,000 (14,500)	110	14	48	94	Recovery in 10 min
67,000 (16,750)	132	10	20	57	Recovery in 25 min
75,000 (18,750)	102	10	18	44	All died in 121-142 min
80,000 (20,000)	95	5	9	19	All died in 66-92 min
105,000 (26,250)	32	4	8	16	All died in 21-32 min
129,000 (32,250)	30	3	6	11	All died in 11-28 min

[a]Lehmann and Schmidt-Kehl, 1936
3 Animals/exposure; sex not given; body weight 17-25 g; times at which effect occurred is average for 3 mice. There was no remarkable irritation of mucous membranes; initially the animals were quiet. Shortly before lethargy set in, spasmodic jumping and rapid respiration were observed. Cyanosis occurred during narcosis.
[b]Time after initiation of exposure when effect was observed.

In another study, DeCeaurriz et al. (1983) exposed groups of 10 male Swiss OF1 mice weighing 20 to 25 g to 0, 1582, 1720, 2194, or 2485 ppm 1,2-dichloroethene (99%) vapors for four hours. Differences in mean total duration of immobility between control and experimental groups were measured over a 3 minute period after exposure in a behavioral despair swimming test. Immobility was defined as cessation of struggling to get out of the water (suggesting pro-longation of escape-directed behavior). A dose-related decrease, ranging from 23 to 71%, in mean duration of immobility was observed in exposed animals when compared to controls. Data are summarized in Table 12.

In a 14-week feeding study, groups of 10 male and 10 female B6C3F1 mice were fed diets with microcapsules containing trans-1,2-dichloroethene (NTP, 2002). Dietary concentrations of 3125, 6250, 12,500, 25,000 and 50,000 ppm microencapsulated

trans-1,2-dichloroethene resulted in average daily doses of 480, 920, 1900, 3850, and 8065 mg/kg for male mice and 450, 915, 1830, 3760, and 7925 mg/kg for female mice. Groups of 10 mice/sex served as untreated and vehicle controls. There was no treatment-related mortality. Mean body weight gain of females in the 12,500, 25,000, and 50,000 ppm groups was decreased approximately 4-7% (p#0.01) compared to vehicle controls. There were no effects on hematology parameters or organ weights, and no treatment-related gross or microscopic lesions were noted.

3.3. Developmental/Reproductive Toxicity

Hurtt et al. (1993) exposed groups of 24 pregnant Crl:CD BR rats to 0, 2000, 6000, or 12,000 ppm trans-1,2-dichloroethene 6 hours/day on days 7-16 of gestation. This study was previously described in section 3.2.2. No other developmental/reproductive data concerning 1,2-dichloroethene were identified.

3.4. Genotoxicity

Neither trans-, cis- or cis-/trans- 1,2-dichloroethene were mutagenic in Salmonella typhimurium strains TA97 (cis-isomer only), TA98, TA100, TA1535, or TA1537, with or without metabolic activation (NTP, 2002; Mortelmans et al., 1986; Zeiger et al., 1988). In CHO cells in vitro, cis-1,2-dichloroethene induced Sister Chromatid Exchanges (SCEs) in the absence of metabolic activation; results were equivocal with S9. The cis-/trans- mixture induced increases in SCE frequency in cultured CHO cells with and without metabolic activation; however, the trans-isomer was negative in this assay (NTP, 2002). Neither isomer nor the isomeric mixture included chromosomal aberrations in CHO cells with or without metabolic activation (NTP, 2002). In vivo genotoxicity studies, trans-1,2-dichloroethene was negative in a mouse bone marrow chromosomal aberration assay (NTP, 2002; Cerna and Kypenova, 1977), in host-mediated gene mutation assays in Salmonella typhimurium and in gene mutation and gene conversion assays in Saccharomyces cerevisiae (Cerna and Kypenova, 1977; Cantelli-Forti and Bronzetti, 1988). Cis-1,2-dichloroethene was positive in a mouse bone marrow chromosomal aberration assay (Cerna and Kypenova, 1977), and in host-mediated gene mutation assays in Salmonella typhimurium and Saccharomyces cerevisiae (Cerna and Kypenova, 1977; Cantelli-Forti and Bronzetti, 1988). Results were equivocal for the cis-isomer in a gene conversion assay in Saccharomyces cerevisiae (Cerna and Kypenova, 1977; Cantelli-Forti and Bronzetti, 1988).

TABLE 12. Immobility in Mice Exposed to 1,2-Dichloroethene Vapors for 4 H[a]

Concentration [mg/m^3(ppm)]	Time (h)	Duration of Immobility (Sec."SE)		Percent Change from Control
		Control	Exposed	
6265 (1582)	4	79.2"10.0	60.6"7.4	-23
6811 (1720)	4	94.5"6.5	51.7"8.3**	-45
8776 (2194)	4	79.2"10.0	33.9"6.6**	-57
9840 (2485)	4	94.0"9.0	26.9"6.2**	-71

[a]DeCeaurriz et al. (1983)
**Significantly different from control, p<0.05.

3.5. Carcinogenicity

No data concerning the carcinogenicity of 1,2-dichloroethene were identified in the available literature.

3.6. Summary

Lethal toxicity data are limited. Four-hour LC_{50} values of 24,100 ppm trans-1,2-dichloroethene and 13,700 ppm cis-1,2-dichloroethene have been reported in rats. No-effect-levels for death for 4-hour exposures were 12,300 ppm for trans-1,2-dichloroethene and 12,100 ppm for cis-1,2-dichloroethene (Kelly, 1999). A 6-hour LC_{50} of 21,723 ppm trans-1,2-dichloroethene has been reported in OF1SPF mice (Gradiski et al., 1978). Also, deaths were observed, following a progression of narcotic effects, in both cats and mice exposed to various regimens of 1,2-dichloroethene (Lehmann and Schmidt-Kehl, 1936). Nonlethal toxicity data indicate that 1,2-dichloroethene has a narcotic effect and that the cis- isomer is more potent than the trans- isomer with respect to narcosis (Lehmann and Schmidt-Kehl, 1936). Narcotic observations indicated a progression from equilibrium effects, followed by lethargy, light narcosis (loss of limb reflex, maintenance of corneal reflex), finally deep narcosis (loss of corneal reflex), and in some cases, as indicated above, death. Narcotic effects were also observed in pregnant rats exposed to 6000 and 12,000 ppm trans-1,2-dichloroethene, and dose-related ocular irritation was observed in pregnant rats exposed to 2000, 6000, and 12,000 ppm. Decreased fetal weight was observed in offspring of these rats exposed to 12,000 ppm trans-1,2-dichloroethene (Hurtt et al., 1993). No treatment-related effects were noted in a 90-day study in rats repeatedly exposed to 4000 ppm trans-1,2-dichloroethene (Kelly, 1998).

