ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
ALLYL CHLORIDE
107-05-1

C_3H_5Cl

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/m3]) 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/m3) 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/m3) 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

Allyl chloride is a yellow or purple industrially produced flammable liquid primarily used to manufacture epichlorohydrin and glycerol. Production facilities located in Europe, North and South America, China, and Japan produce 500-600 thousand tons per year. Allyl chloride is highly flammable and irritating to the skin and mucous membranes. The vapors are irritating to the eyes, nose, and throat. Respiratory irritation, delayed lung injury, kidney and liver injury can result from vapor exposure. Chronic exposures to allyl chloride may lead to neurotoxicity. Exposures to high concentrations of allyl chloride vapor can cause death (Kneupper and Saathoff 1993).

The AEGL-1 values are based on the sensory response experienced by an unknown number of unconditioned personnel during or following five minutes of exposure to allyl chloride (Shell Chemical Co. 1959). Exposure to 3-6 ppm did not cause respiratory, eye, or nose irritation. However, the garlic-like odor of allyl chloride could be detected at this concentration. At concentrations greater than 50 ppm, eye irritation occurred in half of the personnel. Nasal irritation and pulmonary discomfort occurred between 3 and 25 ppm in half of those tested. The authors stated that noticeable irritation of the sensory organs for most people occurred at concentrations ranging from 25-100 ppm. An estimate of the threshold of irritation was calculated by dividing 25 ppm by 3 to yield 8.3 ppm. An intraspecies uncertainty factor of 3 was applied instead of the default value of 10 because allyl chloride is a direct acting irritant and it would protect sensitive populations, those experiencing noticeable irritation below 25 ppm. An uncertainty factor of 10 would result in AEGL-1 values that are lower than concentrations humans have been exposed to with no irritation or physiological changes. Both Torkelson et al. (1959) and the Shell Chemical Co. (1959) reported that humans did not report irritation after being exposed to 3-6 ppm of allyl chloride for 1-5 minutes. An occupational study (Hausler and Lenich 1968) found that workers exposed to 0.5-36 ppm allyl chloride for 6 months had normal liver enzyme activity levels. An interspecies factor of 1 was applied because human data were used to derive AEGL-1 values. The AEGL-1 value was held constant across all exposure time points. That approach was considered appropriate because mild irritant effects generally do not vary greatly over time.

The AEGL-2 values are based on exposure data showing no incapacitating or irreversible effects. Slight eye closure and redness in male and female rats were observed at 300 ppm and females exhibited minimal reversible acute renal tubular degeneration. Complete recovery from irritation occurred at 18-hr postexposure. At the next highest concentration, 500 ppm, moderate eye closure and redness, lethargy, and reversible acute renal tubular degeneration were observed in both sexes, with recovery from irritation and lethargy occurring at 24-hr postexposure (Quast et al. 1982a). These data indicate that the female rat is more sensitive to allyl chloride. The point of departure was 300 ppm based on slight ocular irritation and reversible kidney lesions in female rats. A factor of 3 was used for interspecies uncertainty because allyl chloride is a direct-acting irritant, and data from the more sensitive sex and species (female rat) were used as the point of departure. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Female rats were more sensitive than male rats and mice of both sexes in terms of kidney toxicity which occurred at 300 ppm following a 6-hr exposure. Male rats experienced tubular degeneration at 500 ppm.

Female mice exposed for 6-hr to allyl chloride had reversible tubular degeneration at 800 ppm vs. 1000 ppm in male mice (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Human data did not provide quantitative exposure information, but it suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals. 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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, 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 (NRC 2001). According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NCR 2001), 10-minute values are not to be scaled from an experimental exposure time of greater than 4 hours. Therefore, the 30-minute value was also adopted as the 10-minute value.

The experimental concentration of 800 ppm was selected as the point of departure for AEGL-3 derivation as is was the highest concentration at which no lethality was observed in a rats during or following a 6-hr exposure. The benchmark concentration calculations of the rat data support this approach as the BMC_{01} was 792 ppm and the BMC_{05} was 855 ppm. Neither value was used because of the variability in the animal responses as observed in the standard deviation values of the BMC statistics. Benchmark concentration calculations for the mouse were not used because the data did not show a clear concentration-response compared to the rat data. However, the experimental mouse data support the point of departure because no lethality was observed in male or female mice at 800 ppm but was observed at the next highest concentration, 1000 ppm. A total uncertainty factor of 10 was applied to account for interspecies extrapolation and intraspecies variability. An uncertainty factor of 3 was applied for interspecies variability. Although the mechanism of action is unknown, allyl chloride is a direct-acting eye, nose, and respiratory tract irritant. That mode of action is not expected to differ across species, and the animal data support that claim. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Rats and mice experienced slight to severe eye closure and redness during and following exposures to 200-2000 ppm for 6-hr, with severity increasing with concentration (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Although human data did not provide quantitative exposure information, they suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals. 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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, 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 (NRC 2001). According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline

Levels for Hazardous Chemicals (NCR 2001), 10-minute values are not to be scaled from an experimental exposure time of greater than 4 hours. Therefore, the 30-minute value was also adopted as the 10-minute value.

The calculated values are listed in the table below.

TABLE 1. Summary of AEGL Values for Allyl Chloride

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1[a] (Notable Discomfort)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	Estimate of the threshold for irritation (Shell Chem. Co. 1959)
AEGL–2 (Disabling)	69 ppm (220 mg/m^3)	69 ppm (220 mg/m^3)	54 ppm (170 mg/m^3)	34 ppm (110 mg/m^3)	22 ppm (69 mg/m^3)	Highest concentration with no irreversible or incapacitating effects (Quast et al. 1982a)
AEGL–3 (Lethal)	180 ppm (560 mg/m^3)	180 ppm (560 mg/m^3)	140 ppm (440 mg/m^3)	90 ppm (280 mg/m^3)	60 ppm (190 mg/m^3)	Highest concentration with no lethality (Quast et al. 1982a)

[a] The odor threshold for the pungent garlic-like odor of allyl chloride ranges from 1.2 to 6 ppm. At this concentration, ~50% of the population will notice the distinct odor of chemical.

1. INTRODUCTION

Allyl chloride is an industrially produced liquid used as an intermediate in the manufacture of epichlorohydrin and glycerol. It is also used to synthesize allyl compounds including phenols and bisphenol A, agricultural chemicals, and thermosetting resins for varnishes, plastics, and adhesives (Kneupper and Saathoff 1993).

Allyl chloride does not occur in nature and is manufactured by hot chlorination (400-600ºC) of propylene in a 100% closed system. It is commercially produced in Europe (Germany, Sweden, Holland, Poland, and France) Japan, China, Brazil, and the United States. European production is estimated at 280,000 tons per year. The other countries listed produce an estimated 220-320,000 tons per year (Kneupper and Saathoff 1993). In the United States, allyl chloride is listed as a high production volume chemical (HSDB 2006).

Allyl chloride is highly flammable and irritating to the skin and mucous membranes. The vapors are irritating to the eyes, nose, and throat. Respiratory irritation, delayed lung injury, kidney and liver injury can result from vapor exposure. Exposures to high concentrations of allyl chloride vapor can cause death (Kneupper and Saathoff 1993).

TABLE 2. Allyl Chloride Chemical and Physical Properties

Parameter	Value	References
Synonyms	3-Chloropropene, 3-Chloro-1-propene, 3-chloropropylene, chlorallylene, 1-Chloro-2-propene	O'Neil et al. 2001, AIHA 2006
Chemical formula	C_3H_5Cl	O'Neil et al. 2001
Molecular weight	76.53	O'Neil et al. 2001
CAS Reg. No.	107-05-1	O'Neil et al. 2001
Physical state	Liquid- colorless, yellow, purple, brown, red	O'Neil et al. 2001, NIOSH 2005
Solubility in water	0.36 g/100 g water at 20ºC	ACGIH 1991
Vapor pressure	295 mmHg at 20ºC	AIHA 2006
Vapor density (air =1)	2.64	AIHA 2006
Melting point	-134.5ºC	O'Neil et al. 2001
Boiling point	45ºC	AIHA 2006
Flammability limits	Flash point (closed cup) -31.7ºC; Explosive limits: 3.3% to 11.2%	AIHA 2006
Conversion factors	1 ppm= 3.13 mg/m^3 1 mg/m^3= 0.32 ppm	AIHA 2006

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were located in the available literature.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

Allyl chloride has an irritating, unpleasant, and pungent odor, similar to garlic. The odor threshold ranges from 1.2 to 6 ppm. Torkelson et al. (1959) determined that 10 of 13 volunteers could detect a definite odor when exposed to 3 ppm for one to three minutes. Two or three volunteers entered a chamber and remained for a few minutes. When they left the chamber, each volunteer verbally reported to a tabulator. None reported irritation. The Shell Chemical Co. (1959) found that half of exposed personnel could detect an odor at 3-6 ppm when exposed for 5 minutes. All could detect the odor at 25 ppm. Half of unconditioned personnel had eye irritation between 50 and 100 ppm, and nose irritation and pulmonary discomfort at concentrations lower than 25 ppm. The authors stated that noticeable irritation of the sensory organs for most people occurred at concentrations ranging from 25-100 ppm. The Shell Chemical Co. (1959) did not report the number of people exposed. Amoore and Hautala (1983) lists the air odor threshold as 1.2 ± 2.5 ppm based on the geometric average of all available literature data except extreme and duplicate values. At the threshold limit concentration, 1 ppm, 10-50% of attentive persons would be able to detect that concentration in the air (Amoore and Hautala 1983).

2.2.2. Case Reports

He et al. (1985) reported a case of a 45-year old female employed 4 years as an operator at a factory where allyl chloride and sodium sulphite were used to create sodium allyl sulphonate. She began work in 1972 and upon initial exposure to allyl chloride, suffered lacrimation and chest tightness. The symptoms diminished over time. In September, 1976, she began to

experience tingling in her fingers and toes followed by weakness and cramping in both hands and legs. Two months later, she experienced difficulty walking long distances, gripping small objects, wringing out wet towels, and holding needles firmly. Her medical history, blood and urine chemistry, and physical examinations were normal. Neurological tests revealed bilateral loss of pain, touch, and vibration sensations of fingers and feet. Her finger flexors were moderately weak, tendon reflexes were reduced, and ankle reflexes were absent. In December, 1976, she entered the hospital and was treated with traditional Chinese medicines, vitamins B_1, B_6, and B_{12}, and coenzyme A. After the third week of treatment, steady improvement began. Sensory examinations were normal after 3 months of treatment, and by July, 1977, her ankle reflexes were present and the results of all examinations were normal. The peripheral neuropathy experienced by this worker cannot be attributed to only allyl chloride as the worker was exposed to multiple chemicals in addition to allyl chloride.

2.2.3. Occupational/Epidemiology Studies

2.2.3.1 Studies Noting General Health Effects or No Effects

Hausler and Lenich (1968) examined 45 men and 15 women who had worked in an allyl chloride manufacturing plant for 16 months. The measured concentration of allyl chloride in the plant ranged from 1-113 ppm in different areas. Daily exposure varied due to job functions and the areas in which workers spent their time was not reported. Twenty of the workers had a very strong garlic-like body and breath odor that decreased upon time away from the factory. It returned after one work shift (12 hr) in allyl chloride contaminated air. Some workers had increased liver enzyme activity levels, but it was not stated if the increases were significant or if the values were increased prior to this study. Nor was it reported if the workers with increased enzyme activity worked in specific areas of the plant. The plant was reconstructed and allyl chloride concentrations ranged from 0.5-36 ppm. The liver enzyme activity of the workers was examined 6 months later and “values were back in the normal range”.

Olsen et al. (1994) investigated the mortality experience of workers potentially exposed to epichlorohydrin and allyl chloride at a production plant to determine the cardiovascular effect of exposure. They examined records from the plant, including work history, industrial hygiene, and personal interviews. From the industrial hygiene data, they determined that allyl chloride exposures could have occurred in the glycerin department (1-5 ppm 8-hour time weighted average) and in the allyl chloride production plant (≥ 1 ppm 8-hour time weighted average). Respirator use was required in some jobs in the glycerin department reducing the potential exposure. A total of 1064 employees were included because they had worked a minimum of 1 month in an area of potential exposure between 1956 and 1986. They found no mortality trends that correlated with epichlorohydrin and allyl chloride exposure. The authors noted that the results were limited by the study size and low numbers of observed and expected deaths.

2.2.3.2 Studies Reporting Exposure Concentrations

Doyle and Bales (1977) measured allyl chloride in air samples at an epichlorohydrin production plant in Texas. Air samples were collected in glycerin unit #1 during the three work shifts over a period of five days. The samples were collected for the entire working shift or for the duration of the exposure. Allyl chloride concentrations ranged from non-detectable to 0.69 ppm. Actual worker exposures to the allyl chloride detected were expected to be lower because most jobs required use of organic vapor respirators.

Bales (1978) measured allyl chloride in air at two epichlorohydrin productions plants. Samples were collected over the eight-hr work shift during the three work shifts at each plant. In the chemical operators area, measured concentrations ranged from non-detectable to 0.68 at Plant A and non-detectable to 8.9 ppm at Plant B. The highest concentration (8.9 ppm) occurred once during an operational repair, but the worker wore a cartridge respirator during the repair, reducing the actual exposure level. In the production area, the highest concentrations were 0.3 ppm at Plant A and 0.2 ppm at Plant B. Because of the potential allyl chloride exposure, it was recommended that the plants explore methods to reduce process material losses.

