

アリルクロリドの IARCモノグラフ Vol.36 (1985)

概要

1 曝露データ

アリルクロリドは 1945 年以來ずっと商業的に生産されていて、主としてエピクロロヒドリンの生産において、ほとんど専ら、中間体として用いられている。

2 実験データ

アリルクロリドはその発癌性について、マウス (小型ネズミ) とラット (大型ネズミ) における胃内挿管法、マウスにおける皮膚外用法、反復適用及び 2 段階評価の両法、及びマウスにおける腹腔内注射法によって実験されている。

マウスに対する経口投与後には、扁平上皮細胞乳頭腫および噴門洞 (または前胃) 癌の兆候の軽微な増大が観察された; ラットの場合の実験は評価するには不適當であった。マウスの場合に、皮膚への反復外用の後では、皮膚腫瘍は全く観察されなかった; しかし、12-O-テトラデカノイルホルポール 13-アセテートによる処理の後での 1 回の外用によって、アリルクロリドが発癌の開始剤として働くことの証拠が得られた。A マウスを刺激するための腹腔内注射の後では、肺腺腫の発生のわずかな増加が観察された。

ラットまたはうさぎの場合に、高純度のアリルクロリドの吸入曝露は奇形化を誘起しなかった。

アリルクロリドは細菌に DNA 損傷を起こさせ、また細菌と真菌に対する突然変異誘発性を有した。

3 人についてのデータ

本ワーキンググループは人に対するアリルクロリドの発癌性についての症例報告も疫学的研究も入手できなかった。

4 評価

実験動物の場合に、アリルクロリドの発癌性の証拠は不十分である。

疫学的データがないので、アリルクロリドの人に対する発癌性についての評価は不可能であった。

資料出所 IARCモノグラフ Vol.36 (1985)

ALLYL CHLORIDE

1. Chemical and Physical Data

1.1 Synonyms and trade names

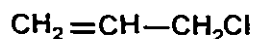
Chem. Abstr. Services Reg. No.: 107-05-1

Chem. Abstr. Name: 1-Propene, 3-chloro-

IUPAC Systematic Name: 3-Chloropropene

Synonyms: AC; chlorallylene; chloroallylene; 1-chloropropene-2; 3-chloropropene-1; 1-chloro-2-propene; 3-chloro-1-propene; α -chloropropylene; 3-chloropropylene; 3-chloro-1-propylene; NCI-C04615; 2-propenyl chloride

1.2 Structural and molecular formulae and molecular weight



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

Mol. wt: 76.5

1.3 Chemical and physical properties of the pure substance

From DeBenedictis (1979), unless otherwise specified

- (a) *Description:* Colourless liquid with a pungent, garlic-like odour (Verschueren, 1977)
- (b) *Boiling-point:* 44.96°C (Beacham, 1978)
- (c) *Freezing-point:* -134.5°C
- (d) *Density:* Specific gravity (20°C), 0.9392
- (e) *Refractive index:* n_D^{20} 1.4160 (Beacham, 1978)
- (f) *Spectroscopy data:* Proton magnetic resonance spectra have been reported (Bothner-By *et al.*, 1966).

- (g) *Solubility*: Slightly soluble (0.36 wt %) in water; miscible with chloroform, diethyl ether, ethanol and petroleum ether (Windholz, 1983)
- (h) *Viscosity*: 0.336 cP at 20°C
- (i) *Volatility*: Vapour pressure, 295.5 mm Hg at 20°C (Beacham, 1978)
- (j) *Stability*: Flash-point (closed-cup), -31.7°C
- (k) *Reactivity*: Reacts as both an olefin (e.g., additions) and an organic halide (e.g., hydrolysis); undergoes a variety of nucleophilic substitution reactions
- (l) *Conversion factor*: 1 ppm = 3.13 mg/m³ at 760 mm Hg and 25°C (Irish, 1963)

1.4 Technical products and impurities

In 1949, allyl chloride was available in the USA as a single grade with a purity of 97% min. Possible impurities were said to be 2-chloropropene, isopropyl chloride, *n*-propyl chloride and traces of 3,3-dichloropropene (Vesper, 1949).

