ALLYL ISOTHIOCYANATE

This substance was considered by previous working groups, in 1984 (IARC, 1985) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 57-06-7

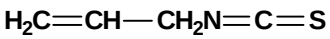
Deleted CAS Reg. No.: 50888-64-7; 50978-48-8; 58391-87-0; 107231-30-1

Chem. Abstr. Name: 3-Isothiocyanato-1-propene

IUPAC Systematic Name: Allyl isothiocyanate

Synonyms: AITC; allyl mustard oil; allyl senevolum; allyl thioisocyanate; 3-isothiocyanato-1-propene; isothiocyanic acid, allyl ester; mustard oil; oleum sinapis; 2-propenyl isothiocyanate; volatile mustard oil; volatile oil of mustard

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_4H_5NS Relative molecular mass: 99.16

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless or pale-yellow, very refractive liquid with a very pungent, irritating odour and acrid taste (Budavari, 1996)

(*b*) *Boiling-point*: 152°C (Lide, 1997)

(*c*) *Melting-point*: –80°C (Lide, 1997)

(*d*) *Density*: 1.0126 g/cm^3 at 20°C (Lide, 1997)

(*e*) *Solubility*: Sparingly soluble in water; very soluble in benzene, ethyl ether and ethanol; miscible with most organic solvents (Budavari, 1996; Lide, 1997)

(*f*) *Vapour pressure*: 1.33 kPa at 38.3°C (Verschueren, 1996)

(*g*) *Octanol/water partition coefficient (P)*: log P, 2.11 (Verschueren, 1996)

(*h*) *Conversion factor*: mg/m^3 = 4.06 × ppm

1.2 Production and use

Information available in 1995 indicated that allyl isothiocyanate was produced in Germany, Japan, Mexico and the United States (Chemical Information Services, 1995).

Allyl isothiocyanate is used as a flavouring agent, in medicine as a rubefacient (counterirritant), as a fumigant, in ointments, in mustard plasters, as an adjuvant, as a fungicide, as a repellent for cats and dogs and as a preservative in animal feed (National Toxicology Program, 1991).

1.3 Occurrence

1.3.1 *Natural occurrence*

Allyl isothiocyanate is the chief constituent of natural mustard oil. It is also found in cooked cabbage, horseradish and black mustard seed (National Toxicology Program, 1991).

1.3.2 *Occupational exposure*

No information on occupational exposure to allyl isothiocyanate was available to the Working Group.

1.3.3 *Dietary intake*

The average daily intake of individuals in the United States was estimated to be less than 6 mg/day on the basis of annual usage in 1970 and estimated exposure to allyl isothiocyanate in foods (Food & Drug Administration, 1975).

1.4 Regulations and guidelines

In the former Czechoslovakia, the 8-h time-weighted average exposure limit for allyl isothiocyanate in workplace air was 0.3 mg/m^3 (International Labor Office, 1991).

No international guidelines for allyl isothiocyanate in drinking-water have been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Allyl isothiocyanate was tested for carcinogenicity by gastric intubation in mice of one strain and in rats of one strain. In mice, no increase in the incidence of tumours was observed. An increased incidence of epithelial hyperplasia and transitional-cell papillomas of the urinary bladder was observed in male rats only, and some subcutaneous fibrosarcomas occurred in female rats given the high dose (IARC, 1985).