Personal air samples from allyl chloride maintenance workers were measured by de Rooij et al. (1997). Breathing zone samples of 136 workers in an organo-chlorine production plant were taken during the work shift for a total of 205 workshifts. In the case of respirator use, the personal air sampler was placed outside of the respirator unit. The concentrations of allyl chloride detected in 86 shifts were below the Dutch 8-hour time weighted average occupational exposure limit of 1 ppm (3 mg/m^3). Thirteen of the shifts had concentrations that were higher, 1.06 to 5.44 ppm (3.3 to 17 mg/m^3). The range of concentrations for the three years combined was 0.032 to 5.44 ppm for shifts with no respirator use (99 shifts) and was 0.032 to 7.36 ppm (0.16 to 2.7 mg/m^3) for shifts with respirator use. Two high air concentrations (up to 62.4 ppm, 195 mg/m^3) were detected in 1992 during workshifts with respirator use.

2.3. Neurotoxicity

Workers at two separate factories where allyl chloride was used to manufacture sodium allyl sulfonate were examined and followed for exposure effects (He et al. 1985; He and Zhang 1985). Factory A began producing sodium allyl sulfonate in 1970 and stopped in 1977. Allyl chloride concentrations in the air were determined to be between 0.832 and 2128 ppm. Twenty-six female workers were examined in 1976 and ten of those examined in 1977 after exposure ceased. Exposures ranged from 2.5 months to 6 years. Factory B, built in 1978, had atmospheric allyl chloride concentrations ranging from 0.832 to 8.04 ppm. Twenty-seven workers (14 male and 13 female) were examined in 1982a. Exposures ranged from 1 year to 4.5 years. The workers completed questionnaires, physical and neurological examinations, and laboratory tests. Factory A workers reported lacrimation and sneezing at initial exposure which decreased as exposures continued. Within two months, most workers had weakness, tingling, and numbness in the distal part of the extremities. Two-thirds of the workers had symmetrical distal sensory deficits, distal muscular decrease, and diminished ankle reflexes. Axonal degeneration of peripheral nerves most likely caused denervation potentials observed in 10 of 19 Factory A workers. Workers of Factory B had similar but milder symptoms than those of Factory A workers. Thirteen workers from Factory B had polyphasic potentials and prolongation of the duration of the motor unit potentials without any denervation potentials. The results indicated that allyl chloride damaged the peripheral nervous system of occupationally exposed workers (He et al. 1985; He and Zhang 1985). Twenty-one of the subjects were clinically treated. They were removed from allyl chloride exposure and treated with various B vitamins, traditional Chinese medicines, acupuncture, and physiotherapy. Steady improvement began at 2 to 4 months and continued through and after 11 months of treatment He et al. (1985). These data are robust, however, the peripheral neuropathy cannot be attributed to only allyl chloride as the workers were exposed to multiple chemicals in addition to allyl chloride.

2.4. Developmental/Reproductive Toxicity

No data were located in the available literature.

2.5. Genotoxicity

Genotoxicity data in humans relevant to the derivation of AEGLs for allyl chloride were not available.

2.6. Carcinogenicity

Allyl chloride is classified as a possible human carcinogen in the US Environmental Protection Agency Integrated Risk Information System (USEPA 1994) based on forestomach tumors in female mice and positive results in genetic toxicity tests (Section 3.5). It is also based on the alkylating nature of allyl chloride and its structural similarities to probable human carcinogens. There are no human carcinogenicity data and no estimate of carcinogenic risk from inhalation exposure (USEPA 1994).

The International Agency for Research on Cancer (IARC) determined there is inadequate evidence in humans for the carcinogenicity of allyl chloride, and that allyl chloride is not classifiable as to its carcinogenicity to humans (IARC 1999).

2.7. Summary

Allyl chloride, an industrially produced liquid, has an irritating odor similar to garlic that can be detected by humans at ~3 ppm. Irritation does not occur at this concentration (Shell Chemical Co. 1959; Torkelson et al. 1959). Human exposure occurs mainly in the factory where it is manufactured. No lethal reports of allyl chloride poisoning have been located, but data from a case report of a non lethal exposure shows initial eye and upper respiratory tract irritation after a short term exposure (He et al. 1985). Workers begin to have garlic-like body and breath odor (Hausler and Lenich 1968) over time. Longer term exposures cause neurological effects on the fingers, arms, toes, feet, and legs. This is supported by reports of neurotoxicity studies of workers at allyl chloride plants. Based on these reports, repeated exposures (2.5 months-6 years) cause weakness, tingling, and numbness in the extremities, and axonal degeneration of peripheral nerves that can be reversed with treatment (He et al. 1985, He and Zhang 1985).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Adams et al. (1940) exposed groups of four or five albino rats one time to allyl chloride vapor to determine the shortest exposure producing 100% lethality in the groups. Rats were placed in either a 10-liter glass jar (two rats exposed for less than 1 hr) or a 154-liter glass-monel chamber (five rats exposed for 30 min or longer) and exposed to 290, 2900, 5800, 14500, or 29300 ppm for 15 min to 9 hr. Allyl chloride liquid (99.5% pure) was sprayed on the chamber sides and allyl chloride vapor was added to the flow of air entering the chamber by pump. The concentration was measured by output of the pump and air flow and checked by collection and

weighing the output. The output was reported to be constant. There were deaths at all concentrations as seen in Table 4. At 290 ppm, eye irritation, drowsiness, and unsteadiness were seen and death occurred within 24 hours. Eye and nose irritation increased with concentration and more rats begin to die during exposure. Unconsciousness occurred within 1 hr of being exposed to 29300 ppm followed shortly by death. Renal damage was observed in the rats consisting of tubular epithelium degeneration, distension of the lumina of the convoluted tubules, moderate congestion, and hemorrhage. The most severe damage was seen in animals exposed to low concentrations for longer periods of time. Pulmonary irritation was seen in the animals exposed to higher concentrations for shorter time periods. Marked congestion, alveolar hemorrhage, and interstitial edema were observed in these animals.

The LC_{50} for rats (n=6) exposed to 90-99% pure allyl chloride for 2 hr in a static inhalation chamber was determined to be 3520 ppm for male rats and 3776 ppm for female rats (Lu et al. 1982). Mean concentration of chamber air was determined from three air samples collected during each exposure analyzed by a gas chromatograph with a flame ionization detector. During exposure, the rats closed their eyes, pawed, and scratched their noses and mouths. Lacrimation and salivation were observed. Death occurred within 24-hr of exposure. Marked pulmonary congestion, hemorrhage, and edema were found in the lungs. Renal tubular degeneration, cloudy swelling, and focal necrosis of the glomeruli epithelium were also seen. There were also dilation of sinusoids and cloudy swelling of hepatocytes observed in the liver. The same effects were noted for rabbits, guinea pigs, mice, and cats. No other information regarding exposure concentrations was reported.

Fischer 344 rats (10/sex/group) were exposed to allyl chloride vapor for 6 hr (allyl chloride 99.8 weight percent) (Quast et al. 1982a). Exposure concentrations were 200, 300, 500, 800, 1000a or 2000 ppm. Groups of rats were also exposed to 1000 ppm allyl chloride from Dow (1000b)Chemical Company or Shell Chemical Company (1000c) to compare toxicological effects of allyl chloride produced by different companies. The exposures took place under dynamic air-flow conditions in a 160-liter glass and stainless steel chamber. The nominal concentration of vapor was calculated as the ratio of the rate of allyl chloride liquid dispensed to the rate of total chamber airflow. The analytical concentration was determined using a gas chromatograph. One male rat died 24-hr post exposure in the 1000 ppm group. One female died in the 1000b ppm group. The animals in these groups had severe palpebral closure and conjunctival hyperemia, nasal discharge, diarrhea, lethargy, and general unthrifty appearance. One male rat died in the 2000 ppm group 24-hr post exposure, and the remaining males were necropsied 48-hr post exposure due to lack of improvement from clinical signs of lethargy, unthrifty appearance, nasal discharge, and severe palpebral closure (eye closure) and conjunctival hyperemia (redness). All females died 24-hr post exposure in the 2000 ppm group. Two of those females died during exposure. The blood urea nitrogen levels in the animals necropsied at 24 hr were increased compared to control. Incidences of kidney changes suggestive of necrosis were increased in these rats. No toxicological differences were observed between allyl chloride produced by Dow Chemical Company and Shell Chemical Company. The calculated $BMCL_{05}$ and BMC_{01} for male and female rats combined were 855 ppm and 792 ppm, respectively.

3.1.2. Mice

The Shell Chemical Company (1959) reported the effects of inhaled allyl chloride on mice.

Twelve of twelve mice died within 24 hr of being exposed to 73,000 ppm for a single 10-min exposure. Nine of twelve died 8 to 47 hr after a single 10-min exposure to 49,266 ppm. Four of four mice died following a 60-min exposure to 1455 ppm with two of the four dying within 24 hr. Pulmonary hemorrhages in the lungs and pleural cavities and enlarged kidneys were observed. The LC_{50}s listed in the report include 24,633 for a 10-min exposure and 1455 ppm for a 60-min exposure. No other information is given in the report.

The LC_{50} for mice (n=10) exposed to allyl chloride in a static inhalation chamber for 2 hr was determined to be 3680 ppm (Lu et al. 1982). During exposure, the mice closed their eyes and pawed and scratched their nose and mouth. Lacrimation, salivation, hypoactivity, hypopnea, and paralysis of hind limbs were also observed. Death occurred within 24 hr of exposure. Marked pulmonary congestion, hemorrhage, and edema were observed in the lungs. Renal tubular degeneration, cloudy swelling, and focal necrosis of the glomeruli epithelium were also seen. There were also dilation of sinusoids and cloudy swelling of hepatocytes observed in the liver. The same effects were noted for rabbits, guinea pigs, cats, and rats. No other information regarding exposure concentrations was reported.

Quast et al. (1982a) exposed B6C3F1 mice to 500, 800, 1000a, 1200, or 2000 ppm allyl chloride for 6 hr. Ten male and female rats were exposed to each concentration. A group of mice were also exposed to 1000b ppm allyl chloride from the Shell Chemical Company. Half of each group was necropsied at 24 hr post exposure and the remaining mice necropsied at 72 hr post exposure. All male mice died in the 1000a pm group, one during exposure and nine 24-hr post exposure. Four females in the same group died 24-hr post exposure. In the Shell 1000b ppm group, eight males died and two females died 24-hr post exposure. In the 1200 ppm group two males died 24 hours post exposure, one male died 72-hours post exposure, and two females died 24-hr post exposure. All animals died in the 2000 ppm, three males and two females during exposure and seven males and eight females 24-hr post exposure. Mice exposed to 1000a, b ppm and 1200 ppm experienced moderate palpebral closure, lethargy, increased blood urea nitrogen levels, and generally unthrifty appearance. Severe palpebral closure and nasal discharge was observed in the animals exposed to 2000 ppm in addition to the other signs. Many mice exhibited kidneys with pale cortex with darker medullary junction. The calculated $BMCL_{05}$ and BMC_{01} were 666 and 696 ppm for females. The calculated $BMCL_{05}$ and BMC_{01} for male mice had P values less than 0.1 and were not reported.

3.1.3. Guinea Pigs

Adams et al. (1940) also exposed guinea pigs (4-5/group) in the same manner as the rats were exposed. However, the guinea pigs were exposed to 290, 2900, or 14500 ppm. There were deaths at all concentrations as seen in Table 4. At 290 ppm, 4 hr of exposure produced drowsiness, unsteadiness, eye irritation, and unconsciousness and death in all five animals within 24-hr. At 2900 ppm nose irritation was observed in addition to the previous signs but unconsciousness did not occur. At the highest concentration, eye and nose irritation, drowsiness, weakness, instability, and labored breathing were observed with death occurring within 24-hr at exposure durations greater than 0.5 hr. Renal damage was observed in the guinea pigs consisting of degeneration of the tubular epithelium, distension of the lumina of the convoluted tubules, moderate congestion, and hemorrhage. The most severe damage was seen in animals exposed to low concentrations for longer periods of time. Kidney damage was the most consistent and characteristic lesion observed. Pulmonary irritation was observed more in the animals exposed

to higher concentrations for shorter time periods. Marked congestion, alveolar hemorrhage, and interstitial edema were observed.

The LC_{50} for guinea pigs (n=4) exposed to allyl chloride in a static inhalation chamber for 2 hr was 1855 ppm (Lu et al. 1982). During exposure, the guinea pigs closed their eyes and pawed and scratched their nose and mouth. Lacrimation, salivation, drowsiness, unconsciousness, and convulsions were also observed. Death occurred within 24-hr of exposure. Marked pulmonary congestion, hemorrhage, and edema were observed in the lungs. Renal tubular degeneration, cloudy swelling, and focal necrosis of the glomeruli epithelium were also seen. There were also dilation of sinusoids and cloudy swelling of hepatocytes observed in the liver. The same effects were noted for rabbits, cats, mice, and rats. No other information regarding exposure concentrations was reported.

3.1.3. Rabbits

The LC_{50} for rabbits (n=2) exposed to allyl chloride for 2 hr in a static inhalation chamber was 7200 ppm (Lu et al. 1982). During exposure, rabbits closed their eyes and pawed and scratched their nose and mouth. Lacrimation, salivation, drowsiness, unconsciousness, and tremors were also observed. Death occurred within 24-hr of exposure. Marked pulmonary congestion, hemorrhage, and edema were observed in the lungs. Renal tubular degeneration, cloudy swelling, and focal necrosis of the glomeruli epithelium were also seen. There were also dilation of sinusoids and cloudy swelling of hepatocytes observed in the liver. The same effects were noted for cats, guinea pigs, mice, and rats. No other information regarding exposure concentrations was reported.

3.1.4. Cat

The LC_{50} for cats (n=2) exposed to allyl chloride for two hours in a static inhalation chamber was 3360 ppm (Lu et al. 1982). During exposure, the cats closed their eyes and pawed and scratched their nose and mouth. Lacrimation, salivation, drowsiness, hypoactivity, and convulsions were observed. The cats also had unsteady gait and ataxia. Death occurred within 24-hr of exposure. Marked pulmonary congestion, hemorrhage, and edema were observed in the lungs. Renal tubular degeneration, cloudy swelling, and focal necrosis of the glomeruli epithelium were also seen. There were also dilation of sinusoids and cloudy swelling of hepatocytes observed in the liver. The same effects were noted for rabbits, guinea pigs, mice, and rats. No other information regarding exposure concentrations was reported.