In 1973, allyl chloride was available in two grades in the USA. A water-washed grade contained 0.01% acidity (as hydrogen chloride) max and an anhydrous grade contained 0.10% acidity max. Both grades met the following specifications: purity, 97% min; apparent specific gravity (20/20°C), 0.935-0.939; and distillation range, 43.0-49.0°C (Bales, 1977).

Allyl chloride is available in western Europe with the following specifications: purity, 97.5% min; water, 200 mg/kg max; specific gravity, 0.932-0.938; and distillation range, 43-50°C.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Allyl chloride was first prepared in 1857 by Cahours and Hofmann by the reaction of allyl alcohol with phosphorus chloride (Vesper, 1949). It was first produced commercially in 1945 from propylene (IARC, 1979a) by means of non-catalytic, high-temperature (500-510°C) chlorination (Beacham, 1978); this method is still used for commercial production (DeBenedictis, 1979).

US production of allyl chloride in 1977 was estimated to have been almost 180 million kg (DeBenedictis, 1979). Only two US companies presently produce it (at three plant locations), and production data are not disclosed (see Preamble, section 8(b)(ii)). Separate data on US imports and exports of allyl chloride are not published.

Allyl chloride is produced commercially by one company in France, one company in the German Democratic Republic, three companies in Germany and one company in the Netherlands.

The commercial production of allyl chloride in Japan started in about 1961. Three Japanese companies currently manufacture it by the chlorination of propylene; 1982 production is estimated to have been 30-40 million kg.

(b) Use

Allyl chloride is used almost exclusively as a chemical intermediate. The major use is as an intermediate for epichlorohydrin (see IARC, 1976). It is also used to make sodium allylsulphonate and a series of allyl amines and quaternary ammonium salts as well as the allyl ethers of a variety of alcohols, phenols and polyols, and a number of barbiturate hypnotic agents.

An estimated 150 million kg of allyl chloride were used as a chemical intermediate (probably unisolated) for epichlorohydrin manufacture in the USA in 1982. Epichlorohydrin is used principally for the manufacture of epoxy resins and glycerol (Beacham, 1978).

Sodium allylsulphonate is made by the reaction of allyl chloride with sodium sulphite; it is used as a component in metal plating baths (DeBenedictis, 1979). US production of this chemical was last reported separately in 1973, when it amounted to 843 thousand kg (US International Trade Commission, 1975).

Allyl chloride is used to make mono-, di-, and triallylamine as well as mixed amines containing other alkyl groups (e.g., diallylmethylamine). These amines find use as such, and as intermediates for other chemicals, such as ambuside (a diuretic), diallyl 2-chloroacetamide (a herbicide) (Beacham, 1978), and several quaternary ammonium salts. The most important allyl amine derivative is believed to be diallyl dimethylammonium chloride, which finds use as a comonomer with acrylamide and other monomers in the production of cationic flocculating agents.

Allyl ethers of polyols such as trimethylol propane have reportedly been used commercially in polyester furniture finishes to improve their drying properties. Another ether made from allyl chloride, allyl starch, was formerly made in commercial quantities in the USA for use in surface coatings (Beacham, 1978).

The following six barbiturate hypnotic agents may be made from allyl chloride: aprobarbital, butalbital, methohexital sodium, secobarbital, talbutal and thiamylal sodium, although one source (Swinyard, 1975) has indicated that such products are made from allyl bromide.

Allyl chloride is also used to make allyl isothiocyanate (see p. 55 of this volume), eugenol (see p. 75 of this volume) and 1,2-dibromo-3-chloropropane (see IARC, 1979b). It has reportedly been used in Japan to make allyl esters (e.g., diallyl phthalate).

Other commercial uses which have been reported for allyl chloride include the synthesis of glycerol chlorohydrins, trichloropropane and cyclopropane (Shell Chemical Corp., 1949).

In Japan, allyl chloride is used as a chemical intermediate for epichlorohydrin (the major use) and other chemicals (e.g., pesticides and pharmaceuticals).

Occupational exposure to allyl chloride has been limited by regulation or recommended guidelines in at least 11 countries. The standards are listed in Table 1.

