

アリルクロリドの I A R C モノグラフ Vol.71 (1999)

概要

アリルクロリドの人に対する発癌性についての証拠は不十分である。

アリルクロリドの発癌性についての動物実験による証拠は不十分である。

総体的評価

アリルクロリドは人に対して発癌性ありと分類することはできない (グループ 3)。

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資料出所 I A R C モノグラフ Vol.71 (1999)

# ALLYL CHLORIDE

Data were last reviewed in IARC (1985) and the compound was classified in *IARC Monographs Supplement 7* (1987).

## 1. Exposure Data

### 1.1 Chemical and physical data

#### 1.1.1 Nomenclature

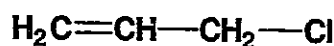
*Chem. Abstr. Serv. Reg. No.:* 107-05-1

*Chem. Abstr. Name:* 3-Chloro-1-propene

*IUPAC Systematic Name:* 3-Chloropropene

*Synonyms:* 3-Chloropropylene; 2-propenyl chloride

#### 1.1.2 Structural and molecular formulae and relative molecular mass



$\text{C}_3\text{H}_5\text{Cl}$

Relative molecular mass: 76.53

#### 1.1.3 Chemical and physical properties of the pure substance

- (a) *Description:* Colourless to pale yellow liquid with an unpleasant pungent odour (Budavari, 1996)
- (b) *Boiling-point:* 45.1°C (Lide, 1997)
- (c) *Melting-point:* -134.5°C (Lide, 1997)
- (d) *Solubility:* Slightly soluble in water (0.36 g/100 g at 20°C); miscible with ethanol, diethyl ether, chloroform and petroleum ether (American Conference of Governmental Industrial Hygienists, 1991; Budavari, 1996)
- (e) *Vapour pressure:* 45 kPa at 20°C; relative vapour density (air = 1), 2.64 (Verschueren, 1996)
- (f) *Flash point:* -31°C, closed cup (Budavari, 1996)
- (g) *Explosive limits:* Upper, 11.1%; lower, 3.3% by volume in air (American Conference of Governmental Industrial Hygienists, 1991)
- (h) *Reactivity:* Highly reactive and flammable (American Conference of Governmental Industrial Hygienists, 1991)
- (i) *Conversion factor:*  $\text{mg/m}^3 = 3.13 \times \text{ppm}$

## 1.2 Production and use

World production of allyl chloride in 1989–90 was estimated to be 500–600 thousand tonnes per year. Production facilities in 1990 were reported in Brazil, China, the Czech Republic, France, Germany, Japan, the Netherlands, Poland and the United States (Kneupper & Saathoff, 1993).

Allyl chloride is used to make intermediates for downstream derivatives such as resins and polymers. Approximately 90% of allyl chloride production is used to synthesize epichlorohydrin, which is used as a basic building block for epoxy resins and in glycerol synthesis. Allyl chloride is also a starting material for allyl ethers of phenols, bisphenol A and phenolic resins, and for some allyl esters. Other compounds made from allyl chloride are quaternary amines used in chelating agents and quaternary ammonium salts, which are used in water clarification and sewage sludge flocculation (Kneupper & Saathoff, 1993).

## 1.3 Occurrence

### 1.3.1 Occupational exposure

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 3000 workers in the United States were potentially exposed to allyl chloride (see General Remarks). Occupational exposure to allyl chloride may occur in its manufacture and in the production of epichlorohydrin, glycerol and a wide range of other chemical products.

### 1.3.2 Environmental occurrence

Although the production and use of allyl chloride may result in its release to the environment, few data are available (United States National Library of Medicine, 1998).

## 1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 3 mg/m<sup>3</sup> as the 8-h time-weighted average threshold limit value for occupational exposures to allyl chloride in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for allyl chloride in drinking-water has been established (WHO, 1993).