TABLE 3. Summary of LC_{50} Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time (hr)	Effect	Reference
Rat	3520 (male)	2	Eye and nose irritation, apnea, death within 24 hours	Lu et al. 1982[a]
Rat	3776 (female)	2	Eye and nose irritation, apnea, death within 24 hours	Lu et al. 1982
Mouse	1,455	1	Pulmonary hemorrhage	Shell Chem.Co. 1959[b]
Mouse	3680 (female)	2	Eye and nose irritation, hypoactivity, hypopnea, hind limbs paralysis	Lu et al. 1982
Mouse	24,633	0.16	Pulmonary hemorrhage	Shell Chem.Co. 1959
Guinea Pig	1856 (male)	2	Eye and nose irritation, lacrimation, salivation	Lu et al. 1982
Rabbit	7200	2	Eye and nose irritation, tremors, convulsions	Lu et al. 1982
Cat	3360	2	Eye and nose irritation, lacrimation, salivation, unconsciousness	Lu et al. 1982

[a] Lu et al. 1982- analytical concentrations
[b] Shell. Chem. Co 1959- no information provided on exposure methods

3.2. Nonlethal Toxicity

3.2.1. Rats

Adams et al. (1940) found that short exposures to allyl chloride vapor were not lethal to albino rats. Rats were placed in either a 10 liter glass jar (two rats) or a 154 liter glass-monel chamber (five rats) and exposed to 290, 2,900, 5,800, 14,500, or 29,300 ppm for 10 min to 3 hr and allowed to recover for 4 wk. Allyl chloride liquid (99.5% pure) was sprayed on the chamber sides and the vapor added to the flow of air entering the chamber. The concentration was measured by output of the pump and air flow and checked by collection and weighing the output. The output was reported to be constant. They determined that the animals were essentially normal. Slight to moderate fibrosis and scarring of the kidney and lungs were observed in the animals exposed to the highest concentrations.

Quast et al. (1982a) exposed Fischer 344 rats (10/sex/group) to 200, 300, 500, 800, 1000a, b (Dow), c (Shell), or 2000 ppm allyl chloride for 6 hr. The exposures took place in a 160 liter glass and stainless steel chamber. The nominal concentration of vapor was calculated as the ratio of the rate of allyl chloride liquid dispensed to the rate of total chamber airflow. The analytical concentration was determined using a gas chromatograph. Necropsies began 24-hr post exposure and were conducted at intervals until 168-hr post exposure. Rats were observed for clinical signs during exposure and recovery. In rats exposed to 800 ppm or less allyl chloride moderate to slight palpebral closure and conjunctival hyperemia were observed. No other signs were noted in rats exposed to 200 or 300 ppm. At 500 ppm and greater, diarrhea, lethargy, and decreased urine and feces were observed. Complete recovery from the observed effects of exposure occurred at 18-hr post exposure for the 200 and 300 ppm groups, 24-hour post exposure for the 500 and 800 ppm groups, and 72-hr post exposure for the 1000a ppm group. Minimal reversible acute renal tubular degeneration was noted in female rats at 300 ppm or

higher and in males at 500 ppm or higher.

3.2.2. Mice

Quast et al. (1982a) exposed B6C3F1 mice (10/sex/group) to 500, 800, 1000a, b (Shell), 1200, or 2000 ppm allyl chloride for 6 hr. The exposures took place in a 160 liter glass and stainless steel chamber. The nominal concentration of vapor was calculated as the ratio of the rate of allyl chloride liquid dispensed to the rate of total chamber airflow. The analytical concentration was determined using a gas chromatograph. Half of each group was necropsied at 24- and 72-hr post exposure. Slight to moderate palpebral closure was observed in mice exposed to 500 and 800 ppm. No other clinical signs were observed in these animals. Complete recovery from observed effects of exposure occurred at 18 and 24-hr post exposure for the 500 and 800 ppm groups, respectively. Females exposed to 1000a, b and 1200 ppm recovered by 24-hr post exposure. Males exposed to 1200 ppm recovered by 48-hr post exposure. Acute renal tubular degeneration (reversible) was observed in female mice at and above 800 ppm and in male mice at or above 1000 ppm.

3.2.3. Guinea Pigs

Adams et al. (1940) exposed guinea pigs (4-5) to allyl chloride vapor in the same manner as the rats were exposed and allowed the animals to recover for four weeks. Guinea pigs were exposed to 290, 2,900, or 14,500 ppm for 15 min to 3 hr. The animals were essentially normal. Slight to moderate fibrosis and scarring of the kidney and lungs were observed in the animals exposed to the highest concentrations.

TABLE 4. Summary of Acute Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time (hr)	Mortality (%)	Effect	Reference
Rat	290	2 3 4 6 7 8 9	0 0 20 20 0 100 100	Drowsiness, unsteadiness, eye irritation, unconsciousness, death within 24 hr	Adams et al. 1940[a]
Rat	2,900	0.5 1 2 2 3 4 4	0 0 80 66 100 100 100	Slight eye and nose irritation, increased death during exposure	Adams et al. 1940
Rat	5,800	0.5 1 2	0 20 100	Eye and nose irritation, drowsiness, death within 24 hr	Adams et al. 1940
Rat	14,500	0.5 1 1.25 1.25 2	0 80 100 100 100	Eye and nose irritation, drowsiness, weakness, instability, labored breathing, death within 24 hr	Adams et al. 1940
Rat	29,300	0.25 0.5 0.5 1	0 100 100 100	Eye and nose irritation, unconsciousness, death within a short time	Adams et al. 1940
Rat	200 300 500 800 1000a 1000b (Dow) 1000c (Shell) 2000	6 hr	0 0 0 0 10 5 0 55	Slight palpebral closure and conjunctival hyperemia; 500 and 800 ppm diarrhea, lethargy; female ≥ 300 ppm and males ≥ 500 ppm acute renal tubular degeneration, recoverable	Quast et al. 1982a[b]
Mouse	73,900	0.16	100	Pulmonary hemorrhage	Shell Chem. Co. 1959[c]
Mouse	500 800 1000 (Dow) 1000 (Shell) 1200 2000	6 hr	0 0 70 50 25 100	Slight to moderate palpebral closure; females 800 ppm acute renal tubular degeneration, recoverable	Quast et al. 1982a
Guinea Pig	290	1 2 4 6 9	0 20 100 100 100	Drowsiness, unsteadiness up to 4 hr; eye irritation, unconsciousness up to 6 hr; death within 24 hr	Adams et al. 1940
Guinea Pig	2,900	0.5 1 2	0 0 100	Slight eye and nose irritation in 2 hr; death after exposure	Adams et al. 1940
Guinea Pig	14,500	0.16 0.25 0.5 0.5 0.5	0 0 50 100 40	Eye and nose irritation, drowsiness, weakness, instability, labored breathing, death within 24 hr	Adams et al. 1940

		0.75 1	100 100		

[a] Nominal Concentrations
[b] Nominal and analytical concentrations
[c] No information provided on exposure methods

3.3. Repeat-Dose Studies

3.3.1. Dogs

Torkelson et al. (1959) exposed a male and female beagle dog to 3 ppm allyl chloride (high purity, analytical concentration) in a vault type stainless steel chamber having a volume of about 3,700 liters. The animals were exposed 7 hr/d, 5 d/wk for a total of 127 to 134 exposures in 180-194 days. The chamber atmosphere was monitored continuously. No treatment related effects were observed in either animal.

3.3.2. Rats

Torkelson et al. (1959) exposed five male and five female rats to 8 ppm allyl chloride for 7 hr/d, 5 d/wk during a 35-day period in a glass walled chamber having a 160-liter capacity. A second set of rats (24/sex/group) was exposed to 3 ppm allyl chloride 7 hr/d, 5 d/wk for a total of 127 to 134 exposures in 180-194 days. Some of these animals were sacrificed immediately after exposure and others were sacrificed following a two-month recovery period. The analytical concentration of the chamber air for the 8 ppm concentration ranged from 7.9-10 ppm with most air samples at 8-8.5 ppm. Air sample concentrations averaged 2.9 ppm with a range of 1.8-3.9 ppm for the 3 ppm exposure. At 8 ppm, female rats had lower spleen weights but nothing of note was found during histopathological examination. Both male and female rats displayed liver and kidney changes. The sinusoids of the liver were dilated, and there was cloudy swelling and focal necrosis. Necrosis of the epithelium and convoluted tubules and proliferation of the interstitial tissues were observed in the kidneys. In the animals exposed to 3 ppm, only the females sacrificed immediately after exposure displayed adverse effects. The livers of these females showed slight lobular degeneration. It was considered a reversible lesion because it was not observed in females rats sacrificed two months after the exposure.

CDF-Fischer 344 rats (10/sex/group) were exposed to 0, 1, 3, 10, or 20 ppm of allyl chloride for 6 hr/d, 5 d/wk except holidays for up to three months (Quast et al. 1982b). The exposure chambers were approximately 14.5 cubic meters in volume. Nominal concentrations were calculated daily and analytical concentration was determined using a gas chromatograph. Some animals were sacrificed after one month of exposure. Clinical observations, body weight, hematology, urinalysis, clinical chemistry, organ weight, gross pathology, and histopathologic examination of the tissues were evaluated. Exposure to allyl chloride did not result in treatment related changes of toxicologic significance. Statistically significant differences noted in the evaluated parameters of the male and female rats of the individual treatment groups were not consistent within the group or across dose groups or were within normal variability.

A 4-day probe and 90-day subchronic study was conducted in male and female Fischer 344 rats (Quast et al. 1982c). The 4-day probe exposed 10 rats/ sex to control and 250 ppm allyl chloride for 4 days. The animals were necropsied on day 5. Female rats exhibited increased relative and absolute liver and kidney weight. The weight increase was not supported by light microscopic examination or clinical chemistry. Histological examination of the tissues revealed

no changes in the liver. Minimal treatment-related effects were noted in the kidneys. There was a slight increase in eosinophilic staining of the cortical epithelial cells and an increase in the number of tubules showing focal collapse and atrophy. The 90-day study exposed 25 rats/sex for 6 hr/d, 5 d/wk to 0, 50, 100, or 250 ppm allyl chloride. Ten rats/sex were sacrificed after one month and the remaining animals were sacrificed at the end of the study. Male and female rats in the 100 and 250 ppm group displayed similar histopathologic kidney changes as the treated females from the 4-day probe study. Animals in the 250 ppm group had a higher number of focal collapsed tubules and atrophy. No other treatment related changes were observed.

3.3.3. Mice

The Shell Chemical Company (1959) reported the effects of allyl chloride on mice following repeated exposures. Concentrations ranging from 1455-2940 ppm were lethal to all mice after 4, 60 min exposures. Ten 60-min exposures to 129 ppm killed 2 of 4 mice. There were no signs in the animals that suggested discomfort or distress. All mice exposed to 129 ppm had pulmonary damage, liver injury, and slight changes in kidneys and spleen. No other details were reported.

B6C3F1 mice (10/sex/group) were exposed to 0, 1, 3, 10, or 20 ppm of allyl chloride for 6 hr/d, 5 d/wk except holidays for up to three months (Quast et al. 1982b). Some animals were sacrificed after one month of exposure. Clinical observations, body weight, hematology, clinical chemistry, organ weight, gross pathology, and histopathologic examination of the tissues were evaluated. No treatment related effects were noted in the parameters evaluated in the mice.

B6C3F1 mice were exposed to 250 ppm and 0, 50, 100, or 250 ppm allyl chloride in a 4-day probe and 90-day subchronic study, respectively (Quast et al. 1982c). Ten mice/sex were exposed to control or 250 ppm allyl chloride in the probe study and necropsied on day 5. Body weight of the males exposed to 250 ppm increased prior to day 5. No histological differences were discernible in the mice. The 90-day study exposed 25 mice/sex for 6 hr/d, 5 d/wk to 0, 50, 100, or 250 ppm allyl chloride. Ten mice/sex were sacrificed after one month and the remaining animals sacrificed at the end of the study. Body weights were not different in the mice during the 90-day study. Female mice exposed to 250 ppm had higher absolute and relative kidney weights, but no histological changes were observed. No other treatment related changes were observed.

3.3.4. Rabbits

Torkelson et al. (1959) exposed one female rabbit to 8 ppm and three male and three female rabbits to 3 ppm allyl chloride. The 28 exposures occurred 7 hr/d, 5 d/ wk to 8 ppm during a 35-day period and 127-134 exposures occurred 7 hr/d, 5 d/wk to 3 ppm during a 180-194 day period. The liver and kidney of the rabbit exposed to 8 ppm were severely affected by exposure. The liver exhibited cloudy swelling and focal necrosis, and necrosis of the epithelium and convoluted tubules were observed in the kidney. No treatment related effects were observed in the rabbits exposed to 3 ppm allyl chloride.

3.3.5. Guinea Pigs

Torkelson et al. (1959) exposed three male guinea pigs to 8 ppm and nine male and nine female guinea pigs to 3 ppm allyl chloride. The 28 exposures occurred 7 hr/d, 5 d/ wk to 8 ppm

during a 35-day period and 127-134 exposures occurred 7 hr/d, 5 d/ wk to 3 ppm during a 180-194 day period. The liver and kidneys of the animals exposed to 8 ppm were severely affected by exposure. Effects noted were cloudy swelling and focal necrosis of the liver and necrosis of the epithelium and convoluted tubules of the kidney. No treatment related effects were observed in the guinea pigs exposed to 3 ppm allyl chloride.

