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International Agency for Research on Cancer



ALLYL CHLORIDE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 107-05-1 *Chem. Abstr. Serv. name*: 3-chloro-1-propene *IUPAC systematic name*: 3-chloropropene *Synonyms*: allyl chloride; 3-chloro-1-propene; 3-chloropropene; 3-chloropropylene; 2-propenyl chloride; α-chloropropylene; chlorallylene; 1-chloro propene-2; 3-chloro-1-propylene; 1-chloro-2-propene; chloroallylene; 3-chloroprene; 3-chloropropene-1; propene, 3-chloro; 2-propenyl chloride.

1.1.2 Structural and molecular formulae, and relative molecular mass

H₂C .Cl

Molecular formula: C₃H₅Cl *Relative molecular mass*: 76.53

1.1.3 Chemical and physical properties of the pure substance

Description: clear colourless liquid with an unpleasant pungent odour *Boiling point:* 44.4 °C (HSDB, 2006)

Melting point: -134.5 °C (HSDB, 2006) Density: 0.938 at 20 °C (O'Neil, 2013) Vapour density: 2.64 (air = 1) (HSDB, 2006) Solubility: slightly soluble in water, 3370 mg/L at 25 °C; miscible with alcohol, chloroform, ether, petrol ether (HSDB, 2006; O'Neil, 2013) Volatility: 368 mm Hg at 25 °C [49.1 kPa] (HSDB, 2006)

Stability: highly flammable (CAMEO, 2019) *Reactivity*: strong reducing agent and decomposes at higher temperatures (CAMEO, 2019) *Flammability*: highly flammable: will be easily ignited by heat, sparks or flames; vapours may form explosive mixtures with air (HSDB, 2006)

Flash point: –27 °C (closed cup) (<u>Krahling</u> et al., 2011)

Auto-ignition temperature: 392 °C (Krahling et al., 2011)

Octanol/water partition coefficient (P): $\log K_{ow} = 1.93$ (estimated) (HSDB, 2006)

Conversion factor: 1 ppm is equivalent to 3.13 mg/m³ at normal temperature (25 °C) and pressure (101.3 kPa).

1.1.4 Technical grade and impurities

Commercial allyl chloride used for the production of dichlorohydrin has a purity of at least 97.5%, and contains mainly 1-chloropropene, 1-chloropropane, and 1,5-hexadiene

as impurities (<u>Krahling et al., 2011</u>). The crude allyl chloride also contains as by-products smaller amounts of other aliphatic and cycloaliphatic hexene and hexadiene isomers, normal hexenes, methylpentenes, methylcyclopentenes and methylcyclopentadienes, and these are also present in the conventionally purified allyl chloride (<u>De Jong & Nisbet, 1998</u>).

1.2 Production and uses

1.2.1 Production

(a) Production process

Allyl chloride is produced on a large scale by the high-temperature (300–600 °C) chlorination of propene. At reactor temperatures higher than 500–510 °C, spontaneous pyrolysis occurs, resulting in the formation of soot and highboiling tars. At reactor temperatures of about 600 °C, benzene can be formed (<u>Krahling et al.,</u> <u>2011</u>).

(b) Production volume

Allyl chloride is listed by the Organisation for Economic Co-operation and Development (OECD) as a High Production Volume chemical (OECD, 2009) Currently the majority of the manufacturing facilities are located in the USA, with fewer sites located in Europe and Asia (ChemSources, 2019). An estimated 800 000 tonnes were produced worldwide in 1997 (Krahling et al., 2011). An overview of historical production volumes in the USA is provided in Table 1.1, with the most recent estimate for 2016 being 113 000-227 000 tonnes. In Canada in 2006, no company reported manufacturing or importing allyl chloride in a quantity greater than or equal to the reporting threshold of 100 kg (Environment Canada, 2009). The quantity reported to be manufactured, imported or in commerce in Canada during the calendar year 1986 was 201 tonnes (Environment Canada, 2009). In 1982, production of allyl chloride in

Japan was reported to range from 30 000 to 40 000 tonnes (<u>IARC</u>, <u>1985</u>). For the European Union, the European Chemicals Agency (ECHA) provides no data on tonnage band as allyl chloride has been registered for use as a chemical intermediate only (<u>ECHA</u>, <u>2019</u>).

1.2.2 Uses

Approximately 90% of all allyl chloride produced is used to synthesize epichlorohydrin, which is used as a basic building block for epoxy resins and in glycerol synthesis (Krahling et al., 2011). Allyl chloride is also used in the manufacture of intermediates for downstream derivatives such as other polymers, resins, and plastic materials, in processes to increase oil production, in the preparation and modification of catalysts, and in the manufacture of pesticides, adhesives, flame retardants, chelating agents, detergents, dyestuffs, flavourings, metal brighteners, perfumes, pharmaceuticals, and urethanes (Olin Corporation, 2016). Acrylic polymers synthesized using allyl chloride are used in personalcare products such as showering soaps or gels, hair conditioners, hair dyes, hair styling gels, hair shampoos, facial cleansers, facial makeup, aftershaves, shaving soaps, creams or foams, skin creams and skin peeling or scrubbing preparations (Environment Canada, 2009).

1.3 Methods of measurement and analysis

1.3.1 Detection and quantification

(a) Air monitoring

In air, allyl chloride can be measured by adsorbing on a coconut shell charcoal, desorption with benzene, and analysis by gas chromatography and flame ionization detection (GC-FID) with an absolute detection limit of 0.01 mg per sample based on National Institute for Occupational Safety and Health (NIOSH)

Year	Reported estimated production volume	Reference
1977	180 thousand tonnes	<u>HSDB (2006)</u>
1979	190 thousand tonnes	<u>HSDB (2006)</u>
1986	> 500 million to 1 billion pounds [~200-500 thousand tonnes]	<u>HSDB (2006)</u>
1990	> 500 million to 1 billion pounds [~200–500 thousand tonnes]	<u>HSDB (2006)</u>
1994	> 1 billion pounds [~500 thousand tonnes]	<u>HSDB (2006)</u>
1998	> 500 million to 1 billion pounds [~200-500 thousand tonnes]	<u>HSDB (2006)</u>
2002	> 500 million to 1 billion pounds [~200–500 thousand tonnes]	<u>HSDB (2006)</u>
2011	629 million pounds [~285 thousand tonnes]	<u>US EPA (2016)</u>
2012	750 million to 1 billion pounds [~340-500 thousand tonnes]	<u>US EPA (2016)</u>
2013-2016	250–500 million pounds [~110–200 thousand tonnes]	<u>US EPA (2016)</u>

Table 1.1 Historical production volumes of allyl chloride in the USA

method 1000 (<u>NIOSH, 1994</u>). The working range is 0.5 to 10 mg/m³ for a 100 L air sample. A similar method based on the use of activated charcoal tubes and desorption using dichloromethane, separation and analysis by GC-FID has been recently described (<u>Li et al., 2015</u>). In a 7.5 L air sample, the minimum detectable concentration was 0.03 mg/m³.

(b) Water analysis

In water, allyl chloride can be measured by capillary column gas chromatography and mass spectrometry with a detection limit of 0.13 μ g/L based on method EPA-NERL 524.2 (NEMI, 1995).

(c) Other matrices

In ground water, aqueous sludges, caustic liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments, allyl chloride can be measured by gas chromatography using photoionization and/or electrolytic conductivity detectors based on method EPA-OSW 8021B (NEMI, 1996a) or by gas chromatography-mass spectrometry (GC-MS) based on method EPA-OSW 8260B (NEMI, 1996b).

(d) Biomarkers

Allylmercapturic acid (ALMA) is established as a urinary biomarker of exposure to allyl chloride in humans. ALMA was identified in urine collected before and after shift from workers occupationally exposed to airborne allyl chloride; the increase in ALMA concentrations in urine during a work shift correlated well with the 8-hour time-weighted average (TWA) personal air exposure to allyl chloride. ALMA was isolated from acidified urine samples, extracted by solidphase extraction and detected with GC-MS (de Rooij et al., 1997). ALMA can also be detected in urine after ingestion of allium vegetables such as garlic (de Rooij et al., 1997). [The Working Group noted that this may limit the usefulness of ALMA as a biomarker of allyl chloride in the general population.]

[The Working Group noted that there was also a quantitative determination for allyl chloride in rat blood samples based on gas chromatography with electron-capture detection (GC-ECD) and GC-MS (Kropscott et al., 1983). This method could be useful for exposure assessment for allyl chloride in humans.]

