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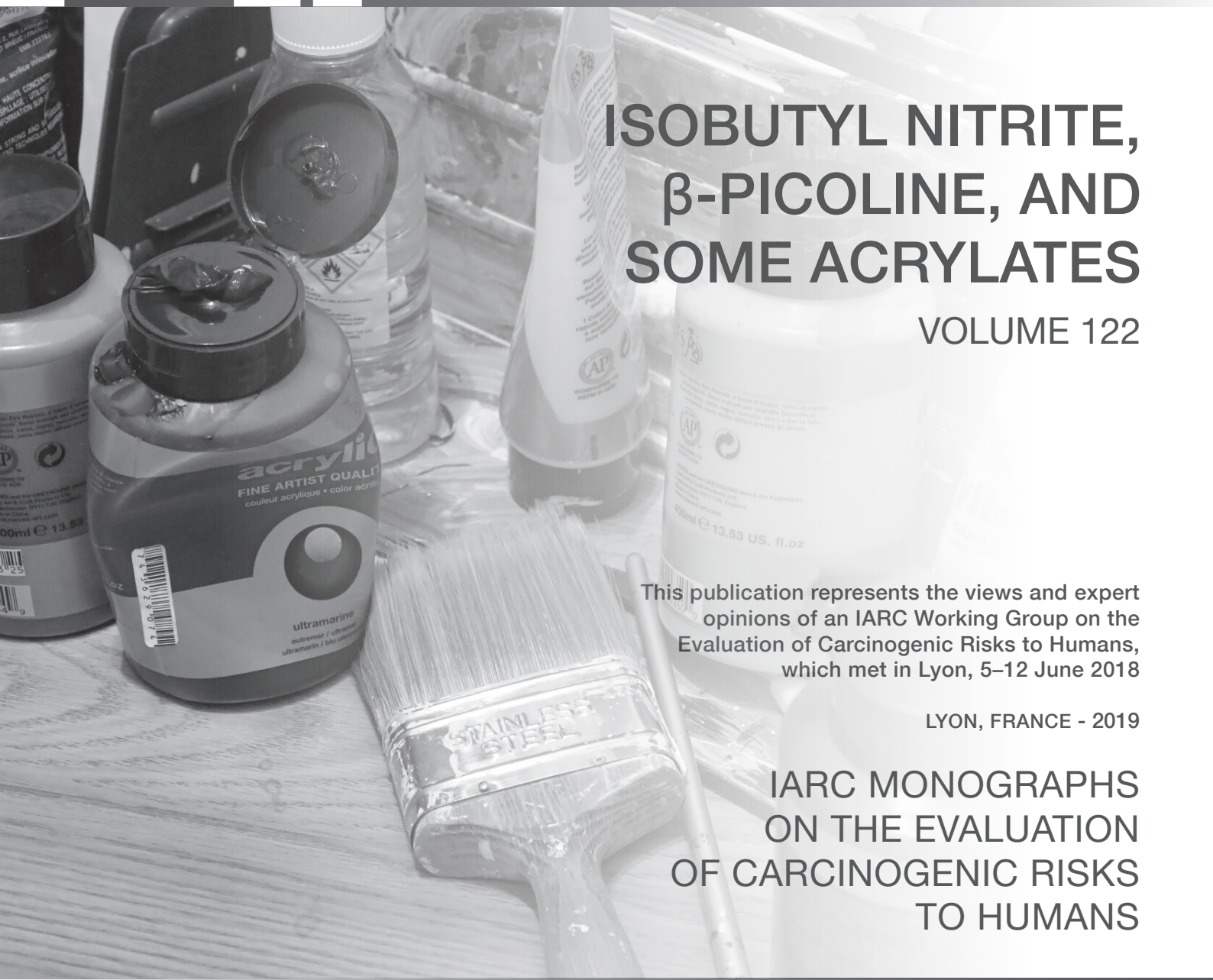


ISOBUTYL NITRITE, β-PICOLINE, AND SOME ACRYLATES

VOLUME 122

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 5–12 June 2018

LYON, FRANCE - 2019

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

ETHYL ACRYLATE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 140-88-5

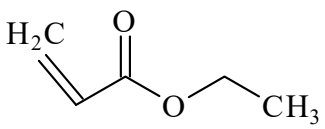
Chem. Abstr. Serv. name: 2-propenoic acid, ethyl ester

IUPAC systematic name: ethyl prop-2-enoate

Synonyms: ethyl propenoate; acrylic acid ethyl ester; ethyl 2-propenoate; ethoxycarbonylethylene.

1.1.2 Structural and molecular formulae, and relative molecular mass

Molecular formula: $C_5H_8O_2$



Relative molecular mass: 100.12

1.1.3 Chemical and physical properties of the pure substance

Description: colourless liquid with an acrid, penetrating odour (Budavari et al., 1996)

Boiling point: 99.4 °C (Lide, 1995)

Melting point: –71.2 °C (Lide, 1995)

Solubility: slightly soluble in water (2% w/v at 20 °C); soluble in chloroform; miscible with diethyl ether and ethanol (Lide, 1995)

Vapour pressure: 29.3 mm Hg [3.9 kPa] at 20 °C

Relative vapour density (air = 1): 3.5 (Verschueren, 1996)

Flash point: 15 °C, open cup (Budavari et al., 1996)

Explosive limits: lower explosive limit, 1.8% by volume in air (ACGIH, 2001)

Conversion factor: 1 ppm = 4.09 mg/m^3 at 1 atm, 25 °C.

1.1.4 Technical products and impurities

Impurities reported in commercial-grade (technical) ethyl acrylate (purity, 99.0–99.5%) include water (0.03–0.10% by weight), acrylic acid (0.0008–0.0090% by weight), and polymerization inhibitors (15–200 mg/kg hydroquinone monomethyl ether or 1000 mg/kg hydroquinone) (HSDB, 2018).

1.2 Production and use

1.2.1 Production process

Ethyl acrylate is produced by several methods, including catalysed esterification of acrylic acid with ethanol (EPA, 2007), reaction of nickel carbonyl and acetylene with ethyl alcohol in the presence of an acid, esterification of acrylic acid

with ethyl alcohol (modified Reppe process), and vinyl chloride reacted at 270 °C at a pressure of 6895 kPa or greater with ethanol in the presence of a cobalt and palladium catalyst (HSDB, 2018). Ethyl acrylate is a monomer that polymerizes readily to a transparent, elastic substance in the presence of light, heat, or a catalyst (EPA, 2007). The monomer is stored with small amounts of hydroquinone or its methyl ether to prevent spontaneous polymerization (ACGIH, 2001).

1.2.2 Production volume

Ethyl acrylate is a chemical with a high production volume (OECD, 2009). The USA produced 160 thousand metric tonnes of ethyl acrylate in 1993, and production was from more than 100 million to 500 million pounds [> 45.4 to 227 thousand metric tonnes] in 2002 (HSDB, 2018). The production rate in the European Union was in excess of 10 thousand metric tonnes per annum (SCOEL, 2004). Production volume in China was 102 674 metric tonnes in 2008 (Chinese Report, 2008) and 108 580 metric tonnes in 2010 (Chinese Report, 2010).

1.2.3 Use

Ethyl acrylate is used primarily as a chemical intermediate during the production of polymers including water-based paints, resins, plastics, and rubber (NIOSH, 2014). It is used as a surface coating for textiles, paper, and leather (such as nubuck and suede), in food-contact materials, and in the production of acrylic fibres, adhesives, and binders (ACGIH, 2001; EPA, 2007; Arkema, 2012). It is one of the principal monomers used worldwide in the production of styrene-based polymers, which can be used for medical and dental items (SCOEL, 2004). It also has limited use as a fragrance in cosmetics and a flavouring agent in food (mostly dairy products and soft drinks) (EPA, 2007; European Commission, 2012; Silano et al., 2017).

1.3 Analytical methods

1.3.1 Detection and quantification

Air sampling for ethyl acrylate is conducted using charcoal adsorbent. Samples are desorbed using carbon disulfide and the extract analysed using gas chromatography with flame ionization detection by United States National Institute for Occupational Safety and Health (NIOSH) Method 1450 (NIOSH, 2003) or United States Occupational Safety and Health Administration (OSHA) Method 92 (OSHA, 2018). NIOSH Method 1450 has a detection limit of 2 µg per sample and OSHA Method 92 has a detection limit of 80 µg/m^3.

Ethyl acrylate can also be analysed in water. The most recently published method found by the Working Group is United States Environmental Protection Agency (EPA) Method 624.1 (EPA, 2016). This method uses a purging chamber that transfers the volatile compounds to the vapour phase, followed by a sorbent trap. The trap is then heated and back-flushed to desorb the purgeables onto a gas chromatography column that is combined with mass spectrometry; the detection limit for ethyl acrylate was not reported. Similar purge and trap methods (Method 8260B) are also reported for other aqueous, solid (including waste and soil), and tissue samples (EPA, 1996).

1.3.2 Exposure assessment and biological markers

No information on biological markers of exposure to ethyl acrylate was available to the Working Group.

Historical exposure to ethyl acrylate was reconstructed for three cohorts, reported in the same study, of acrylic sheet manufacturing workers at two different facilities (Walker et al., 1991). The assessments were made separately for each cohort. For one cohort the assessment was based on monitoring data for methyl methacrylate from 1972 onwards, and on expert judgment

based on production records and interviews with plant personnel. For the other two cohorts only expert judgment was used. The scales for the three cohorts were not directly comparable. The cohort with monitoring data was the only one that had category cut points based on exposure concentrations, with categories of less than 1 ppm [< 4.09 mg/m^3], 1 to less than 5 ppm [4.09 to < 20.5 mg/m^3], 5–24 ppm [20.5–98.2 mg/m^3], and 25 ppm or more [≥ 98.2 mg/m^3]. The highest category of exposure was assigned to workers in the "boil-out" phase of acrylic sheet production and to workers performing hand operations without local exhaust ventilation.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

Ethyl acrylate can be released into the environment in fugitive and stack emissions or in wastewater during its production and use (EPA, 2000). Ethyl acrylate is expected to volatize from water surfaces and is not expected to adsorb to suspended solids and sediment (HSDB, 2018). Based on empirical data and modelling results, ethyl acrylate is not expected to be persistent or bioaccumulate in the environment (Environment Canada/Health Canada, 2011).

(a) Air

Median reported on- and offsite fugitive air releases of ethyl acrylate in the USA reported in the EPA Toxics Release Inventory were 250 pounds [113 kg], 30 pounds [14 kg], 31 pounds [14 kg], and 11 pounds [5.0 kg] for the years 1990, 2000, 2010, and 2016, respectively, with a maximum reported release by a facility of 20 913 pounds [9486.0 kg] in 1990 (EPA, 2017). In 2016, the 89 reporting facilities were primarily in the chemical (82%), hazardous waste (7%), and plastics and rubber (4%) industries. The EPA Toxics Release Inventory emissions reports and other sources of emission data are included in the 2011 National Air Toxics Assessment database, which reported ethyl acrylate emissions of 0–5100 kg (median, 0.0004 kg) per year from 410 facilities (EPA, 2011). More than half of these facilities (236) were wastewater treatment facilities, with a reported maximum air release of 1 kg per year. The Canadian National Pollutant Release Inventory reported mean annual releases of ethyl acrylate into the air of 130, 1800, 26, and 35 kg for the years 1994, 2000, 2010, and 2016, respectively (Government of Canada, 2017).