TABLE 5. Summary of Repeat-Dose Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure	Effect	Reference
Dog M, F	3	7 hr/d, 5 d/wk for 180-190 d	No effect	Torkelson et al. 1959
Rat 24 M, 24 F	3	7 hr/d, 5 d/wk for 180-194 d	Reversible hepatic lobular degeneration	Torkelson et al. 1959
Rat 5 M, 5 F	8	7 hr/d, 5 d/wk for 35 d	Hepatic sinusoid dilation, focal necrosis, cloudy swelling; renal tubule epithelium necrosis	Torkelson et al. 1959
Rat 10 M, 10 F	1 3 10 20	6 hr/d, 5 d/wk for up to 3 months	No effect	Quast et al. 1982b
Rat 10 M, 10 F	250	6 hr/d for 4 d	Kidney- increased cytoplasmic granularity and eosinophilic staining of cortical epithelial cells	Quast et al. 1982c
Rat 25 M, 25 F	50 100 250	6 hr/d, 5 d/wk for 90 d	250 ppm- focal tubule collapse and atrophy	Quast et al. 1982c
Mouse	1455-2940	1 hr repeated 4 times	100% mortality	Shell Chemical Co. 1959
Mouse	129	1 hr repeated 10 times	50% mortality; pulmonary damage, liver injury	Shell Chemical Co. 1959
Mouse 10 M, 10 F	250	6 hr/d for 4 d	No effect	Quast et al. 1982c
Mouse 25 M, 25 F	50 100 250	6 hr/d, 5 d/wk for 90 d	250 ppm- focal tubule collapse and atrophy	Quast et al. 1982c
Rabbit 1 F	3	7 hr/d, 5 d/wk for 35 d	No effect	Torkelson et al. 1959
Rabbit 3 M, 3 F	8	7 hr/d, 5 d/wk for 180-194 d	Hepatic focal necrosis, cloudy swelling; necrosis of epithelium and convoluted tubules of kidney	Torkelson et al. 1959
Guinea Pig 3 M	3	7 hr/d, 5 d/wk for 35 d	No effect	Torkelson et al. 1959
Guinea Pig 9 M, 9 F	8	7 hr/d, 5 d/wk for 180-194 d	Hepatic focal necrosis, cloudy swelling; necrosis of epithelium and convoluted tubules of kidney	Torkelson et al. 1959

3.4. Developmental/Reproductive Toxicity

Pregnant Sprague-Dawley rats (25-39) and New Zealand white rabbits (20-25) were exposed to 98.6% pure allyl chloride (John et al. 1983). The animals were exposed to 30 or 300 ppm allyl chloride (98.6% pure) for seven hours a day on gestation days 6-15 (rats) or 6-18 (rabbits). Animals were exposed in 4.3 cubic meter glass and stainless steel chambers where analytical

concentrations were measured by spectrophotometry. Animals were observed daily and underwent Cesarean section on day 21 (rat) or day 29 (rabbit). Rat dams did not gain as much weight as control dams during the first two exposure days, and dams exposed to 300 ppm had higher absolute liver and kidney weights. Rabbits exposed to 300 ppm gained less weight from days 6-9 of gestation and had higher liver weight. There was a slight delay in skeletal development in rat embryos but no other effects were observed. The authors determined that no teratogenic effects were caused by allyl chloride inhalation exposure in rats or rabbits.

3.5. Genotoxicity

McCoy et al. (1978) found that allyl chloride exhibited genetic activity for *Salmonella typhimurium* TA100 and TA1535 and DNA-modifying activity for *E.coli*. The authors modified the procedure to minimize loss of allyl chloride vapor by using filter discs impregnated with the test agent and sealing the agar plates in plastic bags. There was an increase in revertants, 1.4-fold in TA100 and 1.8-fold in TA1535 in plates without S9. Addition of S9 did not increase mutagenic activity. Allyl chloride inhibited the growth of Pol A1- strain of *E. coli* indicating DNA-modifying activity, and induced gene conversion in *Saccharomyces cerevisiae*. The DNA and gene conversion experiments were conducted in closed systems which greatly reduced evaporation.

3.6. Chronic Toxicity/Carcinogenicity

Strain A mice (10/sex/group) were injected (IP) with allyl chloride to determine if it would induce lung tumors (Theiss et al. 1979). The 0.65, 1.6, and 3.2 mmol/kg doses were injected three times a week for a total of 24 weeks. The lungs of the mice were examined to determine if pulmonary adenomas were induced. Only mice exposed to 3.2 mmol/kg produced a pulmonary adenoma response significant at the 5% level indicating borderline tumorigenicity.

Van Duuren et al. (1979) exposed Ha: ICR Swiss mice to a single dermal application of allyl chloride to test its carcinogenicity. The tumor promoter phorbol myristyl acetate was applied 14 days after allyl chloride. It was applied three times a week for 428-576 days depending on survival. A significant incidence of skin tumors was caused by allyl chloride exposure.

Neudecker et al. (1980) examined the mutagenic properties of halogen and alkyl substituted allyl and allylic compounds in *Salmonella typhimurium* (TA 100) with and without S9 activation mix. Allyl chloride had weak direct mutagenicity which was decreased in the presence of S9 mix. The vinylic chloroolefines and non-allylic isomers tested were not mutagenic without the presence of the S9 mix. Monomethylated and bimethylated allylic chlorides were directly mutagenic, but the activity decreased in the presence of S9.

The limited data for carcinogenicity of allyl chloride in laboratory animals are suggestive of carcinogenicity, but inadequacies in the data limit interpretation (USEPA 1994). However, the alkylating nature of allyl chloride and its epoxide, epichlorohydrin- a probable human carcinogen, support its carcinogenicity.

IARC determined that there is inadequate evidence for the carcinogenicity of allyl chloride in experimental animals (IARC 1999).

3.7. Summary

The effects of acute inhalation exposure of laboratory animals to allyl chloride are described in the above section and Tables 3-4. Repeat dose studies are also listed above and in Table 6. Allyl chloride exposure causes eye, nose, and respiratory tract irritation, depressed activity, renal tubular degeneration, and/or death. Death following acute exposure appeared to be caused by pulmonary hemorrhage, congestion, and edema. Allyl chloride does not appear to cause reproductive or developmental toxicity and its ability to cause cancer is questionable. The data regarding mortality after acute exposure is conflicting with Adams et al. (1940) reporting death in rats and guinea pigs at 290 ppm (2 hr or greater exposure duration) and higher and Quast et al. (1982a) reporting death in rats and mice at 1000 ppm (following 6-hr exposure). Adams et al. (1940) reported nominal concentrations, and the chamber atmosphere was generated by spraying the chamber with allyl chloride liquid and pumping allyl chloride air into the chamber. For exposures shorter than an hour, two animals at a time were placed into a 10 L glass jar and the method of atmosphere generation was not reported. The reliability of the concentrations reported by Adams et al. (1940) is questionable. The data can be used to support effects reported by more reliable studies. This conflict continues in repeat dose studies with Torkelson et al. (1959) finding hepatic and renal lesions in rats, guinea pigs, and rabbits after exposure to 8 ppm for 35 days, but Quast et al. (1982b) discovering no effects in rats exposed to up to 20 ppm for 3 months. The Quast et al. (1982b) and Torkelson et al. (1959) studies are of better quality than the Adams et al. (1940) study. Quast et al. (1982b) suggested the discrepancies could be the result of strain differences, better vapor generating and analytical capabilities, or greater purity of the sample. The reviewer does not have an explanation for the differences between the Torkelson et al. (1959) and Quast et al. (1982b) results.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Van Duuren et al. (1979) suggested that allyl chloride is converted to epichlorohydrin via epoxidation which is oxidized to glycidol and glycidaldehyde.

Male albino rats (137) were given 1 ml allyl chloride solution (12.7 grams total) by subcutaneous injection and urine and bile were collected for 48 hours after injection (Kaye et al. 1972). Urine and bile were also collected for 24 hours prior to injection. Allylmercapturic acid and 2- or 3-hydroxypropyl-mercapturic acid were detected in the urine by chromatograph. *S*-allylglutathione, *S*-allyl-L-cysteine, and allylmercapturic acid were detected in the bile. These results suggested the conjugation of allyl chloride with glutathione.

Allyl mercapturic acid was detected in the urine of male Wistar rats 24 hours after intraperitoneal injection with 5, 15, 25, 35, or 45 mg/kg allyl chloride. It was the major metabolite detected. Two minor metabolites, 3-chloro-2-hydroxypropyl mercapturic acid and α-chlorohydrin, were also detected in the urine. These metabolites suggested the formation of epichlorohydrin from allyl chloride *in vivo* (de Rooij et al. 1996).

The use of urinary mercapturic acids as biomarkers for human allyl chloride exposure was investigated by de Rooij et al. (1997). Male workers volunteered to take part in the study after being informed about the aim, procedure, and potential outcome of the study. The study was conducted during the annual periods in 1991, 1992, and 1993 when no allyl chloride was being

produced, but cleaning and maintenance of the allyl chloride productions installations occurred. None of the workers were involved in the study for two or three consecutive years. Urine samples were taken from the workers before the beginning of the shift and at the end of the shift. Breathing zone samples of 136 workers in an organo-chlorine production plant which produced allyl chloride were taken during the work shift for a total of 205 workshifts. Allylmercapturic acid was the major metabolite of allyl chloride in urine samples taken from the workers. In 1993, the lifestyle factor of garlic consumption of the workers was added to the questionnaire the workers answered. The workers with regular garlic consumption excreted significantly higher amounts of allylmercapturic acid before the workshift began than irregular and non-consumers of garlic. Dermal allyl chloride exposure also increased allylmercapturic acid excretion. A time-course of allylmercapturic acid excretion following allyl chloride exposure was created for each worker. The authors found that the increased allylmercapturic acid concentrations in urine during a workshift correlated well with the 8-hr time weighted average exposure to allyl chloride and that garlic consumption could be a confounder of allylmercapturic acid excretion.

4.2. Mechanism of Toxicity

The mechanism of allyl chloride toxicity is not known, but it is possible that some of the metabolites formed are toxic causing kidney lesions seen in experimental animals. Short-term exposure causes eye and upper respiratory tract irritation. Nose and mouth scratching, eye closure, pawing, drowsiness, lacrimation, salivation, weakness, apnea, and pulmonary hemorrhage were noted in several species following exposure (Adams et al. 1940; Shell Chemical Co. 1959, Lu et al. 1982; Quast et al. 1982a). Liver toxicity including cloudy swelling and focal necrosis was noted in repeat-dose studies in rats, mice, rabbits, and guinea pigs (Shell Chemical Co. 1959; Torkelson et al. 1959).

4.3. Structure Activity Relationships

Neudecker et al. (1980) examined the mutagenic properties of halogen and alkyl substituted allyl and allylic compounds in *Salmonella typhimurium* (TA 100) with and without S9 activation mix. They determined that allylic compounds were directly mutagenic, but a decrease in mutagenicity could be caused by the addition of S9 activation mix.

The IRIS database lists allyl chloride as being structurally similar to dibromochloropropane, a probable human carcinogen (USEPA 1994).

4.4. Other Relevant Information

4.4.1. Species Variability

Based on the results of the available data (Adams et al. 1940; Lu et al. 1982), the guinea pig was somewhat more sensitive than the rat (less than a factor of two). The mouse, cat, and rat had similar susceptibilities, but the rabbit was the least sensitive.

4.4.2. Susceptible Populations

No data were available concerning susceptible populations following inhalation of allyl chloride. However, allyl chloride is an ocular and respiratory irritant. No information on the relative susceptibility of asthmatics and otherwise healthy people to inhaled allyl chloride was

located.

4.4.3. Concurrent Exposure Issues

The majority of allyl chloride produced is used to make epichlorohydrin and concurrent exposure may occur in the workplace.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Torkelson et al. (1959) and the Shell Chemical Co. (1959) exposed humans to allyl chloride and found that odor detection occurred around 3-6 ppm. No irritation was reported by the human volunteers exposed to 3 ppm for 3 min (Torkelson et al. 1959). Shell Chemical Co. (1959) found that noticeable irritation of the sensory organs of most people would occur after exposure to 25-100 ppm. They found that a 5 min exposure to 50-100 ppm caused eye irritation in half of the unconditioned personnel exposed, and less than 25 ppm would cause nasal and pulmonary irritation. Hausler and Lenich (1968) examined workers who were exposed to 1-113 ppm allyl chloride over a 16 month period and found a garlic-like odor of the body and breath of some of the workers. There was also increased liver enzyme activity in some of the workers. When changes to the work place reduced allyl chloride concentrations to 0.5-36 ppm, enzyme activity levels were within normal range.

5.2. Summary of Animal Data Relevant to AEGL-1

None of the acute animal studies had exposure concentrations that resulted in endpoints relevant to AEGL-1. Repeat-dose studies in dogs, rats, rabbits, and guinea pigs found no effects after exposure to 3 ppm for 3 months or longer (Torkelson et al. 1959; Quast et al. 1982a).

5.3. Derivation of AEGL-1

The AEGL-1 values are based on the sensory response experienced by an unknown number of unconditioned personnel during or following five minutes of exposure to allyl chloride (Shell Chemical Co. 1959). Exposure to 3-6 ppm did not cause respiratory, eye, or nose irritation. However, the garlic-like odor of allyl chloride could be detected at this concentration. At concentrations greater than 50 ppm, eye irritation occurred in half of the personnel. Nasal irritation and pulmonary discomfort occurred between 6 and 25 ppm in half of those tested. The authors stated that noticeable irritation of the sensory organs for most people occurred at concentrations ranging from 25-100 ppm. An estimate of the threshold of irritation was calculated by dividing 25 ppm by 3 to yield 8.3 ppm. An intraspecies uncertainty factor of 3 was applied instead of the default value of 10 because allyl chloride is a direct acting irritant and it would protect sensitive populations, those experiencing noticeable irritation below 25 ppm. An uncertainty factor of 10 would result in AEGL-1 values that are lower than concentrations humans have been exposed to with no irritation or physiological changes. Both Torkelson et al. (1959) and the Shell Chemical Co. (1959) reported that humans did not report irritation after being exposed to 3-6 ppm of allyl chloride for 1-5 minutes. An occupational study (Hausler and Lenich 1968) found that workers exposed to 0.5-36 ppm allyl chloride for 6 months had normal liver enzyme activity levels. An interspecies factor of 1 was applied because human data were used. The AEGL-1 value was held constant across all exposure time points. That approach was

considered appropriate because mild irritant effects generally do not vary greatly over time.