New studies

Groups of 20 female A/J mice were given 1 or 5 μmol of allyl isothiocyanate per mouse by gavage in saline or corn oil and then 10 μmol of 4-(methylnitrosamino)-1-(3-pyridyl)butanone (NNK) in 0.1 ml saline or saline alone. Sixteen weeks after these treatments, the animals were killed and pulmonary adenomas were counted. The tumour incidence was 100% in all groups receiving NNK. No statistically significant difference in tumour multiplicity was seen, with 11.1, 11.6 and 9.5 tumour per animal in the controls and in the groups receiving 1 and 5 μmol allyl isothiocyanate, respectively. The incidences of lung adenomas in mice receiving saline were 20 and 10% for those given corn oil and allyl isothiocyanate with multiplicities of 0.3 and 0.2, respectively (Jiao *et al*., 1994a).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Four adult volunteers (two men, two women, aged 20–45) ingested 10 g brown mustard with bread, and a control group of four participants ate bread without mustard. In a second experiment, 20 g of brown mustard were eaten in turkey or chicken sandwiches. In both experiments, urine samples were collected at various intervals up to 48 h following the meal. The major urinary metabolite was *N*-acetyl-*S*-(*N*-allylthiocarbamoyl)-L-cysteine, the *N*-acetylcysteine conjugate of allyl isothiocyanate, but none was found after 12 h. Excretion of this metabolite was dose-dependent (Jiao *et al.*, 1994b).

4.1.2 *Experimental systems*

Male and female Fischer 344 rats (8–10 weeks old) and male and female B6C3F$_1$ mice (6–8 weeks old) were given [^{14}C]allyl isothiocyanate in a solution of ethanol: Emulphor EL-620:water (l:l:8) at doses of 25.2 or 252 μmol/kg [2.5 or 25 mg/kg bw] by gavage, 25 mg/kg bw by injection into a tail vein for studies of distribution or injection into an exposed femoral vein for studies of biliary excretion. The radiolabel was cleared primarily in urine (70–80%) and exhaled air (13–15%), with lesser amounts in faeces (3–5%) in both species. The major metabolite detected in rat and mouse urine was the mercapturic acid, *N*-acetyl-*S*-(*N*-allylthiocarbamoyl)-L-cysteine, while mouse urine also contained three other major and two minor metabolites. The metabolism of allyl isothiocyanate by male and female rats was similar, but the females excreted more than twice as much urine as the males. Major sex- and species-related differences in the tissue distribution of allyl isothiocyanate were restricted to the urinary bladder. Thus, the urinary bladder of male rats contained five times higher concentrations of allyl isothiocyanate-derived radiolabel that that of male mice at early time points, but all of the allyl isothiocyanate-derived radiolabel was cleared from male rat bladder by 24 h (Ioannou

et al., 1984). Similar results were obtained by Bollard *et al.* (1997) after oral administration of allyl isothiocyanate (2.5 or 25 mg/kg bw) to male and female Fischer 344 rats and $B6C3F_1$ mice.

The urinary excretion of allyl isothiocyanate in male Fischer 344 rats did not change with age, but 27-month-old rats showed increased excretion of volatile metabolites and decreased $^{14}CO_2$ production and faecal excretion (Borghoff & Birnbaum, 1986).

Allyl isothiocyanate is a highly reactive compound, which has been shown *in vitro* to form adducts with proteins (Kawakishi & Kaneko, 1987) and glutathione (Kawakishi & Kaneko, 1985).

Oral administration of allyl isothiocyanate, benzyl isothiocyanate or phenethyl isothiocyanate to male Fischer 344 rats inhibited the formation of the α-hydroxylation products of *N*-nitrosopyrrolidine and NNK in liver microsomes (Chung *et al*., 1984).

All of a series of isothiocyanates (including allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, and 1-hexylisothiocyanate) inhibited dealkylation of pentoxyresorufin more readily than that of ethoxyresorufin in liver microsomes prepared from male Fischer 344 rats treated with phenobarbital or 3-methylcholanthrene. Allyl isothiocyanate and its glutathione conjugate were the weakest inhibitors in the series (Conaway *et al*., 1996). The chemopreventive activity of isothiocyanates has been correlated to inhibition of this microsomal enzyme (Yang *et al*., 1994).

Allyl isothiocyanate altered the expression of xenobiotic-metabolizing enzymes such as monooxygenases, amino transferases and glutathione transferases in the liver, small intestine and serum of rats (Lewerenz *et al*., 1988a; Bogaards *et al*., 1990). *N*-Nitrosodimethylamine demethylase activity in rat and human liver microsomes was significantly inhibited by arylalkyl isothiocyanates such as benzyl isothiocyanate and phenethyl isothiocyanate at micromolar concentrations, but very weakly inhibited by allyl isothiocyanate and other alkyl isothiocyanates (Jiao *et al*., 1996).