4. SPECIAL CONSIDERATIONS

4.1. Absorption, Distribution, Metabolism and Disposition

Blood:air partition coefficients, as well as liquid:air and tissue: air partition coefficients for both cis- and trans-1,2-dichloroethene have been reported. The cis-1,2-dichloroethene blood:air partition coefficient was reported as 9.58 and the trans-1,2-dichloroethene blood:air partition coefficient as 6.04. Gargas et al. (1988; 1989) also determined liquid:air and tissue:air partition coefficients for both isomers using 0.9% saline, olive oil, rat blood, rat liver, rat muscle and rat fat tissue. The reported partition coefficients for cis-1,2-dichloroethene are: rat blood:air = 21.6; saline:air = 3.25; olive oil:air = 278; fat:air = 227, liver:air = 15.3, and muscle:air = 6.09. Partition coefficients for trans-1,2-dichloroethene were reported as follows: rat blood:air = 9.58; saline:air = 1.41; olive oil:air = 178; fat:air = 148, liver:air = 8.96, and muscle:air = 3.52. The higher blood:air partition coefficient of the cis-isomer compared with the trans-isomer is likely a major factor in the more rapid and more extensive uptake of the cis-isomer into the systemic circulation and in the greater narcotic potency of the cis-isomer.

No data were located concerning the distribution of cis- or trans-1,2-dichloroethene by any route in any species.

1,2-Dichloroethene is metabolized by the hepatic mixed function oxidase system; it binds to the active site of the cytochrome P450 isoform, CYP2E1, resulting in inhibition of its own metabolism (Costa and Ivanetich, 1982; Barton et al. 1995; Lilly et al., 1998 Hanioka et al., 1998). Both the cis- and trans- isomer are metabolized by CYP2E1 to an epoxide intermediate that covalently binds to proteins, forming S-methylcysteine amino acid adducts (NTP, 2002). The epoxide intermediate is then transformed to 2,2-dichloroacetaldehyde by spontaneous

rearrangement, which is then converted to 2,2-dichloroethanol and 2,2-dichloroacetate by cytolsolic and/or mitochondrial aldehyde and alcohol dehydrogenases (ATSDR, 1996; Costa and Ivanetich, 1982). The aldehyde formed from the cis- isomer yields primarily dichloroethanol with small concentrations of dichloroacetate, while the trans- isomer yields primarily dichloroacetate with only small amounts of dichloroethanol.

Cis-1,2-dichloroethene has a 4-fold greater rate of turnover in hepatic microsomes when compared to the trans- isomer. The elimination of 1,2 dichloroethene follows zero-order kinetics above the metabolic saturation point and first-order kinetics below the saturation point. The cis-isomer has been shown to have a higher rate of first-order clearance than the trans- isomer (ATSDR, 1996).

Inhalation pharmacokinetics were studied in male Wistar rats exposed to cis- or trans-1,2-dichloroethene using a closed inhalation chamber and analyzed with a nonphysiologically constrained, two-compartment model (Filser and Bolt, 1979). The zero-order V_{max} elimination rate for the cis-isomer was 0.67 mg/hour•kg, and the value for the trans-isomer was 2.4 mg/hour•kg. The authors suggested that the low maximal velocities were due to inactivation of CYP450 by reactive epoxy intermediates. Gargas et al. (1990) conducted a study to compensate for enzyme inhibition-resynthesis, and determined V_{max} values of 3 mg/hour•kg for the cis-isomer and 2.49 mg/hour•kg for the trans-isomer.

4.2. Mechanism of Toxicity

1,2-Dichloroethene metabolites modify the heme moiety of cytochrome P-450, resulting in loss of both cytochrome P-450 and heme. The modification may account for the in vivo and in vitro inhibition of metabolism of other cytochrome P-450 substrates by 1,2-dichloroethene. A suicide enzyme inhibition-resynthesis model has been used to describe the metabolism of 1,2-dichloroethene, meaning that the cytochrome P-450 may inactivate itself and enhance the toxicity of other xenobiotics detoxified by the mixed function oxidase system (Gargas et al., 1990). The CYP2E1-catalyzed oxidation of 1,2-dichloroethene to an epoxide, 2,2-dichloroacetaldehyde, and 2,2-dichloroethanol represents metabolic activation. Each of these metabolites is cytotoxic, and collectively, they may be responsible for the hepatic centrilobular fatty degeneration observed in animal studies after 1,2-dichloroethene administration (Kelly, 1999; Lehmann and Schmidt-Kehl, 1936). The more rapid and extensive metabolism of the cis-isomer and the more extensive production of dichloroethanol and its unstable predecessors from the cis-isomer are consistent with this isomer's greater ability to affect the liver (Kelly 1999).

At high concentrations, 1,2-dichloroethene possesses anesthetic properties similar to other chlorinated ethenes. Eger et al. (2001) identified a MAC (minimum alveolar concentration) of 0.0183"0.0031 per cent for trans-1,2-dichloroethene and a MAC of 0.0071"0.0006 per cent for cis-1,2-dichloroethene for induction of anesthesia in rats. These data suggest that the cis-isomer is approximately 2.5-times more potent than the trans-isomer with regard to anesthesia induction. Data presented in this document suggest that the cis- isomer is approximately twice as effective as the trans-isomer in producing narcosis and with regard to lethality. Kelly (1999) reported 4-hour LC_{50} rat values of 24,100 ppm and 13,700 ppm for trans- and cis-1,2-dichloroethene, respectively. Rats exposed to 12,300 ppm trans-1,2-dichloroethene recovered from a lack of stimulus response in approximately 30 minutes, whereas, rats exposed to 12,100 ppm of the cis- isomer took approximately 1 hour to recover from similar effects (Kelly, 1999).

In general, it took animals exposed to the trans- isomer 2 to 3 times longer to lose equilibrium than when exposed to the same concentration of the cis- isomer. For example, data in Tables 10 and 11 indicate that mice exposed to 50,000 mg/m^3 of the cis- isomer lost equilibrium in 5 minutes, whereas it took 15 minutes for mice exposed to the trans- isomer to lose equilibrium. Similarly, cats exposed to 53,000 mg/m^3 of the cis- isomer lost equilibrium in 8 minutes, whereas it took 18-21 minutes for cats exposed to 52,000 mg/m^3 of the trans- isomer to lose equilibrium (Data from Tables 7 and 9).

4.3. Other Relevant Information

4.3.1. Species Variability

Interspecies Variability

Trans-1,2-dichloroethene inhalation lethality data suggest little species variability between rats and mice. Gradiski et al. (1978) reported a 6-hour LC_{50} of 21,723 ppm for mice (however no experimental details were available for this study), and (Kelly, 1999) reported a 4-hour LC_{50} of 24,100 ppm for rats.

McCarty et al. (1991) have shown that for acute exposures the critical brain concentration of halocarbons required to produce a given level of narcosis is relatively constant across species.