1.4 Occurrence and Exposure

1.4.1 Natural occurrence

Allyl chloride has not been reported to occur naturally in the environment.

1.4.2 Environmental occurrence

An overview of environmental exposure measurements of allyl chloride in indoor and outdoor air and in water is provided in <u>Table 1.2</u>. Reported exposures were typically below, or close to, the limit of detection.

The production and use of allyl chloride as a chemical intermediate may result in its release to the environment through various waste streams (HSDB, 2006). On the basis of its physical and chemical properties (see Section 1.1.3) and depending on the compartments to which it is released, allyl chloride is estimated to reside predominantly in air and/or water (Environment Canada, 2009). Allyl chloride is rapidly removed from the atmosphere (calculated half-life for reaction with photochemically produced hydroxyl radicals in air is less than 1 day) (OECD-SIDS, 1996). At slower rates, allyl chloride has also been reported to degrade through reaction with atmospheric ozone (Winer & Atkinson, 1987). Allyl chloride is not susceptible to direct photolysis by sunlight (HSDB, 2006). Concentrations in indoor air are assumed to be low due to its short half-life in air (Environment Canada, 2009).

Volatilization is expected to be the most significant loss process for the allyl chloride in water. Hydrolysis and biodegradation may also occur, but at slower rates (Environment Canada, 2009).

1.4.3 Occupational exposure

Allyl chloride is a highly reactive, toxic, and easily ignitable substance (see Section 1.1.3) and is therefore primarily handled in closed systems (Krahling et al., 2011). Occupational exposure to allyl chloride may occur through inhalation and dermal contact at workplaces where it is produced or used (HSDB, 2006). An overview of measurements of occupational exposure to allyl chloride is provided in Table 1.3. Exposure levels vary widely depending on type of manufacturing plant, job title, country, and year in which the measurements were taken.

1.4.4 Exposure of the general population

Exposure of the general population is possible through inhalation of ambient and indoor air, and the use of personal-care products containing the allyl chloride as a residue (including a potential for dermal exposure). However, residue levels in the personal-care products have been estimated to be very low (0.01%) (Environment Canada, 2009).

Upper-bound estimates of allyl chloride intake for each age group in the general population of Canada from environmental media range from 0.52 µg/kg body weight (bw) per day (in people aged \geq 60 years) to 1.56 µg/kg bw per day (in children aged 0.5–4 years) and indicate that air is the most important source (comprising 99% of total exposure) (Environment Canada, 2009).

1.5 Regulations and guidelines

ECHA harmonized classification labels allyl chloride as a germ cell mutagen (Category 2) and as causing cancer (Category 2) (ECHA, 2019). Table 1.4 gives an overview of various international legally binding exposure limits for allyl chloride collated in the GESTIS database (Information system on hazardous substances of the German Social Accident Insurance; IFA, 2020). Legally binding exposure limits in the USA are consistent with the health-based exposure guidelines of the American Conference of

Location, collection date	Sampling matrix	Number of samples	Exposure level	Exposure range	Limit of detection	Comments	Reference
Ohio, USA, 2015	Air	11	Average, 0.00 ppb	0.02–0.11 ppb [0.06–0.34 μg/m ³]	NR	24-hour samples collected with a whole air sampling system The Working Group noted that the reported average exposure appeared to be inconsistent with the reported range	<u>Ohio EPA (2016)</u>
Olathe, Kansas, USA, 2000	Indoor air	NR	All measurements < LOD	NA	NR	Study of five homes located near an industrial site possibly acting as a point source of allyl chloride emissions	ATSDR (2001), as reported in <u>Environment Canada</u> (2009)
Woodland, California, USA, 1990	Indoor air	NR	All measurements < LOD	NA	0.6 µg/m³	Study of 125 homes	<u>OEHHA (1999)</u>
Denver, Houston, Riverside, St Louis, USA, 1980	Ambient air	NR	All measurements < LOD		0.016 µg/m³	A 24-hour around-the-clock measurement schedule for 1–2 weeks in four cities	<u>Singh et al. (1982)</u>
Pittsburgh, USA, 1981	Ambient air	NR	6 ppt [0.02 μg/m³]	< 1–19 ppt [< 0.003–0.059 µg/m ³]	0.016 µg/m³	A 24-hour around-the-clock measurement schedule for 1–2 weeks	<u>Singh et al. (1982)</u>
Lima, Allen County, Ohio, USA, 1990–1991	Ambient air	21	0.16 µg/m³	Maximum, 0.32 μg/m³	NR		<u>Kelly et al. (1991)</u> as reported in <u>Environment</u> <u>Canada (2009)</u>
32 locations in the USA, 1988–1998	Ambient air	NR	0.266 μg/m³	< 0.156-2.57 µg/m ³	NR		Rosenbaum et al. (1999), as reported in <u>Environment</u> <u>Canada (2009)</u>
Several cities and states in the USA, 2003–2005	Ambient air	NR	Median, 0.16 μg/m³	< LOD-0.19 µg/m ³	NR		<u>US EPA (2009)</u>
Boston, Chicago, Houston, Tacoma, 1991	Ambient air	NR	NA	NA		Qualitative study: 2% of the samples contained allyl chloride	<u>Evans et al. (1992)</u>
Porto Allegre, Brazil, 1996–1997	Ambient air	46	All measurements < LOD		0.1 ppb [0.3 μg/m³]		<u>Grosjean et al. (1999)</u>

Table 1.2 Overview of the occurrence of allyl chloride in outdoor and indoor air and in water

Location, collection date	Sampling matrix	Number of samples	Exposure level	Exposure range	Limit of detection	Comments	Reference
Rousse, Bulgaria, 1995–1996	Ambient air	384	5 out of 384 samples were > LOD	NR	1 μg/m³		Islam & Stancheva (1999)
USA, 1986 or before	Whole water samples	200	$< 0.5 \ \mu g/L$	NR	NR		<u>US EPA (1986)</u>

LOD, limit of detection; NA, not applicable; NR, not reported; ppb, parts per billion; ppt, parts per trillion.

Table 1.2 (continued)

Location, collection date	Occupation description	Number of samples	Exposure level ^b	Exposure range	Comments	Reference
Allyl chloride production factory, the Netherlands, 1991–1993	Multiple job titles	205 workshift samples collected from 136 workers	NR	< 0.1–17 mg/m ³	Personal air monitoring Samples were collected during regular shut-down periods	<u>de Rooij et al.</u> (<u>1997)</u>
Sodium allyl sulfonate manufacturing plant B, China, 1982	Multiple job titles	Unknown number of samples in 27 workers	NR	0.2-25.13 mg/m ³		<u>He & Zhang</u> (1985)
Petrochemical plant, the Netherlands, 1978	Chlorinated hydrocarbon production	Unknown number of samples in 44 workers	4 mg/m ³	< 0.1-54 mg/m ³	Cross-sectional study among men employed for 1–21 years	<u>de Jong et al.</u> (1988)
Sodium allyl sulfonate manufacturing plant A, China, 1976	Multiple job titles	68 area samples collected from 26 workers	2966 mg/m³ c	2.6-6.650 mg/m ³	Location, timing, and duration of samples unknown	<u>He & Zhang</u> (1985)¢
Allyl chloride manufacturing plant, former Soviet Union, before 1978	NR		NR	6.4-140 mg/m ³	Employees occupationally exposed for > 1 year	<u>Kasimova</u> (1978)
Allyl chloride manufacturing plant, USA, 1976	Multiple job titles	100 personal samples	Average levels ranged from 0.47 to 1.9 ppm [1.47 to 6.0 mg/m ³]	< 0.1–5.3 ppm [< 0.3–17 mg/m ³]	Personal air monitoring Samples were collected for six job titles and presented in the publication	<u>NIOSH (1976)</u>
Chemical manufacturing plant, USA, 1975	Multiple job titles	35 personal samples	Average levels ranged from 0.05 to 3.05 ppm [0.16 to 9.55 mg/m ³]	0.005–6.13 ppm [0.015–19.2 mg/m ³]	Samples were collected for seven job titles and presented in the publication	<u>NIOSH (1976)</u>
Allyl chloride manufacturing plant, eastern Germany, 1968	Multiple job titles	60 workers	NR	1–113 ppm [~3–354 mg/m ³]	Samples were collected for five job titles and presented in the publication	<u>Häusler &</u> Lenich (1968)

NR, not reported; ppm, parts per million.

^a Area air monitoring unless indicated otherwise.

^b Arithmetic mean.

^c The Working Group noted that in subsequent communication between the United States Environmental Protection Agency and the authors, the average exposure was reported to be 138 mg/m³ as reported in Environment Canada (2009).