(b) Water

The 75th percentile of the releases into water in the USA reported to the EPA Toxics Release Inventory was 0 pounds for the years 1990, 2000, 2010, and 2016, with a maximum amount of 463 pounds [210 kg] in 1990 and 14 pounds [6.4 kg] in 2016 (EPA, 2017). The Canadian National Pollutant Release Inventory had no reported releases onto land or water from the three reporting facilities (Government of Canada, 2017). Ethyl acrylate has been detected at low levels in wastewater samples (IARC, 1999; EPA, 2017).

1.4.2 Exposure in the general population

Residential exposure to ethyl acrylate may occur through exposure to compounds that contain ethyl acrylate, such as window caulking (NIOSH, 1980b) and acrylic nail compounds (Spencer et al., 2016).

Ethyl acrylate has been detected in food. Dietary exposure from naturally occurring ethyl acrylate has been estimated to be negligible compared with that from flavour additives (Silano et al., 2017). The estimated dietary intake from added ethyl acrylate was 59.1 µg/kg body weight (bw) per day for adults and 149 µg/kg bw per day for children; other dietary sources were estimated to be less than 1 µg/kg bw for both adults and children (Silano et al., 2017). Ethyl acrylate is also used in food-contact materials, and exposure

from this source was estimated to be 6000 µg per person per day or less [≤ 100 µg/kg bw per day] (Silano et al., 2017).

1.4.3 Occupational exposure

Exposure to ethyl acrylate occurs primarily through inhalation and dermal contact during its production, its use as an intermediate (e.g. in resins, coatings, and paints), and during work with products containing ethyl acrylate. Ethyl acrylate has been found in a dental composite resin in Finland (0.9% ethyl acrylate) (Aalto-Korte et al., 2007). Skin sensitization to ethyl acrylate (contact dermatitis) has been reported in nail salon workers exposed to acrylate-based nail treatments (see Section 4.3.1a) (Le et al., 2015; Spencer et al., 2016; DeKoven et al., 2017).

A few studies have quantified ethyl acrylate in the air of workplace settings (Table 1.1). Ethyl acrylate area air concentrations from paint batch mixing in a closed system ranged from less than 0.11 to 5.80 ppm [< 0.45–23.7 mg/m^3] (NIOSH, 1980a). In a chemical manufacturing plant, average concentrations for full-shift samples were 0.2–2.3 ppm [0.8–9.4 mg/m^3] and short-term average concentrations ranged from less than 0.1 to 30.0 ppm [0.4–123 mg/m^3] (SCOEL, 2004). Time-weighted average concentrations of ethyl acrylate at four work sites of a polystyrene production plant were less than 1 to 211 ppb [< 0.004–0.863 mg/m^3] (maximum, 844 ppb [3.45 mg/m^3]) in the breathing zone of workers and less than 1 to 27 ppb [< 0.004–0.11 mg/m^3] (maximum, 241 ppb [0.986 mg/m^3]) in ambient workplace air (Samimi & Falbo, 1982). Ethyl acrylate was detected during laser cutting of plexiglass, acrylic, and lucite, with concentrations ranging from less than 0.4 to 149.0 ppm [< 2–609.4 mg/m^3] in short-term samples (NIOSH, 1990). In various work areas of a chemical plant producing acrylic acid and acrylic acid esters, ethyl acrylate concentrations of 0.2 mg/m^3 or greater were observed in approximately 20% of samples collected between 1988 and 1999 (Tuček et al., 2002).

1.5 Regulations and guidelines

For ethyl acrylate, the 8-hour time-weighted (TWA) average occupational exposure limit is set at 20 mg/m^3 for most countries (see Table 1.2). Only Germany and Switzerland have lower limits of 8 and 10 mg/m^3, respectively. Short-term limit values vary over the range 17–62 mg/m^3. The OSHA standard has a higher 8-hour TWA occupational exposure limit of 100 mg/m^3 with no ceiling value (IFA, 2018; ACGIH, 2001).

The United States Food and Drug Administration has established regulations for the use of monomers, polymers, and copolymers, including ethyl acrylate, in food-contact materials. The proportion of the monomers should not exceed 5% by weight of total polymer units (CFR, 2017).

The European Food Safety Authority has set a safe limit for inclusion of (ethyl acrylate, methyl methacrylate) copolymer in food-contact materials at 2% by weight in rigid polyvinyl chloride and 5% by weight in polylactic acid and polyethylene terephthalate (EFSA, 2011).

2. Cancer in Humans

2.1 Cohort studies of occupational exposure

Only one cohort study of occupational exposure has evaluated the association between exposure to ethyl acrylate and risk of cancer (see Table 2.1).

Mortality from cancer of the colon or rectum was evaluated among workers employed at two plants manufacturing and polymerizing acrylate monomers to make acrylic sheets from 1933 to 1982, in the USA (Walker et al., 1991). Analyses

Table 1.1 Occupational exposure to ethyl acrylate

Industry Location, year	Job/process	Sampling location, duration, no. of workers	Mean	Range	Comments	Reference
Paint company Los Angeles, USA, 1980	Manufacture of polyvinyl acetate emulsion	Breathing zone of workers, full shift, 16	NR	< 0.11–5.80 ppm [< 0.45–23.7 mg/m³]		NIOSH (1980a)
Polystyrene production plant NR, before 1982		Breathing zone of workers, 50 min–7.5 h, 50	< 1–211 ppb [< 0.004–0.863 mg/m³]	< 1–844 ppb [< 0.004–3.45 mg/m³]		Samimi & Falbo (1982)
Polystyrene production plant NR, before 1982		Ambient workplace air, 50 min–7.5 h, 57	< 1–27 ppb [< 0.004–0.11 mg/m³]	< 1–241 ppb [< 0.004–0.986 mg/m³]		Samimi & Falbo (1982)
Laser cutting plastics Longwood (Florida), USA, 1989		Ambient workplace air, short term (< 2 h), 10	34 ppm [140 mg/m³]	< 0.4–149.0 ppm [< 2–610.0 mg/m³]		NIOSH (1990)
Chemical plant NR, 1988–1999	Production of acrylic acid, acrylic acid esters	Ambient workplace air, NR, NR	NR	NR	Results reported as percentage of samples in concentration categories; ethyl acrylate concentrations of > 0.2 mg/m³ were observed in ~20% of air samples	Tuček et al. (2002)
Paint company NR, before 1987		Breathing zone of workers, full shift, NR	0.2–2.3 ppm [0.8–9.4 mg/m³]	NR	Unpublished company data submitted to SCOEL committee in 1987	SCOEL (2004)
Paint company NR, before 1987		Breathing zone of workers, short term, NR	< 0.1 to 30.0 ppm [< 0.4–123 mg/m³]	NR	Unpublished company data submitted to SCOEL committee in 1987	SCOEL (2004)

h, hour; min, minute; NR, not reported; ppb, parts per billion; ppm, parts per million; SCOEL, Scientific Committee on Occupational Exposure Limits

Table 1.2 Occupational exposure limits for ethyl acrylate

Country or region	Concentration (mg/m^3)	Interpretation	Comments
Australia	20	STEL	Ceiling limit value
Austria	20	TWA	
	40	STEL	
Belgium	21	TWA	
	42	STEL	
Canada, Ontario	20	TWA	
	61	STEL	
Canada, Quebec	20	TWA	
	61	STEL	
Denmark	20	TWA	
	40	STEL	
European Union	21	TWA	Indicative occupational exposure limit values
	42	STEL	
Finland	21	TWA	
	42	STEL	
France	21	TWA	Restrictive statutory limit values
	42	STEL	
Germany (AGS)	8.3	TWA	
	16.6	STEL	
Germany (DFG)	8.3	TWA	
	16.6	STEL	
Hungary	10	TWA	
	10	STEL	
Ireland	20	TWA	
	41	STEL	
Italy	21	TWA	Skin notation
	42	STEL	
Latvia	5	TWA	
Netherlands	21	TWA	
	42	STEL	
New Zealand	20	STEL	Ceiling limit value
Poland	20	TWA	
	40	STEL	
Republic of Korea	20	TWA	
Romania	21	TWA	
	42	STEL	
Singapore	20	TWA	
	61	STEL	
Spain	21	TWA	Sensitization notation
	62	STEL	
Sweden	20	TWA	
	40	STEL	
Switzerland	10	TWA	
	42	STEL	
Turkey	21	TWA	
	42	STEL	

Table 1.2 (continued)

Country or region	Concentration (mg/m³)	Interpretation	Comments
UK	21	TWA	
	62	STEL	
USA (OSHA)	100	TWA	
USA (ACGIH)	21	TWA	Upper respiratory tract, eye, and gastrointestinal tract irritation, central nervous system impairment, skin sensitization notations
	62	STEL	

ACGIH, American Conference of Governmental Industrial Hygienists; AGS, Ausschuss für Gefahrstoffe (Committee on Hazardous Substances); DFG, Deutsche Forschungsgemeinschaft (German Research Foundation); OSHA, United States Occupational Safety and Health Administration; STEL, short-term (15-minute) exposure limit; TWA, 8-hour time-weighted average
Compiled from IFA (2018) and ACGIH (2001)

Table 2.1 Occupational cohort studies of exposure to ethyl acrylate

Reference, location, follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases and/or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Walker et al. (1991) USA 1933–1986	3934 white men employed any time between 1933 and 1945 at Bristol facility Exposure assessment method: expert judgement; ordinal 0–5 scale, assessed as co-exposure with methyl methacrylate; ethyl acrylate accounted for 12% of mixture during 1939–1942, with a gradual decline from 7% in 1943 to 0% in 1956	Colon	Time (yr) since exposure at 0 to < 5 dose units			Age, calendar period	Strengths: work histories from company records Limitations: co-exposure to methyl methacrylate; no measurements for period with ethyl acrylate use
			Not exposed	11	0.96 (0.53–1.73)		
			< 5	2	4.39 (1.10–17.60)		
			5–19	5	1.41 (0.59–3.39)		
			≥ 20	31	1.45 (1.02–2.06)		
			Time (yr) since exposure at 5 to < 10 dose units				
			Exposed but at < 5 dose units	17	1.55 (0.96–2.49)		
			< 5	0	0 (0–14.20)		
			5–19	3	1.40 (0.45–4.34)		
			≥ 20	18	1.50 (0.95–2.38)		
			Time (yr) since exposure at 10 to < 15 dose units				
			Exposed but at < 10 dose units	25	1.45 (0.98–2.15)		
			< 5	0	0 (0–26.40)		
			5–19	1	0.84 (0.12–5.93)		
			≥ 20	12	1.76 (1.00–3.10)		
			Time (yr) since exposure at ≥ 15 dose units				
			Exposed but at < 15 dose units	26	1.31 (0.89–1.93)		
			< 5	0	0 (0–33.60)		
			5–19	1	1.13 (0.16–8.05)		
			≥ 20	11	2.40 (1.33–4.34)		
		Colon	Concentration of exposure (dose units) with 20-yr lag				
			Not exposed	12	1.24 (0.71–2.19)		
			0–4	13	1.39 (0.80–2.38)		
			5–9	6	1.16 (0.52–2.58)		
			10–14	1	0.45 (0.06–3.16)		
			≥ 15	11	2.40 (1.33–4.34)		

Table 2.1 (continued)

