ETHYL ACRYLATE

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

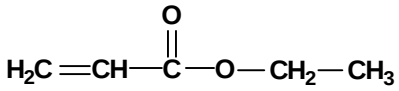
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 140-88-5
Chem. Abstr. Name: 2-Propenoic acid, ethyl ester
IUPAC Systematic Name: Acrylic acid, ethyl ester
Synonym: Ethyl propenoate

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_5H_8O_2$ Relative molecular mass: 100.12

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Liquid with an acrid, penetrating odour (Budavari, 1996)
(*b*) *Boiling-point*: 99.4°C (Lide, 1995)
(*c*) *Melting-point:* –71.2°C (Lide, 1995)
(*d*) *Solubility*: Slightly soluble in water; soluble in chloroform; miscible with diethyl ether and ethanol (Lide, 1995)
(*e*) *Vapour pressure*: 3.9 kPa at 20°C; relative vapour density (air = 1), 3.5 (Verschueren, 1996)
(*f*) *Flash-point*: 15°C, open cup (Budavari, 1996)
(*g*) *Explosive limits*: Lower explosive limit, 1.8% by volume in air (American Conference of Governmental Industrial Hygienists, 1991)
(*h*) *Conversion factor*: $mg/m^3 = 4.09 \times ppm$

1.2 Production and use

Production of ethyl acrylate in the United States in 1993 was reported to be 160 345 tonnes (United States International Trade Commission, 1994).

Ethyl acrylate is used as a monomer in acrylic resins (American Conference of Governmental Industrial Hygienists, 1991).

1.3 Occurrence

1.3.1 *Occupational exposure*

The 1981–83 National Occupational Exposure Survey (NOES) estimated that 34 000 workers in the United States were potentially exposed to ethyl acrylate (NOES, 1997).

National estimates of exposure were not available from other countries.

1.3.2 *Environmental occurrence*

Ethyl acrylate may be released into the environment in escape or stack emissions or in wastewater during its production and use. It is also a volatile component of pineapple and Beaufort cheese (a type manufactured in a small area of the French Alps). It has been detected at low levels in wastewater samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 20 mg/m^3 as the threshold limit value for occupational exposures to ethyl acrylate in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for ethyl acrylate in drinking-water has 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

Ethyl acrylate was tested for carcinogenicity by oral gavage in mice and rats. Dose-related increases in the incidence of squamous-cell papillomas and carcinomas of the forestomach were observed in both species. Ethyl acrylate was tested by inhalation in the same strains of mice and rats; no treatment-related neoplastic lesion was observed. No treatment-related tumour was observed following skin application of ethyl acrylate for lifespan to male mice (IARC, 1986).

3.1 Oral administration

Rat: Three groups of 25 male Fischer 344 rats, two months of age, were treated with 200 mg/kg bw ethyl acrylate (purity, 99%) by gavage in corn oil on five days per week

for six or 12 months. Control rats received 5 mL corn oil/kg bw per day on five days per week for 12 months. Five rats from each treatment group were killed 24 h after the last dose. The remaining rats were killed at 24 months of age. All animals were examined for gross lesions and the stomachs were collected and fixed in formalin. Microscopic examination was restricted to three or four sections of the stomach. No treatment-related neoplastic lesions were observed in the forestomach of rats exposed to ethyl acrylate for six months and autopsied at 24 months of age. After 12 months of ethyl acrylate administration, all rats showed hyperplastic lesions but no neoplastic lesions were detected. However, when rats received ethyl acrylate for 12 months and were killed after nine months of recovery, they developed squamous-cell carcinomas (3/13) and papillomas (1/13) (Ghanayem *et al.*, 1993). [The Working Group noted that histopathological evaluation was limited to the stomach.]

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

De Bethizy *et al*. (1987) administered ethyl [2,3-^{14}C]acrylate to rats orally by gavage at doses of 2, 20 and 200 mg/kg bw. The total recovery in specific tissues and excreta fell with increasing dose from 108% at 2 mg/kg bw to 73% at 200 mg/kg bw. The major metabolite was $^{14}CO_2$, with 52–61% exhaled within 24 h. The proportion of radioactivity excreted in the urine fell with increasing dose, from 28% at 2 mg/kg bw to 8% at 200 mg/kg bw. Three metabolites were identified: 3-hydroxypropionic acid and two mercapturic acids. *N*-Acetyl-*S*-(2-carboxyethyl)cysteine arises by glutathione conjugation of acrylic acid, while *N*-acetyl-*S*-(2-carboxyethyl)cysteine ethyl ester derives from the conjugation of intact ethyl acrylate. The percentage of the dose excreted as these mercapturic acids falls with increasing dose, consistent with depletion of glutathione. Although ethyl acrylate does not reduce non-protein sulfhydryls in the liver, marked and dose-dependent depletion occurs in the forestomach and glandular stomach, which is enhanced by pretreatment of rats with the esterase inhibitor tri(*ortho*-cresyl)phosphate. These data are consistent with the hydrolysis of ethyl acrylate being a systemic detoxication reaction, since acrylic acid has no effect on non-protein sulfhydryl levels.