Country	Limit value, 8 hours		Limit value, short-term		
	ppm	mg/m ³	ррт	mg/m ^{3 c}	
Australia	1	3	2	6	
Austria	1	3	1	3	
Belgium	1	3	2ª	6 ^b	
Canada, Ontario	1	3	2 ^c	6 ^c	
Canada, Québec	1	3	2	6	
Denmark	1	3	2 ^c	6	
Finland	1	3.2	3°	9.5°	
France	1	3			
Hungary		3		3	
Ireland	1	3	2 ^d	6 ^d	
New Zealand	1	3	2	6	
People's Republic of China		2		4 ^c	
Poland		2			
Republic of Korea	1	3	2	6	
Romania	1	3°	2 ^c	6 ^c	
Singapore	1	3	2	6	
Spain	1	3.2	2	6.4	
Sweden	1	3	3°	9°	
Switzerland	1	3	1	3	
USA, NIOSH	1	3	2 ^c	6°	
USA, OSHA	1	3			

Table 1.4 International limit values for occupational exposure to allyl chloride

NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration.

^a Additional indication "D" means that the absorption of the agent through the skin, mucus membranes or eyes is an important part of the total exposure. It can be the result of both direct contact and its presence in the air.

^b 15-minute limit value.

^c 15-minute average value.

^d 15-minute reference period.

From <u>IFA (2020)</u>.

Governmental Industrial Hygienists (<u>ACGIH</u>, <u>2019</u>).

2. Cancer in Humans

Olsen et al. (1994) studied 1064 male employees (12 574 person-years) of a chemical plant in the USA. Of those, 845 person-years were for employment in areas producing allyl chloride and epichlorohydrin, and 6329 personyears in the area producing glycerine where both allyl chloride and epichlorohydrin were used. No increase in cancer mortality was observed among workers exposed to allyl chloride with low co-exposure to epichlorohydrin, compared with workers not exposed to either allyl chloride or epichlorohydrin. The number of cancer deaths in the exposed groups was small (deaths for low allyl chloride/low epichlorohydrin exposure, n = 4; deaths for high allyl chloride/low epichlorohydrin exposure, n = 1). [The Working Group noted that the informativeness of this study was low due to the small number of personyears in the cohort, the high potential for co-exposure to epichlorohydrin, and the minimal adjustment for confounding.]

3. Cancer in Experimental Animals

Allyl chloride has been previously evaluated by the Working Group on two occasions (<u>IARC</u>, <u>1985</u>, <u>1999</u>). Each time, the Working Group concluded that there was *inadequate evidence* in experimental animals for the carcinogenicity of allyl chloride.

3.1 Mouse

See Table 3.1.

3.1.1 Oral administration (gavage)

Groups of 50 male and 50 female B6C3F₁ mice (age, 5-7 weeks) were given allyl chloride (purity, ~98%) in corn oil by gavage (doses described below), 5 days per week, for up to 90 weeks (NCI, 1978). Groups of 20 males and 20 females were included for each vehicle and untreated control group. For males and females, there were two groups treated with allyl chloride for which the dose (mg/kg bw per day) was changed several times throughout the study. In some cases, doses were increased and then reduced, or animals were dosed in cyclic periods, alternating between no treatment and dosing by gavage (for 1 week and 4 weeks, respectively). Finally, dosing was stopped at around study week 76-77 for males at the lower dose and for both treated groups of females. In males at the lower dose, the doses ranged from 0 (during dose cycling and cessation) to 250 mg/kg bw with a TWA of 172 mg/kg bw calculated over 78 weeks. In males at the higher dose, doses ranged from 0 (during dose cycling) to 500 mg/kg bw, with a TWA of 199 mg/kg bw calculated over 78 weeks (surviving mice were removed at 56 weeks) [The Working Group noted that calculation of TWA in males at the higher dose was an underestimate; a more accurate estimate calculated over 56 weeks was 278 mg/kg bw]. In females, the doses ranged from 0 (during dose cycling and

cessation) to 150 mg/kg bw and 300 mg/kg bw for the lower and higher dose, respectively, with TWAs of 129 and 258 mg/kg bw, respectively, for 78 weeks. Dosing in the vehicle control groups was stopped at weeks 76–77 to correspond with groups dosed with allyl chloride.

Survival was reduced in males at the higher dose, resulting in removal of surviving mice (10/50) at week 56. Survival in all other groups of males and females was deemed adequate for assessment of carcinogenicity. Body weights of males were similar in treated and control groups throughout the study. Body weights of females at the lower and higher dose were slightly lower than those of controls beginning at weeks 20 and 10, respectively. All mice underwent complete necropsy and full histopathological examination.

In male and female mice, there were occurrences of squamous cell papilloma (females only) and squamous cell carcinoma of the forestomach in treated groups that were not observed in control groups, and were considered rare for the testing facility. Due to high mortality in males at the higher dose, tumour analysis in males was time-adjusted to include only those mice that survived at least 52 weeks. In males at the lower dose, there was an incidence of 2/36 (5.6%) of squamous cell carcinoma of the forestomach; metastases of these tumours were observed in both males. No squamous cell carcinomas of the forestomach were observed in the 10 males at the higher dose fitting the above survival criteria. Tumour incidence in females was analysed on the basis of the full study duration. In females, the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach was 3/47 (6.4%) and 3/45 (6.7%) at the lower and higher dose, respectively. While none of these tumour rates were statistically significantly increased according to the Fisher exact (pairwise) test, the Cochran-Armitage test, or the Peto (trend) test, all rates exceeded those for concurrent (0%) and historical (1/180; 0.6% for

Table 3.1 Studies of carcinogenicity with allyl chloride in mice and rats							
Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments			
Full carcinogenicity Mouse, B6C3F ₁ (F) Age, 5–7 wk 90 wk <u>NCI (1978)</u>	Oral (gavage) Purity, ~98% Corn oil 0 (untreated control), 0 (vehicle control), 129, 258 mg/kg bw (TWA) 5 days/wk 20, 20, 50, 50 16, 18, 40, 34	<i>Forestomach</i> Squamous cell papillom 0/20, 0/19, 3/47, 3/45 Squamous cell papillom 0/20, 0/19, 1/47, 3/45 Squamous cell carcinom 0/20, 0/19, 2/47, 0/45	na or carcinoma (combined) NS (Cochran-Armitage or Fisher exact test; see comments) na NS (Cochran-Armitage or Fisher exact test; see comments) na NS (Cochran-Armitage or Fisher exact test; see comments)	Principal limitations: two-dose study; study duration less than most of lifespan; problematic dosing regimen, doses were changed multiple times throughout the study in both exposed groups due to overt toxicity; small number of mice for control groups Other comments: treatment for 78 wk; no significant effect of treatment on survival; incidence of squamous cell papilloma or carcinoma (combined) of the forestomach in historical controls was 1/180 for female B6C3F ₁ mice			
Full carcinogenicity Mouse, Ha:ICR Swiss (F) Age, 6–8 wk 62–85 wk <u>Van Duuren et al.</u> (1979)	Skin application Purity, NR Acetone Application of 0.1 mL acetone (control), or of 31.0 or 94.0 mg allyl chloride in 0.2 mL acetone, 3×/wk for study duration 30, 30, 30 NR	<i>Any tumour type</i> No significant increase		Principal limitations: small number of mice per group; females only; chemical purity, NR; limited gross and histopathological evaluations performed Other comments: duration of study, NR specifically for allyl chloride; survival of allyl chloride-treated mice, NR			
Full carcinogenicity Mouse, Ha:ICR Swiss (F) Age, 6–8 wk ≤ 631 days (90 wk) <u>Van Duuren et al.</u> (1979)	Subcutaneous injection Purity, NR Trioctanoin Injection in left flank of 0.05 mL trioctanoin (control) or of 1.5 mg of allyl chloride in 0.05 mL trioctanoin, 1×/wk for study duration 30, 30 NR	<i>Any tumour type</i> No significant increase		Principal limitations: small number of mice per group; females only; chemical purity, NR; limited gross and histopathological evaluations performed Other comments: duration of study for allyl chloride, \leq 549 days (78 wk); duration of study for controls, \leq 631 days; survival of allyl chloride- treated mice, NR			

