and females, respectively) allyl chloride (technical grade; purity, 98%) per day in corn oil by gavage on five days per week. Due to toxicity the doses were reduced on two occasions; average time-weighted doses over a 78-week treatment period were 57 and 77 mg/kg bw for low- and high-dose males and 55 and 73 mg/kg bw for low- and high-dose females, respectively. All surviving animals were maintained without further treatment up to a maximum of 110 weeks. A group of 20 rats of each sex was treated with corn oil alone and served as vehicle controls, and a further group of 20 rats of each sex served as untreated controls. In the high-dose group, 50% of males had died by week 14 and 50% of females by week 38; the number of animals at risk for developing tumours was insufficient for analysis of these results. In the low-dose group, 50% of males were still alive at 77 weeks and 50% of females at 99 weeks; no increased incidence of tumours related to treatment was observed (National Cancer Institute, 1977; Weisburger, 1977).

(*b*) *Skin application*

Mouse: Groups of 30 female Ha:ICR Swiss mice, six to eight weeks of age, received skin applications of 31 or 94 mg allyl chloride (technical grade) [purity unspecified] in 0.2 ml acetone three times per week for 440-594 days. No skin tumour was observed in treated animals, and the incidence of other tumours did not differ significantly from that in controls. No skin tumour occurred in 30 controls treated with 0.1 ml acetone alone (Van Duuren *et al.*, 1979).

In a two-stage mouse-skin assay, groups of 30 female Ha:ICR Swiss mice, aged six to eight weeks, received a single skin application of 94 mg allyl chloride (technical grade) [purity unspecified] in 0.2 ml acetone, followed 14 days later by thrice-weekly applications of 5 µg phorbol myristyl acetate [12-*O*-tetradecanoylphorbol 13-acetate, TPA] in 0.2 ml acetone for life (median survival, 428-576 days). Seven papillomas were found in 6/90 control animals treated three times weekly with 5 µg TPA alone. A total of 10 papillomas was found in 7/30 treated mice ($p < 0.025$). The first tumour appeared at day 197 in the allyl chloride-treated group and at day 449 in the TPA-treated controls (Van Duuren *et al.*, 1979).

(*c*) *Intraperitoneal administration*

Mouse: Groups of 10 male and 10 female A/St mice, six to eight weeks of age, received intraperitoneal injections in tricaprylin of allyl chloride (technical grade, without further purification) three times weekly for eight weeks at total-dose levels of 15.6, 38.4 and 76.8 mmol/kg bw (1.2, 2.9 and 5.9 g/kg bw). Controls received tricaprylin alone. All animals were killed 24 weeks after the first injection, when the numbers of survivors were 16/20, 20/20, 20/20 and 20/20 in the control, low-, medium- and high-dose groups, respectively. The numbers of lung adenomas seen grossly per mouse in animals of both sexes combined were 0.19 $\pm$ 0.1, 0.60 $\pm$ 0.20, 0.50 $\pm$ 0.27 and 0.60 $\pm$ 0.15 in the control, low-, medium- and high-dose groups, respectively. The incidence of lung tumours in the high-dose group differed statistically from that in controls by one of two statistical tests ($p < 0.05$) (Theiss *et al.*, 1979).

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The oral LD_{50}s of allyl chloride (purity, >99 %) have been reported to be 425 mg/kg bw in mice and 460 mg/kg bw in rats. In mice, the oral LD_{50} of a commercial-grade sample (purity, 90%) was 550 mg/kg bw. Inhalation studies in a static exposure system gave the

following LC_{50} values for two-hour exposures: female mice, 11 500 mg/m^3; rats, approximately 11 400 mg/m^3; and guinea-pigs, 5800 mg/m^3 (Lu *et al.*, 1982). Exposure by inhalation to 2000 ppm (6200 mg/m^3) allyl chloride vapour for four hours was lethal for 1/6 rats (Smyth & Carpenter, 1948).