Reference, location, follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases and/or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Walker et al. (1991) (cont.)		Rectum	Exposure concentration (dose units) with 20-yr lag			Age, calendar period	
			Not exposed	2	0.72 (0.18–2.88)		
			0–4	6	2.52 (1.13–5.60)		
			5–9	0	0 (0–2.98)		
			10–14	1	1.85 (0.26–13.10)		
			≥ 15	3	2.83 (0.91–8.76)		
Walker et al. (1991) USA 1946–1986	6548 white men hired between 1946 and 1982 at Bristol facility Exposure assessment method: expert judgement; semiquantitative scale: 0, 1–< 5, 5–24, ≥ 25 ppm, assessed as co-exposure with methyl methacrylate; ethyl acrylate accounted for 6% in 1946 and gradually declined to 0% in 1956	Colon	Exposure concentration (dose units) with 20-yr lag			Age, calendar period	Strengths: work histories from company records Limitations: co-exposure to methyl methacrylate; no measurements for period with ethyl acrylate use
			Not exposed	8	0.98 (0.49–1.95)		
			0–4	6	1.08 (0.49–2.41)		
			5–9	1	1.26 (0.18–8.92)		
Walker et al. (1991) USA 1943–1986	3381 white men employed between 1943 and 1982 at Knoxville facility Exposure assessment method: expert judgement; ordinal 0–3 scale, assessed as co-exposure with methyl methacrylate; ethyl acrylate accounted for 7% in 1943 and gradually declined to 0% in 1956	Colon	Exposure concentration (dose units) with 20-yr lag			Age, calendar period	Strengths: work histories from company records Limitations: co-exposure to methyl methacrylate; no measurements for period with ethyl acrylate use
			Not exposed	0	0 (0–4.63)		
			0–4	17	1.85 (1.15–2.98)		
			5–9	1	0[a] (0–3.66)		
			10–14	0	0 (0–5.52)		
			≥ 15	1	0.63 (0.09–4.44)		

CI, confidence interval; ppm, parts per million; yr, year

[a] The Working Group noted that the value in the original paper appeared to be erroneous; it should be 1/1.01 = 0.99

were conducted for three cohorts: (i) 3934 white men hired during 1933–1945 at the Bristol facility; (ii) 6548 white men hired during 1946–1982 at the Bristol facility; and (iii) 3381 white men employed during 1943–1982 at the Knoxville facility. Follow-up continued from the first day of employment until 1986. Semiquantitative estimates of co-exposure to vapours of ethyl acrylate and methyl methacrylate were estimated from employer work history records, production records, and interviews with plant personnel separately for each group, and were not directly comparable between groups (see Section 1.3.2). Three compounds were used for acrylic sheet manufacture in these facilities, namely, methyl methacrylate (88–100%), ethyl acrylate (0–12%), and butyl lactate (0–2%). The percentage of ethyl acrylate was 12% between 1940 and 1943, reduced to 7% in 1943, and decreased gradually to 1% between 1943 and 1955; it was eliminated in 1956. In the Bristol cohort with the earliest hire dates, excess mortality from cancer of the colon occurred 20 years or more after cumulative exposure to ethyl acrylate and methyl methacrylate combined at specified concentrations. Compared with the general population, standardized mortality ratios (SMRs) were 1.45 (95% confidence interval, CI, 1.02–2.06), 1.50 (95% CI, 0.95–2.38), 1.76 (95% CI, 1.00–3.10), and 2.40 (95% CI, 1.33–4.34) at cumulative exposures of 0 to < 5, 5 to < 10, 10 to < 15, and ≥ 15 units, respectively. A cumulative exposure of 5 units was achieved by working 3 years or more in jobs rated a score of 5 on a 0–5 scale, where a score of 5 corresponded to the "boil-out" phase of acrylic sheet production. Excess mortality from cancer of the colon was also observed in workers exposed to ethyl acrylate at low concentrations (> 0 to < 5 units). These workers may have been co-exposed to solvents such as ethylene dichloride, methylene chloride, acetone, and methyl methacrylate monomer. [The Working Group noted that these co-exposures could not be ruled out for the other cumulative exposure groups.] Mortality from cancer of the rectum was significantly and non-significantly elevated in the same categories that showed excess rates of mortality from cancer of the colon, and was based on small numbers of cases. In the Bristol cohort with later hire dates, no excess mortality from cancer of the colon or rectum was observed. In the Knoxville cohort, an excess mortality of cancer of the colon was observed 20 years or more after accumulating 0–4 units of exposure (rate ratio, 1.95; 95% CI, 1.15–2.98). Analyses of higher-exposure categories were limited because of small numbers. No excess mortality from cancer of the rectum was observed in the Knoxville cohort.

[The Working Group noted that the Walker et al. (1991) paper was based on five internal reports that are not publicly available. Only the results of mortality from cancer of the colon and rectum were reported. Walker et al. noted in the introduction that there were no excesses of cancer of the respiratory system. The strengths of this study included a medium-sized cohort and good follow-up time; however, it has several important limitations. Ethyl acrylate exposure co-occurred with exposure to methyl methacrylate and, as a result, the observed increased risks cannot be solely attributed to ethyl acrylate. Ethyl acrylate exposure occurred over a short time period (1939–1956). Exposure metrics concerned inhalation exposure only; they did not consider dermal exposure, which may have been important. Exposure assessment for two cohorts was based on expert judgment; for one cohort (Bristol hires during 1946–1982) the exposure assessment was partly based on measurements of methyl methacrylate and not of ethyl acrylate. Finally, outcome ascertainment considered mortality from and not incidence of cancer.]

Mortality risk was also evaluated in a cohort of 4324 acrylic sheet manufacturing workers in two facilities in the UK (Tomenson et al., 2000). Decreased mortality risks in the subcohort with more than minimal exposure to methyl methacrylate were observed for all causes (SMR, 94)

and for cancer of the colon and rectum (SMR, 92) based on comparisons with the general population; the standardized mortality ratio for all cancers combined was 104. No exposure–response associations were observed with cumulative exposure to methyl methacrylate. [The Working Group noted that this cohort may have been exposed to ethyl acrylate, but this exposure was not assessed.]

2.2 Case–control studies

No results from case–control studies that evaluated cancer risk in relation to ethyl acrylate exposure were available to the Working Group.

Aliphatic esters were evaluated in a series of analyses in a general-population case–control study in Montreal, Canada, with cases and controls identified between 1979 and 1985. In analyses of 257 cases and 533 population controls, an excess risk of cancer of the rectum with substantial exposure to aliphatic esters based on expert judgment of subject-reported work histories was observed (odds ratio, OR, 3.0; 95% CI, 1.4–6.8; 10 cases) (Dumas et al., 2000). The increased risk of cancer of the colon with substantial exposure to aliphatic esters was 1.5 (90% CI, 0.8–3.0; 9 cases) (Siemiatycki, 1991). [The Working Group noted that aliphatic esters may include ethyl acrylate, in addition to thousands of aliphatic esters of other acids.]

3. Cancer in Experimental Animals

Ethyl acrylate was previously reviewed by the Working Group (*IARC Monographs* Volume 39, IARC, 1986; Supplement 7, IARC, 1987; and Volume 71, IARC, 1999. The Working Group for Volume 71 concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of ethyl acrylate. This section provides an evaluation of the studies of carcinogenicity in experimental animals reviewed previously, and of all new studies.

See Table 3.1

3.1 Mouse

3.1.1 Oral administration

In a well-conducted study, groups of 50 male and 50 female B6C3F$_1$ mice (age, 7 weeks) were given ethyl acrylate (purity, 99.0–99.5%; stabilized with 15 ppm of the monoethyl ether of hydroquinone) at a dose of 0, 100, or 200 mg/kg bw by gavage in corn oil for 5 days per week for 103 weeks (NTP, 1986). In males and females, survival was comparable between exposed groups and the control group. Mean body weights of females exposed at the lower dose were at least 10% less than those of controls during the last 22 weeks of the study. Mean body weights of exposed males and females exposed at the higher dose were comparable to controls. The incidence of squamous cell papilloma – 0/48 (*P* for trend, 0.001), 4/47 (9%), 9/50 (*P* = 0.004) (18%) – squamous cell carcinoma – 0/48 (*P* for trend, 0.017), 2/47 (4%), 5/50 (*P* = 0.040) (10%) – and squamous cell papilloma or carcinoma (combined) – 0/48 (*P* for trend, < 0.001), 5/47 (11%), 12/50 (*P* < 0.001) (24%) – of the forestomach were significantly increased in all males at the higher dose, and there was a significant positive trend in the formation of these tumours in exposed males. The incidence of squamous cell papilloma or carcinoma (combined) of the forestomach – 1/50 (2%), (*P* for trend, 0.018), 5/49 (10%), 7/48 (*P* = 0.028) (15%) – in female mice exposed at the higher dose was significantly increased, and there was a significant positive trend in exposed females. The incidence of non-neoplastic lesions of the forestomach was dose-related in male and female mice; these lesions included ulceration, inflammation, epithelial hyperplasia, and hyperkeratosis.

Table 3.1 Studies of carcinogenicity with ethyl acrylate in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 7 wk 104–106 wk NTP (1986)	Gavage Ethyl acrylate, 99.0–99.5% Corn oil 0, 100, 200 mg/kg bw for 5 d/wk for 103 wk 50, 50, 50 28, 36, 30	*Forestomach* Squamous cell papilloma 0/48*, 4/47 (9%), 9/50** (18%) Squamous cell carcinoma 0/48*, 2/47 (4%), 5/50** (10%) Squamous cell papilloma or carcinoma (combined) 0/48*, 5/47 (11%), 12/50** (24%)	*P = 0.001 (trend), life-table test; **P = 0.004, life-table test *P = 0.017 (trend), life-table test; **P = 0.040, life-table test *P < 0.001 (trend), life-table test; **P < 0.001, life-table test	Principal strengths: well-conducted study Several non-neoplastic lesions, including ulceration, inflammation, epithelial hyperplasia, and hyperkeratosis, were observed in the forestomach of male mice in a dose-related manner Historical incidence for gavage studies for stomach tumours: 5/881 (0.6%)
Full carcinogenicity Mouse, B6C3F$_1$ (F) 7 wk 104–106 wk NTP (1986)	Gavage Ethyl acrylate, 99.0–99.5% Corn oil 0, 100, 200 mg/kg bw for 5 d/wk for 103 wk 50, 50, 50 27, 35, 26	*Forestomach* Squamous cell papilloma 1/50 (2%), 4/49 (8%), 5/48 (10%) Squamous cell carcinoma 0/50, 1/49 (2%), 2/48 (4%) Squamous cell papilloma or carcinoma (combined) 1/50* (2%), 5/49 (10%), 7/48** (15%)	NS NS *P = 0.018 (trend), life-table test; **P = 0.028, life-table test	Principal strengths: well-conducted study Several non-neoplastic lesions, including ulceration, inflammation, epithelial hyperplasia, and hyperkeratosis, were observed in the forestomach of female mice in a dose-related manner Historical incidence for gavage studies for stomach tumours: 8/901 (0.9%)
Full carcinogenicity Mouse, B6C3F$_1$ (M) 7–9 wk 27 mo Miller et al. (1985)	Inhalation (whole-body) Ethyl acrylate, > 99.5% None 0 (control A), 0 (control B), 25, 75, 225 ppm for 6 h/d, 5 d/wk for 6 mo (then unexposed for 21 mo) 60, 61, 75, 76, 69 NR	*Thyroid*: follicular cell adenoma 1/60 (2%), 1/61 (2%), 1/75 (1%), 0/76, 7/69* (10%)	*P < 0.05 compared with control groups, Fisher exact test	Principal strengths: well-conducted study Approximately 60 mice per control group and 75 mice per exposed group at the beginning of the experiment; the number of mice at the start is the effective number of mice According to Miller et al. (1985), a historical rate for thyroid follicular cell adenoma as high as 16% has been reported in male B6C3F$_1$ control groups in other studies, but no reference was cited