Table 3.1 (contin	nued)			
Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, Crj:BDF1 (M) Age, 6 wk 104 wk JBRC (2003a)	Inhalation (whole-body exposure) Purity, > 98% Air 0, 50, 100, 200 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 35, 35, 33, 0	<i>Harderian gland</i> : adeno 3/50, 4/50, 14/50*, 8/50 <i>Lung</i> : bronchioloalveola 4/50, 13/50*, 11/50*, 3/50	ma Trend, <i>P</i> < 0.01 (Peto test); * pairwise test, <i>P</i> < 0.05 (Fisher exact test) ar adenoma Trend, <i>P</i> < 0.01 (Peto test); *pairwise test, <i>P</i> < 0.05 (Fisher exact test)	Principal strengths: multiple-dose study; GLP study; males and females used; study covered most of lifespan Principal limitations: decreased survival in males at 200 ppm had an impact on interpretation of tumour incidence dose-response relationship Other comments: incidence of Harderian gland adenoma exceeded the upper bound of the historical control range (all routes) at 100 and 200 ppm: males, 51/1196 (average, 4.3%; range, 0–10%); lower incidence of tumours in the group at 200 ppm may be attributed to lower survival
Full carcinogenicity Mouse, Crj:BDF1 (F) Age, 6 wk 104 wk JBRC (2003a)	Inhalation (whole-body exposure) Purity, > 98% Air 0, 50, 100, 200 ppm 6 h/day, 5 days/wk 50, 50, 49, 50 27, 26, 25, 6	<i>Harderian gland</i> : adeno 0/50, 4/50, 8/49**, 9/50** <i>Lung</i> : bronchioloalveola 0/50, 3/50, 6/49*, 5/50*	ma Trend, <i>P</i> < 0.01 (Peto and Cochran–Armitage tests); **pairwise test, <i>P</i> < 0.01 (Fisher exact test) ar adenoma Trend, <i>P</i> < 0.01 (Peto test) and <i>P</i> < 0.05 (Cochran– Armitage test); *pairwise test, <i>P</i> < 0.05 (Fisher exact test)	Principal strengths: multiple-dose study; GLP study; males and females used; study covered most of lifespan Principal limitations: low survival rate in all groups; treatment-related decreased survival at 200 ppm

2.1 (continued)

Table 3.1 (contin	ble 3.1 (continued)						
Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments			
Full carcinogenicity Mouse, A/St (M+F, combined) Age, 6–8 wk 24 wk <u>Theiss et al. (1979)</u>	Intraperitoneal injection Purity, NR Tricaprylin 0 (vehicle control), 15.6, 38.4, 76.8 mmol/kg bw total dose 3 injections/wk, total of 24 injections 20, 20, 20, 20 16, 20, 20, 20	Lung All gross tumours (most Average number of tumours per animal: 0.19 ± 0.10 , 0.60 ± 0.20 , 0.50 ± 0.27 , $0.60 \pm 0.15^*$	ly adenomas) *P < 0.05 (either <i>t</i> -test or χ ² test)	Principal strengths: multiple-dose study; males and females used Principal limitations: short duration; small number of mice per group; sexes combined in analysis; chemical purity, NR; limited gross and histopathological evaluations performed (a few lung surface nodules were examined histologically to confirm the typical morphological appearance of pulmonary adenomas) Other comments: tumour incidence presented as average number of lung tumours per mouse, eliminating the ability to analyse incidence by mice affected or by tumour multiplicity; number of mice per group at start, 10 M + 10 F			
Initiation-promotion (tested as initiator) Mouse, Ha:ICR Swiss mice (F) Age, 6–8 wk 61–82 wk <u>Van Duuren et al.</u> (1979)	Skin application Purity, NR Acetone Single application of 0.2 mL acetone (TPA-only control) or 94.0 mg allyl chloride in 0.2 mL acetone, followed by (after 14 days without treatment) 0.0050 mg TPA in 0.2 mL acetone 3×/wk for study duration 90, 30 NR, NR	Skin Squamous cell papilloma 6/90, 7/30* Squamous cell carcinom 2/90, 0/30	a *P < 0.05 (χ² test) a [NS]	Principal limitations: chemical purity, NR Other comments: duration of study, NR specifically for allyl chloride; survival of allyl chloride-treated mice, NR			

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Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (M) Age, 6 wk 104 wk JBRC (2003c)	Inhalation (whole-body exposure) Purity, > 98% Air 0, 20, 50, 100 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 33, 40, 24	<i>Urinary bladder</i> : transi 0/50, 1/50, 0/50, 5/50* <i>Thyroid</i> Follicular cell adenoma (combined) 1/50, 3/50, 4/50, 5/49 Follicular cell adenoma 1/50, 2/50, 2/50, 4/49 C-cell carcinoma 0/50, 1/50, 0/50, 3/49 <i>Peritoneum</i> : mesothelic 0/50, 1/50, 4/50, 4/50 <i>Lung</i> Bronchioloalveolar ader 5/50, 0/50, 4/50, 8/50 Bronchioloalveolar ader (combined) 5/50, 1/50, 6/50, 9/50 <i>Skin</i> : keratoacanthoma 1/50, 0/50, 2/50, 4/50 <i>Mammary gland</i> : fibroa 0/50, 0/50, 3/50, 3/50	tional cell carcinoma Trend, $P \le 0.01$ (Peto and Cochran–Armitage tests); *pairwise test, $P \le 0.05$ (Fisher exact test) or adenocarcinoma Trend: $P \le 0.05$ (Peto test) Trend: $P \le 0.05$ (Peto test) Trend: $P \le 0.05$ (Peto test) Trend: $P \le 0.05$ (Peto and Cochran–Armitage tests) ma Trend: $P \le 0.01$ (Peto test); $P \le 0.05$ (Cochran– Armitage test) noma Trend: $P \le 0.05$ (Peto test) noma or carcinoma Trend: $P \le 0.05$ (Peto test) noma or carcinoma Trend: $P \le 0.05$ (Peto test) Trend: $P \le 0.05$ (Peto and Cochran–Armitage tests) denoma Trend: $P \le 0.05$ (Peto and Cochran–Armitage tests)	Principal strengths: multiple-dose study; GLP study; males and females used; study covered mos of lifespan Other comments: survival was significantly reduced in males at 100 ppm; historical control incidence of urinary bladder transitional cell carcinoma was 0/1398 [assumed to be for all route year range and routes not specified]; historical control range of thyroid follicular cell adenoma or adenocarcinoma (combined; all routes), 39/1393 (average, 2.8%; range, 0–8%)

Table 3.1 (continued)

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (F) Age, 6 wk 104 wk J <u>BRC (2003c)</u>	Inhalation (whole-body exposure) Purity, > 98% Air 0, 20, 50, 100 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 40, 34, 34, 34	<i>Any tumour type</i> No significant increase	NS	Principal strengths: multiple-dose study; GLP study; males and females used; study covered most of lifespan Other comments: no significant effect of treatment on survival

bw, body weight; F, female; GLP, good laboratory practice; h, hour; M, male; NR, not reported; NS, not significant; TPA, 12-O-tetradecanoylphorbol-13-acetate; ppm, parts per million; TWA, time-weighted average; wk, week.

males and for females) controls. In addition, a high incidence of non-neoplastic lesions (hyperkeratosis and acanthosis) of the forestomach was observed in groups of male and female mice treated with the lower or higher dose of allyl chloride, which was not observed in mice in the control groups (NCI, 1978). [Principal limitations included the poor survival in males at the higher dose, the inconsistent dosing regimen resulting in TWA doses with poor spacing and no dose– response relationship, the small number of mice in the control groups, the two-dose study, and less-than-lifespan exposure. The Working Group concluded that the study in male mice was inadequate for the evaluation.]

3.1.2 Skin application

Groups of 30 female Ha:ICR Swiss mice (age, 6-8 weeks) were given dorsal applications of allyl chloride [purity not reported] at a dose of 0 (in 0.1 mL of acetone), 31.0, or 94.0 mg/application per mouse (in 0.2 mL of acetone) to the shaved skin (Van Duuren et al., 1979), three times per week for the study duration. Study duration was not reported for this specific chemical, but a range of 62-85 weeks was provided for the set of nine chemicals tested in the study. Similarly, survival was not specifically reported. At termination of the experiment, routine sections of the skin, liver, stomach, and kidney were taken for histopathological examination. There were no significant or unusual histological findings in this study. Repeated skin application of allyl chloride did not induce any papillomas of the skin, and the incidence of lung papilloma and of papilloma of the forestomach was similar in control and treated mice. One adenocarcinoma of the glandular stomach was observed in a mouse at the highest dose. [Principal limitations included the limited gross and histopathological evaluations, small number of animals per group, use of females only, chemical purity not reported,

study duration and number of surviving mice not specifically reported.]