Intraspecies Variability

de Jong and Eger (1975) compared the MAC (minimum alveolar concentration) of nine anesthetics required to induce adequate anesthesia in 50% (AD_{50}) or 95% (AD_{95}) of patients. The ratios of AD_{95}:AD_{50} ranged from 1.1 to 1.4, suggesting a steep concentration-response curve in the vapor concentration required to produce anesthesia.

Gregory et al.(1969) examined the MAC (minimum alveolar concentration) of halothane required to induce anesthesia in 8 age groups (0-0.5 years, 0.5-2.5 years, 2.5-6 years, 7-11 years, 12-18 years, 19-30 years, 31-55 years, and 70-96 years). The number of patients per age group ranged from 8 to 24. The MAC was found to be the highest in newborns (1.08%) and lowest in the elderly (0.64%). These data suggested relatively little intraspecies variability with regard to age.

Stevens et al. (1975) also found little variability with regard to age when comparing MAC of isoflurane required for anesthesia. The MAC were 1.28%"0.01 for age range 19-30 years, 1.15%"0.06 for age range 32-55 years, and 1.05%"0.05 for age over 55 years.

4.3.2. Unique Physicochemical Properties

1,2-Dichloroethene is highly flammable and will produce toxic fumes of hydrogen chloride when burning. It also forms explosive hazards when combined with metals and alloys, and will detonate by heat, impact, or friction when mixed with nitric acid (ATSDR, 1996).

4.3.3. Concurrent Exposure Issues

No information was located concerning exposure to 1,2-dichloroethene in conjunction with other chemicals that might be found concurrently in the workplace or environment. However, as previously described, 1,2-dichloroethene is metabolized by and may inhibit cytochrome P-450. Thus, 1,2-dichloroethene may potentiate the toxicity of compounds that are normally detoxified through cytochrome P-450 dependent metabolism and may antagonize the toxicity of compounds that are activated by cytochrome P-450. Ethanol in alcoholic beverages induces CYP2E1, and isozyme involved in the metabolic activation of 1,2-dichloroethene and other halocarbons, and thus may enhance the metabolic activation and increase liver toxicity of chlorinated hydrocarbons, including 1,2-dichloroethene. Also, as previously described in section 3.2.2, Freundt and Macholz (1978) observed prolonged hexobarbital sleeping time and zoxazolamine paralysis time in rats treated with 1,2-dichloroethene, suggesting that 1,2-dichloroethene may inhibit P-450 catalyzed detoxification of other chemicals.

4.4. Temporal Extrapolation

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). Data were unavailable for an empirical derivation of n in the equation, $C^n \times t = k$. In the absence of chemical specific data, an n of 3 will be applied to extrapolate to shorter time periods, and an n of 1 will be applied to extrapolate to longer time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Although use of an exponent 'n' of 1 for extrapolating from shorter-term to longer-term time points may often overestimate risks for volatile organic compounds (VOCs) (Bruckner et al., 2004), this approach is considered appropriate for 1,2-dichloroethylene. For most well-metabolized VOCs, such as trichloroethylene, blood concentrations rapidly attain near steady-state during inhalation exposures. As a consequence, adverse effects typically increase only modestly with time for the longer exposure periods (once steady-state is reached). However, cis- and trans-1,2-dichloroethylene are unique in that they are suicide inhibitors (the trans- isomer is a more potent suicide inhibitor than the cis-isomer) (Lilly et al., 1998). As a result, blood and brain concentrations of 1,2-dichloroethylene should continue to increase during prolonged exposures, rather than reaching near steady-state. It is the parent compounds are responsible for producing the CNS depression.

Furthermore, although Barton et al. (1995) published a model that was used to predict interactions between trans-1,2-dichloroethylene and other halocarbons, it has not been validated for humans; and thus was not used for time scaling of this chemical.

5. RATIONALE AND AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data indicate that a concentration of 275 ppm trans-1,2-dichloroethene for 5 minutes had no effect, a concentration of 825 ppm trans-1,2-dichloroethene caused slight dizziness after 5 minutes, and slight eye irritation was observed at a concentration of 950 ppm for 5 minutes (Lehmann and Schmidt-Kehl, 1936). The odor threshold is 17 ppm (ATSDR, 1996).

5.2. Animal Data Relevant to AEGL-1

Signs of dose-related ocular irritation were observed in pregnant rats exposed to 2000, 6000, and 12,000 trans-1,2-dichloroethene 6 hours/day during days 7-16 of gestation (Hurtt et al., 1993). The irritation was observed immediately following exposure(s). At 2000 ppm the ocular irritation was considered minor, and thus consistent with the definition of AEGL-1, because 13/24 animals exhibited clear eye discharge, but only 3/24 animals exhibited periocular wetness. If significant discharge were occurring, a greater number of animals would be expected to exhibit periocular wetness.

5.3. Derivation of AEGL-1

Since human data are available, they will be used to derive AEGL-1 values. The NOEL for eye irritation of 825 ppm was used as the point of departure (Lehmann and Schmidt-Kehl, 1936). This value was divided by an uncertainty factor of 3 to protect sensitive individuals and is considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set. (Using the full uncertainty factor of 10, yields an AEGL-1 value of 83 ppm; no effects were noted in humans exposed to 275 ppm). The values were held constant across the 10- and 30-minute, 1-, 4-, and 8-hour exposure time points since mild irritantancy is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect. The animal data previously described in this report (Section 4.2) suggest that the cis- isomer is approximately twice as toxic as the trans- isomer with regard to narcosis and lethality in experimental animals. Therefore, a modifying factor of 2 was applied in the derivation of the cis- isomer values only. Although the AEGL-1 point-of-departure is a NOEL for eye irritation, the use of the modifying factor is justified for the cis-isomer because slight dizziness, a possible mild narcotic effect, was noted at the concentration used as starting point for the derivation of the AEGL-1.

The values for AEGL-1 are given in Table 13 (trans-isomer) and Table 14 (cis-isomer).

TABLE 13. AEGL-1 for trans-1,2-Dichloroethene [ppm (mg/m^3)]

AEGL Level	10-min.	30-min.	1-h	4-h	8-h
AEGL-1	280 (1109)	280 (1109)	280 (1109)	280 (1109)	280 (1109)

TABLE 14. AEGL-1 for cis-1,2-Dichloroethene [ppm (mg/m^3)]

AEGL Level	10-min	30-min	1-h	4-h	8-h
AEGL-1	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)

6. RATIONALE AND AEGL-2

6.1. Human Data Relevant to AEGL-2

Human data indicate that a concentration of 1000 ppm trans-1,2-dichloroethene caused dizziness in two subjects after 10 minutes (Lehmann and Schmidt-Kehl, 1936). Higher

concentrations caused greater dizziness, drowsiness, burning of the eyes, intracranial pressure and nausea.