TABLE 6. AEGL-1 Values for Allyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to AEGL-2 are available.

6.2. Summary of Animal Data Relevant to AEGL-2

Fischer 344 rats exposed to 200, 300, 500, or 800 ppm allyl chloride for 6 hr experienced eye redness and closure during exposure and were found to have reversible acute tubular degeneration at 300 ppm or higher (Quast et al. 1982a). Other symptoms including diarrhea, lethargy, and decreased urine and feces were observed at 500 and 800 ppm. B6C3F1 mice exposed to 500 or 800 ppm had eye closure with no other clinical signs. Reversible acute tubular degeneration was observed in female mice at 800 ppm (Quast et al. 1982a).

6.3. Derivation of AEGL-2

The AEGL-2 values are based on exposure data showing no incapacitating or irreversible effects. Slight eye closure and redness in male and female rats were observed at 300 ppm and females exhibited minimal reversible acute renal tubular degeneration. Complete recovery from irritation occurred at 18-hr postexposure. At the next highest concentration, 500 ppm, moderate eye closure and redness, lethargy, and reversible acute renal tubular degeneration were observed in both sexes, with recovery from irritation and lethargy occurring at 24-hr postexposure (Quast et al. 1982a). These data indicate that the female rat is more sensitive to allyl chloride. The point of departure was 300 ppm based on slight ocular irritation and reversible kidney lesions in female rats. A factor of 3 was used for interspecies uncertainty because allyl chloride is a direct-acting irritant, and data from the more sensitive sex and species (female rat) were used as the point of departure. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Female rats were more sensitive than male rats and mice of both sexes in terms of kidney toxicity which occurred at 300 ppm following a 6-hr exposure. Male rats experienced tubular degeneration at 500 ppm. Female mice exposed for 6-hr to allyl chloride had reversible tubular degeneration at 800 ppm vs. 1000 ppm in male mice (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Human data did not provide quantitative exposure information, but it suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals.

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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, 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 (NRC 2001). According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NCR 2001), 10-minute values are not to be scaled from an experimental exposure time of greater than 4 hours. Therefore, the 30-minute value was also adopted as the 10-minute value.

TABLE 7. AEGL-2 Values for Allyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
69 ppm (220 mg/m^3)	69 ppm (220 mg/m^3)	54 ppm (170 mg/m^3)	34 ppm (110 mg/m^3)	22 ppm (69 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data with quantitative exposure concentration were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data were available for rats, mice, guinea pigs, rabbits, and cats. Adams et al. (1940) found lethality in rats and guinea pigs exposed to 290- 29300 ppm exposed from 10 min to 9 hours. Several 2-hr LC_{50}s were reported for the male rat 3520 ppm, female rat 3776 ppm, female mouse 3680 ppm, male guinea pig 1856 ppm, rabbit 7200 ppm, and cat 3360 ppm (Lu et al. 1982). Quast et al. (1982a) exposed rats to 200-2000 ppm mice to 500-2000 ppm and observed increased mortality in rats and mice exposed to concentrations equal to and greater than 1000 ppm. The $BMCL_{05}$ and BMC_{01} for rats were 855 and 792 ppm, and for female mice, the $BMCL_{05}$ and BMC_{01} were 666 and 696 ppm.

Although data from Adams et al. (1940) were available and showed lethality at lower concentrations than Quast et al. (1982a), the data were not used to derive AEGL values because the study is not as reliable and robust as the Quast et al. (1982a) study. This was determined due to the questionable method in which the chamber atmospheres were generated- spraying the sides of the chamber with liquid and adding to the air flow. No information was reported with respect to atmosphere generation for the 10 L glass jar in which 2 animals at a time were placed for exposures lasting less than 1 hour. Data from Lu et al. (1982) were also not used to derive AEGL values due to lack of information. All species experienced the same effects, but the authors mentioned if effects were more prominent in individual species. They stated that the guinea pig was somewhat more susceptible and had more prominent sensory irritation, but individual species data or concentration range for the guinea pig was not provided.

7.3. Derivation of AEGL-3

The data set used for deriving AEGL-3 values is from Quast et al. (1982a) and provides

exposure response data for rats and mice exposed to allyl chloride for 6 hr at concentrations ranging from 200 to 2000 ppm. The 1000 ppm concentration resulted in mortality in both species 24-72 hours post exposure. The rats and mice exposed to 800 ppm had moderate palpebral closure and conjunctival hyperemia, and this was the highest experimental concentration at which mortality did not occur.

The experimental concentration of 800 ppm was selected as the point of departure for AEGL-3 derivation as is was the highest concentration at which no lethality was observed in a rats during or following a 6-hr exposure. The benchmark concentration calculations of the rat data support this approach as the BMC_{01} was 792 ppm and the BMC_{05} was 855 ppm. Neither value was used because of the variability in the animal responses as observed in the standard deviation values of the BMC statistics. Benchmark concentration calculations for the mouse were not used because the data did not show a clear concentration-response compared to the rat data. However, the experimental mouse data support the point of departure because no lethality was observed in male or female mice at 800 ppm but was observed at the next highest concentration, 1000 ppm. A total uncertainty factor of 10 was applied to account for interspecies extrapolation and intraspecies variability. An uncertainty factor of 3 was applied for interspecies variability. Although the mechanism of action is unknown, allyl chloride is a direct-acting eye, nose, and respiratory tract irritant. That mode of action is not expected to differ across species, and the animal data support that claim. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Rats and mice experienced slight to severe eye closure and redness during and following exposures to 200-2000 ppm for 6-hr, with severity increasing with concentration (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Although human data did not provide quantitative exposure information, they suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals.

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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, 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 (NRC 2001). According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NCR 2001), 10-minute values are not to be scaled from an experimental exposure time of greater than 4 hours. Therefore, the 30-minute value was also adopted as the 10-minute value.

TABLE 8. AEGL-3 Values for Allyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
180 ppm (560 mg/m^3)	180 ppm (560 mg/m^3)	140 ppm (440 mg/m^3)	90 ppm (280 mg/m^3)	60 ppm (190 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values are derived from human exposures for the estimate of the threshold for irritation (8.3 ppm) of the sensory organs (Shell Chemical Co. 1959). AEGL-2 values are based on experimental concentrations that were neither incapacitating nor irreversible in rats (300 ppm) exposed for 6 hours (Quast et al. 1982a). AEGL-3 values are based on the highest concentration that did not cause lethality in rats (800 ppm) exposed for 6 hours (Quast et al. 1982a). AEGL values for allyl chloride are listed in the table below.

TABLE 9. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Notable Discomfort)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)	2.8 ppm (8.8 mg/m^3)
AEGL-2 (Disabling)	69 ppm (220 mg/m^3)	69 ppm (220 mg/m^3)	54 ppm (170 mg/m^3)	34 ppm (110 mg/m^3)	22 ppm (69 mg/m^3)
AEGL-3 (Lethal)	180 ppm (560 mg/m^3)	180 ppm (560 mg/m^3)	140 ppm (440 mg/m^3)	90 ppm (280 mg/m^3)	60 ppm (190 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

All currently available standards and guidelines are shown in the table below. The standards and guidelines applicable to an 8 hr workday are similar to the 8 hr AEGL 1 indicating it is applicable to the general population. The ERPGs set at higher levels that the derived AEGL 2 and 3 indicate the conservative endpoint chosen for those values.

TABLE 10. Extant Standards and Guidelines for Allyl Chloride

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	2.8 ppm	2.8 ppm	2.8 ppm	2.8 ppm	2.8 ppm
AEGL-2	69 ppm	69 ppm	54 ppm	34 ppm	22 ppm
AEGL-3	180 ppm	180 ppm	140 ppm	90 ppm	60 ppm
ERPG-1 (AIHA)[a]			3 ppm		
ERPG-2 (AIHA)			40 ppm		
ERPG-3 (AIHA)			300 ppm		
PEL-TWA (OSHA)[b]					1 ppm
IDLH (NIOSH)[c]		250 ppm			
REL-TWA (NIOSH)[d]					1 ppm
REL-STEL (NIOSH)[e]					2 ppm
TLV-TWA (ACGIH)[f]					1 ppm
TLV-STEL (ACGIH)[g]					2 ppm
MAC (The Netherlands)[h]					1 ppm

[a]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 is based on the human data that showed detectable odor at 3-6 ppm and uncomfortable nasal and pulmonary irritation at less than 25 ppm.
- 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 protective action. The ERPG-2 is based on human data showing an absence of effects in workers repeatedly exposed to levels below 36 ppm. Although there may be some irritation at this level, it is expected to be slight.
- 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 is based on the acute inhalation data that showed deaths in the most sensitive species, the guinea pig, after a 2-hour exposure to 3200 pm, or a 4-hour exposure to 320 ppm, but no deaths after 1 hour at 3200 ppm or 3 hours at 320 ppm.

[b]OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[c]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005) is defined as the time-weighted average concentration for up to a 10-hour workday during a 40-hr workweek.

[e]NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH 2005) is defined as a 15-minute time weighted average exposure that should not be exceeded at any time during the workday.

[f]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 1991) 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.

[g]ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit) (ACGIH 1991) is defined as a 15-minute TWA

exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

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

8.3. Data Adequacy and Research

The data reported for human exposure to allyl chloride is available for determining threshold of irritation. Conflicting quantitative animal data are available showing respiratory, ocular, and nasal irritation as well as lethality. Additional data providing information regarding lethality would be useful to determine where the mortality threshold lies and what effects occur below that threshold. More studies using a various species would also be helpful to determine if one species is more sensitive than another and if allyl chloride does cause irreversible effects.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Study: Shell Chemical Co. 1959. Allyl Chloride. Industrial Hygiene Bulletin No. SC-57-80. New York: Shell Chemical Co., Industrial Hygiene Department, January 1959. pp. 1-4.

Toxicity endpoint: Estimate of the threshold of irritation

Time scaling: None

Uncertainty factors: An intraspecies uncertainty factor of 3 was applied instead of the default value of 10 because allyl chloride is a direct acting irritant and it would protect sensitive populations, those experiencing noticeable irritation below 25 ppm. An uncertainty factor of 10 would result in AEGL-1 values that are lower than concentrations humans have been exposed to with no irritation or physiological changes. Both Torkelson et al. (1959) and the Shell Chemical Co. (1959) reported that humans did not report irritation after being exposed to 3-6 ppm of allyl chloride for 1-5 minutes. An occupational study (Hausler and Lenich 1968) found that workers exposed to 0.5-36 ppm allyl chloride for 6 months had normal liver enzyme activity levels. An interspecies factor of 1 was applied because human data were used to derive AEGL-1 values.

Modifying factor: None

Calculations: 25 ppm/ 3 = 8.3 ppm
8.3 ppm/ 3 = 2.8 ppm

The AEGL level was held constant across all exposure time points. That approach was considered appropriate because mild irritant effects generally do not vary greatly over time.

10-minute AEGL-1 2.8 ppm

30-minute AEGL-1 2.8 ppm

1-hour AEGL-1 2.8 ppm

4-hour AEGL-1 2.8 ppm

8-hour AEGL-1 2.8 ppm

Derivation of AEGL-2

Key Study: Quast, J.F., J.W, Henck, D.J. Schuetz, D.A. Dittenber, and M.J. McKenna. 1982a. Allyl Chloride- Acute Studies. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents. Final Report, Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, MI (June 4, 1982).

Toxicity endpoints: AEGL-2 values were based upon the highest concentration for slight eye closure and redness following a 6 hour exposure and the lowest concentration (300 ppm) at which female rats manifested reversible kidney tubular degeneration. This estimate of a threshold for irreversible effects was justified because of the absence of exposure-response data related to irreversible or other serious, long-lasting effects.

Time scaling: 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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, 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 (NRC 2001). The 30-minute value was also adopted as the 10-minute value.

Uncertainty factors: A factor of 3 was used for interspecies uncertainty because allyl chloride is a direct-acting irritant, and data from the more sensitive sex and species (female rat) were used as the point of departure. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Female rats were more sensitive than male rats and mice of both sexes in terms of kidney toxicity which occurred at 300 ppm following a 6-hr exposure. Male rats experienced tubular degeneration at 500 ppm. Female mice exposed for 6-hr to allyl chloride had reversible tubular degeneration at 800 ppm vs. 1000 ppm in male mice (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Human data did not provide quantitative exposure information, but it suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals.

Modifying factor: None

Calculations: 300 ppm/10 = 30 ppm

$C^3 \times t = k$

$(30 \text{ ppm})^3 \times 360 \text{ min} = 9720000 \text{ ppm}^3 \cdot \text{min}$

$C^1 \times t = k$

$30 \text{ ppm} \times 360 \text{ min} = 10800 \text{ ppm min}$

10-minute AEGL-2 $C^3 \times 30 \text{ min} = 9720000 \text{ ppm}^3 \cdot \text{min}$

$C = 69 \text{ ppm}$

1	30-minute AEGL-2	C^3 x 30 min = 9720000 ppm^3·min
2		C = 69 ppm
3	1-hour AEGL-2	C^3 x 60 min = 9720000 ppm^3·min
4		C = 54 ppm
5	4-hour AEGL-2	C^3 x 240 min = 9720000 ppm^3·min
6		C = 34 ppm
7	8-hour AEGL-2	C x 480 min = 10800 ppm min
8		C = 22 ppm

Derivation of AEGL-3

Key Study: Quast, J.F., J.W, Henck, D.J. Schuetz, D.A. Dittenber, and M.J. McKenna. 1982a. Allyl Chloride- Acute Studies. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents. Final Report, Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, MI (June 4, 1982).