3.1.3 Subcutaneous injection

Groups of 30 female Ha:ICR Swiss mice (age, 6-8 weeks) were injected subcutaneously with allyl chloride [purity not reported] at a dose of 0 (in 0.05 mL of trioctanoin) or 1.5 mg/injection per mouse (in 0.05 mL of trioctanoin) in the left flank (Van Duuren et al., 1979), weekly for the study duration. Study duration was up to 78 weeks for the treated group and up to 90 weeks for controls. Survival was not specifically reported. At termination of the experiment, routine sections of the liver and injection sites were taken for histopathological examination. The only tumour observed was a fibrosarcoma at the injection site in one mouse treated with allyl chloride. [Principal limitations included the limited gross and histopathological evaluations, small number of animals per group, use of females only, absence of reporting of chemical purity, and number of surviving animals not specifically reported.]

3.1.4 Inhalation

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female Crj:BDF1 [B6D2F₁/Crlj] mice (age, 6 weeks) were treated by whole-body inhalation with allyl chloride (purity, > 98%; in air) at a concentration of 0, 50, 100, or 200 ppm for 6 hours per day, 5 days per week, for up to 104 weeks (JBRC, 2003a, b). Survival was significantly reduced in males and females at 200 ppm: 0/50 males survived past week 97, and 6/50 females remained at study termination. Survival in the groups of males and females at 50 and 100 ppm was similar to that in controls. Average body weights in the groups of males and females at 200 ppm to 200 ppm were lower than in the respective controls groups. All mice

underwent complete necropsy and full histopathological examination.

In male and female mice, there was a significant increase (Fisher exact test) in the incidence of adenoma of the Harderian gland in the groups at 100 ppm (males, P < 0.05; females, P < 0.01) and 200 ppm (females, P < 0.01), with a significant positive trend (Peto test, *P* < 0.01; males and females). There were also occurrences of nonneoplastic lesions (Harderian gland hyperplasia) in all groups of treated males, and in one female at 100 ppm. In male and female mice, there was a significant increase (Fisher exact test) in the incidence of bronchioloalveolar adenoma in the groups at 50 ppm (males, P < 0.05), 100 ppm (males and females, P < 0.05), and 200 ppm (females, P < 0.05), with a significant positive trend (Peto test, P < 0.01; males and females). [The Working Group noted the strengths of this well-conducted study that complied with GLP: the use of males and females and multiple doses.]

3.1.5 Intraperitoneal injection

Groups of 20 (10 males and 10 females, combined) strain A/St mice (age, 6-8 weeks) were given intraperitoneal injections of allyl chloride [purity not reported] at a dose of 0 (vehicle only, tricaprylin), 0.65, 1.60, or 3.20 mmol/kg bw, three times per week for a total of 24 doses (Theiss et al., 1979). Total injected doses amounted to 0 (vehicle), 15.6, 38.4, and 76.8 mmol/kg bw. Necropsies were performed 24 weeks after the first injection. All treated mice survived until study termination; survival in the tricaprylin vehicle-control group was 16/20. [Body weights were not reported in this study.] Histopathological evaluation was limited to the lungs, and findings were reported as average number of lung tumours per mouse. A few lung surface nodules were examined histologically to confirm the typical morphological appearance of pulmonary adenoma. There was a significant increase (P < 0.05, either *t*-test or χ^2 test) in the

average number of lung tumours per mouse in the group at 76.8 mmol/kg (0.60 ± 0.15) compared with vehicle controls (0.19 ± 0.10). The average numbers of lung tumours per mouse in the other dosed groups were similar to those in the group at 76.8 mmol/kg, but were not statistically significantly increased. [Principal limitations included the short exposure duration and small number of mice per group, that the sexes were combined in the analysis, the limited gross and histopathological evaluations, and that chemical purity and tumour incidences were not reported.]

3.1.6 Initiation-promotion

In the study described by Van Duuren et al. (1979), allyl chloride was assessed as a tumour initiator. A group of 30 female Ha:ICR Swiss mice (age, 6–8 weeks) were given a single dorsal application of allyl chloride [purity not reported] at a dose of 94.0 mg/mouse (in 0.2 mL of acetone) to the shaved skin. After application, mice remained untreated for 14 days, and then received applications of 0.0050 mg of 12-O-tetradecanoylphorbol-13-acetate (TPA) in 0.2 mL of acetone, three times per week for the study duration. A group of 90 females - serving as TPA-only controls - received 0.0050 mg of TPA (in 0.2 mL of acetone), three times per week for the study duration. Study duration was not specifically reported for this chemical, but a range of 61-82 weeks was provided for the set of nine chemicals tested in the study. [Survival and body weights were not reported in this study, although survival was described as being "very good" in the treated group.]

Histopathological evaluation was limited to the skin. There was a significant increase (P < 0.05, χ^2 test) in the incidence of skin squamous cell papilloma (7/30, 23.3%) in the group receiving allyl chloride plus TPA compared with TPA-only controls (6/90, 6.7%). There was also a reduced time to first tumour in the group receiving allyl chloride plus TPA (197 days) compared with TPA-only controls (449 days). All tumours in the group receiving allyl chloride plus TPA were squamous cell papillomas, while two mice in the TPA-only group (2/90) also developed skin squamous cell carcinomas (Van Duuren et al., 1979). [Principal limitations included the limited gross and histopathological evaluation, and that chemical purity was not reported.]

3.2 Rat

See <u>Table 3.1</u>.

3.2.1 Oral administration (gavage)

Groups of 50 male and 50 female Osborne-Mendel rats (age, 6-7 weeks) were given allyl chloride (purity, ~98%) in corn oil by gavage (doses described below), 5 days per week for up to 110 weeks (NCI, 1978). Groups of 20 males and 20 females were included for each vehicle and untreated control group. In both males and females, doses in the groups treated with allyl chloride were reduced throughout the study, with cessation of dosing beginning in weeks 78-80 for all groups. The lower dose in males ranged from 55 to 70 mg/kg bw with a TWA of 57 mg/kg bw, calculated based on the number of weeks for which the rats were dosed. The higher dose in males ranged from 55 to 140 mg/kg bw, with a TWA of 77 mg/kg bw. In females, the lower dose was 55 mg/kg bw until dosing cessation, resulting in a calculated TWA of 55 mg/kg bw. In females the higher dose ranged from 55 to 110 mg/kg bw with a TWA of 73 mg/kg bw. Dosing in the vehicle-control groups was stopped at week 78 to correspond with that in groups dosed with allyl chloride. All rats underwent complete necropsy and full histopathological examination.

Survival was lower in male and female rats than in controls, with a significant association between increasing dose and mortality (P < 0.001, Tarone test). Survival at study termination was 14% for males at the lower dose, 0% for males at the higher dose (compared with 20–35% for male controls), 38% for females at the lower dose, and 12% for females at the higher dose (compared with 65–75% for female controls). Body weights of male rats at the higher dose were significantly reduced compared with those of controls at the end of the study, with a consistent trend of bodyweight loss beginning around week 50. Treated females (lower and higher dose) had somewhat lower body weights than controls. There was no effect on tumour incidence that was attributed to exposure to allyl chloride. [Principal limitations included the poor survival in treated and control males and females, the inconsistent dosing regimen resulting in TWA doses with poor spacing and no dose-response relationship, the small number of animals in control groups, and the two-dose study. The Working Group concluded that the study in male and female rats was inadequate for the evaluation.]

3.2.2 Inhalation

In a study that complied with GLP, groups of 50 male and 50 female F344/DuCrj (Fischer) rats (age, 6 weeks) were treated by whole-body inhalation with allyl chloride (purity, > 98%; in air) at a concentration of 0, 25, 50, or 100 ppm for 6 hours per day, 5 days per week, for up to 104 weeks (JBRC, 2003c, d). Survival was reduced in the males at 100 ppm (48%) compared with controls (76%); survival in other groups of exposed males was similar to that in controls. Exposure to allyl chloride had no impact on body weight in male or female rats. All rats underwent complete necropsy and full histopathological examination.

In male rats, there was a significant increase (P < 0.05, Fisher exact test) in the incidence of transitional cell carcinoma of the urinary bladder in the group at 100 ppm (5/50) compared with controls (0/50), with a significant positive trend (P < 0.01, Peto and Cochran–Armitage tests). There were also occurrences of non-neoplastic

lesions: transitional epithelium hyperplasia, nodular hyperplasia, and squamous cell metaplasia in the urinary bladder.

