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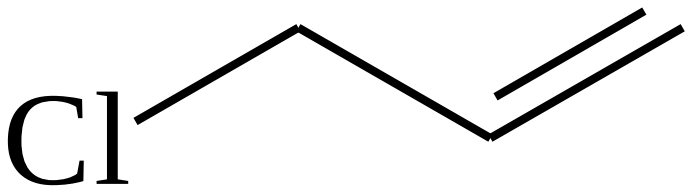
Allyl Chloride



Molecular Weight: 76.5

CAS Registry No.: 107-05-1

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Listing History: Allyl Chloride

- Listed under Proposition 65 on January 1, 1990
- Based on a report U.S. EPA (U.S. EPA, 1987)
  - Limited animal data
  - Supporting evidence: mutagenicity, metabolism to epichlorohydrin, alkylation properties.
- Classified as a Group C carcinogen (U.S. EPA, 1990)

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Reviews by Other Authoritative Bodies

- IARC
  - Group 3 carcinogen (IARC, 1985; 1987, 1999)
    - Inadequate evidence in experimental animals and humans
- NCI
  - “Suggestive evidence” (NCI, 1978)
    - Male and female $B6C3F_1$ mice, low incidence of rare forestomach neoplasms
    - No convincing evidence in rats of either sex

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Human Carcinogenicity Data: Allyl Chloride

- Three occupational epidemiological studies: potential exposure to allyl chloride
  - Enterline *et al*., 1990: leukemia
  - Olsen *et al*., 1994
  - Tsai *et al*., 1996

None of these studies is informative about the carcinogenic effects of allyl chloride.

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Forestomach Tumors B6C3F$_1$ Mice (NCI, 1978)

		Dose, mg/kg$_{bw}$-day			
Tumor Site and Type		vehicle	untreated	low	high
Males			0	175	199
Forestomach	Squamous Cell Carcinoma	0/20	0/20	2/46*	No survivors
Females			0	129	258
Forestomach	Squamous Cell Carcinoma	0/20	0/20	2/48	0/45
	Squamous Cell Papilloma	0/20	0/20	1/48	3/45

*Metastases and additional leiomyosarcoma of the forestomach.

Precancerous lesions of the forestomach in exposed animals of both sexes

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Lung Adenomas in Strain A Mice (Theiss *et al*., 1979)

		Dose, mg/kg$_{bw}$			
Tumor Site and Type		control	low	mid	high
(Sexes combined)		0	0.65	1.6	3.2
Lung	Adenoma: Tumors per mouse	0.19 ± 0.10	0.6 ± 0.20	0.5 ± 0.27	0.60* ± 0.15

i.p. injection 3 times per week for 8 weeks

*Significant relative to control by one of two tests used by study authors: carcinogenic effect was considered “intermediate”.

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Gavage Studies in Osborne-Mendel Rats (NCI, 1978)

		Dose, mg/kg_{bw}-day		
Tumor Site and Type		control	low	high
Males	No increased	0	57	77*
Females	tumor incidences	0	55	73*

78 w + 31-32 w observation

* Severe early mortality in both sexes in high-dose groups.

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Skin Painting Studies in Mice (Van Duuren *et al*., 1979)

- Skin carcinogenicity:
  - 94 mg or 31 mg in acetone, 3 times per week (lifetime)
  - No tumors observed
- Initiation/promotion:
  - single application of 94 mg allyl chloride. After 14 d, 2.5 µg PMA 3 times per week
  - Skin papillomas in 7/30 mice, a significant ($p<0.025$) increase compared to PMA alone (9/120, 6/90)

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Genotoxicity of Allyl Chloride

Species, strain	End-point	Result
Salmonella typhimurium		
100 (base substitution)	Reverse mutation	+
1535 (base substitution)	"	+
1538 (frame shift)	"	-
Escherischia coli		
Pol^+/Pol^-	DNA modification	+
WP_2, WP_2uvrA	Reverse mutation	+
Saccharomyces cerevisiae		
D4	Gene conversion	+
JD1	"	+
Aspergillus nidulans	Gene segregation	+
Rat liver - epithelial type cells, *in vitro*	Clastogenicity	-
HeLa cells, *in vitro*	Unscheduled DNA synthesis	+

Alkylating Activity

- Allyl chloride, a direct acting mutagen, binds to DNA *in vitro*
  - 3 guanine & 2 adenine adducts
- Metabolic activation enhances mutagenic activity
  - epichlorohydrin - DNA binding and DNA adducts *in vivo* & guanine adduct *in vitro*
  - glycidaldehyde - DNA adducts *in vivo* & *in vitro*

Structure-Activity Comparisons

- Several allyl compounds are known mutagens and/or carcinogens
- The proposed metabolites epichlorohydrin and glycidaldehyde are listed as causing cancer under Proposition 65

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Summary: Allyl Chloride

- Oral exposure: rare squamous cell forestomach tumors in male and female mice
- The confidence in these findings is reduced by:
  - Severe toxicity and mortality, and resulting low power of the study
  - Marginal statistical significance of the results
- The confidence in these findings is increased by:
  - Precancerous lesions in the forestomach of both sexes of mice
  - Genotoxicity in a number of test systems
  - DNA alkylation
  - Structural relationship to other known mutagens and carcinogens
  - Apparent formation of known carcinogens as its metabolites