## 2. Studies of Cancer in Humans

Olsen *et al.* (1994) reported on the results of a retrospective cohort mortality study of workers in Texas, United States, with potential exposure to epichlorohydrin (see this volume) and allyl chloride. The cohort consisted of 1064 men employed in the epoxy resin, glycerine and allyl chloride/epichlorohydrin production areas of a large chemical facility between 1957 and 1986. Follow-up was carried out until 1989. Mortality was

compared with national rates and company rates for other facilities. There was no exposure to allyl chloride in the epoxy resin area. Exposures to allyl chloride were estimated to be between 1 and 5 ppm [3.1 and 15.7 mg/m<sup>3</sup>] in the glycerine area before 1970 and occasionally in some jobs in the allyl chloride/epichlorohydrin area, although respiratory protection may have been worn by these workers. There were 66 deaths (standardized mortality ratio (SMR), 0.8; 95% confidence interval (CI), 0.6–1.0). Ten cancers were observed (SMR, 0.5; 95% CI, 0.2–0.9, compared with national rates) in the entire cohort and no association between site-specific cancer risks and exposure to allyl chloride was observed.

### 3. Studies of Cancer in Experimental Animals

Allyl chloride was tested for carcinogenicity by gavage in mice and rats, by skin application in mice, both by repeated application and in a two-stage assay, and by intraperitoneal injection in mice. Following its oral administration to mice in an experiment that was compromised by high mortality in males, a nonsignificant increase in the incidence of squamous cell papillomas and carcinomas of the forestomach was observed in both sexes; the experiment in rats was inadequate for evaluation. No skin tumours were observed in mice following repeated skin applications; however, a single application followed by treatment with 12-*O*-tetradecanoylphorbol 13-acetate (TPA) increased the incidence of tumour-bearing mice from 6/90 in the TPA controls to 7/30 in treated mice ( $p < 0.025$ ) and reduced the time to first papilloma from 449 days to 197 days. Following intraperitoneal injection in strain A mice, there was a marginal increase in the multiplicity of lung adenomas (IARC, 1985).

## 4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

### 4.1 Absorption, distribution, metabolism and excretion

#### 4.1.1 *Humans*

No data were available to the Working Group.

#### 4.1.2 *Experimental systems*

Allyl chloride is presumed to be metabolized to allyl alcohol, which could then be further metabolized via two pathways to form either acrolein or glycidol, from which a variety of metabolites could result. Metabolites identified in rat urine are 3-hydroxypropylmercapturic acid and allyl mercapturic acid and its sulfoxide. Allyl glutathione and *S*-allyl-L-cysteine have been detected in the bile of dosed rats. In-vitro metabolism of allyl chloride results in haem destruction in microsomal cytochrome P450 (IARC, 1985).

Activation of allyl chloride to genotoxic substances appears to involve aldehydes, since inhibition of aldehyde dehydrogenase by cyanamide increases the mutagenic activity in *Salmonella typhimurium* TA100; on the other hand neither SKF525 nor 1,1,1-trichloropropene-2,3-oxide affect the mutagenicity, so that metabolic activation via an epoxide is unlikely (Neudecker & Henschler, 1986).

## 4.2 Toxic effects

### 4.2.1 Humans

Workers exposed to allyl chloride at concentrations ranging from 1 to 113 ppm [3–350 mg/m<sup>3</sup>] for 16 months showed enzymatic evidence of liver damage, which was reversible. One report described impaired kidney function in workers exposed to unknown concentrations. A reversible polyneuropathy was also described (IARC, 1985). A later study in China indicated that two-thirds of 26 workers in one factory exposed to allyl chloride at concentrations of 2.6–6650 mg/m<sup>3</sup> for 2.5–6 years during the production of allyl sulfonate from allyl chloride and sodium sulfite developed symptoms and signs of polyneuropathy. Thirteen of 27 workers in another factory in China who were exposed to allyl chloride at concentrations in the range of 0.2–25.1 mg/m<sup>3</sup> for 1–4.5 years showed similar but much milder symptoms of neuropathy, without evident neurological signs (He & Zhang, 1985; He *et al.*, 1985).

No evidence of liver or kidney dysfunction was found in 73 male workers employed for an average of 8.2 years (range, 0.5–23 years) in a plant in the Netherlands producing allyl chloride, 1,3-dichloropropene, epichlorohydrin and hexachlorocyclopentadiene. Mean allyl chloride concentrations ranged from 0.21 to 2.89 mg/m<sup>3</sup>; the values for hexachlorocyclopentadiene ranged from 0.01 to 0.23 mg/m<sup>3</sup>. Exposures to 1,3-dichloropropene and epichlorohydrin were well below the current maximum allowable concentrations. The results of the liver and kidney function tests were compared with those of 35 men in the same plant who were not occupationally exposed to these chemicals (Boogaard *et al.*, 1993).