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (F) 7–9 wk 27 mo Miller et al. (1985)	Inhalation (whole-body) Ethyl acrylate, > 99.5% None 0 (control A), 0 (control B), 25, 75, 225 ppm for 6 h/d, 5 d/wk for 6 mo (then unexposed for 21 mo) 64, 61, 78, 76, 66 NR	*Any tumour type* No significant increase in the incidence of any neoplastic lesion	NS	Principal strengths: well-conducted study Approximately 60 mice per control group and 75 mice per exposed group at the beginning of the experiment; the number of mice at the start is the effective number of mice
Full carcinogenicity Rat, F344/N (M) 7 wk 104–105 wk NTP (1986)	Gavage Ethyl acrylate, 99.0–99.5% Corn oil 0, 100, 200 mg/kg bw for 5 d/wk for 103 wk 50, 50, 50 41, 32, 34	*Forestomach* Squamous cell papilloma 1/50* (2%), 15/50** (30%), 29/50** (58%) Squamous cell carcinoma 0/50*, 5/50** (10%), 12/50*** (24%) Squamous cell papilloma or carcinoma (combined) 1/50* (2%), 18/50** (36%), 36/50** (72%) *Pancreas* Acinar cell adenoma or carcinoma (combined) 0/49, 4/50* (8%), 0/49 Acinar cell adenoma 0/49, 3/50 (6%), 0/49 Acinar cell carcinoma 0/49, 1/50 (2%), 0/49	 *P < 0.001 (trend), life-table test; **P < 0.001, life-table test *P < 0.001 (trend), life-table test; **P = 0.019, life-table test; ***P < 0.001, life-table test *P < 0.001 (trend), life-table test; **P < 0.001, life-table test *P = 0.041, life-table test NS by more appropriate incidental tumour test NS NS	Principal strengths: well-conducted study Several non-neoplastic lesions, including inflammation, epithelial hyperplasia, and hyperkeratosis, were observed in the forestomach of male rats in a dose-related manner Historical incidence for gavage studies for stomach tumours: 5/967 (0.5%) No pancreatic acinar cell hyperplasia in exposed rats

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Rat, F344/N (F) 7 wk 104–105 wk NTP (1986)	Gavage Ethyl acrylate, 99.0–99.5% Corn oil 0, 100, 200 mg/kg bw for 5 d/wk for 103 wk 50, 50, 50 36, 36, 42	*Forestomach* Squamous cell papilloma 1/50* (2%), 6/50 (12%), 9/50** (18%) Squamous cell carcinoma 0/50, 0/50, 2/50 (4%) Squamous cell papilloma or carcinoma (combined) 1/50* (2%), 6/50 (12%), 11/50** (22%)	*P = 0.018 (trend), life-table test; **P = 0.021, life-table test NS *P = 0.005 (trend), life-table test; **P = 0.008, life-table test	Principal strengths: well-conducted study Several non-neoplastic lesions, including inflammation, epithelial hyperplasia, and hyperkeratosis, were observed in the forestomach of female rats in a dose-related manner Historical incidence for gavage studies for stomach tumours: 5/973 (0.5%)
Full carcinogenicity Rat, F344 (M) 3 mo 21 mo Ghanayem et al. (1994)	Gavage Ethyl acrylate, 99% Corn oil 0 (vehicle control) for 12 mo, 200 mg/kg bw for 6 mo, 200 mg/kg bw for 12 mo, 0 (vehicle control) for 12 mo + 9 mo recovery, 200 mg/kg bw for 6 mo + 15 mo recovery, and 200 mg/kg bw for 12 mo + 9 mo recovery; 5×/wk for 6 or 12 mo months and then held untreated until killed aged 24 mo NR NR	*Forestomach* Squamous cell papilloma 0/5, 0/5, 0/5, 0/16, 0/18, 1/13 (8%) Squamous cell carcinoma 0/5, 0/5, 0/5, 0/16, 0/18, 3/13 (23%) Squamous cell papilloma or carcinoma (combined) 0/5, 0/5, 0/5, 0/16, 0/18, 4/13* (13%)	[NS] [NS] *[P = 0.03, Fisher exact test]	Principal limitations: no data provided on survival, body weight, or observations on any organ except the forestomach; short durations of exposure; use of only one dose; small number of rats at each time point The study is not a true carcinogenicity study and focused on determining the time required for sustained forestomach hyperplasia to produce neoplastic transformation

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Rat, F344 (M) 7–9 wk 27 mo Miller et al. (1985)	Inhalation (whole-body) Ethyl acrylate, > 99.5% None 0 (control A), 0 (control B), 25, 75, 225 ppm for 6 h/d, 5 d/wk for 6 mo (then unexposed for 21 mo) 60, 60, 76, 75, 71 NR	*Thyroid*: follicular cell adenoma or carcinoma (combined) 1/60 (2%), 0/60, 5/76* (7%), 2/75 (3%), 3/71 (4%)	*$P < 0.05$ compared with combined control groups, Fisher exact test	Principal strengths: well-conducted study Approximately 60 rats per control group and 75 rats per exposed group at the beginning of the experiment; the number of rats at the start is the effective number of rats
Full carcinogenicity Rat, F344 (F) 7–9 wk 27 mo Miller et al. (1985)	Inhalation (whole-body) Ethyl acrylate, > 99.5% None 0 (control A), 0 (control B), 25, 75, 225 ppm for 6 h/d, 5 d/wk for 6 mo (then unexposed for 21 mo) 59, 62, 77, 78, 70 NR	*Any tumour type* No significant increase in the incidence of any neoplastic lesion	NS	Principal strengths: well-conducted study Approximately 60 rats per control group and 75 rats per exposed group at the beginning of the experiment; the number of rats at the start is the effective number of rats

bw, body weight; d, day; F, female; h, hour; M, male; mo, month; NR, not reported; NS, not significant; ppm, parts per million; wk, week

3.1.2 Skin application

(a) C3H/HeJ mice

DePass et al. (1984) tested ethyl acrylate as a complete carcinogen on mouse skin. A group of 40 male C3H/HeJ mice (age, 74–79 days) were exposed to neat ethyl acrylate (purity, 99%) at a dose of 25 µL (~23 mg) on clipped dorsal skin three times per week for their lifetime. A group of 40 male mice were given skin applications of 20 mg of acetone three times per week for their lifetime, and served as controls. Survival was comparable between the group exposed to ethyl acrylate and the acetone control group. No skin tumours or adverse effects were reported in the group exposed to ethyl acrylate or the acetone control group. [The Working Group concluded that this study was inadequate for the evaluation of the carcinogenicity of ethyl acrylate because of the use of only one sex and one dose, the lack of appropriate unexposed control group, and the lack of body-weight data.]

(b) Genetically engineered mice

Groups of 10–15 female homozygous Tg.AC mice (age, 10–12 weeks) were exposed to ethyl acrylate [purity not given] at 30 mg in 200 µL acetone by skin application three times per week for 20 weeks. A group of 10–15 female mice treated concurrently with the vehicle solvent [not reported] served as negative controls. After 20 weeks, 50% of the mice exposed to ethyl acrylate averaged 0.6 papillomas of the skin per mouse. [No information was given on the results for control mice.] Ethyl acrylate was reported to be "inactive" [not tumorigenic] in Tg.AC mice, and no gross systemic effects were observed at the end of the study (20 weeks) (Tennant et al., 1995). [The Working Group noted that the study used only one dose and one sex, there was a small number of mice in the exposed and control groups, no information on body weight or the survival of exposed mice was provided, no histopathology was performed, and no results were provided for controls. The study was judged inadequate for the evaluation of the carcinogenicity of ethyl acrylate.]

In another skin application study with homozygous Tg.AC mice (Nylander-French & French, 1998), four groups of 10 female Tg.AC mice (age, 12 weeks) were exposed to ethyl acrylate at 0 (control), 60, 300, or 600 µmol (purity, 99%) in 200 µL acetone three times per week for 20 weeks. No significant difference in survival was observed between exposed and control groups. Body weight was lower in the group exposed at the highest dose. There was no significant increase in the incidence or multiplicity of papilloma of the skin in any of the exposed groups compared with the acetone control group. [The Working Group noted that the study used only one sex, there was a small number of mice in exposed and control groups, and that no histopathology was performed on organs other than the skin. The study was judged inadequate for the evaluation of the carcinogenicity of ethyl acrylate.]

3.1.3 Inhalation

In a well-conducted study, groups of [approximately] 75 male and 75 female B6C3F$_1$ mice (age, 7–9 weeks) were exposed by whole-body inhalation to ethyl acrylate vapour (purity, > 99.5%) at concentrations of 25, 75, or 225 ppm (100, 310, or 920 mg/m^3) for 6 hours per day, 5 days per week, for 27 months (Miller et al., 1985). Two separate groups of [approximately] 60 males and 60 females served as unexposed controls. Exposure of males and females to the highest dose (225 ppm) was stopped after 6 months because of a significant decrease in body-weight gain. The mice were held without further treatment for up to 21 months. The survival of exposed groups of male and female mice was similar to or better than that of both control groups. The mean body-weight gains of males and females in the groups at 75 ppm and 225 ppm were significantly lower

than that in both control groups throughout the study. A non-significant decrease in body-weight gain was also observed in males and females at 25 ppm during the last 8 months of the study. There was a significant increase in the incidence of follicular cell adenoma of the thyroid in male mice exposed to ethyl acrylate at 225 ppm for 6 months and held for an additional 21 months (controls, combined, 2/121 (2%); lowest dose, 1/75 (1%); intermediate dose, 0/76; highest dose, 7/69 (10%), $P < 0.05$, Fisher exact test). [The authors reported that the historical rate for follicular cell adenoma of the thyroid has been as high as 16% in male $B6C3F_1$ control groups in other studies, but did not cite a reference for this.] There was no significant increase in the incidence of any tumours in females.

3.2 Rat

3.2.1 Oral administration

In a well-conducted study, groups of 50 male and 50 female Fischer 344/N rats (age, 7 weeks) were given ethyl acrylate (purity, 99–99.5%; stabilized with 15 ppm of the monoethyl ether of hydroquinone) at a dose of 0, 100, or 200 mg/kg bw, by gavage in corn oil, 5 days per week for 103 weeks (NTP, 1986). In males and females, survival was comparable between exposed groups and the control group. Mean body weights of all groups of exposed males and females were comparable to those of controls throughout the study. In male rats, the incidence of squamous cell papilloma – 1/50 (*P* for trend, < 0.001), 2%; 15/50 and 29/50 ($P < 0.001$), 30% – squamous cell carcinoma – 0/50 (*P* for trend, < 0.001), 5/50 (P = 0.019), 10%, 12/50 ($P < 0.001$), 24% – and squamous cell papilloma or carcinoma (combined) – 1/50 (*P* for trend, < 0.001), 2%; 18/50 (36%) and 36/50 ($P < 0.001$), 72% – of the forestomach were significantly increased in all treated groups, and there was a significant positive trend in the incidence of these tumours in exposed male rats. In female rats, the incidence of squamous cell papilloma – 1/50 (*P* for trend, 0.018), 2%, 6/50 (12%), 9/50 ($P = 0.021$), 18% – and squamous cell papilloma or carcinoma (combined) – 1/50 (*P* for trend, 0.005), 2%, 6/50 (12%), 11/50 ($P = 0.008$), 22% – of the forestomach was significantly increased in the group at the higher dose, and there was a significant positive trend in the incidence of these tumours in exposed female rats; squamous cell carcinomas of the forestomach were only observed in two females exposed at the higher dose. The incidence of non-neoplastic lesions of the forestomach was dose-related in male and female rats; these lesions included inflammation, epithelial hyperplasia, and hyperkeratosis. The combined incidence of acinar cell adenoma (3/50) and carcinoma (1/50) of the pancreas in male rats at the lower dose (4/50) was higher (significant by the life-table test, $P = 0.041$, not significant by the more appropriate incidental tumour test) than that in the vehicle controls (0/49). There was no acinar cell hyperplasia of the pancreas in exposed males.