In male rats, there was also a significant positive trend (P < 0.05, Peto trend test) in the incidence of follicular cell adenoma, and follicular cell adenoma or adenocarcinoma (combined) of the thyroid gland. There was a significant positive trend (P < 0.01, Peto trend test; P < 0.05, Cochran-Armitage trend test) in the incidence of peritoneal mesothelioma in males. There was a significant positive trend (P < 0.05, Peto and Cochran-Armitage trend tests) in the incidence of thyroid C-cell carcinoma, skin keratoacanthoma, and mammary gland fibroadenoma in males. There was a significant positive trend (P < 0.05, Peto trend test) in the incidence of bronchioloalveolar adenoma, and bronchioloalveolar adenoma or carcinoma (combined) in males.

There was no significant increase in tumour incidence in female rats. [The Working Group noted the strengths of this well-conducted GLP study covering most of the lifespan: the use of males and females and multiple doses.]

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

In workers exposed by inhalation to allyl chloride at concentrations at or below 3 mg/m³ (the 8-hour TWA occupational exposure limit for many countries worldwide), ALMA was a major urinary metabolite, whereas traces of 3-hydroxypropylmercapturic acid (HPMA) were detected in only a few urine samples. As noted in Section 1.3.1(d), ALMA is an established urinary biomarker of exposure to allyl chloride. The calculated end-of-shift mean urinary excretion of ALMA in workers exposed to an 8-hour TWA air concentration of allyl chloride of 3 mg/m³ was 352 μ g/g creatinine. This value was proposed as a biological exposure index for human exposure to allyl chloride (de Rooij et al., 1997). ALMA was also detected in the urine of people consuming garlic (de Rooij et al., 1996a; Verhagen et al., 2001).

No data from human cells in vitro were available to the Working Group.

4.1.2 Experimental systems

(a) Experimental systems in vivo

In male albino rats dosed subcutaneously with allyl chloride (1 mL of 10% v/v solution in oil, equivalent to 94 mg per rat), ALMA, its sulfoxide, and HPMA were identified as urinary metabolites, while S-allylglutathione and S-allyl-L-cysteine were detected in the bile. Kaye et al. (1972) proposed metabolic steps to convert allyl chloride to ALMA and its sulfoxide, as well as four possible metabolic pathways for the conversion of allyl chloride to HPMA, initiated at either C-1 or C-3 of allyl chloride.

The intraperitoneal dosing of male Wistar rats with allyl chloride (5-45 mg/kg bw) resulted in the detection of urinary ALMA (30% of the administered dose) and HPMA (< 3%) (de Rooij et al., 1996b; Fig. 4.1). In addition, two minor metabolites were identified, a-chlorohydrin (0.13%) and 3-chloro-2-hydroxypropylmercapturic acid (0.21%), indicative of the metabolic conversion of allyl chloride to epichlorohydrin. Pre-treatment of rats with pyrazole (cytochrome P450 CYP2E1 inducer), β-naphthoflavone (CYP1A1/2 inducer), and phenobarbital (CYP2B1/2 inducer) had little to no impact on the urinary excretion of ALMA. In contrast to the results of <u>de Rooij et al. (1996b</u>), the urinary yield of HPMA in male Sprague-Dawley rats dosed orally with allyl chloride (76 mg/kg bw) was 21.5% (Sanduja et al., 1989).

Studies of other adverse effects indirectly confirmed distribution to target tissues.



Fig. 4.1 Proposed metabolic scheme for allyl chloride in rats

ECH, epichlorohydrin; ALMA, allylmercapturic acid; HPMA, 3-hydroxypropylmercapturic acid; α-CH, α-chlorohydrin; CHPMA, 3-chloro-2hydroxypropylmercapturic acid; R, N-acetyl-cysteinyl.

Reproduced with permission from <u>de Rooij et al. (1996b)</u>. Biotransformation of allyl chloride in the rat. Influence of inducers on the urinary metabolic profile. *Drug Metab Dispos*, 24(7):765–772. [The Working Group noted that formation of allyl alcohol as a metabolic intermediate is uncertain.]

Inhalation exposure of rats, guinea-pigs, and rabbits for 5 weeks caused histological damage to the liver and kidney (Torkelson et al., 1959). Mice treated orally for 2–7 weeks developed focal kidney damage (He et al., 1981). Studies on acute and subchronic toxicity after exposure by inhalation in male rats showed dose-dependent adverse effects on the testis and suppression of the reflexes (Guseinov et al., 1981; Guseinov, 1982).

(b) Experimental systems in vitro

Emmert et al. (2006) (see Section 4.2) showed a greater mutagenicity of allyl chloride in a metabolically competent *Salmonella typhimurium* strain encoding production of CYP2E1 than in a conventional Ames test, indicating a major role of CYP2E1 in the metabolic activation of allyl chloride. On the other hand, for a series of allylic compounds including allyl chloride, good correlation was found between mutagenicity in a conventional Ames test and direct alkylating properties (Eder et al., 1980). [The Working Group noted that metabolic activation is a modifying factor, but not the principal factor in the biotransformation and mutagenicity of allyl chloride.]

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether allyl chloride is electrophilic or can be metabolically activated to electrophiles; is genotoxic; or alters cell proliferation,

cell death, or nutrient supply. Insufficient data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

Allyl chloride gave positive results in the 4-(4-nitrobenzyl)pyridine (NBP) alkylation test (Eder et al., 1982). The NBP-alkylation test results correlated with direct mutagenicity potency observed in S. typhimurium TA100 (Henschler et al., 1983). Moreover DNA adducts were formed after exposure in isolated perfused rat liver (Eder & Zugelder, 1990) and in salmon sperm DNA in vitro (Eder et al., 1987) (see Table 4.4 and Table 4.5, respectively). The alkylated bases identified (N³-allyladenine, N⁶-allyladenine, N²-allylguanine, N⁷-allylguanine and O⁶-allylguanine) contained the allyl moiety. He et al. (1995) showed that allyl chloride has the ability to covalently cross-link axonal cytoskeletal proteins. A study in rats treated by subcutaneous injection of allyl chloride 5 days per week for 3 months showed no evidence of cross-linking of neurofilament proteins from the spinal cord (Nagano et al., 1993).

4.2.2 Is genotoxic

<u>Table 4.1</u>, <u>Table 4.2</u>, <u>Table 4.3</u>, <u>Table 4.4</u> and <u>Table 4.5</u> summarize studies of the genetic and related effects of allyl chloride.

- (a) Humans
- (i) Exposed humans

See <u>Table 4.1</u>.

A cross-sectional epidemiological study of 44 men engaged in the production of various chlorinated hydrocarbons, including allyl chloride and epichlorohydrin, analysed cytogenetic end-points in blood samples (de Jong et al., 1988). The workers involved in this study had been employed in this plant for periods of between 1 and 21 years and exposures to allyl chloride were reported as 4 mg/m³ (arithmetic mean; range, < 0.1-54). The frequencies of chromatid gaps, chromatid and chromosome breaks, and total aberrations were statistically significantly higher than those in the control group investigated during the same year. [The Working Group noted the complex nature of exposures and that no individual measurements of exposure to allyl chloride were reported.]

(ii) Human cells in vitro

See <u>Table 4.2</u>.

In human cells in vitro, the unscheduled DNA synthesis assay provided inconsistent results for allyl chloride: a test on human embryonic intestinal cells gave negative results with and without metabolic activation (McGregor, 1981), while a study in the HeLa S3 cell line (human cervical cancer) gave positive results without metabolic activation (not tested with metabolic activation) (Schiffmann et al., 1983).

(b) Experimental systems

(i) Non-human mammals in vivo

See <u>Table 4.3</u>.

After inhalation exposure to allyl chloride (1 or 25 ppm for 7 hours per day), rats did not show an increase in the frequency of chromosomal aberrations when treated for a single day, or of micronucleus formation, or dominant lethal mutations when treated for 5 consecutive days, and exposed mice did not demonstrate sperm abnormalities (McGregor, 1981). After oral administration, allyl chloride failed to induce micronucleus formation in exposed mice (Rim & Kim, 2015). [The Working Group noted the absence of direct evidence of target tissue exposure in these genotoxicity tests.]

(ii) Non-human mammalian cells in vitro See Table 4.4.

Table 4.1 Genetic and related effects of allyl chloride in exposed humans

End-point	Tissue, cell type (if specified)	Location, date, setting, scenario	No. of exposed and controls	Agent, exposure level (mean, range, units)	Response (significance)	Covariates controlled	Comments	Reference
Chromosomal aberration	Peripheral blood, lymphocytes	Netherlands, 1978, plant producing various chlorinated hydrocarbons, including epichlorohydrin and allyl chloride	44, 27ª	Allyl chloride: 4 (< 0.1–54) mg/m ³ Epichlorohydrin: 1 (< 0.1–3) mg/m ³	(+) ^b (<i>P</i> < 0.05)	Sex, age and smoking habits	Confounding exposure (epichlorohydrin)	<u>de Jong</u> et al. (1988)

^a Participants engaged in manufacture of bisphenol A (diphenylolpropane) by reaction of phenol and acetone. These chemicals are not believed to be associated with the induction of chromosomal damage.