It has been suggested that co-exposure to allyl chloride and epichlorohydrin may increase the risk of heart disease mortality. A study population of workers at a plant in Texas, United States, was divided into groups with a likelihood of exposure to allyl chloride in conjunction with high, moderate, low or nil exposure to epichlorohydrin. The SMR for heart disease mortality was 1.2 for 160 workers for whom exposure to allyl chloride and high/moderate exposure to epichlorohydrin had occurred, compared with 0.6 for 35 workers with low/nil co-exposure to epichlorohydrin, 0.7 for 88 workers who were probably not exposed to allyl chloride but who had potentially been heavily exposed to epichlorohydrin and 0.5 for 116 workers who also were probably not exposed to allyl chloride but had had light exposure to epichlorohydrin (Enterline *et al.*, 1990). It has been argued that important confounders and specific exposure data were not considered (Ross, 1990) and the need for further research on this apparent association has been stressed (Enterline, 1990).

A retrospective cohort mortality study in Texas, United States (see also Section 2) failed to confirm an effect of co-exposure upon mortality (Olsen *et al.*, 1994). However,

the authors noted that the results were limited by the cohort size, duration of follow-up, relatively small numbers of observed and expected deaths and the level of potential exposure to epichlorohydrin.

#### 4.2.2 *Experimental systems*

Following inhalation exposure to allyl chloride, necrosis in the respiratory tract was the usual cause of death in rats and guinea-pigs. Major systemic effects were degenerative changes in kidney and liver in rats, guinea-pigs and rabbits inhaling 8 ppm [25 mg/m<sup>3</sup>] for 7 h per day on five days per week for five weeks, whereas 3 ppm [9.3 mg/m<sup>3</sup>] for six months under the same conditions produced no observed effect in these species or in dogs. Exposure of rabbits and cats to allyl chloride atmospheres of 206 mg/m<sup>3</sup> for 6 h per day on six days per week for three months resulted in partially reversible flaccid paralysis with muscular atrophy in rabbits; cats were less affected. Exposure to 17.5 mg/m<sup>3</sup> had no effect in either species. Subcutaneous injection of 50 mg/kg bw allyl chloride also resulted in peripheral neuropathy in rabbits (IARC, 1985).

Mice treated orally with 300 or 500 mg/kg bw allyl chloride on three days per week for two to 17 weeks developed focal kidney damage and degeneration in many peripheral nerves and roots (He *et al.*, 1981), confirming earlier observations in other species. Peripheral nerve fibre degeneration was also confirmed in rabbits treated by subcutaneous injection (He *et al.*, 1985).

Male ICR mice were given single subcutaneous injections of allyl chloride at dose levels of 496–1037 mg/kg bw (LD<sub>50</sub> by this route being 621 mg/kg bw; 95% CI, 522–739 mg/kg bw). Mice dying within 24 h showed consistent, severe haemorrhage and oedema of the lung and inconsistent, non-dose-related damage to the liver and kidney. The latter was not observed in mice killed on day 7, when histopathological changes were confined to the testes (Omura *et al.*, 1993), a novel finding.

### 4.3 **Reproductive and developmental effects**

#### 4.3.1 *Humans*

No data were available to the Working Group.

#### 4.3.2 *Experimental systems*

Inhalation exposure to allyl chloride of high purity was not teratogenic to either rats or rabbits (IARC, 1985). However, intraperitoneal administration of allyl chloride (80 mg/kg bw) to pregnant rats on gestation days 1–15 was reported to increase the frequencies of resorptions and of fetuses with short snout and protruding tongue. The authors intended to investigate possible reasons for the differences between the results from the two studies (Hardin *et al.*, 1981).

#### 4.4 Genetic and related effects

##### 4.4.1 Humans

No data were available to the Working Group.

##### 4.4.2 Experimental systems (see Table 1 for references)

Allyl chloride caused DNA damage in bacteria, was mutagenic to bacteria and fungi and induced gene conversion in yeast. It also induced chromosomal aberrations in cultured Chinese hamster lung cells, this activity being greater in the absence of an exogenous activation system. Allyl chloride can bind to isolated DNA, although it is a weak alkylating agent. Five alkylated bases have been identified: *N*3-allyladenine, *N*<sup>6</sup>-allyl-adenine, *N*<sup>2</sup>-allylguanaine, *N*7-allylguanaine and *O*<sup>6</sup>-allylguanaine (Eder *et al.*, 1987).