In a study to investigate the association between exposure to ethyl acrylate and hyperplasia of the forestomach and carcinogenicity in the forestomach in rats, two groups of [number at start unspecified] male Fischer 344 rats (age, 3 months) were given ethyl acrylate (purity, 99%; stabilized with 15–20 ppm of the monoethyl ether of hydroquinone) at a dose of 200 mg/kg bw by gavage in corn oil for 5 days per week for 6 or 12 months. A control group received corn oil only for 12 months. Five rats from each treatment group and the control group were killed 24 hours after the last dose. The remaining rats were killed at age 24 months. All rats were examined for gross lesions and the stomachs were collected and examined microscopically. No treatment-related neoplastic lesions were observed in the forestomach of rats exposed to ethyl acrylate for 6 months, with (0/18) or without (0/5) a recovery period. All rats exposed to ethyl acrylate for 12 months and then killed showed hyperplastic lesions of the forestomach (5/5 compared with

0/5 in corn oil controls), but no neoplastic lesions. However, when rats were exposed to ethyl acrylate for 12 months and killed after 9 months of recovery, they developed squamous cell carcinoma (3/13, 23%) and papilloma (1/13, 8%) – combined incidence, 4/13 (31%) [$P = 0.03$, Fisher exact test] – of the forestomach, compared with none in the controls (0/16) (Ghanayem et al., 1993, 1994). [The Working Group noted the use of only one sex and dose, the small number of animals, the lack of data on survival and body weight, and that histopathological evaluation was limited to the forestomach.]

3.2.2 Inhalation

In a well-conducted study, groups of [approximately] 75 male and 75 female Fischer 344 rats (age, 7–9 weeks) were exposed by whole-body inhalation to ethyl acrylate vapour (purity, > 99.5%) at a concentration of 25, 75, or 225 ppm (100, 310, or 920 mg/m^3) for 6 hours per day, 5 days per week, for 27 months (Miller et al., 1985). Two separate groups of [approximately] 60 males and 60 females served as unexposed controls. Exposure of males and females at the highest dose (225 ppm) was stopped after 6 months because of a significant decrease in body-weight gain. These rats were held without further treatment for up to 21 months. Survival of exposed groups of males and females was lower than, but not significantly different from, that of the control groups throughout the study. The mean body-weight gains of male and female rats in the groups at 75 ppm and 225 ppm were significantly lower than those in both control groups throughout the study. There was a significant increase in the incidence of follicular cell adenoma or carcinoma (combined) of the thyroid in male rats exposed to ethyl acrylate at 25 ppm for 27 months: control, combined, 1/120 (1%); lowest dose, 5/76 (7%), $P < 0.05$, Fisher exact test; intermediate dose, 2/75 (3%); highest dose, 3/71 (4%). There was no significant increase in the incidence of any tumours in females.

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

Data on absorption, distribution, metabolism, and excretion of ethyl acrylate in humans were not available to the Working Group.

4.1.2 Experimental systems

In adult male Fischer 344 rats given single doses of 2,3-[^{14}C]-ethyl acrylate at a dose of 100, 200, or 400 mg/kg bw by oral gavage in corn oil, analysis of the stomach contents showed that more than 90% of all doses administered was absorbed within 4 hours (Ghanayem et al., 1987). Ethyl acrylate was rapidly distributed to all major organs and tissues (Ghanayem et al., 1987; Frederick et al., 1992). Ghanayem et al. (1987) demonstrated that in male Fischer 344 rats the highest concentrations of 2,3-[^{14}C]-ethyl acrylate-derived radiolabel were found in the forestomach, a target organ for carcinogenesis induced by ethyl acrylate (IARC, 1986, 1999; NTP, 1986), and in three non-target organs, the glandular stomach, small intestine, and liver, 4 hours after a single oral dose of 2,3-[^{14}C]-ethyl acrylate at 100, 200, or 400 mg/kg bw. The level of 2,3-[^{14}C]-ethyl acrylate-derived radiolabel in the rat forestomach remained greater than in other organs 24 hours after exposure to 2,3-[^{14}C]-ethyl acrylate at 200 mg/kg bw.

The major route for ethyl acrylate excretion is CO_2 exhalation (Ghanayem et al., 1987). This was demonstrated by the fact that approximately 70% of ethyl acrylate was exhaled as $^{14}CO_2$ within

24 hours of exposure to 2,3-[^{14}C]-ethyl acrylate at 200 mg/kg bw. Similar findings have been reported by deBethizy et al. (1987), who demonstrated that approximately 60% of 2,3-[^{14}C]-ethyl acrylate given by oral gavage to adult male Sprague-Dawley rats (n = 3 rats per group) at a dose of 2, 20, or 200 mg/kg bw was eliminated in 8 hours and 75% was eliminated in 24 hours by $^{14}CO_2$ exhalation. Approximately 10% of a dose of 2,3-[^{14}C]-ethyl acrylate of 200 mg/kg bw given by oral gavage was excreted in the urine, in the form of *N*-acetyl-(2-carboxyethyl)cysteine and *N*-acetyl-(2-carboxyethyl)cysteine ethyl ester, and 4% was excreted in the faeces (Ghanayem et al., 1987). In addition to *N*-acetyl-(2-carboxyethyl) cysteine and *N*-acetyl-(2-carboxyethyl)cysteine ethyl ester, two separate studies also identified the presence of 3-hydroxypropionic acid in the urine of rats exposed to ethyl acrylate (deBethizy et al., 1987; Linhart et al., 1994). In the first study, deBethizy et al. (1987) showed that 3-hydroxypropionic acid was present in the urine of adult male Sprague-Dawley rats in the 0–6-hour period after oral exposure to 2,3-[^{14}C]-ethyl acrylate at 200 mg/kg bw. In the second study, Linhart et al. (1994) reported a significant increase of 3-hydroxypropionic acid in the urine of adult female Wistar rats 24 hours after intraperitoneal injection of ethyl acrylate at 2.0 mmol/kg bw.

Several studies investigated the metabolism of ethyl acrylate in rats (see Fig. 4.1). Ethyl acrylate is rapidly metabolized, as demonstrated by its short metabolic half-life (Miller et al., 1981; Frederick et al., 1992). There are two main metabolic routes in ethyl acrylate metabolism: (i) enzymatic hydrolysis of ethyl acrylate to acrylic acid and ethanol catalysed by carboxylesterases, with a subsequent high-efficiency conversion of both metabolites to CO_2 (Miller et al., 1981; Silver & Murphy, 1981; Ghanayem et al., 1987); and (ii) binding of ethyl acrylate to glutathione (GSH) and proteins (deBethizy et al., 1987; Ghanayem et al., 1987; Frederick et al., 1992).

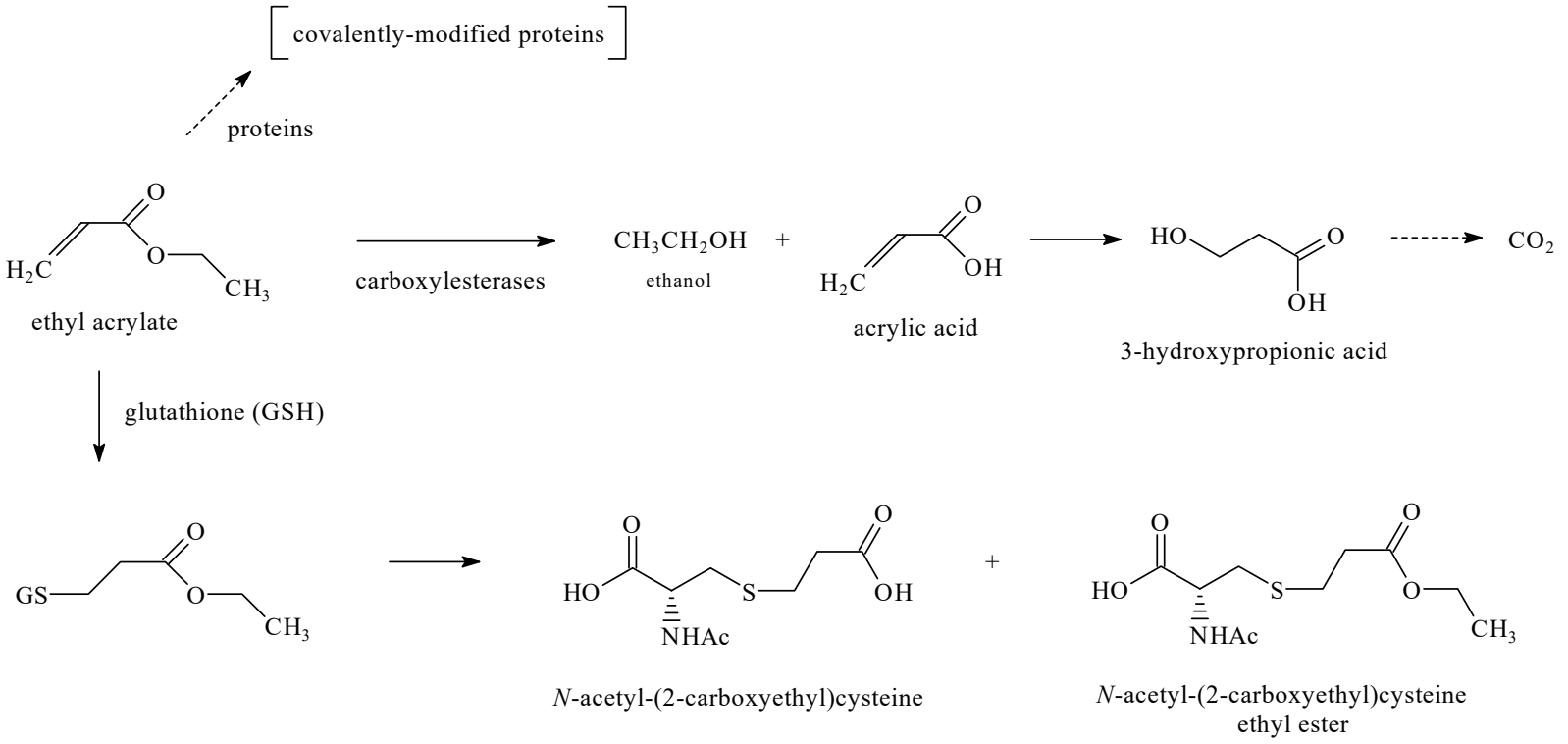
Three studies investigated enzymatic hydrolysis of ethyl acrylate in a reaction mediated by carboxylesterase (Miller et al., 1981; Frederick et al., 1992; McCarthy & Witz, 1997). In two studies, Miller et al. (1981) and Frederick et al. (1992) demonstrated significant carboxylesterase activity towards ethyl acrylate by tissue homogenates from Fischer 344 rats in vitro. In a separate study, McCarthy & Witz (1997) reported a high efficiency of ethyl acrylate enzymatic hydrolysis by purified porcine liver carboxylesterase.