Toxicity endpoint: The AEBL-3 values were based upon the highest experimental concentration with no mortality (800 ppm) following a 6 hour exposure in rats.

Time scaling: $C^n \times t = k$, temporal scaling, using n = 3 when extrapolation to shorter time points and n = 1 when extrapolating to longer time points due to lack of data to derive the value of n (NRC 2001). The 30-minute value was adopted for the 10-minute value.

Uncertainty factors: An uncertainty factor of 3 was applied for interspecies variability. Although the mechanism of action is unknown, allyl chloride is a direct-acting eye, nose, and respiratory tract irritant. That mode of action is not expected to differ across species, and the animal data support that claim. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Rats and mice experienced slight to severe eye closure and redness during and following exposures to 200-2000 ppm for 6-hr, with severity increasing with concentration (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Although human data did not provide quantitative exposure information, they suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals.

Modifying factor: None

Calculations: 800 ppm/10 = 80 ppm

$C^3 \times t = k$

$(80\ ppm)^3 \times 360\ min = 18432000\ ppm^3 \cdot min$

$C^1 \times t = k$

$80\ ppm \times 360\ min = 28800\ ppm\ min$

10-minute AEGL-3	$C^3 \times 30\ min = 18432000 ppm^3 \cdot min$
	$C = 180\ ppm$
30-minute AEGL-3	$C^3 \times 30\ min = 18432000 ppm^3 \cdot min$
	$C = 180\ ppm$
1-hour AEGL-3	$C^3 \times 60\ min = 18432000 ppm^3 \cdot min$
	$C = 140\ ppm$
4-hour AEGL-3	$C^3 \times 240\ min = 18432000 ppm^3 \cdot min$
	$C = 90\ ppm$

1	8-hour AEGL-3	C^1 x 480 min = 28800 ppm·min
2		C = 60 ppm

1 # APPENDIX B: Time-Scaling Calculations

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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, 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 (NRC 2001). According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NCR 2001), 10-minute values are not to be scaled from an experimental exposure time of greater than 4 hours. Therefore, the 30-minute value was also adopted as the 10-minute value.

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3 # APPENDIX C: Derivation Summary for Allyl Chloride AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR
Allyl Chloride (CAS Reg. No. 107-05-1)
DERIVATION SUMMARY

AEGL-1 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
2.8 ppm	**2.8 ppm**	**2.8 ppm**	**2.8 ppm**	**2.8 ppm**

Key Reference: Shell Chemical Co. 1959. Allyl Chloride. Industrial Hygiene Bulletin No. SC-57-80. New York: Shell Chemical Co., Industrial Hygiene Department, January 1959. pp. 1-4.

Test Species/Strain/Number: Humans/ unconditioned personnel

Exposure Route/Concentrations/Durations: Inhalation/ 3-6 ppm/ 5 min

Effects:
3-6 ppm No effects
< 25 ppm Threshold, nasal irritation$_{50}$ and pulmonary discomfort$_{50}$
50-100 ppm Threshold, eye irritation$_{50}$

Endpoint/Concentration/Rationale: Estimate of the threshold of irritation, 25 ppm/3 = 8.3 ppm

Uncertainty Factors/Rationale:
An intraspecies uncertainty factor of 3 was applied instead of the default value of 10 because allyl chloride is a direct acting irritant and it would protect sensitive populations, those experiencing noticeable irritation below 25 ppm. An uncertainty factor of 10 would result in AEGL-1 values that are lower than concentrations humans have been exposed to with no irritation or physiological changes. Both Torkelson et al. (1959) and the Shell Chemical Co. (1959) reported that humans did not report irritation after being exposed to 3-6 ppm of allyl chloride for 1-5 minutes. An occupational study (Hausler and Lenich 1968) found that workers exposed to 0.5-36 ppm allyl chloride for 6 months had normal liver enzyme activity levels. An interspecies factor of 1 was applied because human data were used to derive AEGL-1 values. The AEGL-1 value was held constant across all exposure time points. That approach was considered appropriate because mild irritant effects generally do not vary greatly over time.

Modifying Factor: none

Animal to Human Dosimetric Adjustment: none

Time Scaling: none

Data Adequacy: The studies were considered adequate for AEGL-1 derivation. Humans were used as subjects and there was no clear and convincing evidence that the research was fundamentally unethical (e.g. investigators intended to harm the subjects). Support was supplied by Torkelson et al. 1959 in which 13 human volunteers did not report irritation after exposure to 3 ppm for one to three minutes.

AEGL-2 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
69 ppm	**69 ppm**	**54 ppm**	**34 ppm**	**22 ppm**

Key Reference: Quast, J.F., J.W, Henck, D.J. Schuetz, D.A. Dittenber, and M.J. McKenna. 1982a. Allyl Chloride- Acute Studies. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents. Final Report, Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, MI (June 4, 1982).

Test Species/Strain/Number: Rat/Fischer 344/ 10/sex/group

Exposure Route/Concentrations/Durations: Inhalation to 200, 300, 500, 800, 1000, 2000 for 6 hr

Effects:

200 ppm Slight eye closure, red eyes
300 ppm Slight eye closure, red eyes, acute tubular degeneration (females only)
500 ppm Moderate eye closure, red eyes, lethargy, diarrhea, acute renal tubular degeneration
800 ppm Moderate eye closure, red eyes, lethargy, diarrhea, acute renal tubular degeneration
1000a ppm Severe eye closure, red eyes, nasal discharge; lethargy, diarrhea, acute renal tubular degeneration
1000b ppm Severe eye closure, red eyes, nasal discharge; lethargy, diarrhea, acute renal tubular degeneration
1000c ppm Severe eye closure, red eyes, nasal discharge; lethargy, diarrhea, acute renal tubular degeneration
2000 ppm Severe eye closure, red eyes, nasal discharge; lethargy, diarrhea, acute renal tubular degeneration

Endpoint/Concentration/Rationale: Highest concentration for slight eye redness and closure at 300 ppm for 6 hr, reversible acute tubular degeneration in females

Uncertainty Factors/Rationale:

A factor of 3 was used for interspecies uncertainty because allyl chloride is a direct-acting irritant, and data from the more sensitive sex and species (female rat) were used as the point of departure. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Female rats were more sensitive than male rats and mice of both sexes in terms of kidney toxicity which occurred at 300 ppm following a 6-hr exposure. Male rats experienced tubular degeneration at 500 ppm. Female mice exposed for 6-hr to allyl chloride had reversible tubular degeneration at 800 ppm vs. 1000 ppm in male mice (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Human data did not provide quantitative exposure information, but it suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied. Insufficient data

Time Scaling: In the absence of an empirically derived exponent (n), and to obtain AEGL values, $C^n \times t = k$, temporal scaling, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. 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 ranges from 0.8 to 3.5 (ten Berge et al. 1986).

Data Adequacy: The study was considered adequate for AEGL-2 derivation. It was well-designed and performed, adequate numbers of animals were used, and although an endpoint consistent with AEGL-2 definition and toxicity of allyl chloride was not observed, the data can be used to derive AEGL-2 values.

AEGL-3 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
180 ppm	180 ppm	140 ppm	90 ppm	60 ppm

Key Reference: Quast, J.F., J.W, Henck, D.J. Schuetz, D.A. Dittenber, and M.J. McKenna. 1982a. Allyl Chloride- Acute Studies. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents. Final Report, Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, MI (June 4, 1982).

Test Species/Strain/Number: Rat/Fischer 344/ 10/sex/group

Exposure Route/Concentrations/Durations: Inhalation to 200, 300, 500, 800, 1000, 2000 for 6 hr

Effects:
200 ppm 0% mortality; red eyes, eye closure
300 ppm 0% mortality; minimal acute renal tubular degeneration (females only)
500 ppm 0% mortality; lethargy, diarrhea, acute renal tubular degeneration
800 ppm 0% mortality; lethargy, diarrhea, acute renal tubular degeneration
1000a ppm 10% morality; nasal discharge; lethargy, diarrhea, acute renal tubular degeneration
1000b ppm 5% morality; nasal discharge; lethargy, diarrhea, acute renal tubular degeneration
1000c ppm 0% morality; nasal discharge; lethargy, diarrhea, acute renal tubular degeneration
2000 ppm 55% mortality; nasal discharge; lethargy, diarrhea, acute renal tubular degeneration

Endpoint/Concentration/Rationale: Highest concentration with no mortality/800 ppm for 6 hr

Uncertainty Factors/Rationale:
An uncertainty factor of 3 was applied for interspecies variability. Although the mechanism of action is unknown, allyl chloride is a direct-acting eye, nose, and respiratory tract irritant. That mode of action is not expected to differ across species, and the animal data support that claim. Adams et al. (1940) reported that rats and guinea pigs experienced eye, nose, and pulmonary irritation during acute exposures (10 min-9 hr), and Lu et al. (1982) reported closing eyes, pawing, scratching the nose and mouth, lacrimation, and salivation as signs of irritation in mice, rats, guinea pigs, rabbits, and cats exposed for 2 hr. Rats and mice experienced slight to severe eye closure and redness during and following exposures to 200-2000 ppm for 6-hr, with severity increasing with concentration (Quast et al. 1982a). An intraspecies uncertainty factor of 3 was applied. Although human data did not provide quantitative exposure information, they suggested that allyl chloride is a direct-acting irritant and described effects similar to those seen in rats, guinea pigs, and mice, eye, nose, and respiratory tract irritation, following acute exposures (Torkelson et al. 1959; Shell Chemical Co. 1959; He et al. 1985). Although data on sensitive populations are lacking for allyl chloride, as a direct-acting irritant for acute exposures, the mode of action is not expected to differ among individuals.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None, insufficient data.

Time Scaling: In the absence of an empirically derived exponent (n), and to obtain AEGL values, $C^n \times t = k$, temporal scaling, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. 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 ranges from 0.8 to 3.5 (ten Berge et al. 1986).

Data Adequacy: The study was considered adequate for AEGL-3 derivation. It was well-designed and performed, adequate numbers of animals were used. An endpoint consistent with the AEGL-3 definition and toxicity of allyl chloride was observed.

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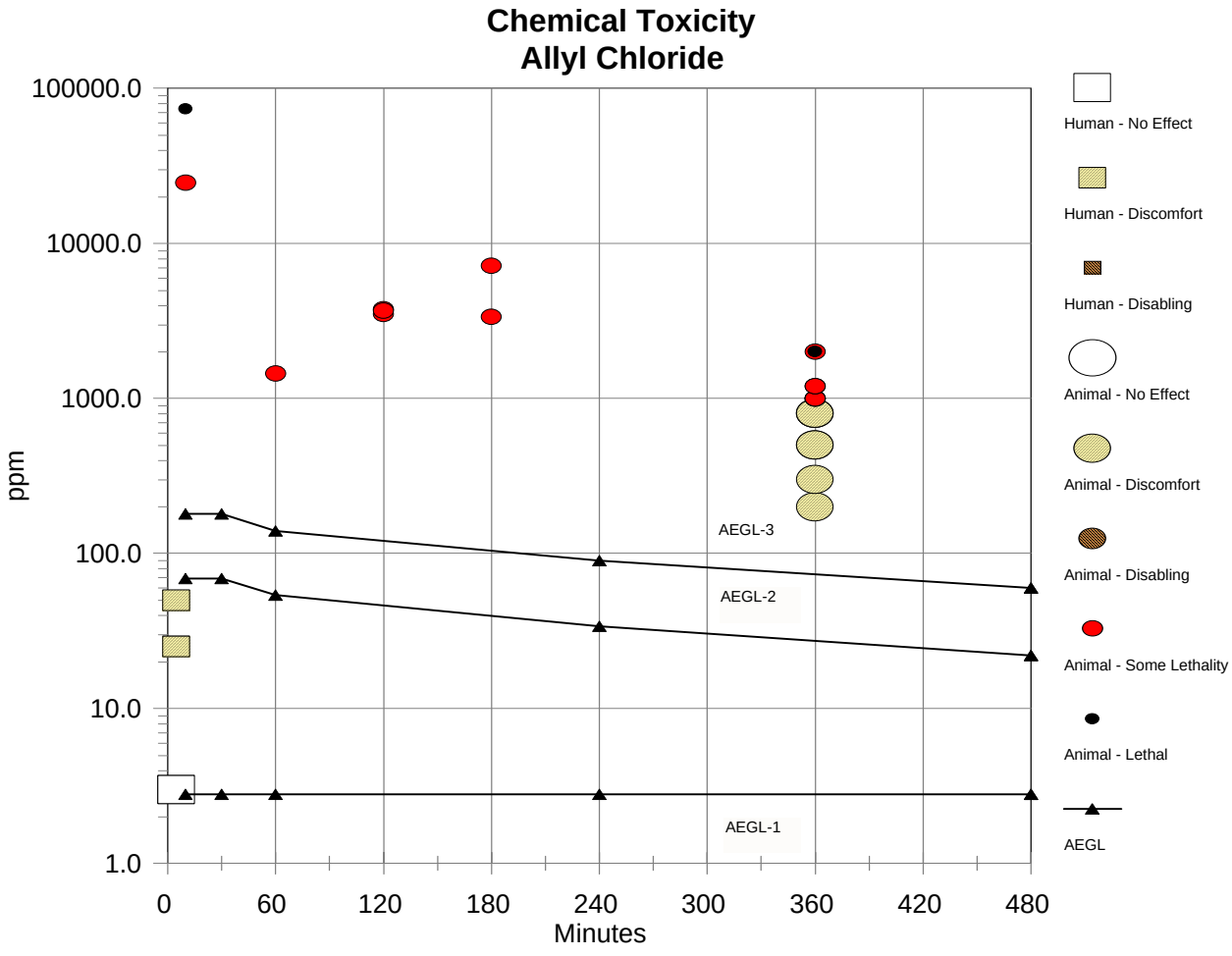
2 **APPENDIX D: Category Plot for Allyl Chloride**