6.2. Animal Data Relevant to AEGL-2

Narcosis was observed in pregnant rats exposed to 6000 and 12,000 trans-1,2-dichloroethene 6 hours/day during days 7-16 of gestation (Hurtt et al., 1993). Cats exposed to 43,000 mg/m^3 (10,750 ppm) trans-1,2-dichloroethene exhibited effects on equilibrium after 57 minutes and lethargy after 325 minutes of exposure, while cats exposed to 20,000 mg/m^3 (5000 ppm) cis-1,2-dichloroethene exhibited head and leg spasms after 120 minutes (Lehmann and Schmidt-Kehl, 1936). Mice exposed to 45,000 mg/m^3 (11,250 ppm) trans-1,2-dichloroethene exhibited effects on equilibrium after 19 minutes, lethargy after 115 minutes, and loss of reflex after 155 minutes of exposure, while mice exposed to 27,000 mg/m^3 (6750 ppm) cis-1,2-dichloroethene exhibited effects on equilibrium after 13 minutes, lethargy after 91 minutes, and loss of reflex after 82 minutes of exposure (Lehmann and Schmidt-Kehl, 1936). The total exposure times of mice for the trans- and cis- isomers were 155 and 150 minutes, respectively. The trans- exposed mice recovered 5-10 minutes after the end of the exposure period, and the cis- exposed mice recovered within 3-19 minutes after exposure.

6.3. Derivation of AEGL-2

The narcosis observed in the well-conducted study of pregnant rats exposed to 6000 ppm of the trans- isomer was used to derive AEGL-2 values for the 4- and 8-hour time points. Uncertainty factors of 3 each (total UF=10) were applied for both inter- and intraspecies differences. The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975). This total uncertainty factor of 10 was applied for AEGL-2 values for both the cis- and trans-isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The 10-, 30-, and 60-minute values extrapolated with n=3 would be 1400 ppm for 10- and 30-minutes and 1100 ppm for 1-hour. However, these values are within the range of exposure times and concentrations in which healthy adult humans responded with symptoms reaching a level of severe dizziness (Lehmann and Schmidt-Kehl, 1936). Dizziness was seen in humans after exposure to 1000 ppm for 10 minutes, and the exposure lasted for 30 minutes. Therefore, the 10-minutes, 30-minutes, and 1-hour values were set as maximum exposure values of 1000 ppm for anesthetic effects in humans.

The animal data previously described in this report (Section 4.2) suggest that the cis-isomer is approximately twice as toxic than the trans- isomer with regard to narcosis and lethality in experimental animals. Therefore, a modifying factor of 2 was applied in the derivation of the cis- isomer values only.

The values for AEGL-2 are given in Table 15 (trans-isomer) and Table 16 (cis-isomer).

TABLE 15. AEGL-2 for trans-1,2-Dichloroethene [ppm (mg/m^3)]

AEGL Level	10-min.	30-min.	1-h	4-h	8-h
AEGL-2	1000 (3960)	1000 (3960)	1000 (3960)	690 (2724)	450 (1782)

TABLE 16. AEGL-2 for cis-1,2-Dichloroethene [ppm (mg/m^3)]

AEGL Level	10-min	30-min	1-h	4-h	8-h
AEGL-2	500 (1980)	500 (1980)	500 (1980)	340 (1346)	230 (911)

7. RATIONALE AND AEGL-3

7.1. Human Data Relevant to AEGL-3

Although there has been a report of a human fatality associated with accidental exposure to 1,2-dichloroethene, the exposure concentration and duration are not known (Hamilton, 1934). Dizziness, intracranial pressure and nausea were observed in two human subjects exposed to 1700 ppm trans-1,2-dichloroethene for 5 minutes (Lehmann and Schmidt-Kehl, 1936).

7.2. Animal Data Relevant to AEGL-3

Four-hour rat LC_{50} values of 24,100 ppm and 13,700 ppm were reported for trans- and cis-1,2-dichloroethene, respectively (Kelly, 1999). In the same study, no deaths were reported for 4-hour exposures at 12,300 ppm for the trans- isomer and at 12,100 ppm for the cis- isomer (Kelly, 1999). No histopathological changes were noted in the liver, heart, kidney, or lungs in any of the rats in the Kelly (1999) study. Exposure of cats to cis-1,2-dichloroethene at concentrations ranging from 5000 to 28,500 ppm for 9 to 360 minutes resulted in death at various times after exposure (Lehmann and Schmidt-Kehl, 1936). Varying degrees of equilibrium effects, lethargy, light narcosis, and/or deep narcosis were observed in cats prior to death. Decreases in combined and mean female fetal weight were observed in pregnant rats exposed to 12,000 ppm trans-1,2-dichloroethene for 6 hours/day on days 7-16 of gestation. In another study, female Wistar rats exhibited severe fatty degeneration of hepatic lobules and kupffer cells, pulmonary capillary hyperemia, alveolar septum distention, pneumonic infiltration, and fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation after exposure to 3000 ppm trans-1,2-dichloroethene for 8 hours (Freundt et al., 1977). However, these pathology data are contradicted by a recent study showing no treatment-related effects in rats exposed to up to 4000 ppm trans-1,2-dichloroethene 6 hours/day, 5 days/week for 90 days (Kelly, 1998).

7.3. Derivation of AEGL-3

The concentration (12,300 ppm) causing no death in rats exposed to trans-1,2-dichloroethene for 4 hours was used as the basis of AEGL-3 for the 4- and 8-hour time points. An uncertainty factor of 3 was applied for interspecies differences because rat and mouse

lethality data indicate little species variability with regard to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). An intraspecies UF of 3 was also applied and is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975). The total uncertainty factor of 10 was applied for AEGL-3 values for both the cis- and trans-isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The 10-, 30-, and 60-minute values extrapolated with n=3 are 3500, 2500, and 2000 ppm respectively. However, these values are within the range of exposure times and concentrations in which healthy humans responded with severe dizziness. Dizziness, intracranial pressure, and nausea were observed at 1700 ppm. Therefore, the 10-, 30-, and 60-minute values were set at 1700 ppm because healthy adult humans exposed for 5 minutes to 1700 ppm experienced dizziness, intracranial pressure (unspecified) and nausea which persisted for ½ hour after exposure (Lehmann and Schmidt-Kehl, 1936). Similar effects were seen with exposures of humans to 2200 ppm for 5 minutes which resulted in severe dizziness, intracranial pressure (unspecified) and nausea which persisted for ½ hour after exposure. The animal data previously described in this report (Section 4.2) suggest that the cis- isomer is approximately twice as toxic than the trans- isomer with regard to narcosis and lethality in experimental animals. Therefore, a modifying factor of 2 was applied in the derivation of the cis- isomer values only. (Although the concentration causing no death observed in the cis- isomer rat experiment could be used to derive AEGL-3 values for this isomer, the approach of dividing the trans- values by 2 was chosen to be consistent with the AEGL-1 and AEGL-2 derivations.).