Allyl chloride has strong irritating properties. Inhalation of vapours produces inflammatory and necrotizing effects in the respiratory ducts and lung damage is the usual cause of death in rats and guinea-pigs. The major systemic effects are degenerative changes of kidney and to a lesser extent of the liver (Adams *et al.*, 1940). Long-term inhalation studies, in which rabbits and cats were exposed to 206 mg/m^3 allyl chloride vapour for six hours per day on six days per week for three months, resulted in the development in rabbits of flaccid paralysis with muscular atrophy, which were in part reversible after cessation of exposure; cats were affected to a lesser extent. Exposure to 17.5 mg/m^3 under comparable conditions was tolerated without adverse effects (Lu *et al.*, 1982).

All of six rabbits injected subcutaneously with 50 mg/kg bw allyl chloride three times for one week followed by 100 mg/kg bw three times a week for up to 11 weeks developed peripheral neuropathy (He *et al.*, 1980).

Inhalation exposure of rats, guinea-pigs and rabbits to 8 ppm (24.8 mg/m^3) allyl chloride vapour in a dynamic-flow system for seven hours per day, on five days per week for five weeks caused histological damage to the livers and kidneys, whereas exposure to 3 ppm (9.3 mg/m^3) for six months under the same conditions caused no observable toxic effect in rats, guinea-pigs, rabbits or dogs (Torkelson *et al.*, 1959).

In a bioassay gavage study (described in section 3.1), rats received daily time-weighted average doses of 57 or 77 (males) and 55 or 73 (females) mg/kg bw allyl chloride in corn oil for 78 weeks. A slight depression of body-weight gain was observed in the high-dose groups, but a dose-dependent reduction in mean survival times was seen in both the high- and low-dose groups. Hunched appearance and some respiratory distress were also reported. Mice received daily time-weighted average doses of 172 or 199 (males) and 129 or 258 (females) mg/kg bw. No depression of body weight was observed, but a significant decrease in mean survival times, accompanied by loss of equilibrium and abdominal distention, was reported in high-dose males (National Cancer Institute, 1977).

Effects on reproduction and prenatal toxicity

Groups of 25-39 Sprague-Dawley rats and 20-25 New Zealand white rabbits were exposed *via* inhalation to 0, 30 or 300 ppm (0, 93 or 930 mg/m^3) allyl chloride (purity, 98.6%) vapour for seven hours per day on gestation days 6-15 (rats) or 6-18 (rabbits). Exposure to 300 ppm resulted in decreased maternal weight gain during the first two or three days of exposure. Only minor alterations of the foetal skeleton were seen, including delayed ossification of the sternebrae and vertebral centra among rats at the highest exposure level (John *et al.*, 1983).

A group of 10-15 Sprague-Dawley rats received intraperitoneal injections of 80 mg/kg bw allyl chloride [purity unspecified] in corn oil on days 1-15 of gestation. Foetuses were examined on day 21 of gestation. Maternal heart, liver, spleen and kidney weights were significantly increased by treatment, but no histopathological change was evident. There were significant increases in the occurrence of oedematous foetuses and foetuses with short snout and protruding tongue in treated litters (Hardin *et al.*, 1981).

[The Working Group noted that these studies differed in the route of administration.]

Absorption, distribution, excretion and metabolism

Male rats dosed subcutaneously with allyl chloride (1 ml of a 10% v/v solution in arachis oil) excreted mercapturic acids in the urine which were identified as 3-hydroxypropylmercapturic acid and allylmercapturic acid and its sulphoxide (Kaye *et al.*, 1972). This suggests that allyl chloride is metabolized through two different pathways (see also Fig. 1, General Remarks on the Substances Considered, p. 32). Allylglutathione and *S*-allyl-L-cysteine have been detected in the bile of a rat given allyl chloride (Kaye *et al.*, 1972).

Allyl chloride in the presence of NADPH and oxygen partially destroyed rat hepatic microsomal cytochrome P-450 with loss of haem (Patel *et al.*, 1981).

Allyl chloride exerts direct alkylating properties *in vitro* (Eder *et al.*, 1980, 1982a,b).

Mutagenicity and other short-term tests (see also 'Appendix: Activity Profiles for Short-Term Tests', p. 329).

Allyl chloride is positive in the bacterial $polA^+/polA^-$ DNA-repair assay with *Escherichia coli* (McCoy *et al.*, 1978).