Linhart *et al*. (1994) reported increases in urinary levels of 3-hydroxypropanoic, lactic and acetic acids after administration of ethyl acrylate to rats.

Potter and Tran (1992) showed that ethyl acrylate reacts spontaneously with glutathione and protein sulfhydryl groups in many tissues: in liver alone, conjugation with glutathione was catalysed by cytosolic glutathione *S*-transferase. Miller *et al*. (1981)

showed a major role for the liver in the hydrolysis of ethyl acrylate, the order of activities among tissues being liver >> blood >> lung > kidney. The hydrolysis of ethyl acrylate in various regions of the nose and respiratory tract was region-dependent (Frederick *et al*., 1994): high activity was found in homogenates of the dorsal meatus and olfactory septum, with much lower activity in respiratory epithelium. This distribution of activity does not correlate well with the distribution of cytotoxicity of ethyl acrylate after inhalation exposure. Stott and McKenna (1985) found that ethyl acrylate was hydrolysed in homogenates of mouse nasal epithelium.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Frederick *et al*. (1990) treated male Fischer 344/N rats with 0, 2, 20, 50, 100 and 200 mg/kg bw ethyl acrylate by daily gavage for two weeks. Another group of animals received 200, 1000, 2000 and 4000 ppm (mg/L) in the drinking-water for two weeks. In the 20–200 mg/kg bw dose range, dose-dependent irritation of the forestomach, but not of the glandular stomach, was observed. In the animals dosed with ethyl acrylate in the drinking-water, much lower effects were observed at corresponding dose levels. Dosage of 200 mg/kg bw led to a reduction of about 90% in non-protein sulfhydryl content in the forestomach, but not in the glandular stomach or the liver. Interestingly, Ghanayem *et al*. (1991a) found that sulfhydryl-containing agents (cysteine and cysteamine) enhanced ethyl acrylate-induced oedema of the forestomach, whereas depletion of the sulfhydryl content by fasting or pretreatment with diethyl maleate was protective.

In Fischer 344 rats of both sexes receiving a single dose of 100, 200 or 400 mg/kg bw ethyl acrylate, dose- and time-dependent occurrence of mucosal and submucosal oedema, vacuolization of the tunica muscularis of the forestomach and mild submucosal oedema in the glandular stomach were observed (Ghanayem *et al*., 1985a). Equivalent subcutaneous or intraperitoneal dosing did not produce similar gastric lesions. Profound gastric toxicity was also obtained with methyl or ethyl acrylate, while acrylic acid, *n*-butyl acrylate, methyl and ethyl propionate and methacrylic acid esters were inactive (Ghanayem *et al*., 1985b). Depending on dose and time, forestomachs of rats either returned to normal or showed (reversible) mucosal hyperplasia (Ghanayem *et al*., 1991b; Gillette & Frederick, 1993), while submucosal fibrosis became more prevalent in high-dose animals with time (Ghanayem *et al*., 1986a). Another study (Ghanayem *et al*., 1993) provided evidence that a certain time of sustained hyperplasia of the forestomach is required for effective tumorigenesis of ethyl acrylate in the forestomach of rats.

Daily gavage doses of 100 and 200 mg/kg bw ethyl acrylate on five days per week for two weeks resulted in a dramatic increase in forestomach epithelial cell proliferation in male Fischer 344 rats (Ghanayem *et al*., 1986b).

Exposure of male and female Fischer 344 rats and B6C3F$_1$ mice to 0, 0.1 or 0.31 mg/L ethyl acrylate vapour for 6 h per day on five days per week for 27 months resulted in dose-dependent occurrence of basal-cell hyperplasia, an increase in intra-epithelial glands, respiratory metaplasia and diffuse atrophy of the olfactory epithelium in rats, and in hyperplasia of submucosal glands and respiratory metaplasia of olfactory epithelium in mice (Miller *et al.*, 1985). Inhalation exposure of male Wistar rats to 1000 mg/m^3 ethyl acrylate for 6 h led to a significant increase in urinary thioether excretion (Vodička *et al.*, 1990). The average concentrations of ethyl acrylate in inhaled air that caused 50% depletion of non-protein sulfhydryl groups were estimated at 41.7 mmol/m^3 for blood, 50.4 mmol/m^3 for liver, 63.8 mmol/m^3 for lung and 81.5 mmol/m^3 for brain.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

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)

In single studies, ethyl acrylate did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* but did induce mitotic recombination in *Saccharomyces cerevisiae.* It was not mutagenic to bacteria.