Four studies investigated the metabolic pathways involved in the reactions binding ethyl acrylate to GSH and proteins (Ghanayem et al., 1987; Frederick et al., 1990, 1992; Potter & Tran, 1992).

Potter & Tran (1992) demonstrated a rapid and time-dependent non-enzymatic conjugation of 2,3-[^{14}C]-ethyl acrylate to GSH in Fischer 344 rats, with a second-order rate constant of 32.8 M^{-1} min^{-1}. Similarly, a second-order rate constant of 26.6 M^{-1} min^{-1} was found for the reaction of GSH conjugation with ethyl acrylate in vitro (McCarthy et al., 1994). The conjugation of ethyl acrylate with GSH is also demonstrated by the fact that the major ethyl acrylate metabolites detected in the urine of Fischer 344 rats given a single dose of ethyl acrylate at 100, 200, or 400 mg/kg bw by oral gavage were *N*-acetyl-(2-carboxyethyl)cysteine, the degradation product of an acrylic-acid–GSH adduct, and *N*-acetyl-(2-carboxyethyl)cysteine ethyl ester, a metabolite resulting from direct conjugation of ethyl acrylate with GSH (Ghanayem et al., 1987).

In addition to conjugation with GSH, ethyl acrylate exhibits a high binding efficiency for proteins (Ghanayem et al., 1987; Potter & Tran, 1992). In particular, Ghanayem et al. (1987) demonstrated that 24 hours after Fischer 344 rats were given radiolabelled ethyl acrylate at a dose of 200 mg/kg bw by oral gavage, most of the 2,3-[^{14}C]-ethyl acrylate-derived radiolabel in the forestomach was irreversibly bound to proteins, whereas in the liver most of the 2,3-[^{14}C]-ethyl

Fig. 4.1 Proposed metabolic pathways for ethyl acrylate in rats in vivo



The *N*-acetyl-(2-carboxyethyl)cysteine conjugate may also stem from glutathione addition to acrylic acid. Protein binding derived from ethyl acrylate has been detected in rat forestomach, but the specific adducts have not been characterized

Compiled by the Working Group

acrylate-derived radiolabel was bound to lipids. The concentration of protein-bound 2,3-[^{14}C]-ethyl acrylate-derived radiolabel in the forestomach was fivefold that in the liver.

4.2 Mechanisms of carcinogenesis

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016) in the following order: is genotoxic; alters cell proliferation, cell death, or nutrient supply; and induces chronic inflammation. Insufficient data were available for evaluation of the other key characteristics of carcinogens.

4.2.1 Genetic and related effects

Table 4.1, Table 4.2, Table 4.3, and Table 4.4 summarize the studies evaluated and considered to be the most representative of the genetic and related effects of ethyl acrylate.

(a) Humans

See Table 4.1

In one study, cytogenetic analysis was carried out in peripheral blood lymphocytes of 60 controls and 60 workers exposed in 1987, 1992, 1993 (exposed group only), and 1997 during production of acrylic acid, acrylic acid esters, and acrylate dispersions (Tuček et al., 2002). The average exposure duration was 13 ± 5 years. The mean percentage of aberrant cells in both groups remained in normal range when analysed annually; however, in an overall analysis of all results, a borderline statistically significant (P = 0.05) increase in chromosomal aberrations in peripheral lymphocytes was seen in exposed workers. [The Working Group noted that the effects could not be attributed to ethyl acrylate specifically.]

In human cells in vitro, Fowler et al. (2012) analysed the effect of exposure to ethyl acrylate on micronucleus induction in human TP53-competent primary cultures of lymphocytes (HuLy), TK6 lymphoblastoid cells, and HepG2 liver cells for 3 hours followed by a 21-hour recovery period in two independent experiments. There was significant formation of micronuclei at concentrations that induced some cytotoxicity in HuLy cells, TK6 cells, and in HepG2 cells (in one of two tests). In a separate experiment involving 24-hour exposures in two independent trials (Fowler et al., 2012), there was no increase in the frequency of micronucleus formation in HuLy cells at a concentration that induced some cytotoxicity, but frequency of micronucleus formation was increased in TK6 cells and in HepG2 cells in one of the two trials.

In the human TK6 lymphoblast TP53-competent) and WIL2-NS lymphoblast (TP53-mutant) cell lines exposed to ethyl acrylate at concentrations below the predefined cytotoxicity cut-off and in the presence of cytochalasin B there was a slight induction of micronuclei that did not meet the criteria for either a positive or a negative response (Whitwell et al., 2015). In a separate experiment in the absence of cytochalasin B, the results of exposure of TK6 and WIL2-NS cells to ethyl acrylate were negative.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.2

Several studies investigated the genotoxic effects of exposure to ethyl acrylate in experimental animals in vivo. A single dose of 1.0 mL of 4% ethyl acrylate in corn oil by gastric tube did not increase DNA damage in the forestomach squamous epithelium in male Fischer 344 rats as measured by the alkaline elution assay (Morimoto et al., 1990). In female homozygous transgenic Tg.AC (v-Ha-ras) mice, ethyl acrylate did not alter the migration of DNA isolated from peripheral blood leukocytes after up to 20 weeks of dermal topical application of ethyl acrylate at 60, 300, and 600 µmol per mouse (n = 9 mice per dose) three times per week, as measured by the alkaline comet assay (Tice et al., 1997). Further,

Table 4.1 Genetic and related effects of ethyl acrylate in human cells in vitro

End-point	Tissue, cell line	Results[a]		Concentration (μg/mL) (LEC or HIC)	Comments	References
		Without exogenous activation	With exogenous activation			
Micronucleus formation	Lymphocytes (HuLy)	+	NT	38, 50	Positive results observed at cytotoxic concentrations; 3 h exposure with 21 h recovery	Fowler et al. (2012)
	Lymphoblast TK6 cells	+	NT	20, 25	Positive results observed at cytotoxic concentrations; 3 h exposure with 21 h recovery	
	HepG2 hepatocarcinoma cells	+/–	NT	96	Positive in one of two experiments at the same dose; 3 h exposure with 21 h recovery	
	Lymphocytes (HuLy)	–	NT	10	24 h exposure	
	Lymphoblast TK6 cells	+/–	NT	10	Positive in one of two experiments at the same dose; 24 h exposure	
	HepG2 hepatocarcinoma cells	+/–	NT	77	Positive in one of two experiments; 24 h exposure	
Micronucleus formation	Lymphoblast TK6 cells	–	NT	6		Whitwell et al. (2015)
	Lymphoblast WIL2-NS cells	–	NT	9		
	Lymphoblast TK6 cells	+/–	NT	6	In the presence of cytochalasin B	
	Lymphoblast WIL2-NS cells	+/–	NT	9	In the presence of cytochalasin B	

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

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study); the level of significance was set at $P < 0.05$ in all cases

Table 4.2 Genetic and related effects of ethyl acrylate in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
DNA strand breaks	Rat, Fischer 344 (M)	Forestomach	–	1.0 mL	Via gastric tube, 4% ethyl acrylate in corn oil, ×1		Morimoto et al. (1990)
DNA strand breaks	Mouse, Tg.AC transgenic (F)	Peripheral blood leukocytes	–	600 µmol	Skin application, 3×/wk for 20 wk		Tice et al. (1997)
Point mutations, deletions	Mouse, *gpt* delta transgenic (M)	Stomach, liver	–	50 mg/kg bw	Gavage, ×1/d for 28 d		Ellis-Hutchings et al. (2018)
Micronucleus formation	Mouse, BALB/c (M)	Bone marrow	+	225 mg/kg bw	Intraperitoneal injection, ×2		Przybojewska et al. (1984)
Micronucleus formation	Mouse, BALB/c (M)	Bone marrow	+/–	812 mg/kg bw	Intraperitoneal injection, ×2	Positive in one of two experiments at the same dose; observation made 30 h after second dose	Ashby et al. (1989)
Micronucleus formation	Mouse, C57BL/6J (M, F)	Bone marrow	–	738 mg/kg bw	Intraperitoneal injection, ×1	Observations made 24, 48, and 72 h after dose	
Micronucleus formation	Mouse, C57BL/6J (M)	Bone marrow	–	738 mg/kg bw	Intraperitoneal injection, ×2	Observation made 30 h after second dose	
Micronucleus formation	Mouse, Tg.AC transgenic (F)	Peripheral blood leucocytes	–	600 µmol	Skin application, ×60		Tice et al. (1997)
Micronucleus formation Sister-chromatid exchange Chromosomal aberrations	Mouse, C57BL/6J (M)	Splenocytes	– – –	1000 mg/kg bw	Intraperitoneal injection, ×1		Kligerman et al. (1991)

bw, body weight; d, day; F, female; h, hour; HID, highest effective dose; LED, lowest effective dose; M, male; wk, week

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study); the level of significance was set at $P < 0.05$ in all cases

Table 4.3 Genetic and related effects of ethyl acrylate in non-human mammalian cells in vitro

End-point	Species, cell line	Results[a]		Concentration (μg/mL) (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA double-strand breaks	Mouse lymphoma L5178Y	+	NT	40	Positive results observed at cytotoxic concentrations	Ciaccio et al. (1998)
Gene mutation, *Tk*	Mouse lymphoma L5178Y	+	NT	20		McGregor et al. (1988)
Gene mutation, *Tk*	Mouse lymphoma L5178Y	+	NT	20	Positive results observed at cytotoxic concentrations	Moore et al. (1988)
Gene mutation, *Tk*	Mouse lymphoma L5178Y	+	NT	20	Positive results observed at cytotoxic concentrations	Moore et al. (1989)
Gene mutation, *Tk*	Mouse lymphoma L5178Y	+	+	20	Positive results observed at cytotoxic concentrations	Dearfield et al. (1991)
Gene mutation, *Tk*	Mouse lymphoma L5178Y	+	NT	20	Positive results observed at cytotoxic concentrations	Ciaccio et al. (1998)
Gene mutation, *Hprt*	Chinese hamster ovary	–	NT	23		Moore et al. (1989)
Gene mutation, *Hprt*	Chinese hamster ovary	–	NT	80		Moore et al. (1991)
Chromosomal aberrations, *Tk*	Mouse lymphoma L5178Y	+	NT	20	Positive results observed at cytotoxic concentrations	Moore et al. (1988)
Chromosomal aberrations, *Tk*	Mouse lymphoma L5178Y	+	NT	20	Positive results observed at cytotoxic concentrations	Moore et al. (1989)
Chromosomal aberrations, *Hprt*	Chinese hamster ovary	+	NT	21	Positive results observed at cytotoxic concentrations	
Chromosomal aberrations	Chinese hamster ovary	–	+	Not clearly indicated		Loveday et al. (1990)
Micronucleus formation	Mouse leukaemia L5178Y	+/–	NT	12, 18		Whitwell et al. (2015)

Table 4.3 (continued)