4.2 Toxic effects

4.2.1 *Humans*

Allyl isothiocyanate irritates the mucous membranes and induces eczematous or vesicular skin reactions (Gaul, 1964). Contact dermatitis was reported in a waitress who handled salad plants, and patch tests with radishes and with allyl isothiocyanate produced positive reactions (Mitchell & Jordan, 1974).

Allyl isothiocyanate was cytostatic and cytotoxic towards a human colon carcinoma cell line, HT29; this activity was reduced when the cells were treated with sodium butyrate or dimethylformamide (Musk & Johnson, 1993a). The authors speculated that allyl isothiocyanate protects against the development of colorectal cancer by selectively inhibiting the growth of transformed cell clones within the gastrointestinal mucosa.

4.2.2 *Experimental systems*

The oral LD_{50} of allyl isothiocyanate dissolved in corn oil was reported to be 339 mg/kg bw in rats (Jenner *et al*., 1964); in mice, the subcutaneous LD_{50} of a 10%

solution of allyl isothiocyanate in corn oil was 80 mg/kg bw (Klesse & Lukoschek, 1955). The compound strongly irritates skin and mucous membranes (Gosselin *et al*., 1982).

A single administration of the compound in corn oil by gavage caused growth retardation and dose-related, non-specific signs of toxicity at doses of 200 and 400 mg/kg bw in rats and 100–800 mg/kg bw in mice. In a 14-day experiment in which mice and rats received doses of 3–50 and 25–400 mg/kg bw, respectively, dose-dependent thickening of the stomach mucosa was seen. Rats also showed adhesion of the stomach wall to the peritoneum, and mice given the highest dose developed thickening of the urinary bladder wall. Doses of ≥ 200 mg/kg bw in rats and of ≥ 50 mg/kg bw in mice were lethal. In a study lasting 103 weeks, daily doses of 12 or 25 mg/kg bw caused a slight, dose-related decrease in body-weight gain and mean survival time, and an increased incidence of cytoplasmic vacuolization was noted in the livers of male mice (National Toxicology Program, 1982).

Administration to rats of 0.5 mg allyl isothiocyanate by intraperitoneal injection of 0.1% in the diet for 30 days resulted in reduced blood clotting and prothrombin times, an increase in total plasma phospholipids, increased concentrations of total lipids and cholesterol in the liver and decreased activity of D-amino acid oxidase (Muztar *et al*., 1979a,b) and xanthine oxidase (Huque & Ahmad, 1975). Feeding allyl isothiocyanate increased the urine volume and increased the uric acid, creatinine and glucose concentrations in the urine of Sprague-Dawley rats (Muztar *et al*., 1979b).

Allyl isothiocyanate exerts slight goitrogenic activity. Rats weighing 150–320 g given 2–4 mg as a single dose by gavage in water showed inhibited uptake of iodine into the thyroid gland (Langer & Štolc, 1963). Studies *in vitro* indicated that this effect may be due to inhibition of inorganic iodide storage and of organic binding of iodine (Langer & Greer, 1968).

Male outbred rats (Shoe; WIST) (70–90 g) were given allyl isothiocyanate in paraffin oil by gavage at doses of 0, 10, 20 or 40 mg/kg bw on five days per week for up to six weeks (Lewerenz *et al*., 1988b). The highest dose decreased body weight and thymus weight, reduced the blood glucose and serum globulin concentrations, increased the percentage of neutrophils and decreased the percentage of lymphocytes after two weeks; changes in urinary specific gravity, a slight but significant increase in aspartate aminotransferase activity and histological changes in the kidneys, indicative of renal dysfunction, were also seen at this dose. This investigation did not show that allyl isothiocyanate had a goitrogenic effect, as reported by Langer and Štolc (1963). There were no significant changes in thyroid weight in rats treated for up to four weeks.