The values for AEGL-3 are given in Table 17 (trans-isomer) and Table 18 (cis-isomer).

TABLE 17. AEGL-3 FOR trans-1,2-Dichloroethene [ppm (mg/m^3)]

AEGL Level	10-min	30-min	1-h	4-h	8-h
AEGL-3	1700 (6732)	1700 (6732)	1700 (6732)	1200 (4752)	620 (2455)

TABLE 18. AEGL-3 FOR cis-1,2-DICHLOROETHENE [ppm (mg/m^3)]

AEGL Level	10-min	30-min	1-h	4-h	8-h
AEGL-3	850 (3366)	850 (3366)	850 (3366)	620 (2455)	310 (1228)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 19 (trans- isomer) and Table 20 (cis- isomer). AEGL-1 values were based

on a NOEL for ocular irritation in humans. AEGL-2 values were based on narcosis in rats (4-and 8-hr) or anesthetic effects in humans (10-, 30-, and 60-min). AEGL-3 values were based on a no-effect-level for death in rats (4- and 8-hr) or dizziness, intracranial pressure, and nausea in humans (10-, 30-, and 60-min).

TABLE 19. Relational Comparison of AEGL Values For trans-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	280 (1109)	280 (1109)	280 (1109)	280 (1109)	280 (1109)
AEGL-2 (Disabling)	1000 (3960)	1000 (3960)	1000 (3960)	690 (2724)	450 (1782)
AEGL-3 (Lethality)	1700 (6732)	1700 (6732)	1700 (6732)	1200 (4752)	620 (2455)

TABLE 20. Relational Comparison of AEGL Values for cis-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)
AEGL-2 (Disabling)	500 (1980)	500 (1980)	500 (1980)	340 (1346)	230 (911)
AEGL-3 (Lethality)	850 (3366)	850 (3366)	850 (3366)	620 (2455)	310 (1228)

8.2. Other Exposure Criteria

TABLE 21. Extant Standards and Guidelines for 1,2-Dichloroethene

Guideline	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
	Trans-isomer				
AEGL-1	280 ppm	280 ppm	280 ppm	280 ppm	280 ppm
AEGL-2	1000 ppm	1000 ppm	1000 ppm	690 ppm	450 ppm
AEGL-3	1700 ppm	1700 ppm	1700 ppm	1200 ppm	620 ppm
	cis-isomer				
AEGL-1	140 ppm	140 ppm	140 ppm	140 ppm	140 ppm
AEGL-2	500 ppm	500 ppm	500 ppm	340 ppm	230 ppm
AEGL-3	850 ppm	850 ppm	850 ppm	620 ppm	310 ppm
NIOSH IDLH[a]	1000 ppm				
NIOSH REL[b]					200 ppm
OSHA PEL[c]					200 ppm
ACGIH TLV-TWA[d]					200 ppm
German MAK[e]					200 ppm
Dutch MAC[f]					200 ppm

[a] IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2003) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. The IDLH for 1,2-dichloroethene is based on acute inhalation toxicity data in humans.

[b]NIOSH REL (Recommended Exposure Limits) (NIOSH 2003) is defined analogous to the ACGIH TLV-TWA.

[c]OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (NIOSH 2003) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/wk.

[d]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2003) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e]MAK (Maximale rbeitsplatzkonzentration [Maximum Workplace Concentration]) DFG [Deutsche Forschungsgemeinschaft] (German Research Association) 2002 is defined analogous to the ACGIH-TLV-TWA.

[f]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000, is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Quality and Research Needs

Data from human studies are sparse. Exposure times are short-term, ranging from only 5 to 30 minutes. Furthermore, the only quantitative human data are from 1936, and although the study appears to be thorough and well described, it is likely that analytical measurements were not as precise as those used today. Data from animal studies are more abundant and encompass a wider range of exposure periods. More recent animal studies include greater numbers of experimental animals and almost certainly improved methodology.

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APPENDIX A: Time Scaling Calculations for 1,2-Dichloroethene

AEGL-1 for 1,2-Dichloroethene

Key Study: Lehmann and Schmidt-Kehl, 1936

Toxicity endpoint: 825 ppm, 5 min: NOEL for ocular irritation in humans

Scaling: None: values were held constant across time points

Uncertainty factors: 3 for intraspecies variability (trans- and cis-1,2-dichloroethene)

Modifying factor: 2 for differential isomer toxicity (cis-1,2-dichloroethene only)

10-, and 30-min, 1-, 4-, and 8-h AEGL-1

825 ppm) 3 = 275 ppm

trans-1,2-dichloroethene AEGL-1 = 280 ppm

cis-1,2-dichloroethene AEGL-1 = 280 ppm) 2 = 140 ppm

AEGL-2 for 1,2-Dichloroethene

Key Studies: Lehmann and Schmidt-Kehl, 1936 (10-, 30-, and 60-min)
Hurtt et al., 1993 (4- and 8-h)

Toxicity endpoints: Anesthetic effects in humans (10-, 30-, and 60-min)
Narcosis in rats (4- and 8-h)

Scaling: Maximum exposure level at 10-, 30-, and 60-min.
$(6000 \text{ ppm})^3 \times 6 \text{ h} = 1.3 \times 10^{12} \text{ ppm}^3\text{h}$ (4-h)
$(6000 \text{ ppm})^1 \times 6 \text{ h} = 36{,}000 \text{ ppm}^1\text{h}$ (8-h)

Uncertainty factors: 3 for intraspecies variability (trans- and cis-1,2-dichloroethene; 4- and 8-h)
3 for interspecies variability (trans- and cis-1,2-dichloroethene; 4- and 8-h)

Modifying factor: 2 for differential isomer toxicity (cis-1,2-dichloroethene only)

<u>10-, and 30-min, and 1-h AEGL-2</u>

trans-1,2-dichloroethene AEGL-2 = 1000 ppm

cis-1,2-dichloroethene AEGL-1 = 1000 ppm) 2 = 500 ppm

<u>4 h AEGL-2</u>

$C^3 \times 4 \text{ h} = 1.3 \times 10^{12} \text{ ppm}^3\text{hr}$
$C^3 = 3.25 \times 10^{11}$ ppm
C = 6875 ppm
4 h trans-1,2-dichloroethene AEGL-2= 6868 ppm/10 = 690 ppm

4 h cis-1,2-dichloroethene AEGL-2 = 6868 ppm/20 = 340 ppm

<u>8 h AEGL-2</u>

$C^1 \times 8 \text{ h} = 36{,}000 \text{ ppm}^1\text{hr}$
$C^1 = 4500$ ppm
C = 4500 ppm
8 h trans-1,2-dichloroethene AEGL-2 = 4500 ppm/10 = 450 ppm