^b (+), positive in a study of limited quality.

Table 4.2 Genetic and related effects of allyl chloride in human cells in vitro

End-point	Tissue, cell line	Resultsª		Concentration	Reference	
		Without metabolic activation	With metabolic activation	(LEC or HIC)		
Unscheduled DNA synthesis	Human embryonic intestinal cells	-	-	9900 μg/mL	<u>McGregor (1981)</u>	
Unscheduled DNA synthesis	HeLa S3 cell line (human cervix)	+	NT	1 mM [76.5 μg/mL]	Schiffmann et al. (1983)	

HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested.

^a +, positive; –, negative.

Table 4.3 Genetic and related effects of allyl chloride in non-human mammals in vivo

End-point	Species, strain, (sex)	Tissue	Results ^a	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Chromosomal aberration	Rat (M and F)	Bone marrow	-	1 and 25 ppm	Inhalation, 7 h per day, \times 1 day, sampling after 6, 24, and 48 h		<u>McGregor (1981)</u>
Micronucleus formation	Rat (M and F)	Bone marrow	-	1 and 25 ppm	Inhalation, 7 h per day, × 5 days, sampling after 6, 24, and 48 h		<u>McGregor (1981)</u>
Dominant lethal test	Rat (M) (treated) and (F) (not treated)	Ovary and uterus	-	1 and 25 ppm	Inhalation, 7 h per day, \times 5 days		<u>McGregor (1981)</u>
Sperm abnormality test	Mouse (M)	Testis, cauda epididymis	-	1 and 25 ppm	Inhalation, 7 h per day, \times 5 days		<u>McGregor (1981)</u>
Micronucleus formation	Mouse, ICR (M)	Bone marrow; polychromatic erythrocytes	(-)	400 mg/kg bw	Oral, single treatment [not specified but assumed], sampling 24 h later	Single treatment followed by only one sampling time	<u>Rim & Kim</u> (2015)

bw, body weight; F, female; h, hour; HID, highest ineffective dose; LED, lowest effective dose (units as reported); M, male; ppm, parts per million.

^a+, positive; –, negative; (–), negative in a study of limited quality (see OECD TG 474) (OECD, 2014).

Table 4.4 Genetic and related effects of allyl chloride in non-human mammal cells in vitro

End-point	Species, tissue, cell line	Results ^a		Concentration	Comments	Reference
		Without metabolic activation	With metabolic activation	(LEC or HIC)		
DNA-binding (adduct formation, HPLC)	Rat (perfusion of isolated liver)	+	NT	300 mg/liver ^b		<u>Eder & Zugelder</u> (1990)
Chromosomal aberrations	Rat liver RL1 cells	-	NT	25 μg/mL		<u>Dean et al.</u> (1985)
Chromosomal aberrations	Chinese hamster lung (CHL) cells	+	+	400 μg/mL	No data on cytotoxicity; the culture bottle was sealed and cultured standing after adding the test substances	<u>JETOC (1997a)</u>
Chromosomal aberrations	Chinese hamster lung (CHL) fibroblast cells	(-)	(-)	3 mM [~230 μg/mL]	Highest concentration is lower than that recommended by OECD TG 473 (OECD, 2016)	<u>Rim & Kim</u> (2014)

HIC, highest ineffective concentration; HPLC, high-performance liquid chromatography; LEC, lowest effective concentration; NT, not tested.

^a +, positive; –, negative; (–), negative in a study of limited quality.

^b Test substance was administered to the isolated liver in portions every 15 minutes over a period of 3-4 hours directly into the perfusion medium through the tube leading to the portal vein using a syringe.

Test system	End-point	Results ^a		Concentration (LEC or HIC)	Reference
(species, strain)		Without metabolic activation	With metabolic activation		
Drosophila melanogaster	Sex-linked recessive lethal test	-	NA	150 ppm	McGregor (1981)
Saccharomyces cerevisiae D4	Gene conversion	+	NT	14 μg/mL	<u>McCoy et al. (1978)</u>
Saccharomyces cerevisiae JD1	Gene conversion	+	+	NR	<u>Dean et al. (1985)</u>
Aspergillus nidulans	Forward mutation	-	NT	40 μL/plate [37 600 μg/plate]	<u>Bignami et al. (1980)</u>
Aspergillus nidulans	Mitotic segregation	-	NT	0.6 mL/20 L desiccator ^ь [0.03 μg/mL]	<u>Crebelli et al. (1984)</u>
Salmonella typhimurium TA1535	Reverse mutation	-	-	10 μL/plate ^c [9400 μg/plate]	<u>McCoy et al. (1978)</u>
Salmonella typhimurium TA1535	Reverse mutation	-	+	1 μL/plated [940 μg/plate]	<u>McCoy et al. (1978)</u>
Salmonella typhimurium TA1535	Reverse mutation	+	+	1 μL/plateº (-S9) [940 μg/plate] 5 μL/plateº (+S9) [4700 μg/plate]	<u>McCoy et al. (1978)</u>
Salmonella typhimurium TA1535	Reverse mutation	-	+	10 μL/plate [9400 μg/plate]	<u>Bignami et al. (1980)</u>
Salmonella typhimurium TA1535	Reverse mutation	+	-	5000 μg/plate	<u>JETOC (1997b)</u>
Salmonella typhimurium TA100	Reverse mutation	-	-	10 μL/plate [9400 μg/plate]	<u>Bignami et al. (1980)</u>
Salmonella typhimurium TA100	Reverse mutation	+	-	15 μmol/mL [1150 μg/mL]	<u>Eder et al. (1980)</u>
Salmonella typhimurium TA100	Reverse mutation	+	NT	0.1 μL/9 L desiccator ^ь [0.01 μg/mL]	<u>Norpoth et al. (1980)</u>
Salmonella typhimurium TA100	Reverse mutation	+	NT	0.05 μg/mL ^b	<u>Simmon et al. (1981)</u>
Salmonella typhimurium TA100	Reverse mutation	+ (w)	+	250 μg/plate	<u>Neudecker &</u> <u>Henschler (1985)</u>
Salmonella typhimurium TA100	Reverse mutation	NT	+	235 μg/plate	<u>Neudecker &</u> Henschler (1986)
Salmonella typhimurium TA100	Reverse mutation	+	-	2500 μg/plate	<u>JETOC (1997b)</u>
Salmonella typhimurium TA100, TA1538	Reverse mutation	-	-	10 μL/plate ^d [9400 μg/plate]	<u>McCoy et al. (1978)</u>
<i>Salmonella typhimurium</i> TA1535, TA100, TA98, TA1538	Reverse mutation	-	-	4000 μg/plate	<u>Dean et al. (1985)</u>
Salmonella typhimurium TA98, TA1537	Reverse mutation	-	-	5000 μg/plate	<u>JETOC (1997b)</u>
Salmonella typhimurium strain YG7108 ^f	Reverse mutation	NT	+	500 μL/plate	<u>Emmert et al. (2006)</u>

Table 4.5 Genetic and related effects of allyl chloride in non-mammalian and acellular systems in vitro

Table 4.5 (continued)

Test system	End-point	Results ^a		Concentration (LEC or HIC)	Reference
(species, strain)		Without metabolic activation	With metabolic activation		
Salmonella typhimurium strain YG7108pin3ERb5§	Reverse mutation	+	NT	300 μg/plate	<u>Emmert et al. (2006)</u>
Escherichia coli WP2 and WP2uvrA	Reverse mutations	+	+	NR [highest dose 4000 µg/plate]	<u>Dean et al. (1985)</u>
Escherichia coli WP2uvrA/pKM101	Reverse mutation	+	+	5000 μg/plate	<u>JETOC (1997b)</u>
Escherichia coli pol A+/pol A-	Differential toxicity (spot test)	+	NT	10 μL/plate [9400 μg/plate]	<u>McCoy et al. (1978)</u>
Streptomyces coelicolor	Reverse mutation Forward mutation	+ +	NT NT	10 μL/plate [9400 μg/plate] 10 μL/plate [9400 μg/plate]	<u>Bignami et al. (1980)</u>
Salmon sperm DNA	Binding (covalent) to DNA	+ (w)	NT	9000 μg/mL	<u>Eder et al. (1987)</u>

HIC, highest ineffective concentration; LEC, lowest effective concentration (units as reported); NA, not applicable; NR, not reported; NT, not tested; ppm, parts per million; S9, $9000 \times g$ supernatant.