Both glutathione and L-cysteine conjugates of allyl isothiocyanate were cytotoxic to RL-4 rat hepatocytes. Since glutathione conjugates cannot enter the cell, their toxicity was suggested to be due to release of free isothiocyanates (Bruggeman *et al*., 1986).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Allyl isothiocyanate has been tested for developmental toxicity by exposing CD-1 mice to doses of up to 28 mg/kg bw per day, Wistar rats to 18.5 mg/kg bw per day, Syrian hamsters to 23.8 mg/kg bw per day and Dutch-belted rabbits to 12.3 mg/kg bw per day throughout their respective major organogenesis periods. No evidence of maternal toxicity and no treatment-related malformations were observed in any species. There was some increase in the incidence of resorbed fetuses in mice, the average number of live pups per litter being 9.9 at the highest dose and 11 in the controls, while the percentage of dead implants was 14 at this dose and 5.7 in the controls. No adverse developmental effects were seen when limited numbers of Wistar rats received up to 120 mg/kg bw by oral intubation on day 12 or 13 gestation. When Holtzman rats received up to 100 mg/kg bw by subcutaneous injection on days 8 and 9 of gestation, the incidence of resorptions was increased at the high dose (IARC, 1985).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

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

Inconsistent results for gene mutation in *Salmonella typhimurium* TA100 and TA98 were found with and without exogenous metabolic activation. Allyl isothiocyanate did not induce gene mutation in *Salmonella* strains TA1535, TA1537 or TA1538 in the absence of exogenous metabolic activation, but it induced mutation in *Escherichia coli* with exogenous metabolic activation. Allyl isothiocyanate at a very high dose induced chromosomal aberrations in *Allium cepa*. Sex-linked recessive lethal mutations were induced in *Drosophila melanogaster*. The compound induced gene mutation in mouse lymphoma L5178Y cells in the absence of exogenous metabolic activation. It did not induce sister chromatid exchange in Chinese hamster ovary cells in the absence of exogenous metabolic activation, but inconsistent results were obtained in assays for chromosomal aberration in mammalian cells *in vitro*. In single studies, allyl isothiocyanate was reported to induce aneuploidy and cell transformation in a Chinese hamster cell line at the extremely low concentration of 5 pg/mL and chromosomal aberrations in human cells *in vitro*, but it did not induce aneuploidy or cell transformation in human fibroblasts *in vitro*. It did not induce dominant lethal mutations in mice and did not give rise to unscheduled DNA synthesis in the liver of rats exposed *in vivo*.

Mustard oil, which is reported to contain more than 90% allyl isothiocyanate, induced sex-linked recessive lethal mutations in *Drosophila melanogaster* but did not induce aneuploidy. It did not induce chromosomal aberrations in human embryonic lung cells *in vitro* and did not induce any 'genetic effect' in *Saccharomyces cerevisiae* in a host-mediated assay. It did not induce chromosomal aberrations in bone marrow or dominant lethal mutations in rats treated *in vivo*.