The US Environmental Protection Agency (EPA) (1983) requires that notification be given whenever discharges containing 454 kg or more of allyl chloride are made into waterways,

Table 1. National occupational exposure limits for allyl chloride^a

Country	Year	Concentration		Interpretation ^b	Status
		mg/m ³	ppm		
Australia	1978	3	1	TWA	Guideline
Belgium	1978	3	1	TWA	Regulation
Finland	1981	3	1	TWA	Guideline
		9	3	STEL	
German Democratic Republic	1979	3	-	TWA	Regulation
		6	-	Maximum (30 min)	
Germany, Federal Republic of	1984	3	1	TWA ^c	Guideline
Italy	1978	3	1	TWA	Guideline
Netherlands	1978	3	1	TWA	Guideline
Romania	1975	3	-	TWA	Regulation
		6	-	Maximum	
Switzerland	1978	3	1	TWA	Regulation
USA ^d					
OSHA	1978	3	1	TWA	Regulation
		-	300	Maximum (30 min) ^e	
ACGIH	1984/85	3	1	TWA	Guideline
		6	2	STEL	
NIOSH	1976	3	1	TWA	Guideline
		9	3	Ceiling (15 min)	
Yugoslavia	1971	3	1	Ceiling	Regulation

^aFrom International Labour Office (1980); National Institute for Occupational Safety and Health (1980); National Finnish Board of Occupational Safety and Health (1981); American Conference of Governmental Industrial Hygienists (1984); Deutsche Forschungsgemeinschaft (1984)

^bTWA, time-weighted average; STEL, short-term exposure limit

^cCarcinogenic risk notation added

^dOSHA, Occupational Safety and Health Administration; ACGIH, American Conference of Governmental Industrial Hygienists; NIOSH, National Institute for Occupational Safety and Health

^eSkin irritant notation added

but has proposed that this be revised to require notification when discharges containing 2270 kg are made.

As part of the Hazardous Materials Regulations of the US Department of Transportation (1982), shipments of allyl chloride are subject to a variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material.

2.2 Occurrence

(a) Natural occurrence

Allyl chloride has not been reported to occur in nature.

(b) Occupational exposure

It has been estimated that approximately 5000 workers in the USA are potentially exposed to allyl chloride. Occupations involving potential exposure to allyl chloride have been reported to include producers of allyl chloride, epichlorohydrin (crude epichlorohydrin can contain 10-15% allyl chloride), glycerol, diallyldimethylammonium chloride, allyl alcohol (by a process no longer in current use) and medicinal products (National Institute for Occupational Safety and Health, 1976).

Occupational exposure has been reported in a plant producing allyl chloride in the German Democratic Republic. The data are summarized in Table 2.

Table 2. Occupational exposure to allyl chloride at various locations in an allyl chloride plant in the German Democratic Republic^a

Plant area	Concentration (mg/m ³)
Laboratory	3
Filling	19
Production	53-59
Tank storage	43-310
Pump room	189-350

^aFrom Häusler and Lenich (1968)

Results of personnel monitoring at two US allyl chloride plants are summarized in Tables 3 and 4.

Table 3. Levels of allyl chloride at a US allyl chloride manufacturing site^a

Job classification	No. of samples	Concentration ^b (mg/m ³)		
		High	Low	Average
Control room, operator A	6	2.82	0.59	1.40
Control room, operator C	8	2.91	0.74	1.77
Instrument	4	14.63 ^c	0.37	6.70
Laboratory	4	2.20	0.71	1.24
Shift foreman	4	12.49 ^c	0.37	4.03
Maintenance	4	18.88 ^c	2.42	9.46
Class 2 operator	5	19.00 ^c	0.016	5.36
Head packaging operator	2	0.28	0.062	0.16
Chief material-handling technician	2	0.96	0.40	0.58

^aFrom National Institute for Occupational Safety and Health (1976)

^bIt is possible that high values are caused by acetone interference.

^cPotential exposure; protective equipment was worn during sampling operations and process upsets.