8 h cis-1,2-dichloroethene AEGL-2 = 4500 ppm/20 = 230 ppm

AEGL-3 for 1,2-Dichloroethene

Key Studies: Lehmann and Schmidt-Kehl, 1936 (10-, 30-, and 60-min)
Kelly, 1999 (4- and 8-h)

Toxicity endpoint: Nausea, intracranial pressure, dizziness in humans (10-, 30-, and 60-min)
No-effect-level for death in rats (4- and 8-h)

Scaling: Maximum exposure level at 10-, 30-, and 60-min.
$(12{,}300\ ppm)^3 \times 4\ h = 7.44 \times 10^{12}\ ppm^3 \cdot h$ (4-h)
$(12{,}300\ ppm)^1 \times 4\ h = 49{,}200\ ppm \cdot h$ (8-h)

Uncertainty factors: 3 for intraspecies variability (trans- and cis-1,2-dichloroethene; 4- and 8-h)
3 for interspecies variability (trans- and cis-1,2-dichloroethene; 4- and 8-h)

Modifying factor: 2- for differential isomer toxicity (cis-1,2-dichloroethene only)

<u>10, and 30-min and 1-h AEGL-3</u>

trans-1,2-dichloroethene AEGL-3 = 1700 ppm

cis-1,2-dichloroethene AEGL-3 = 1700) 2 = 850 ppm

<u>4 h AEGL-3</u>

$C^3 \times 4\ h = 7.44 \times 10^{12}\ ppm^3 \cdot h$
$C^3 = 1.86 \times 10^{12}\ ppm$
$C = 12298\ ppm$
4 h trans-1,2-dichloroethene AEGL-3= 12298 ppm/10 = 1200 ppm

4 h cis-1,2-dichloroethene AEGL-3 = 12298 ppm/20 = 620 ppm

<u>8 h AEGL-3</u>

$C^1 \times 8\ h = 49{,}200\ ppm^3 \cdot h$
$C^1 = 6150\ ppm$
$C = 6150\ ppm$
8 h trans-1,2-dichloroethene AEGL-3 = 6150 ppm/10 = 620 ppm

8 h cis-1,2-dichloroethene AEGL-3 = 6150 ppm/20 = 310 ppm

APPENDIX B: Derivation Summary Tables for 1,2-Dichloroethene (trans-and cis- isomers)

ACUTE EXPOSURE GUIDELINES FOR 1,2-DICHLOROETHENE DERIVATION SUMMARY

AEGL-1 VALUES: trans 1,2-Dichloroethene				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
280 ppm	**280 ppm**	**280 ppm**	**280 ppm**	**280 ppm**

Key Reference: Lehmann, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116:9-268.

Test Species/Strain/Number: Human subjects/ 2

Exposure Route/Concentrations/Durations:
Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min

Effects:
275 ppm No effects (5 min. Total exposure)
825 ppm Slight dizziness after 5 min. (10 min. exposure); determinant for AEGL-1
950 ppm Slight burning of eyes (5 min.)
1000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure)
1200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)
1700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea (5 min exposure)
2200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)

Endpoint/Concentration/Rationale: 825 ppm for 5 min.; no effect level for eye irritation; odor present.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable, human data used.
Intraspecies: 3 - Considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set. (Utilizing the full uncertainty factor of 10, yields an AEGL-1 value of 83 ppm; no effects were noted in humans exposed to 275 ppm).

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment:
Not applicable; human data used

Time Scaling: Values were held constant across time since minor irritation is a threshold effect and is not likely to increase over time.

Data Quality and Research Needs:
Although the values developed are considered to be protective, data are sparse due to the exposure of only two subjects.

1

AEGL-2 VALUES: trans 1,2-Dichloroethene				
10 min	30 min	1-h	4 h	8 h
1000 ppm	1000 ppm	1000 ppm	690 ppm	450 ppm
Key Reference: Lehmann, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268. (10-, and 30-min and 1-h)			Key Reference: Hurtt, M.E., Valentine, R., and Alvarez, L. 1993. Developmental toxicity of inhaled *trans*-1,2-dichloroethylene in the rat. Fund. Appl. Toxicol. 20: 225-230. (4- and 8-h)	
Test Species/Strain/Number: Human subjects/ 2			Test Species/Strain/Number: rat/Crl:CD BR pregnant females/24/group	
Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min.			Exposure Route/Concentrations/Durations: 0, 2000, 6000, or 12,000 ppm, 6 h/d, d 7-16 of gestation	
Effects: 275 ppm No effects (5 min.) 825 ppm Slight dizziness after 5 min. 950 ppm Slight burning of eyes (5 min.) 1000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure) 1200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure) 1700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea 2200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)			Effects: 2000 ppm Clear ocular discharge (after single 6-h exposure) 6000 ppm Narcosis, ocular irritation (after single 6-h exposure) 12,00 ppm Ocular irritation, narcosis, lethargy, decreased body weight gain	
Endpoint/Concentration/Rationale: 1000 ppm for 10 min.; threshold for anesthetic effects			Endpoint/Concentration/Rationale: 6000 ppm, 6 h/narcosis	
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: Not applicable - human data used. Intraspecies:1 -threshold for anesthetic effect			Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 Intraspecies: 3 The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975).	
Time Scaling: held constant at threshold for anesthetic effects			Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (8-hr) or 3 (4-h)	
Data Quality and Research Needs: Although recent studies are well conducted, human and animal data are in apparent conflict.				

1

AEGL-3 VALUES: trans 1,2-Dichloroethene				
10 min	**30 min**	**1-h**	**4 h**	**8 h.**
1700 ppm	**1700 ppm**	**1700 ppm**	**1200 ppm**	**620 ppm**
Key Reference: Lehmann, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268. (10-,and 30-min and 1-h)			Key Reference: Kelly, D.P. 1999. *trans*-1,2-dichloroethylene and *cis*-1,2-dichloroethylene: inhalation median lethal concentration (LC_{50}) study in rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. Laboratory Project ID: DuPont-2806. (4-and 8-h)	
Test Species/Strain/Number: Human subjects/ 2			Test Species/Strain/Number: Rat/Crl:CD (SD)/5/sex/group	
Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min			Exposure Route/Concentrations/Durations: Inhalation/ 0, 12300, 22500, 28100, or 34100 ppm/4 hr	
Effects: 275 ppm No effects (5 min.) 825 ppm Slight dizziness after 5 min. 950 ppm Slight burning of eyes (5 min.) 1000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure) 1200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure) 1700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea 2200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)			Mortality: 12,300 ppm 0/10 22,500 ppm 4/10 28,100 ppm 7/10 34,100 ppm 10/10	
Endpoint/Concentration/Rationale: 1700 ppm for 3 min.; dizziness, intracranial pressure, nausea			Endpoint/Concentration/Rationale: 12300 ppm, 4 hr/ NOEL for death	
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies:Not applicable - human data used. Intraspecies 1 - conservative AEGL-3 endpoint			Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 Intraspecies: 3 An uncertainty factor of 3 was applied for interspecies differences because rat and mouse lethality data indicate little species variability with regard to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975).	
Time Scaling: Held constant across time points; conservative AEGL-3 endpoint			Time Scaling: $c^n \times t = k$, where the exponent,n, is the conservative default of 1 (8-hr) or 3 (4-h)	
Data Quality and Research Needs: Although recent studies are well conducted, human and animal data are in apparent conflict.				