^a +, positive; –, negative; + (w), weak positive.

^b Salmonella typhimurium or Aspergillus nidulans, on Petri dishes, were exposed to allyl chloride vapour in a 9 L or 20 L desiccator, respectively.

^c Standard plate incorporation.

^d Filter discs impregnated with test agent put on surface of agar.

^e Preincubation.

^f Strain YG7108 is similar to strain TA1535, except that it has a methyltransferase deficiency.

^g Strain YG7108pin3ERb5 is strain YG7108 that carries plasmid *pin3ERb5*.

In several tests for chromosomal aberration, allyl chloride gave variable outcomes. Allyl chloride gave negative results in a study in rat liver cells without metabolic activation (Dean et al., 1985); the test was not carried out with metabolic activation. In Chinese hamster lung cells, allyl chloride gave positive results with and without metabolic activation (JETOC, 1997a), but negative results in another study that investigated allyl chloride at lower concentrations (Rim & Kim, 2014) [The Working Group noted that the highest dose investigated in the most recent study appeared to be too low.]

(iii) Non-mammalian and acellular systems in vitro

See Table 4.5.

Allyl chloride produced gene mutations in bacteria (McCoy et al., 1978; Bignami et al., 1980; Eder et al., 1980; Norpoth et al., 1980; Simmon et al., 1981; Dean et al., 1985; Neudecker & Henschler, 1985, 1986; JETOC, 1997b; Emmert et al., 2006) and induced gene conversion in fungi (McCoy et al., 1978; Dean et al., 1985). Allyl chloride gave negative results in the sex-linked recessive lethal test in *Drosophila melanogaster* (McGregor, 1981), and in tests for forward mutation (Bignami et al., 1984) in *Aspergillus nidulans*.

4.2.3 Alters cell proliferation, cell death, or nutrient supply

In $B6C3F_1$ mice exposed orally to allyl chloride for 90 weeks (NCI, 1978), a high incidence of non-neoplastic lesions (hyperkeratosis and acanthosis) of the forestomach was observed in males and females.

In Crj:BDF1 mice exposed to allyl chloride by inhalation for 104 weeks (JBRC, 2003a, b), there were occurrences of non-neoplastic lesions such as hyperplasia of the Harderian gland in all groups of treated males. In F344/DuCrj rats exposed to allyl chloride by inhalation for 104 weeks (JBRC, 2003c, d), there were occurrences of transitional epithelium hyperplasia, nodular hyperplasia, and squamous cell metaplasia in the urinary bladder in male rats at the highest dose.

4.3 Data relevant to comparisons across agents and end-points

The analysis of the bioactivity in vitro of the agents reviewed in IARC Monographs Volume 125 was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the Government of the USA (Thomas et al., 2018). Allyl chloride was one of thousands of chemicals tested across the large assay battery of the Tox21 and ToxCast research programmes as of 1 September 2019 (US EPA, 2019a). Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is publicly available (US EPA, 2019a). The Working Group noted that the metabolic capacity of the cell-based assays is variable, and generally limited, as acknowledged in Kavlock et al. (2012).]

Allyl chloride was tested (at concentrations of up to 100 μ M) in 403 assays and was found to be inactive in almost all. Active responses were observed in six assays (<u>US EPA, 2019b</u>). For nuclear receptors, borderline activity (potency of < 50% and/or activity observed only at the highest concentration tested) was found for the pregnane X receptor response element (PXRE), activation of human vascular endothelial growth factor receptor 1 (hVEGFR1), estrogen receptor a (ER α) agonism in two assays, estrogen receptor β (ER β) antagonism, and TP53 activation.

5. Summary of Data Reported

5.1 Exposure characterization

Allyl chloride (CAS No. 107-05-01) is a High Production Volume chemical that is almost exclusively used in the production of epichlorohydrin, a basic building block for epoxy resins and the synthesis of glycerol. Minor uses of allyl chloride also include the synthesis of a variety of miscellaneous products including other allyl chemicals, pesticides, pharmaceuticals, adhesives, and personal-care products. A wide range of occupational exposure levels to allyl chloride have been reported in air where this chemical is produced and used, but exposures of the general population have not been reported.

5.2 Cancer in humans

The only available study of allyl chloride was conducted in a cohort of male employees from a chemical plant in the USA. The study was considered uninformative due to the small number of person-years with exposure to allyl chloride, the high potential for co-exposure to epichlorohydrin, and the minimal adjustment for confounding.

5.3 Cancer in experimental animals

Allyl chloride was tested for carcinogenicity in four different strains of male and/or female mice in one study of each of the following routes of exposure: whole-body inhalation, intraperitoneal injection, skin application, subcutaneous injection, gavage, and skin application as initiator in an initiation–promotion study. Allyl chloride was tested in two different strains of male and female rats in one study of whole-body inhalation, and in one study of administration by gavage.

The inhalation study in male and female rats was well-conducted under good laboratory practice (GLP). In male rats, exposure to allyl chloride resulted in a significant positive trend and increase in the incidence of transitional cell carcinoma of the urinary bladder. In male rats, there were also significant positive trends in the incidence of follicular cell adenoma, follicular cell adenoma or adenocarcinoma (combined), and C-cell carcinoma of the thyroid, bronchioloalveolar adenoma, and bronchioloalveolar adenoma or carcinoma (combined) of the lung, peritoneal mesothelioma, keratoacanthoma of the skin, and mammary gland fibroadenoma. There were no significant increases in tumour incidence in female rats in this inhalation study. The gavage study in male and female rats was inadequate for the evaluation of the carcinogenicity of allyl chloride.

The study of inhalation in male and female mice was well-conducted under GLP and resulted in significant positive trends and increases in the incidence of Harderian gland adenoma and lung bronchioloalveolar adenoma in males and females.

In the study of intraperitoneal injection, there was a significant increase in the average number of lung tumours by gross observation (mostly adenomas) per animal in male and female mice (combined). In the initiation–promotion study in female mice, there was a significant increase in the incidence of skin papilloma. The studies of skin application and subcutaneous injection in female mice gave negative results.

In the study of gavage in female mice, there was a non-significant increase in the incidence of forestomach tumours. The study of gavage in male mice was inadequate for the evaluation of the carcinogenicity of allyl chloride.

5.4 Mechanistic evidence

In humans exposed by inhalation to allyl chloride at low concentrations (at or below 3 mg/m³), allylmercapturic acid (ALMA) was detected in the urine. ALMA and its sulfoxide were detected in the urine of rats exposed to allyl chloride subcutaneously or intraperitoneally. ALMA also can be detected in the urine after ingestion of allium vegetables such as garlic.

Overall, the mechanistic evidence is suggestive but incoherent across different experimental systems. Regarding the key characteristics of carcinogens, allyl chloride is electrophilic and alkylates DNA, but the evidence that it is genotoxic is incoherent across studies in different experimental systems. Allyl chloride gave generally positive results in the Ames test, but gave negative results in the two studies of genotoxicity in vivo in rodents, and yielded inconsistent results in the few studies in vitro in human and mammalian experimental systems. There is suggestive evidence that allyl chloride alters cell proliferation, cell death, or nutrient supply, based on the increased incidence of nodular hyperplasia of transitional epithelium and squamous cell metaplasia in the urinary bladder at the highest dose in male rats exposed chronically by inhalation. For other key characteristics of carcinogens, there is a paucity of available data. Allyl chloride was found to be mostly without effects in the assay battery of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes in the USA.

6. Evaluation and Rationale

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Mechanistic evidence

There is *limited mechanistic evidence*.

6.4 Overall evaluation

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

6.5 Rationale

Allyl chloride was evaluated as Group 3 because the evidence of cancer in humans is inadequate, the evidence of cancer in experimental animals is *limited*, and the mechanistic evidence is limited. The evidence of cancer in humans was *inadequate* as only one, non-informative, study was available. The evidence of carcinogenicity in experimental animals was *limited* as malignant neoplasms were induced in one species (rat) and one sex (males). A small minority of the Working Group considered the evidence in experimental animals to be *sufficient* on the basis of tumour multiplicity in target tissues, and proposed a classification of possibly carcinogenic to humans (Group 2B). The mechanistic evidence was limited as the findings regarding key characteristics of carcinogens were suggestive, but incoherent across different experimental systems.

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