End-point	Species, cell line	Results[a]		Concentration (µg/mL) (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Micronucleus formation	V79 Chinese hamster lung fibroblasts	+	NT	1, 4	Positive results observed at cytotoxic concentrations; 24 h exposure	Fowler et al. (2012)
	V79 Chinese hamster lung fibroblasts	+	NT	16, 20	Positive results observed at cytotoxic concentrations; 3 h exposure with 21 h recovery	
	Chinese hamster lung	+	NT	7, 14	Positive results observed at cytotoxic concentrations; 24 h exposure	
		+	NT	39, 40	Positive results observed at cytotoxic concentrations; 3 h exposure with 21 h recovery	
	Chinese hamster ovary	–	NT	10, 12	24 h exposure	
		+	NT	20, 32	Positive results observed at cytotoxic concentrations; 3 h exposure with 21 h recovery	
Sister-chromatid exchange	Chinese hamster ovary	–	+	Not clearly indicated		Loveday et al. (1990)

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

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study); the level of significance was set at $P < 0.05$ in all cases

Table 4.4 Genetic and related effects of ethyl acrylate in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without exogenous metabolic activation	With exogenous metabolic activation			
Drosophila melanogaster	Sex-linked recessive lethal mutations	–		40 000 ppm feed		Valencia et al. (1985)
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	+/–	+/–	3333 µg/plate	Inconsistent result from two different laboratories, one positive and one negative	Haworth et al. (1983)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	2000 µg/plate		Waegemaekers & Bensink (1984)
Salmonella typhimurium TA102	Reverse mutation	–	–	15–5000 µg/plate		Kirkland et al. (2016)
Salmonella typhimurium YG7108pin3Erb5	Reverse mutation	–	–	2000 µg/plate		Emmert et al. (2006)
Saccharomyces cerevisiae D61.M	Homozygosis by mitosis	–	NT	733 µg/mL		Zimmermann & Mohr (1992)
	Homozygosis by mitosis	+	NT	733 µg/mL	In combination with propionitrile	

HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested; ppm, parts per million

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study); the level of significance was set at $P < 0.05$ in all cases

the frequency of micronucleated peripheral blood polychromatic or normochromatic erythrocytes was not increased after 20 weeks of treatment.

No increase in the occurrence of point mutations or deletions was seen in the stomach or liver of male *gpt* delta mice (age, 40 weeks; $n = 6$ per group) exposed to ethyl acrylate at 8, 20, or 50 mg/kg bw per day in corn oil by oral gavage for 28 days (Ellis-Hutchings et al., 2018).

Two studies (Przybojewska et al., 1984; Ashby et al., 1989) investigated micronuclei induction by ethyl acrylate in mice. Przybojewska et al. (1984) reported that in male BALB/c mice exposed to ethyl acrylate by two intraperitoneal injections at 225, 450, 900 ($n = 4$ mice per dose), or 1800 mg/kg bw ($n = 2$ mice) separated by 24 hours, significantly increased micronuclei induction in the bone marrow was observed. Ashby et al. (1989) observed a significant induction of micronuclei in male BALB/c mice ($n = 10$ mice) 30 hours after two intraperitoneal injections of ethyl acrylate at 812 mg/kg bw in one of two experiments. In contrast, in two separate experiments in male and female C57BL/6J mice, observations made 24, 48, or 72 hours after a single intraperitoneal injection, or 30 hours after two intraperitoneal injections separated by 24 hours, of ethyl acrylate at 738 mg/kg bw did not reveal induction of micronuclei in the bone marrow (Ashby et al., 1989). However, a statistically significant bone-marrow toxicity, indicated by a decreased polychromatic:normochromatic erythrocyte ratio, was observed 48 and 72 hours after exposure of male and female mice to ethyl acrylate (Ashby et al., 1989).

In male C57BL/6 mice, ethyl acrylate did not increase the frequency of chromosomal aberrations, sister-chromatid exchange, or micronucleus formation in splenocytes 24 hours after a single intraperitoneal injection of ethyl acrylate at 125, 250, 500, or 1000 mg/kg bw (Kligerman et al., 1991).

(ii) Non-human mammalian cells in vitro

See Table 4.3

Ethyl acrylate induced DNA double-strand breaks in L5178Y $Tk^{+/-}$ lymphoma cells (Ciaccio et al., 1998).

In a study of mutations at the hypoxanthine-guanine phosphoribosyltransferase (*Hgprt*) gene, ethyl acrylate gave negative results in the standard and suspension protocols using Chinese hamster ovary (CHO) cells (Moore et al., 1991).

In contrast to experimental animal studies in vivo, ethyl acrylate produced a consistently positive response when tested in the mouse lymphoma assay or other non-human mammalian cell clastogenicity assays in vitro (Johannsen et al., 2008). Four studies (McGregor et al., 1988; Moore et al., 1988, 1989; Dearfield et al., 1991) that were reviewed in the previous monograph (IARC, 1999) examined the genotoxic activity of ethyl acrylate in the mouse heterozygous L5178Y $Tk^{+/-}$ lymphoma cell assay. The results of these studies demonstrated that exposure of mouse L5178Y lymphoblast cells to ethyl acrylate without exogenous metabolic activation by a post-mitochondrial rat S9 liver homogenate (S9 mix) increased mutation frequency. Furthermore, Moore et al. (1988) reported a dose-dependent increase in the mutation frequency after exposure of L5178Y $Tk^{+/-}$ lymphoma cells. Similar results were obtained in a later independent study (Ciaccio et al., 1998) that showed a concentration-dependent increase in mutation frequency in L5178Y $Tk^{+/-}$ lymphoma cells exposed to ethyl acrylate. It should be noted that positive genotoxic activity of ethyl acrylate in these mouse L5178Y $Tk^{+/-}$ lymphoma cell studies was primarily observed at concentrations that induced some cytotoxicity (McGregor et al., 1988; Moore et al., 1988, 1989; Dearfield et al., 1991; Ciaccio et al., 1998).

Loveday et al. (1990) reported that exposure of CHO cells to ethyl acrylate [concentration not clearly indicated] induced chromosomal aberrations and sister-chromatid exchange in

cells with, but not without, metabolic activation. Chromosomal aberrations were induced in L5178Y *Tk*$^{+/-}$ lymphoma and CHO cells exposed to ethyl acrylate, without metabolic activation (Moore et al., 1988, 1989).

Micronuclei were induced when V79, CHO, and Chinese hamster lung (CHL) cells were exposed to ethyl acrylate without metabolic S9 activation for 3 hours at concentrations that induced some cytotoxicity, followed by a 21-hour recovery (Fowler et al., 2012). In a separate experiment reported by Fowler et al. (2012), micronuclei were induced in V79 and CHL cells, but not in CHO cells, when the exposure was for 24 hours.

In the mouse Tp53-mutant lymphoma L5178Y cell line, exposure to ethyl acrylate for 24 hours induced a small dose-dependent, but statistically significant, induction of micronuclei that did not meet the criteria for either a positive or a negative response (Whitwell et al., 2015).

(iii) Non-mammalian experimental systems

See Table 4.4

Valencia et al. (1985) reported that ethyl acrylate was not mutagenic in *Drosophila melanogaster*.

Several reports showed negative results in the Ames assay (Waegemaekers & Bensink, 1984; Johannsen et al., 2008; Kirkland et al., 2016). Haworth et al. (1983) reported inconsistent results from two different laboratories, one positive and one negative.

Ethyl acrylate lacked mutagenicity in the Ames test with the metabolically competent *Salmonella typhimurium* YG7108 strain containing the plasmid pin3ERb$_5$ that encodes a complete electron transport chain, including CYP450 (CYP) reductase, cytochrome b_5, and CYP2E1 (Emmert et al., 2006).

Ethyl acrylate did not induce genetic alterations in *Saccharomyces cerevisiae* D61.M when applied alone; however, when ethyl acrylate was applied in combination with propionitrile, a strong inducer of chromosomal malsegregation, chromosome loss was observed (Zimmermann & Mohr, 1992).

4.2.2 Altered cell proliferation, cell death or nutrient supply

(a) Humans

No data in exposed humans were available to the Working Group.

In human cells in vitro, exposure to ethyl acrylate for 18 hours had a strong cytotoxic effect in normal human epidermal keratinocytes and normal human dermal fibroblasts (0.1 µmol/well), and normal human bronchial epithelium cells (1.0 µmol/well), as determined by the MTT [(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (Nylander-French & French, 2000).

In the primary human gingival fibroblast and human submandibular gland adenocarcinoma cell lines, ethyl acrylate was not cytotoxic at concentrations of less than 10 µM as determined by the MTT assay. Cytotoxicity was seen at 100 µM, although no cell viability was found with ethyl acrylate at 1 mM (Fujisawa et al., 2000). Cytotoxicity was also observed in human HuLy cells, TK6 cells, and HepG2 cells (see Section 4.2.1 above).

Ethyl acrylate increased caspase3/7 activity in TK6 cells at concentrations of 6–12 µg/mL, and in WIL2-NC lymphoblast cells at concentrations of 6–16 µg/mL (Whitwell et al., 2015).

(b) Experimental systems

(i) Non-human mammals in vivo

In male and female C57BL/6J mice given a single intraperitoneal injection of ethyl acrylate at 738 mg/kg bw, statistically significant bone marrow toxicity was observed after 48 and 72 hours (Ashby et al., 1989).

Several studies examined the effect of ethyl acrylate on cell proliferation using different experimental approaches.

In a 2-year study of carcinogenicity in B6C3F$_1$ mice and Fischer 344/N rats exposed to ethyl acrylate via oral gavage (5 days per week, for 103 weeks), hyperplasia was seen in the forestomach (NTP, 1986). The incidence of hyperplasia was greater in the group exposed to ethyl acrylate at 200 mg/kg bw (26/50 male and 30/50 female B6C3F$_1$ mice, and 46/50 male and 49/50 female Fischer 344/N rats) compared with the group exposed to ethyl acrylate at 100 mg/kg bw (17/50 male and 12/50 female B6C3F$_1$ mice, and 41/50 male and 34/50 female Fischer 344/N rats). Hyperplasia of the bile duct was also seen in female Fischer 344 rats at both doses, with chronic exposure in the 2-year bioassay (NTP, 1986).

In a later study, Frederick et al. (1990) examined the forestomach and the glandular stomach of male Fischer 344 rats (n = 10 rats per dose) exposed to ethyl acrylate by oral gavage at 0.04, 0.2, 0.4, 1.0, 2.0, or 4.0% w/v (corresponding to 2, 10, 20, 50, 100, or 200 mg/kg bw) for 5 days per week for 2 weeks. At doses of 20 mg/kg bw or more, a dose-dependent increase in the incidence and severity of diffuse epithelial hyperplasia in the forestomach mucosa was seen. No treatment-related effects were observed in rats exposed to ethyl acrylate at doses of 10 mg/kg bw or less. An increased incidence and severity of diffuse epithelial hyperplasia in the forestomach was accompanied by an equal severity of hyperkeratosis. In contrast, no epithelial lesions were found in the glandular stomach in rats in any experimental group. Similarly, with exposure via drinking-water, diffuse epithelial hyperplasia in the forestomach mucosa was observed in all rats exposed to ethyl acrylate at concentrations of 1000, 2000, or 4000 ppm (99, 197, or 369 mg/kg bw), with the severity increasing in a dose-dependent manner. Hyperkeratosis, in conjunction with diffuse epithelial hyperplasia, was observed in rats exposed to ethyl acrylate at concentrations of 2000 and 4000 ppm.