1

AEGL-1 VALUES- cis 1,2-Dichloroethene				
10 min	**30 min**	**1 h**	**4 h.**	**8 h**
140 ppm	**140 ppm**	**140 ppm**	**140 ppm**	**140 ppm**

Key Reference: Lehman, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268.

Test Species/Strain/Number: Human subjects/ 2

Exposure Route/Concentrations/Durations:
Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm trans-isomer for 5-30 min

Effects:
- 275 ppm No effects (5 min Total exposure)
- 825 ppm Slight dizziness after 5 min (10 min. exposure); determinant for AEGL-1
- 950 ppm Slight burning of eyes (5 min)
- 1000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure)
- 1200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)
- 1700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea (5 min exposure)
- 2200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)

Endpoint/Concentration/Rationale: 825 ppm for 5 min.; no effect level for eye irritation; odor present.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable, human data used.
Intraspecies: 3 - considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set.

Modifying Factor:
2; differential isomer toxicity, the cis-isomer has been reported to be approximately twice as toxic as the trans isomer. Although the AEGL-1 point-of-departure is a NOEL for eye irritation, the use of the modifying factor is justified for the cis-isomer because slight dizziness, a possible mild narcotic effect, was noted at the concentration used as starting point for the derivation of the AEGL-1.

Animal to Human Dosimetric Adjustment: Not applicable; human data used

Time Scaling: Values were held constant across time since minor irritation is a threshold effect and is not likely to increase over time.

Data Quality and Research Needs:
Although the values developed are considered to be protective, data are sparse due to the exposure of only two subjects.

1

<table>
<tr><th colspan="5">AEGL-2 VALUES: cis 1,2-Dichloroethene</th></tr>
<tr><td>10 min.</td><td>30 min.</td><td>1-h</td><td>4 h</td><td>8 h</td></tr>
<tr><td>500 ppm</td><td>500 ppm</td><td>500 ppm</td><td>340 ppm</td><td>230 ppm</td></tr>
<tr><td colspan="3">Key Reference: Lehmann, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268. (10-, and 30-min and 1-h)</td><td colspan="2">Key Reference: Hurtt, M.E., Valentine, R., and Alvarez, L. 1993. Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat. Fund. Appl. Toxicol. 20: 225-230. (4-and 8-h)</td></tr>
<tr><td colspan="3">Test Species/Strain/Number:
Human subjects/ 2</td><td colspan="2">Test Species/Strain/Number:
rat/Crl:CD BR pregnant females/24/group</td></tr>
<tr><td colspan="3">Exposure Route/Concentrations/Durations:
Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min</td><td colspan="2">Exposure Route/Concentrations/Durations:
0, 2000, 6000, or 12,000 ppm, 6 h/d, d 7-16 of gestation</td></tr>
<tr><td colspan="3">Effects: (exposure to trans-isomer)
275 ppm No effects (5 min.)
825 ppm Slight dizziness after 5 min.
950 ppm Slight burning of eyes (5 min.)
1000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure)
1200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)
1700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea
2200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)</td><td colspan="2">Effects: (exposure to trans-isomer)
2000 ppm Clear ocular discharge (after single 6-h exposure)
6000 ppm Narcosis, ocular irritation (after single 6-h exposure)
12,00 ppm Ocular irritation, narcosis, lethargy, decreased body weight gain</td></tr>
<tr><td colspan="3">Endpoint/Concentration/Rationale:
1000 ppm for 10 min.; threshold for anesthetic effects</td><td colspan="2">Endpoint/Concentration/Rationale: 6000 ppm, 6 h/narcosis</td></tr>
<tr><td colspan="3">Uncertainty Factors/Rationale:
Total uncertainty factor: 1
Interspecies: Not applicable - human data used.
Intraspecies: 1 -threshold for anesthetic effect</td><td colspan="2">Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975).</td></tr>
<tr><td colspan="3">Modifying Factor: 2; differential isomer toxicity, the cis-isomer has been reported to be approximately twice as toxic as the trans isomer</td><td colspan="2">Modifying Factor: 2; differential isomer toxicity, the cis-isomer has been reported to be approximately twice as toxic as the trans isomer</td></tr>
<tr><td colspan="3">Time Scaling: held constant at threshold for anesthetic effects</td><td colspan="2">Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (8-h) or 3 (4-h)</td></tr>
<tr><td colspan="5">Data Quality and Research Needs:
Although recent studies are well conducted, human and animal data are in apparent conflict.</td></tr>
</table>