Table 4. Results of allyl chloride monitoring at a US manufacturing plant^a

Job classification	Eight-hour TWA ^b			Peak (up to 15 min)			Comments
	No. of TWAs	Range (mg/m ³)	Mean ^c (mg/m ³)	No. of samples	Range (mg/m ³)	Mean ^c (mg/m ³)	
Loading	8	1.2-9.9	5.9	5	19.2-122.5	60.5	Loading operators wear breathing masks. Drum-loading measurements were taken prior to installation of ventilation system. Tank car and tank truck loading rate is 2-3 h/day for each.
Operators, except 70 for G-300		<0.3-11.2	1.46	15	0.3-95.2	35.0	Evaluations are for routine operations and do not include shut-down or start-up periods when full breathing apparatus is worn.
G-300 operators	5	0.3-16.4	- ^d	-	-	-	
Shift foreman	16	0.3-10.5	1.89	-	-	-	

^aFrom National Institute for Occupational Safety and Health (1976)

^bTWA, time-weighted average

^cThis represents the arithmetic mean, which is an overestimate of the central tendency of distribution; the data appear to follow a log-normal distribution with a lower geometric mean.

^dFour of five samples contained <1 mg/m³.

Occupational exposure to allyl chloride associated with the production of epichlorohydrin has been reported. Data reported on US units in 1976 are summarized in Table 5 (which mainly reflects potential exposures, since protective equipment was generally used) and Table 6. Data on US manufacturing facilities from reports made in 1977 and 1978 are shown in Table 7.

Table 5. Levels of allyl chloride at a US epichlorohydrin unit^a

Job classification	No. of samples	Concentration ^b (mg/m ³)		
		High	Low	Average
Control room, operator A	5	3.44 ^c	0.12	1.52
Instrument Laboratory	2	3.84 ^c	0.96	2.42
Laboratory	6	10.60 ^c	0.12	4.96
Shift foreman	3	14.48 ^c	1.21	5.86
Epichlorohydrin helper	4	8.40 ^c	0.16	2.73
Control finisher	2	4.40 ^c	0.84	2.64
Maintenance	13	1.58	0.16	0.62

^aFrom National Institute for Occupational Safety and Health (1976)

^bIt is possible that high values are caused by acetone interference.

^cPotential exposure; protective equipment was worn during sampling operations and process upsets.

Table 6. Occupational exposure to allyl chloride at a US epichlorohydrin-manufacturing site^a

Job classification	Eight-hour TWA ^b			Peak (up to 15 min)			Comments
	No. of TWAs	Range	Mean ^c (mg/m ³)	No. of samples	Range (mg/m ³)	Mean ^c (mg/m ³)	
Marine cargo inspection	-	-	-	5	<0.3-8.4	2.8	Gauging and inspecting crude epichlorohydrin barges. Exposure is limited to about 13-20 min/barge and 2-3 barges/month. Allyl chloride is a contaminant (10-15%) in crude epichlorohydrin.
Dockman	1	<0.3	-	7	<0.3-18.6	4.7	Connecting and disconnecting barge loading lines on crude epichlorohydrin barges

^aFrom National Institute for Occupational Safety and Health (1976)

^bTWA, time-weighted average

^cThis represents the arithmetic mean, which is an overestimate of the central tendency of distribution; the data appear to follow a log-normal distribution with a lower geometric mean.

Table 7. Occupational exposure to allyl chloride at various locations in epichlorohydrin manufacturing facilities^a

Job classification	Plant	No. of samples	Time-weighted average (mg/m ³) ^b	
			Range	Median
Chemical operators	A	8	<0.16-2.11	0.56
	B	12	<0.16-27.6	<0.16
	C	6	<0.3-44.2	1.43
	C	5	<0.3-1.59	0.64
	C	5	<0.3-0.95	0.32
Foremen Epichlorohydrin production	C	5	<0.03-2.06	0.32
	A	3	<0.16-0.93	0.53
	B	3	<0.16-0.62	0.53
	B	1	0.53	0.53
	C	6	<0.3-0.95	[0.21]
Epoxide plant production	C	1	--	0.31
	C	1	--	<0.3
Tank truck loading	B	1	<0.16	<0.16
	C	1	--	<0.3
Pipe fitters	A	3	<0.16	<0.16
Control room area	B	3	<0.16	<0.16
	C	5	<0.3-0.95	[<0.3]
	C	1	0.3	<0.16
Glycerol production area	B	1	0.32-0.54	[0.44]
	C	2	0.32-0.54	[0.44]

^aFrom Bales (1978)

^bTime-weighted average concentration to which workers may be exposed for a normal eight-hour working day of a 40-hour week; figures in square brackets were calculated by the Working Group.