The mutagenicity of allyl chloride for *Salmonella typhimurium* TA1535 and TA100 but not TA1538 can be demonstrated if precautions are taken to prevent its escape due to volatility (McCoy *et al.*, 1978; Bignami *et al.*, 1980; Eder *et al.*, 1980; Norpoth *et al.*, 1980; Simmon, 1981; Eder *et al.*, 1982a,b); its activity is greatly decreased by the presence of an exogenous metabolic system (Eder *et al.*, 1980, 1982a,b).

Allyl chloride is mutagenic to *Streptomyces coelicolor* but not to *Aspergillus nidulans* (Bignami *et al.*, 1980); it induces gene conversions in *Saccharomyces cerevisiae* (McCoy *et al.*, 1978).

(*b*) *Humans*

Toxic effects

Workers exposed to concentrations of allyl chloride ranging from 1-113 ppm (3-350 mg/m^3) for 16 months were reported to have developed liver damage, as determined by serum enzyme activities, which was shown to be reversible after cessation or minimization of exposure (Häusler & Lenich, 1968). In another study of exposure to unknown concentrations of allyl chloride, workers were reported to have impaired kidney function (Ali-Zade, 1979). Both motor and sensory neurotoxic damage at the distal parts of the extremities (similar to that seen after exposure to *n*-hexane or tri-*ortho*-cresyl phosphate) was reported in 17 industrial workers, which was reversible after cessation of exposure and treatment; however, this effect recurred after return to work. The same symptoms were induced in rabbits exposed under similar laboratory conditions (He *et al.*, 1980).

Effects on reproduction and prenatal toxicity

Potential adverse effects of allyl chloride (as well as the structurally similar epichlorohydrin and 1,3-dichloropropene) on male fertility were investigated in employees of a glycerol factory in Texas, USA (Venable *et al.*, 1980). In general, no difference in a variety of sperm counts was found between 64 exposed and 63 control workers, although a subgroup of 10 workers exposed to all three chemicals had a significantly lowered sperm count in comparison to the remainder of the study group. The eight-hour time-weighted average for all of these chemicals was estimated to have been <1 ppm (<3.1 mg/m^3) during the five years

immediately preceding the study. Two other subgroups, exposed to epichlorohydrin and allyl chloride or 1,3-dichloropropane and allyl chloride, showed no evidence of decreased sperm counts. [The Working Group noted the multiple exposures evaluated, the possible exposure of controls to other chemicals, as well as possible variations in individual sample collections and processing time, making this study inadequate for the evaluation of the effects of allyl chloride on semen quality.]

No data were available to the Working Group on absorption, distribution, excretion and metabolism or on mutagenicity and chromosomal effects.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Allyl chloride has been produced commercially since 1945 and is used almost exclusively as a chemical intermediate, principally in the production of epichlorohydrin.

4.2 Experimental data

Allyl chloride has been tested for carcinogenicity by intragastric intubation in mice and rats, by skin application in mice, both by repeated application and in a two-stage assay, and by intraperitoneal injection in mice. Following its oral administration to mice, a nonsignificant increase in the incidence of squamous-cell papillomas and carcinomas of the forestomach was observed; the experiment in rats was inadequate for evaluation. No skin tumour was observed in mice following repeated skin applications; however, a single application followed by treatment with 12-*O*-tetradecanoylphorbol 13-acetate gave some evidence that allyl chloride acts as an initiator. Following its intraperitoneal injection to strain A mice, a slight increase in the incidence of lung adenomas was observed.

Inhalation exposure to allyl chloride of high purity did not induce teratogenicity in rats or rabbits.

Allyl chloride caused DNA damage in bacteria, and was mutagenic to bacteria and fungi.

Overall assessment of data from short-term tests: allyl chloride[a]

	Genetic activity			
	DNA damage	Mutation	Chromosomal effects	Cell transformation
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects				
Mammalian cells (*in vitro*)				
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity: *Limited*				Cell transformation: No data

[a]The groups into which the table is divided and the symbol + are defined on pp. 17-18 of the Preamble; the degrees of evidence are defined on p. 18.

4.3 Human data

No case report or epidemiological study of the carcinogenicity of allyl chloride to humans was available to the Working Group.

4.4 Evaluation[1]

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

In the absence of epidemiological data, no evaluation could be made of the carcinogenicity of allyl chloride to humans.

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[1]For definitions of the italicized terms, see the Preamble, pp. 15-16.

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