1

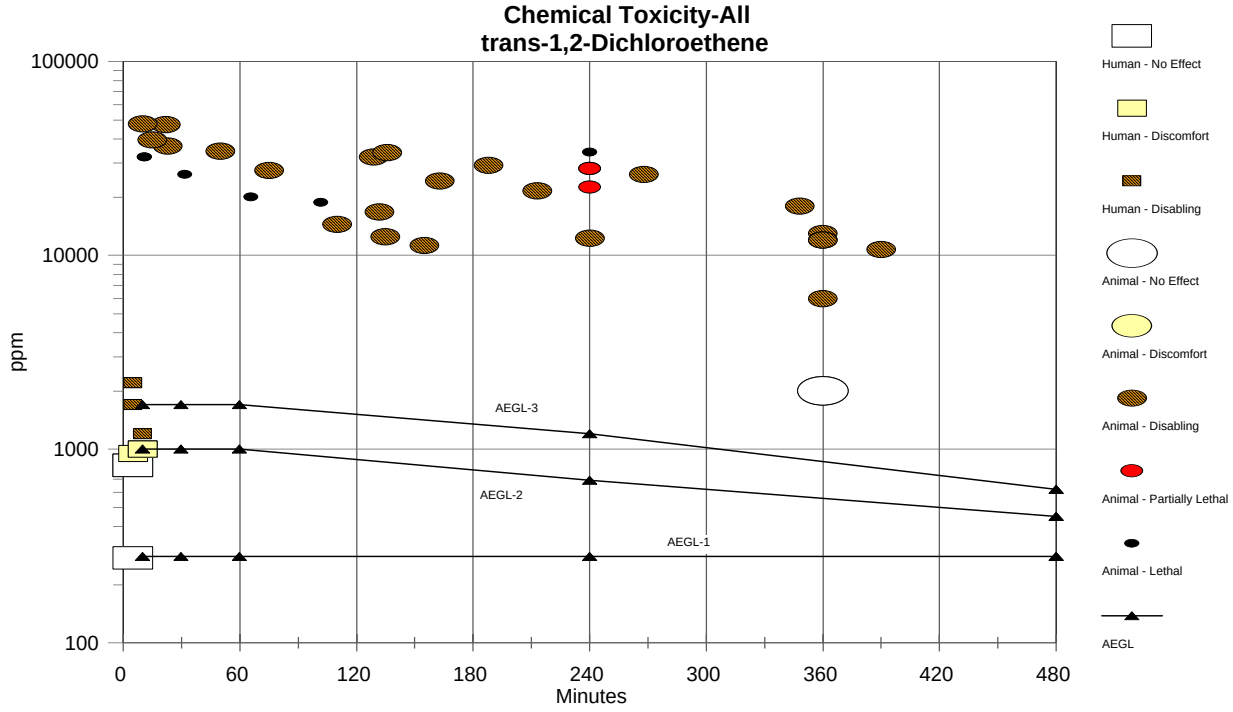
AEGL-3 VALUES: cis 1,2-Dichloroethene				
10 min	**30 min**	**1-h**	**4 h**	**8 h**
850 ppm	**850 ppm**	**850 ppm**	**620 ppm**	**310 ppm**
Key Reference: Lehmann, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268. (10-, and 30-min and 1-h)			Key Reference: Kelly, D.P. 1999. trans-1,2 dichloroethylene and cis-1,2 dichloroethylene: inhalation median lethal concentration (LC_{50}) study in rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. Laboratory Project ID: DuPont-2806. (4- and 8-h)	
Test Species/Strain/Number: Human subjects/ 2			Test Species/Strain/Number: rat/Crl:CD (SD)/5/sex/group	
Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min			Exposure Route/Concentrations/Durations: Inhalation/ 0, 12300, 22500, 28100, or 34100 ppm trans-isomer/4 h	
Effects: (exposure to trans-isomer) 275 ppm No effects (5 min.) 825 ppm Slight dizziness after 5 min. 950 ppm Slight burning of eyes (5 min.) 1000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure) 1200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure) 1700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea 2200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)			Mortality: (exposure to trans-isomer) 12,300 ppm 0/10 22,500 ppm 4/10 28,100 ppm 7/10 34,100 ppm 10/10	
Endpoint/Concentration/Rationale: 1700 ppm for 3 min.; dizziness, intracranial pressure, nausea			Endpoint/Concentration/Rationale: 12100 ppm, 4 hr/ NOEL for death	
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: Not applicable - human data used. Intraspecies: 1 - conservative AEGL-3 endpoint			Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3- Intraspecies: 3 An uncertainty factor of 3 was applied for interspecies differences because rat and mouse lethality data indicate little species variability with regard to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al., 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al., 1969; Stevens et al., 1975; deJong and Eger, 1975).	
Modifying Factor: 2; differential isomer toxicity, the cis-isomer has been reported to be approximately twice as toxic as the trans isomer			Modifying Factor: 2; differential isomer toxicity, the cis-isomer has been reported to be approximately twice as toxic as the trans isomer	
Time Scaling: held constant across time points; conservative AEGL-3 endpoint			Time Scaling: $c^n \times t = k$, where the exponent,n, is the conservative default of 1 (8-h) or 3 (4-h)	
Data Quality and Research Needs: Although recent studies are well conducted, human and animal data are in apparent conflict.				

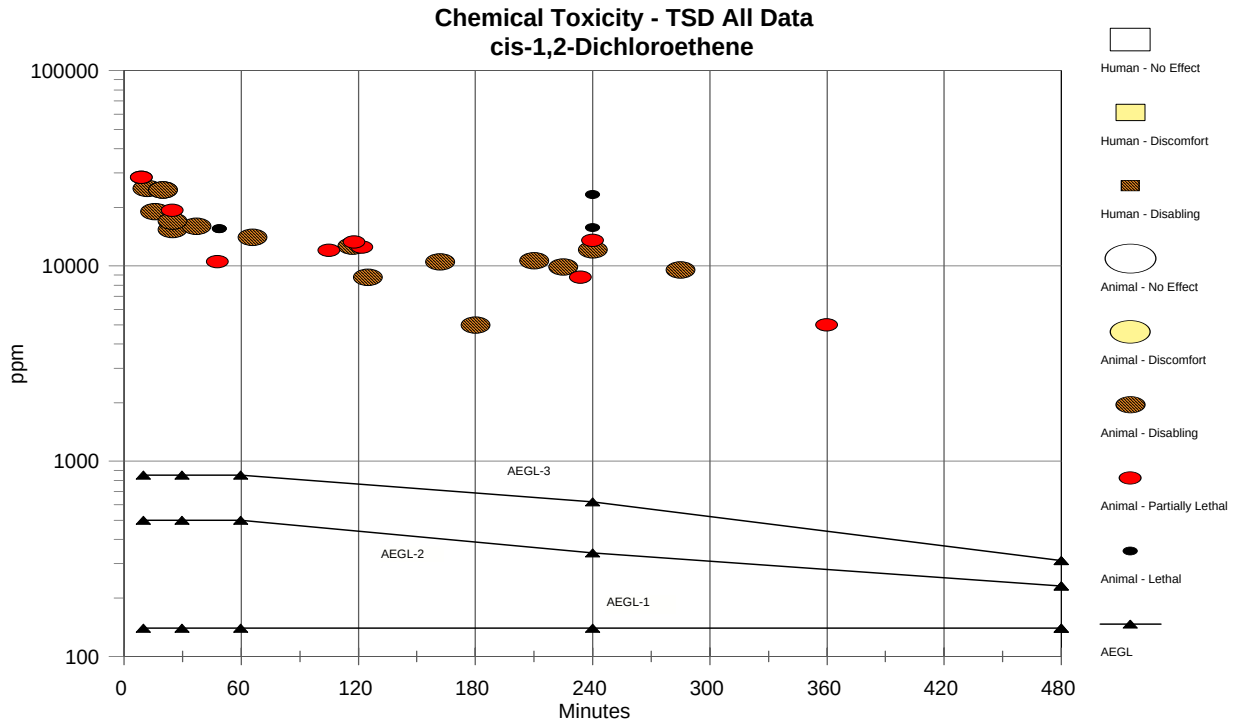
2

APPENDIX C: CATEGORY PLOTS

trans-1,2-Dichloroethene

cis-1,2-Dichloroethene




Chemical Toxicity - TSD All Data
cis-1,2-Dichloroethene
100000
10000
1000
100
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

1