Table 1. Genetic and related effects of allyl isothiocyanate

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA98, reverse mutation	+	NT	25	Yamaguchi (1980)
Salmonella typhimurium TA100, TA98, reverse mutation	–	–	500 µg/plate	Kasamaki *et al*. (1982)
Salmonella typhimurium TA100, TA1535, TA98 reverse mutation	–	–	0.1 µL/plate	Eder *et al*. (1980)
Salmonella typhimurium TA1535, TA1537, TA1538, reverse mutation	–	–	100 µg/plate	Yamaguchi (1980)
Salmonella typhimurium TA100, reverse mutation	–	+	0.25 µL/plate	Neudecker & Henschler (1985)
Escherichia coli WP67, reverse mutation	–	+	99	Rihová (1982)
Allium cepa, chromosomal aberrations	+	NT	20 000	Sharma & Sharma (1962)
Drosophila melanogaster, sex-linked recessive lethal mutations	+		NR	Auerbach & Robson (1944)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	0.4	McGregor *et al.* (1988)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	NT	3.0	Musk *et al.* (1995)
Chromosomal aberrations, Chinese hamster B241 cells *in vitro*	+	NT	0.0001	Kasamaki *et al*. (1982)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	NT	3.0	Musk *et al.* (1995)
Chromosomal aberrations, Chinese hamster B241 cells *in vitro*	+	NT	0.0005	Kasamaki *et al.* (1987)
Chromosomal aberrations, transformed Indian muntjac cells *in vitro*	–	NT	0.8	Musk & Johnson (1993b)
Aneuploidy, Chinese hamster B241 cells *in vitro*	+	NT	0.0005	Kasamaki *et al.* (1987)
Cell transformation, Chinese hamster B241 cells with confirmation *in vivo*	+	NT	0.0005	Kasamaki *et al.* (1987)
Chromosomal aberrations, human HAIN-55 fibroblasts *in vitro*	+	NT	0.002	Kasamaki *et al.* (1987)
Aneuploidy, human HAIN-55 cells *in vitro*	–	NT	0.002	Kasamaki *et al.* (1987)
Cell transformation, human HAIN-55 cells *in vitro*	–	NT	0.002	Kasamaki *et al.* (1987)
Dominant lethal mutation, mice *in vivo*	–		19 ip × 1	Epstein *et al*. (1972)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Unscheduled DNA synthesis, rat hepatocytes *in vivo*	–		125 po × 1	Bechtel *et al.* (1998)
Mustard oil reported to contain > 90% allyl isothiocyanate				
Drosophila melanogaster, sex-linked recessive lethal mutations	+		NR, spray	Auerbach & Robson (1947)
Drosophila melanogaster, aneuploidy	–		NR, spray	Auerbach & Robson (1947)
Chromosomal aberrations, human embryonic lung cells *in vitro*	–	NT	10	Food & Drug Administration (1975)
Host-mediated assay, *Saccharomyces cerevisiae* in mouse peritoneal cavity	–		130 po × 1	Food & Drug Administration (1975)
Chromosomal aberrations, rat bone-marrow cells *in vivo*	–		100 po × 1	Food & Drug Administration (1975)
Dominant lethal mutation, rats *in vivo*	–		100 po × 1	Food & Drug Administration (1975)

[a] +, positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro test, µg/mL; in-vivo test, mg/kg bw per day; ip, intraperitoneal; NR, not reported; po, oral

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to allyl isothiocyanate occurs as a result of its presence in foods as the chief constituent of mustard oil and as a flavouring agent.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Allyl isothiocyanate was tested for carcinogenicity in one experiment in mice and one experiment in rats by oral administration. No increase in tumour incidence was observed in mice. An increased but low incidence of transitional-cell hyperplasia and papillomas of the urinary bladder was observed in male rats, and there was a low incidence of subcutaneous fibrosarcomas in female rats given the high dose.

5.4 Other relevant data

Major sex- and species-related differences in the tissue distribution of allyl isothiocyanate were restricted to the urinary bladder, where higher concentrations of allyl isothiocyanate-derived radiolabel were found in the bladders of male rats than in mice or female rats. Rodents and humans both metabolize allyl isothiocyanate to *N*-acetyl-*S*-(*N*-allyl thiocarbamoyl)-L-cysteine. Allyl isothiocyanate appears to be an irritant in both rodents and humans.

Allyl isothiocyanate was not teratogenic to mice, rats, hamsters or rabbits, but resorptions were seen in mice and rats.

No data were available on the genetic and related effects of allyl isothiocyanate in humans. The available data do not allow a conclusion about the genotoxicity of allyl isothiocyanate in expertimental systems *in vivo*. There is evidence for genotoxic effects in mammalian cells *in vitro*. It was not mutagenic to bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

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