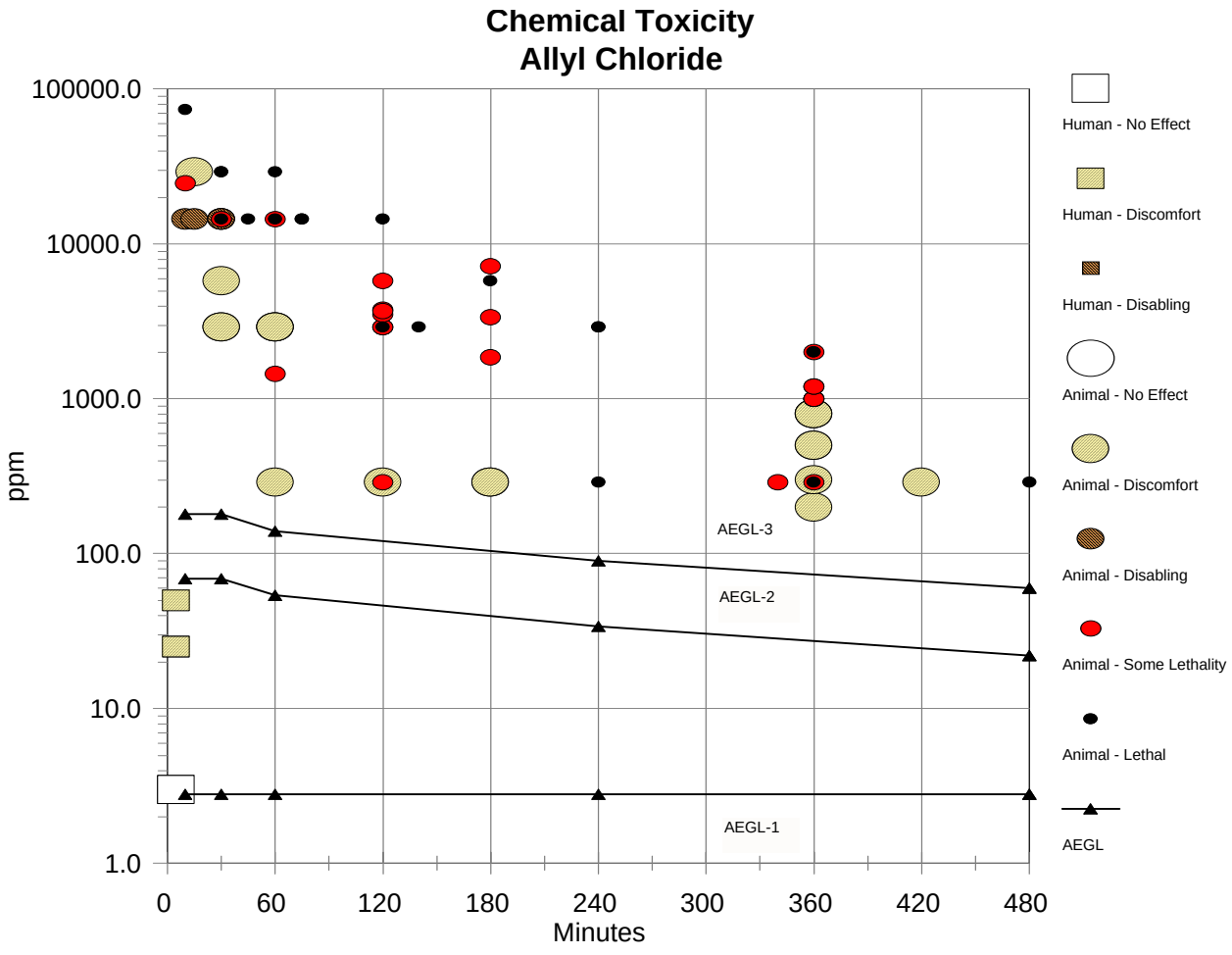
The following category plot was created omitting the data from Adams et al. (1940).



1 Category Plot Data- Adams et al. 1940 omitted

							For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal
Source	Species	Sex	Exposures #	ppm	Time (min)	Category	Comments
NAC/AEGL-1				2.8	10	AEGL	
NAC/AEGL-1				2.8	30	AEGL	
NAC/AEGL-1				2.8	60	AEGL	
NAC/AEGL-1				2.8	240	AEGL	
NAC/AEGL-1				2.8	480	AEGL	
NAC/AEGL-2				69	10	AEGL	
NAC/AEGL-2				69	30	AEGL	
NAC/AEGL-2				54	60	AEGL	
NAC/AEGL-2				34	240	AEGL	
NAC/AEGL-2				22	480	AEGL	
NAC/AEGL-3				180	10	AEGL	
NAC/AEGL-3				180	30	AEGL	
NAC/AEGL-3				140	60	AEGL	
NAC/AEGL-3				90	240	AEGL	
NAC/AEGL-3				60	480	AEGL	
Torkelson et al. 1959	human	M	1	3	3	0	Odor detection
Shell Chemical Co. 1959	human		1	3	5	0	50% odor detection
Shell Chemical Co. 1959	human		1	50	5	1	50% eye irritation
Lu et al. 1982	guinea pig	M	1	1856	180	SL	50% mortality
Lu et al. 1982	rabbit		1	7200	180	SL	50% mortality
Lu et al. 1982	cat		1	3360	180	SL	50% mortality
Lu et al. 1982	rat	M	1	3520	120	SL	50% mortality
Lu et al. 1982	rat	F	1	3776	120	SL	50% mortality
Quast et al. 1982a	rat		1	200	360	1	Slight eye closure, red eyes
Quast et al. 1982a	rat		1	300	360	1	Slight eye closure, red eyes
Quast et al. 1982a	rat		1	500	360	1	Renal tubular degeneration
Quast et al. 1982a	rat		1	800	360	1	Renal tubular degeneration
Quast et al. 1982a	rat		1	1000	360	SL	5% mortality, eye closure
Quast et al. 1982a	rat		1	1000	360	SL	5% mortality, eye closure
Quast et al. 1982a	rat		1	2000	360	SL	Lethargy, eye closure
Shell Chemical Co. 1959	mouse		1	73900	10	3	100% mortality
Shell Chemical Co. 1959	mouse		1	24633	10	SL	50% mortality
Shell Chemical Co. 1959	mouse		1	1455	60	SL	50% mortality
Lu et al. 1982	mouse		1	3680	120	SL	50% mortality
Quast et al. 1982a	mouse		1	500	360	1	Slight-moderate eye closure
Quast et al. 1982a	mouse		1	800	360	1	Renal tubular degeneration
Quast et al. 1982a	mouse		1	1000	360	SL	70% mortality
Quast et al. 1982a	mouse		1	1000	360	SL	50% mortality
Quast et al. 1982a	mouse		1	1200	360	SL	25% mortality
Quast et al. 1982a	mouse		1	2000	360	3	100% mortality
Shell Chemical Co. 1959	human		1	25	5	1	Nose and pulmonary irritation

The following category plot was created including all the data in which the conflicts in data can be observed very well.



1 Category Plot Data- All Data

							For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal
Source	Species	Sex	Exposures #	ppm	Time (min)	Category	Comments
NAC/AEGL-1				2.8	10	AEGL	
NAC/AEGL-1				2.8	30	AEGL	
NAC/AEGL-1				2.8	60	AEGL	
NAC/AEGL-1				2.8	240	AEGL	
NAC/AEGL-1				2.8	480	AEGL	
NAC/AEGL-2				69	10	AEGL	
NAC/AEGL-2				69	30	AEGL	
NAC/AEGL-2				54	60	AEGL	
NAC/AEGL-2				34	240	AEGL	
NAC/AEGL-2				22	480	AEGL	
NAC/AEGL-3				180	10	AEGL	
NAC/AEGL-3				180	30	AEGL	
NAC/AEGL-3				140	60	AEGL	
NAC/AEGL-3				90	240	AEGL	
NAC/AEGL-3				60	480	AEGL	
Torkelson et al. 1959	human	M	1	3	3	0	Odor detection
Shell Chemical Co. 1959	human		1	3	5	0	50% odor detection
Shell Chemical Co. 1959	human		1	50	5	1	50% eye irritation
Adams et al. 1940	guinea pig		1	290	60	1	Drowsiness and unsteadiness
Adams et al. 1940	guinea pig		1	290	120	SL	20% mortality
Adams et al. 1940	guinea pig		1	290	180	1	Drowsiness and unsteadiness
Adams et al. 1940	guinea pig		1	290	240	3	100% mortality
Adams et al. 1940	guinea pig		1	290	360	3	100% mortality
Adams et al. 1940	guinea pig		1	290	540	3	100% mortality
Adams et al. 1940	guinea pig		1	2900	30	1	Eye and nose irritation
Adams et al. 1940	guinea pig		1	2900	60	1	Eye and nose irritation
Adams et al. 1940	guinea pig		1	2900	120	3	100% mortality
Adams et al. 1940	guinea pig		1	14500	10	2	Eye and nose irritation
Adams et al. 1940	guinea pig		1	14500	15	2	Eye,nose irritation, hypopnea
Adams et al. 1940	guinea pig		1	14500	30	SL	50% mortality
Adams et al. 1940	guinea pig		1	14500	30	3	100% mortality
Adams et al. 1940	guinea pig		1	14500	30	SL	66% mortality
Adams et al. 1940	guinea pig		1	14500	45	3	100% mortality
Adams et al. 1940	guinea pig		1	14500	60	3	100% mortality
Lu et al. 1982	guinea pig	M	1	1856	180	SL	50% mortality
Lu et al. 1982	rabbit		1	7200	180	SL	50% mortality
Lu et al. 1982	cat		1	3360	180	SL	50% mortality
Adams et al. 1940	rat		1	290	120	1	Drowsiness, unsteadiness
Adams et al. 1940	rat		1	290	180	1	Drowsiness, unsteadiness
Adams et al. 1940	rat		1	290	340	SL	20% mortality, eye irritation
Adams et al. 1940	rat		1	290	360	SL	20% mortality, eye irritation
Adams et al. 1940	rat		1	290	420	1	Drowsiness, unsteadiness

Adams et al. 1940	rat		1	290	480	3	100% mortality
Adams et al. 1940	rat		1	290	540	3	100% mortality
Adams et al. 1940	rat		1	2900	30	1	Eye and nose irritation
Adams et al. 1940	rat		1	2900	60	1	Eye and nose irritation
Adams et al. 1940	rat		1	2900	60	1	Eye and nose irritation
Adams et al. 1940	rat		1	2900	120	SL	80% mortality
Adams et al. 1940	rat		1	2900	120	SL	66% mortality
Adams et al. 1940	rat		1	2900	140	3	100% mortality
Adams et al. 1940	rat		1	2900	240	3	100% mortality
Adams et al. 1940	rat		1	2900	240	3	100% mortality
Adams et al. 1940	rat		1	5800	30	1	Eye and nose irritation
Adams et al. 1940	rat		1	5800	120	SL	20% mortality
Adams et al. 1940	rat		1	5800	180	3	100% mortality
Adams et al. 1940	rat		1	14500	30	2	Eye, nose irritation; instability
Adams et al. 1940	rat		1	14500	30	2	Eye, nose irritation; instability
Adams et al. 1940	rat		1	14500	60	SL	80% mortality
Adams et al. 1940	rat		1	14500	75	3	100% mortality
Adams et al. 1940	rat		1	14500	75	3	100% mortality
Adams et al. 1940	rat		1	14500	120	3	100% mortality
Adams et al. 1940	rat		1	29300	15	1	Eye and nose irritation
Adams et al. 1940	rat		1	29300	30	3	100% mortality
Adams et al. 1940	rat		1	29300	30	3	100% mortality
Adams et al. 1940	rat		1	29300	60	3	100% mortality
Lu et al. 1982	rat	M	1	3520	120	SL	50% mortality
Lu et al. 1982	rat	F	1	3776	120	SL	50% mortality
Quast et al. 1982a	rat		1	200	360	1	Slight eye closure, red eyes
Quast et al. 1982a	rat		1	300	360	1	Slight eye closure, red eyes
Quast et al. 1982a	rat		1	500	360	1	Renal tubular degeneration
Quast et al. 1982a	rat		1	800	360	1	Renal tubular degeneration
Quast et al. 1982a	rat		1	1000	360	SL	5% mortality, eye closure
Quast et al. 1982a	rat		1	1000	360	SL	5% mortality, eye closure
Quast et al. 1982a	rat		1	2000	360	SL	Lethargy, eye closure
Shell Chemical Co. 1959	mouse		1	73900	10	3	100% mortality
Shell Chemical Co. 1959	mouse		1	24633	10	SL	50% mortality
Shell Chemical Co. 1959	mouse		1	1455	60	SL	50% mortality
Lu et al. 1982	mouse		1	3680	120	SL	50% mortality
Quast et al. 1982a	mouse		1	500	360	1	Slight-moderate eye closure
Quast et al. 1982a	mouse		1	800	360	1	Renal tubular degeneration
Quast et al. 1982a	mouse		1	1000	360	SL	70% mortality
Quast et al. 1982a	mouse		1	1000	360	SL	50% mortality
Quast et al. 1982a	mouse		1	1200	360	SL	25% mortality
Quast et al. 1982a	mouse		1	2000	360	3	100% mortality
Shell Chemical Co. 1959	human		1	25	5	1	Nose and pulmonary irritation

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1 **Appendix E: Benchmark Concentration Calculations**

BMDS MODEL RUN $BMCL_{05}$- Quast et al. 1982a male and female rat

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The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 9
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -8.23753
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-20.1087	3.86631	-27.6865	-12.5308
slope	2.66416	0.53452	1.61653	3.7118