### 5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of allyl chloride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of allyl chloride.

#### Overall evaluation

Allyl chloride is *not classifiable as to its carcinogenicity to humans (Group 3)*.

### 6. References

- American Conference of Governmental Industrial Hygienists (1991) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Vol. 1, Cincinnati, OH, pp. 37-42
- American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs® and BEIs®*, Cincinnati, OH, p. 15
- Biggami, M., Conti, G., Conti, L., Crebelli, R., Misuraca, F., Puglia, A.M., Randazzo, R., Sciandrello, G. & Carere, A. (1980) Mutagenicity of halogenated aliphatic hydrocarbons in *Salmonella typhimurium*, *Streptomyces coelicolor* and *Aspergillus nidulans*. *Chem.-biol. Interact.*, **30**, 9-23
- Boogaard, P.J., Rocchi, P.S.J. & van Sittert, N.J. (1993) Effects of exposure to low concentrations of chlorinated hydrocarbons on the kidney and liver of industrial workers. *Br. J. ind. Med.*, **50**, 331-339
- Budavari, S., ed. (1996) *The Merck Index*, 12th ed., Whitehouse Station, NJ, Merck & Co., p. 53
- Eder, E., Neudecker, T., Lutz, D. & Henschler, D. (1980) Mutagenic potential of allyl and allylic compounds. Structure-activity relationship as determined by alkylating and direct in vitro mutagenic properties. *Biochem. Pharmacol.*, **29**, 993-998
- Eder, E., Neudecker, T., Lutz, D. & Henschler, D. (1982) Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs. kinetic investigation. *Chem.-biol. Interact.*, **30**, 303-315

Table 1. Genetic and related effects of allyl chloride

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECD, <i>Escherichia coli</i> pol A <sup>+</sup> /pol A <sup>-</sup> differential toxicity (spot test)	+	NT	9400	McCoy <i>et al.</i> (1978)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	9400/disk	McCoy <i>et al.</i> (1978)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	(+)	2350	Bignami <i>et al.</i> (1980)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	+	(+)	1150	Eder <i>et al.</i> (1980)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	+	NT	0.02	Norpoth <i>et al.</i> (1980)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	+	NT	0.05 <sup>c</sup>	Simmon (1981)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	+	(+)	NG	Eder <i>et al.</i> (1982)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	(+)	+	250	Neudecker & Henschler (1985)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	NT	+	235	Neudecker & Henschler (1986)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	(+)	+	940/disk	McCoy <i>et al.</i> (1978)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	+	2350	Bignami <i>et al.</i> (1980)
SA8, <i>Salmonella typhimurium</i> TA1538, reverse mutation	-	-	9400/disk	McCoy <i>et al.</i> (1978)
SCG, <i>Saccharomyces cerevisiae</i> D4, gene conversion	+	NT	14	McCoy <i>et al.</i> (1978)
STF, <i>Streptomyces coelicolor</i> , forward mutation	+	NT	4700	Bignami <i>et al.</i> (1980)
STR, <i>Streptomyces coelicolor</i> , reverse mutation	+	NT	4700	Bignami <i>et al.</i> (1980)
ANF, <i>Aspergillus nidulans</i> , forward mutation	-	NT	18800	Bignami <i>et al.</i> (1980)



Table 1 (contd)

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster lung CHL cells <i>in vitro</i>	+	+	400	JETOC (1997)
BID, Binding (covalent) to DNA <i>in vitro</i>	(+)	NT	9000	Eder <i>et al.</i> (1987)

<sup>a</sup> +, positive; (+), weak positive; -, negative; NT, not tested

<sup>b</sup> LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; NG, not given

<sup>c</sup> Cells were exposed to allyl chloride vapour; dose = µg/mL in air.