The majority of exposures were within the time-weighted average (TWA) for allyl chloride recommended by the National Institute for Occupational Safety and Health. Although at plants B and C levels for two chemical operators reached 27.6 and 44.2 mg/m³ (TWA), respectively, these samples were considered abnormal since they were taken during the repairing of processing machinery; the operators were wearing cartridge respirators so that actual exposure was considered to be significantly less.

(c) Air

Diurnal urban air samples, collected in the USA from Denver, CO, Houston, TX, Riverside, CA, and St Louis, MO, were found to contain <16 ng/m³ of allyl chloride, whereas samples from Pittsburgh, PA, were found to contain a mean of 64 ng/m³. None was detected in Chicago, IL, or Staten Island, NY (Singh *et al.*, 1982).

2.3 Analysis

Typical methods for the analysis of allyl chloride in various matrices are summarized in Table 8.

Table 8. Methods for the analysis of allyl chloride

Sample matrix	Sample preparation	Assay procedure ^a	Limit of detection	Reference
Air	Trap onto Tenax-GC; desorb thermally	GC/FID	not given	Brown & Purnell (1979)
	Trap onto charcoal; desorb with benzene	GC/FID	1.8-7.19 mg/m ³ (range of validation)	National Institute of Occupational Safety and Health (1977)
	Concentrate on a glass wool trap at liquid oxygen temperature; desorb thermally	GC/EC	<3 ng/m ³ (\pm 15%)	Singh <i>et al.</i> (1982)
	--	GC	0.2 mg/m ³	Yu <i>et al.</i> (1981)
	Trap onto Tenax-GC; desorb thermally	GC/MS	83 ng/m ³	Krost <i>et al.</i> (1982)
Waste water	Sparge with an inert gas; trap volatiles onto Tenax-GC; desorb thermally	GC/MS	2 μ g/l	Spingarn <i>et al.</i> (1982)

^aAbbreviations: GC/FID, gas chromatography/flame ionization detection; GC/EC, gas chromatography/electron capture detection; GC, gas chromatography; GC/MS, gas chromatography/mass spectroscopy

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female B6C3F₁ mice, five weeks old, were given doses of 172 or 199 and 129 or 258 mg/kg bw (low- or high-dose males and females, respectively) allyl chloride (technical grade; purity, 98%) per day in corn oil by gavage on five days per week for 78 weeks. Groups of 20 animals of each sex received corn oil alone and served as vehicle controls, and a further 20 animals of each sex served as untreated controls. Animals were maintained without further exposure through week 92. There was excessive mortality in male mice; 48% of mice in the high-dose group had died by week 27, and the 10 mice surviving longer than 48 weeks were killed at week 56. Survival rates in other groups at the end of the study were 8/20, 14/20 and 23/50 in untreated controls, vehicle controls and the low-dose group, respectively. Of the females, 70-90% of mice were still alive at the end of the study. Treatment-related lesions were observed in the forestomachs of animals of both sexes. A metastasizing squamous-cell carcinoma was found in 2/46 low-dose male mice, but not in high-dose (0/50), vehicle-control (0/20) or untreated (0/18) males. Acanthosis and hyperkeratosis of the forestomach were found in 9/46 low-dose and 19/50 high-dose, but not in control males. In females, a squamous-cell carcinoma was found in 2/48 low-dose, but not in high-dose (0/45), vehicle-control (0/19) or untreated (0/20) groups. Squamous-cell papillomas were observed in three high-dose and in one low-dose female. Acanthosis and hyperkeratosis of the forestomach occurred in 17 low-dose and 25 high-dose females, but not in controls. The incidence of forestomach tumours in male and female mice was not statistically different from that in controls (National Cancer Institute, 1977; Weisburger, 1977). [The Working Group noted the high mortality in treated males.]

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, six weeks of age, were given initial doses of 70 and 140, and 55 and 110 mg/kg bw (low-dose and high-dose males