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.2347	9			
Fitted model	-25.9189	2	3.36829	7	0.849
Reduced model	-49.1955	1	49.9214	8	<.0001
AIC:	55.8378				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	20	0.000
200.0000	0.0000	0.000	0	20	-0.000
~~~~~~

300.0000	0.0000	0.000	0	20	-0.003
500.0000	0.0002	0.004	0	20	-0.062
800.0000	0.0107	0.215	0	20	-0.466
1000.0000	0.0441	0.881	0	20	-0.960
1000.0000	0.0441	0.881	2	20	1.219
1000.0000	0.0441	0.881	1	20	0.129
2000.0000	0.5562	11.124	11	20	-0.056

Chi^2 = 2.65 d.f. = 7 P-value = 0.9156

Benchmark Dose Computation

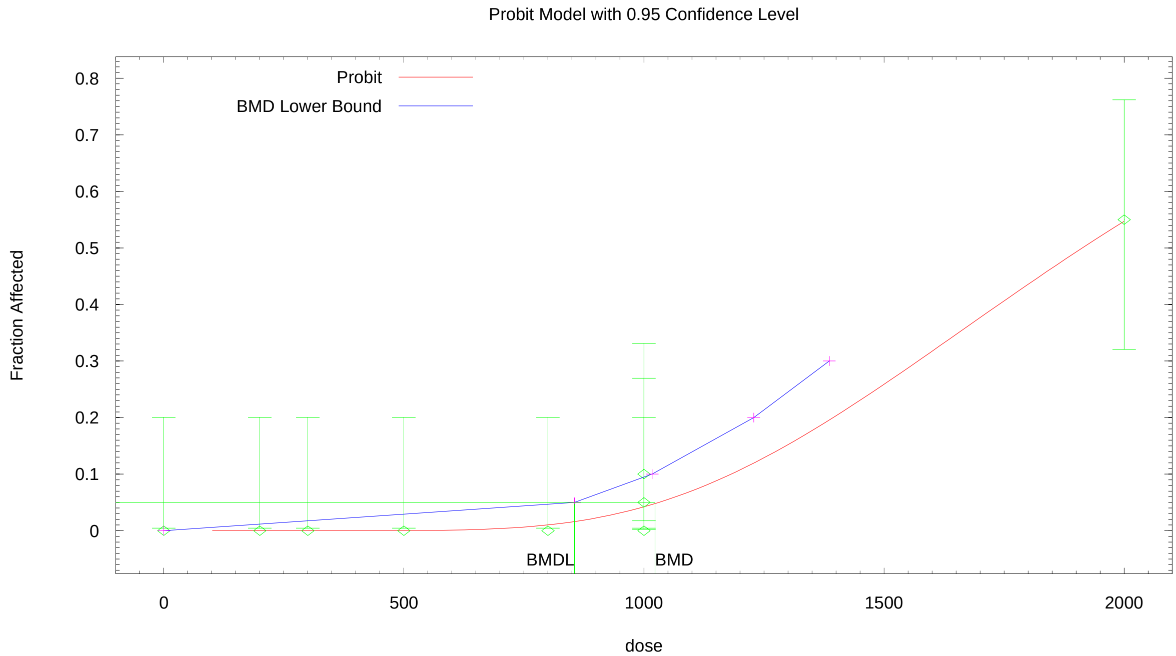
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1022.93

BMDL = 855.085



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BMDS MODEL RUN BMC_{01}- Quast et al. 1982a male and female rat

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The form of the probability function is:

P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 9
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
~~~~~~

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
background = 0
intercept = -8.23753
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-20.1087	3.86631	-27.6865	-12.5308
slope	2.66416	0.53452	1.61653	3.7118

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

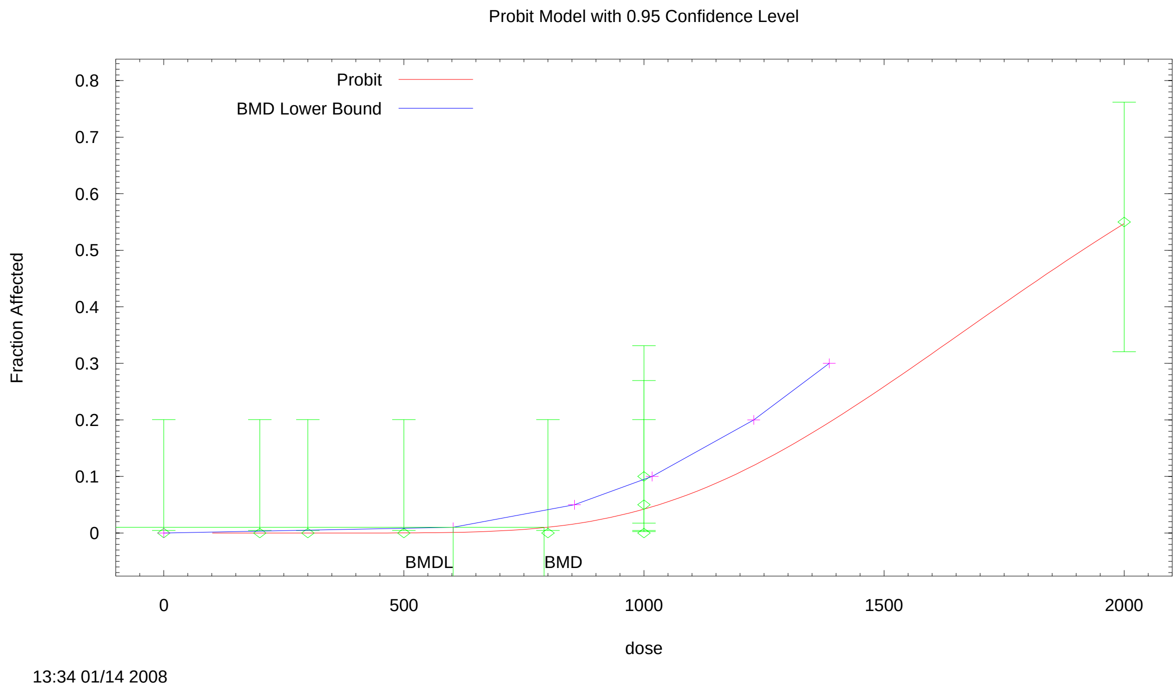
Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.2347	9			
Fitted model	-25.9189	2	3.36829	7	0.849
Reduced model	-49.1955	1	49.9214	8	<.0001
AIC:	55.8378				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	20	0.000
200.0000	0.0000	0.000	0	20	-0.000
300.0000	0.0000	0.000	0	20	-0.003
500.0000	0.0002	0.004	0	20	-0.062
800.0000	0.0107	0.215	0	20	-0.466
1000.0000	0.0441	0.881	0	20	-0.960
1000.0000	0.0441	0.881	2	20	1.219
1000.0000	0.0441	0.881	1	20	0.129
2000.0000	0.5562	11.124	11	20	-0.056

Chi^2 = 2.65 d.f. = 7 P-value = 0.9156
Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 792.052
BMDL = 602.77



BMDS MODEL RUN $BMCL_{05}$- Quast et al. 1982a female mouse
Male mouse or combined data not shown; P<0.00001

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The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -17.4183
slope = 2.43645

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1
~~~~~~

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-28.352	7.77563	-43.5919	-13.112
slope	3.97635	1.11108	1.79867	6.15403

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-16.7382	7			
Fitted model	-19.8902	2	6.30409	5	0.2777
Reduced model	-39.9033	1	46.3303	6	<.0001
AIC:	43.7804				

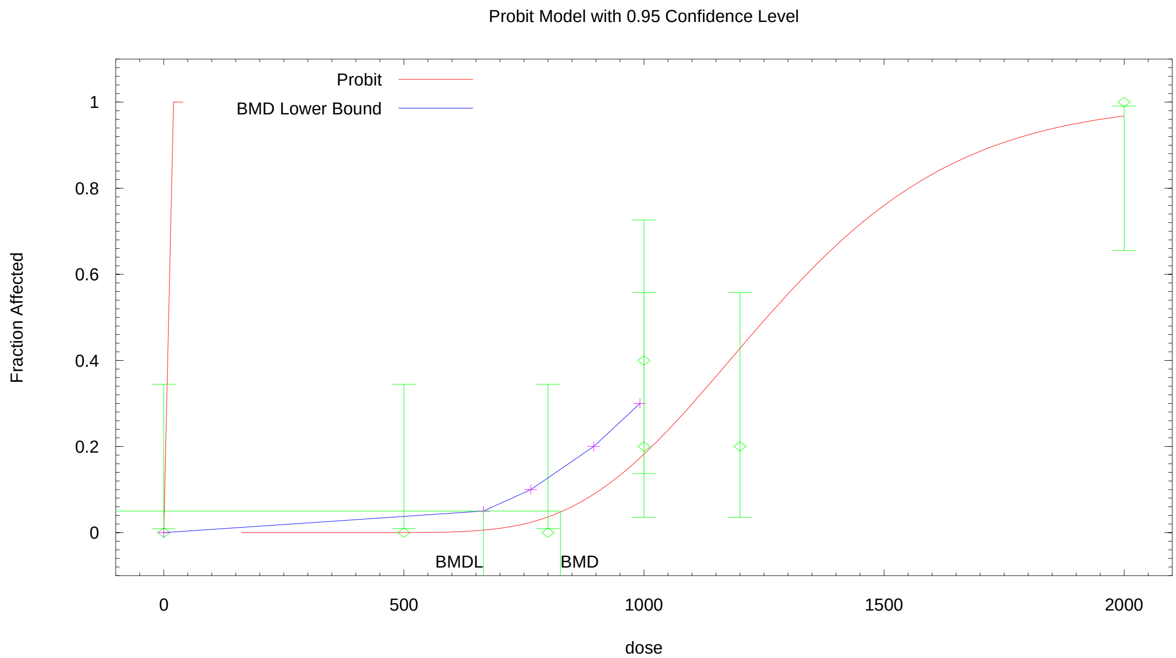
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
500.0000	0.0001	0.001	0	10	-0.037
800.0000	0.0382	0.382	0	10	-0.630
1000.0000	0.1883	1.883	4	10	1.713
1000.0000	0.1883	1.883	2	10	0.095
1200.0000	0.4367	4.367	2	10	-1.509
2000.0000	0.9694	9.694	10	10	0.562

Chi^2 = 5.93 d.f. = 5 P-value = 0.3126

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 825.909
BMDL = 665.554



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BMDS MODEL RUN BMC_{01}- Quast et al. 1982a female mouse

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The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -17.4183
slope = 2.43645

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1
~~~~~~

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-28.352	7.77563	-43.5919	-13.112
slope	3.97635	1.11108	1.79867	6.15403

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-16.7382	7			
Fitted model	-19.8902	2	6.30409	5	0.2777
Reduced model	-39.9033	1	46.3303	6	<.0001
AIC:	43.7804				

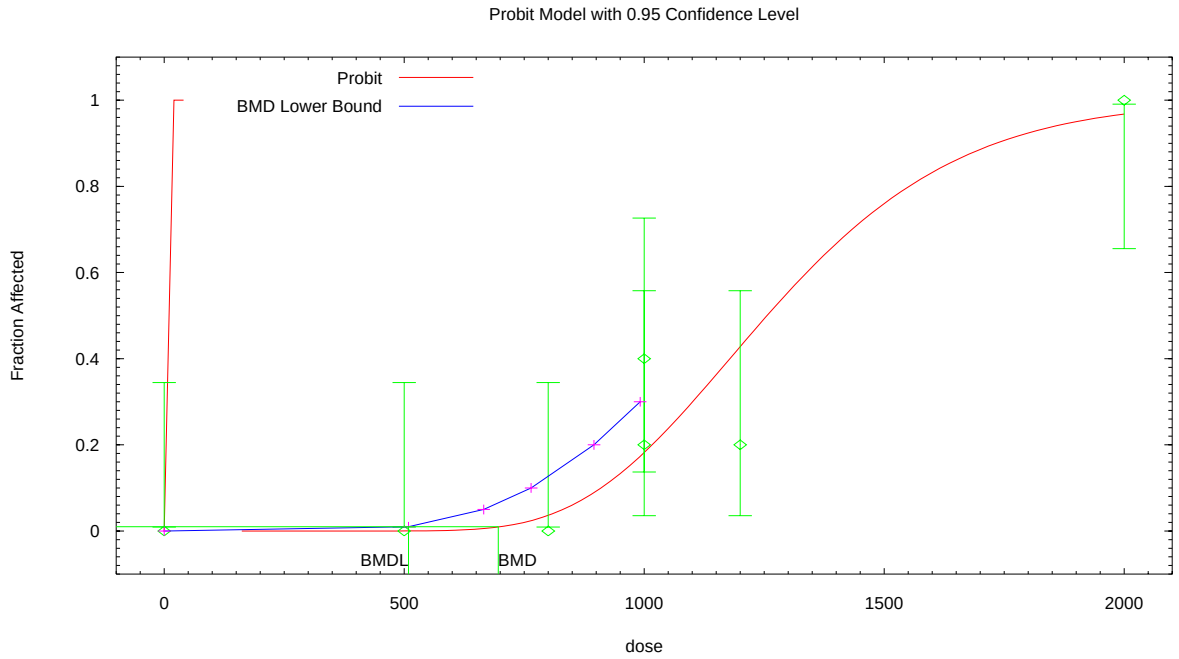
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
500.0000	0.0001	0.001	0	10	-0.037
800.0000	0.0382	0.382	0	10	-0.630
1000.0000	0.1883	1.883	4	10	1.713
1000.0000	0.1883	1.883	2	10	0.095
1200.0000	0.4367	4.367	2	10	-1.509
2000.0000	0.9694	9.694	10	10	0.562

Chi^2 = 5.93 d.f. = 5 P-value = 0.3126

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 695.824
BMDL = 509.114



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