- Eder, E., Lutz, D. & Jörns, M. (1987) Allylic compounds bind directly to DNA: investigation of the binding mechanisms *in vitro*. *Chem.-biol. Interact.*, **61**, 97-108
- Enterline, P.E. (1990) Author's reply. *Br. J. ind. Med.*, **47**, 789-790
- Enterline, P.E., Henderson, V. & Marsh, G. (1990) Mortality of workers potentially exposed to epichlorohydrin. *Br. J. ind. Med.*, **47**, 269-276
- Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. & Shelby, M.D. (1989) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*. III. Results with 27 chemicals. *Environ. mol. Mutag.*, **13**, 133-193
- Hardin, B.D., Bond, G.P., Sikov, M.R., Andrew, F.D., Beliles, R.P. & Niemeier, R.W. (1981) Testing of selected workplace chemicals for teratogenic potential. *Scand. J. Work. Environ. Health*, **7** (Suppl. 4), 66-75
- He, F. & Zhang, S.L. (1985) Effects of allyl chloride on occupationally exposed subjects. *Scand. J. Work. Environ. Health*, **11** (Suppl. 4), 43-45
- He, F., Jacobs, J.M. & Scaravilli, F. (1981) The pathology of allyl chloride neurotoxicity in mice. *Acta neuropathol. berl.*, **55**, 125-133
- He, F., Lu, B.Q., Zhang, S., Dong, S., Yu, A. & Wang, B. (1985) Chronic allyl chloride poisoning. An epidemiology, clinical, toxicological and neuropathological study. *G. ital. Med. Lav.*, **7**, 5-15
- IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 36, *Allyl Compounds, Aldehydes, Epoxides and Peroxides*, Lyon, pp. 39-54
- IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Lyon, p. 56
- International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 96-97
- JETOC (1997) *Mutagenicity Test Data of Existing Chemical Substances*, Suppl., Tokyo, Japan Chemical Industry Ecology-Toxicology and Information Center, pp. 278-279
- Kneupper, C. & Saathoff, L. (1993) Chlorocarbons, -hydrocarbon, (allyl chloride). In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 6, New York, John Wiley, pp. 59-69
- Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics*, 78th Ed., Boca Raton, FL, CRC Press, p. 3-288
- McCoy, E.C., Burrows, L. & Rosenkranz, H.S. (1978) Genetic activity of allyl chloride. *Mutat. Res.*, **57**, 11-15
- Neudecker, T. & Henschler, D. (1985) Mutagenicity of chloro-olefins in the *Salmonella*/mammalian microsome test. I. Allyl chloride mutagenicity re-examined. *Mutat. Res.*, **157**, 145-148
- Neudecker, T. & Henschler, D. (1986) Mutagenicity of chloroolefins in the *Salmonella*/mammalian microsome test. III. Metabolic activation of the allylic chloropropenes allyl chloride, 1,3-dichloropropene, 2,3-dichloro-1-propene, 1,2,3-trichloropropene, 1,1,2,3-tetrachloro-2-propene and hexachloropropene by S9 mix via two different metabolic pathways. *Mutat. Res.*, **170**, 1-9

- NOES (1997) *National Occupational Exposure Survey 1981-83*, Unpublished data as of November 1997, Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, United States National Institute for Occupational Safety and Health
- Norpoth, K., Reisch, A. & Heinecke, A. (1980) Biostatistics of Ames-test data. In: Norpoth, K.H. & Garner, R.C., eds, *Short-term Test Systems for Detecting Carcinogens*, New York, Springer-Verlag, pp. 312-322
- Olsen, G.W., Lacy, S.E., Chamberlin, S.R., Albert, D.L., Arceneaux, T.G., Bullard, L.F., Stafford, B.A. & Boswell, J.M. (1994) Retrospective cohort mortality study of workers with potential exposure to epichlorohydrin and allyl chloride. *Am. J. ind. Med.*, **25**, 205-218
- Omura, M., Itonaga, Y., Komatsu, H., Mangen, Z., Hirata, M., Tanaka, A. & Inoue, N. (1993) The acute toxicity of allyl chloride by subcutaneous injection in mice. *Fukuoka Acta med.*, **84**, 427-432
- Ross, C.E. (1990) Mortality among workers exposed to epichlorohydrin. *Br. J. ind. Med.*, **47**, 789-790
- Simmon, V.F. (1981) Applications of the *Salmonella*/microsome assay. In: Stich, H.F. & San, R.H.C., eds, *Short-term Tests for Chemical Carcinogens*, New York, Springer-Verlag, pp. 120-126
- United States National Library of Medicine (1998) *Hazardous Substances Data Bank (HSDB)*, Bethesda, MD [Record No. 178]
- Verschueren, K. (1996) *Handbook of Environmental Data on Organic Chemicals*, 3rd Ed., New York, Van Nostrand Reinhold, pp. 160-161
- WHO (1993) *Guidelines for Drinking Water Quality*, 2nd Ed., Vol. 1. *Recommendations*, Geneva