In mammalian cells treated *in vitro*, it induced mutation at the *tk* locus in mouse L5178Y lymphoma cells, in the absence of exogenous metabolic activation, but not at the *hprt* locus in Chinese hamster ovary CHO cells. It induced chromosomal aberrations in mouse L5178Y lymphoma cells, Chinese hamster ovary CHO and Chinese hamster lung CHL cells *in vitro.*

In a single study, ethyl acrylate failed to induce DNA binding in forestomach or liver of rats when given by gavage at doses up to 400 mg/kg (Ghanayem *et al.*, 1987) [The Working Group noted the inadequate method for determining DNA binding.] It induced micronucleus formation in mouse bone marrow and weakly in mouse splenocytes; another study performed under the same conditions was negative. In single studies, ethyl acrylate failed to induce sister chromatid exchanges or chromosomal aberrations in mouse splenocytes *in vivo*. It did not induce DNA damage in peripheral white blood cells of mice or in the forestomach of rats treated *in vivo*.

4.4.3 *Mechanistic considerations*

Ethyl acrylate appears to be clastogenic to mammalian cells *in vitro*. The preferential induction of small colonies rather than large ones in the mouse lymphoma L5178Y *tk* mutagenicity assay is thought to indicate that mutations arise from chromosomal damage rather than by point mutation. The clastogenic activity of ethyl acrylate seen *in vitro* is

Table 1. Genetic and related effects of ethyl acrylate

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1666	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	670	Waegemaekers & Bensink (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1666	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	670	Waegemaekers & Bensink (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1666	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	670	Waegemaekers & Bensink (1984)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	670	Waegemaekers & Bensink (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1666	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	670	Waegemaekers & Bensink (1984)
SCH, *Saccharomyces cerevisiae* D61.M, homozygosis by mitotic recombination or gene conversion	+	NT	733	Zimmermann & Mohr (1992)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		40 000 ppm feed	Valencia *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	20	Moore *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	(+)	NT	20	McGregor *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	20	Moore *et al.* (1989)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	(+)	20	Dearfield *et al.* (1991)
GCO Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	–	NT	23	Moore *et al.* (1989)
GCO Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	–	NT	80	Moore *et al.* (1991)
SIM, Sister chromatid exchange, mouse splenocytes *in vitro*	–	NT	25	Kligerman *et al.* (1991)
CIM, Chromosomal aberrations, mouse splenocytes *in vitro*	(+)	NT	2	Kligerman *et al.* (1991)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
CIM, Chromosomal aberrations, mouse lymphoma L5178Y cells *in vitro*	+	NT	20	Moore *et al.* (1988)
CIM, Chromosomal aberrations, mouse lymphoma L5178Y cells *in vitro*	+	NT	20	Moore *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	21	Moore *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster lung cells *in vitro*	+	NT	9.8	Ishidate *et al.* (1981)
DVA, DNA strand breaks, Fischer 344 rat forestomach *in vivo*	–	NT	4% po × 1	Morimoto *et al.* (1990)
DVA, DNA strand breaks, Tg.AC mouse peripheral blood leukocytes *in vivo*	–		12 µg/mouse skin × 3/wk 20 wk	Tice *et al.* (1997)
SVA, Sister chromatid exchange, C57BL/6 mouse splenocytes *in vivo*	–		1000 ip × 1	Kligerman *et al.* (1991)
MVM, Micronucleus test, C57BL/6 mouse splenocytes *in vivo*	(+)		1000 ip × 1	Kligerman *et al.* (1991)
MVM, Micronucleus test, BALB/c mouse bone marrow *in vivo*	+		225 ip × 2	Przybojewska *et al.* (1984)
MVM, Micronucleus test, BALB/c and C57BL/6J mouse bone marrow *in vivo*	–		812 ip × 2	Ashby *et al.* (1989)
MVM, Micronucleus test, C57BL/6J mouse bone marrow *in vivo*	–		738 ip × 2	Ashby *et al.* (1989)
MVM, Micronucleus test, Tg.AC mouse peripheral blood cells *in vivo*	–		12 µg/mouse skin × 3/wk 20 wk	Tice *et al.* (1997)
CVA, Chromosomal aberrations, C57BL/6 mouse splenocytes *in vivo*	–		1000 ip × 1	Kligerman *et al.* (1991)

[a] +, positive; (+), weak positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal; po, oral; wk, week

not readily expressed *in vivo*. Ethyl acrylate did not bind to deoxyribonucleosides *in vitro* (McCarthy *et al.*, 1994).

5. Evaluation

No epidemiological data relevant to the carcinogenicity of ethyl acrylate were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethyl acrylate.

Overall evaluation

Ethyl acrylate is *possibly carcinogenic to humans (Group 2B)*.

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