Several studies from one research group investigated the role of cell proliferation in forestomach carcinogenesis induced by ethyl acrylate in rats (Ghanayem et al., 1991a,b,c, 1993, 1994). In the first report, Ghanayem et al. (1991a) showed that exposure of male Fischer 344 rats (n = 5 per group) to ethyl acrylate at a dose of 100 or 200 mg/kg bw per day by oral gavage for 14 consecutive days resulted in hyperplasia in the forestomach, the severity of which was dose-dependent. In several other studies (Ghanayem et al., 1991b,c, 1993, 1994), exposure of Fischer 344 rats to ethyl acrylate at 100 or 200 mg/kg bw by oral gavage for 5 days per week for 13 weeks induced mucosal hyperplasia in the forestomach (Ghanayem et al., 1991b). This was largely reversed after 8 weeks and 19 months of cessation of exposure for the groups exposed at 100 and 200 mg/kg bw, respectively. In two subsequent studies, the effect of exposure to ethyl acrylate at 200 mg/kg bw by oral gavage on hyperplasia in the forestomach was investigated. In the first of these studies, Ghanayem et al. (1993) reported that exposure of male Fischer 344 rats (n = 5 rats per group) at 200 mg/kg bw by oral gavage for 5 days per week for 6 and 12 months resulted in the development of mucosal hyperplasia in the forestomach in all exposed rats. This hyperplasia was reversed 15 months after cessation of treatment in all rats exposed for 6 months, but was sustained in 8 out of 13 rats (62%) 9 months after cessation of treatment in rats exposed for 12 months. This finding was confirmed in the second study (Ghanayem et al., 1994), which showed persistence of hyperplasia in the forestomach in 10 out of 13 rats (77%) 9 months after cessation of treatment in rats exposed to ethyl acrylate at 200 mg/kg bw for 12 months. Importantly, in 30% of rats exposed at 200 mg/kg bw for 12 months, the hyperplasia progressed to neoplasia.

Two articles reported the effect of ethyl acrylate on the extent of cell proliferation in the forestomach of exposed Fischer 344 rats (Gillette & Frederick, 1993; Ghanayem et al.,

1994). Gillette & Frederick (1993) reported the results of three experiments on the induction of epithelial S-phase activity in the Fischer 344 rat forestomach and glandular stomach. In the first experiment, a significant and prolonged elevation in the number of S-phase cells in the forestomach after a single gavage exposure to ethyl acrylate at 200 mg/kg bw in corn oil was evident 10 hours after treatment and remained elevated for 48 hours. In contrast to the forestomach, the glandular stomach response showed a marked increase of the S-phase activity 16 and 20 hours after treatment, which rapidly returned to normal levels 28 hours after treatment. In the second experiment, a significant induction of S-phase cells was seen in the forestomach and glandular stomach in a dose-dependent manner in rats exposed to ethyl acrylate at a concentration of 20 mg/kg bw or more. In the third experiment, in rats exposed to ethyl acrylate by oral gavage at 200 mg/kg bw in corn oil 5 days per week for 2 weeks, a significant elevation in the number of S-phase cells in the forestomach of exposed rats was detected at each post-dose time interval (6, 12, 18, and 24 hours).

In the study by Ghanayem et al. (1994), the exposure of Fischer 344 rats to ethyl acrylate by oral gavage at 200 mg/kg bw for 5 days per week for 12 months markedly increased the number of bromodeoxyuridine-stained nuclei in basal and squamous epithelial cells of the forestomach mucosa.

(ii) Non-human mammalian cells in vitro

An increase in the frequency of cell death in mouse fibroblast L929 (NCTC) cells was seen after exposure to ethyl acrylate at a concentration of 40, 70, or 100 µg/mL for 16 hours (Yang & Duerksen-Hughes, 1998). A dose-dependent increase in cytotoxicity was seen after exposure to ethyl acrylate at 0, 65, 80, 90, and 100 µg/mL for 24 hours in the Chinese hamster CHL/IU cell line when a relative population doubling index was used instead of the traditional relative cell count index (Fujita et al., 2016). Cytotoxicity was also observed in rodent V79, CHO, and CHL cells (see Section 4.2.1 above).

4.2.3 Chronic inflammation

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Several studies reported chronic inflammation in the forestomach of mice and rats exposed to ethyl acrylate. In the 2-year studies of carcinogenicity, inflammation of the forestomach was reported in male and female Fischer 344/N rats and B6C3F$_1$ mice exposed to ethyl acrylate at 100 or 200 mg/kg bw (NTP, 1986).

Exposure of Fischer 344 rats (n = 10 rats per group) to ethyl acrylate 5 days per week, for 2 weeks by oral gavage, but not by drinking-water, induced inflammation in the forestomach (Frederick et al., 1990). Concentrations of 100 and 200 mg/kg bw in corn oil resulted in submucosal inflammation in the forestomach in 6 and 10 rats, respectively, which was accompanied by a submucosal oedema in the forestomach in 2 and 9 rats, respectively. A lower incidence of inflammation was seen in the glandular stomach (1 and 6 out of 10 rats exposed at 100 and 200 mg/kg bw, respectively). In contrast, inflammation was not seen in the forestomach or the glandular stomach of Fischer 344 rats given drinking-water containing ethyl acrylate at 369 mg/kg bw per day for 2 weeks.

In rats, a single oral dose of ethyl acrylate consistently induced inflammation in the forestomach in two separate studies. deBethizy et al. (1987) reported that in male Sprague-Dawley rats (n = 3 rats per group), a single exposure to ethyl acrylate at 200 mg/kg bw by oral gavage resulted in a significant oedema and increased forestomach weight 72 hours after treatment. Ghanayem et al. (1991c) demonstrated a dose-dependent forestomach oedema in male Fischer 344 rats 4 hours

after a single exposure to ethyl acrylate at 100, 200, or 400 mg/kg bw by oral gavage in corn oil. No significant changes in the glandular stomach were observed.

Daily exposure to ethyl acrylate at 8, 20, or 50 mg/kg bw by oral gavage in corn oil for 28 days resulted in inflammatory cell infiltration in the forestomach of *gpt* delta transgenic mice (Ellis-Hutchings et al., 2018).

4.2.4 Other mechanisms

Several studies reported depletion of GSH, the principal cellular non-protein thiol, induced in human cells in vitro and in experimental systems by exposure to ethyl acrylate; these are discussed in the following sections.

(a) Humans

No data in exposed humans were available to the Working Group.

In human cells in vitro, Nylander-French & French (2000) reported a decrease in intracellular sulfhydryl concentrations in normal human epidermal keratinocytes and normal human bronchial epithelium cells treated with ethyl acrylate at 0.01 µmol/well in 96-well plates for 18 hours.

(b) Experimental systems

(i) Non-human mammals in vivo

Three studies investigated the effect of ethyl acrylate on the concentration of non-protein sulfhydryl (NPSH) in tissues of exposed rats. deBethizy et al. (1987) examined the tissue concentrations of NPSH in adult male Sprague-Dawley rats (n = 3 rats per group) that were given a single dose of ethyl acrylate at 2, 20, or 200 mg/kg bw by gavage. A dose-dependent depletion of NPSH was seen in all analysed tissues (forestomach, glandular stomach, liver, and blood), with the greatest decrease in the NPSH content observed in the forestomach and glandular stomach. In male Wistar rats exposed to ethyl acrylate by 6-hour inhalation, a dose-dependent depletion of NPSH was reported in the livers at concentrations of 20–80 mmol/m^3 and in blood at exposure concentrations of 40–80 mmol/m^3 (Vodička at al., 1990). Frederick et al. (1990) showed a rapid depletion of NPSH, primarily GSH, in the forestomach of male Fischer 344 rats exposed to ethyl acrylate at 200 mg/kg bw by oral gavage for 5 days per week for 2 weeks (Frederick et al., 1992). A less pronounced effect was seen on the NPSH content in the glandular stomach. In contrast, exposure to ethyl acrylate did not alter the NPSH concentration in the liver. Exposure at 20 mg/kg bw had a negligible effect on the NPSH content of the forestomach, and no effect on the concentrations of NPSH in the glandular stomach and liver.

Significantly decreased levels of both GSH and oxidized glutathione (GSSG) were seen in the forestomach of male C57BL/6 mice (n = 5 mice per group) 3 hours after exposure to ethyl acrylate at 0, 20, 50, or 100 mg/kg bw by oral gavage in corn oil. The relative GSH/GSSG ratio was not altered (Ellis-Hutchings et al., 2018).

(ii) Non-human mammalian cells in vitro

In heterozygous L5178Y *Tk*$^{+/-}$ mouse lymphoma cells, exposure to ethyl acrylate at 10, 20, 30, 40, or 50 µg/mL for 4 hours resulted in time- and concentration-dependent reduction of the NPSH concentrations (Ciaccio et al., 1998).

4.3 Other adverse effects

4.3.1 Irritancy and sensitization

(a) Humans

The major reported adverse effects of ethyl acrylate exposure in humans include sensory irritation in the nose and eyes (Hoffmeyer et al., 2016, 2017; Kleinbeck et al., 2017) and contact dermatitis (Le et al., 2015; Spencer et al., 2016; DeKoven et al., 2017).

(b) Experimental systems

Three studies of the skin irritating effect of ethyl acrylate in mice (Hayes & Meade, 1999; Warbrick et al., 2001; Dearman et al., 2007) produced contradictory results. In the first study (Hayes & Meade, 1999), no skin irritating effect of ethyl acrylate was found in the murine local lymph node assay and in the mouse ear swelling test in $B6C3F_1$ mice. In two later studies in CBA mice (Warbrick et al., 2001; Dearman et al., 2007), the skin-irritating effect of ethyl acrylate was demonstrated in the murine local lymph node assay.

An increased incidence of retinopathy and cataracts was reported in male and female Fischer 344/N rats exposed to ethyl acrylate at 100 mg/kg bw in 2-year studies of carcinogenicity (NTP, 1986). Additionally, in studies of short-term exposure to ethyl acrylate by inhalation, leukopenia was observed in adrenalectomized male Sprague-Dawley rats (Brondeau et al., 1990) and hyperglycaemia was seen in male Wistar rats (Vodička et al., 1990).

4.4 Data relevant to comparisons across agents and end-points

See the monograph on isobutyl nitrite in the present volume.

5. Summary of Data Reported

5.1 Exposure data

Ethyl acrylate is a high production volume chemical that is produced worldwide. It is used in the production of polymers for water-based paints, resins, plastics, and rubber, and in the production of acrylic fibres, adhesives, and binders. Ethyl acrylate is also used in surface coatings for textiles, paper, leather, and food-contact materials, and as a food flavouring agent. Occupational exposure may occur among chemical and paint manufacturing workers, nail salon workers, and dental technicians. A small number of studies have characterized occupational air exposures to ethyl acrylate in polystyrene production, paint mixing, and laser cutting of plexiglass, acrylic, and lucite materials. Exposure to the general population occurs from food flavouring additives and food-contact materials, and through materials containing ethyl acrylate, such as window caulking and acrylic nail products. Exposure concentrations in the environment and the general population have not been reported.

5.2 Cancer in humans

One cohort study found an increased risk of mortality from cancer of the colon and rectum among acrylic sheet manufacturing workers exposed to methyl methacrylate and ethyl acrylate. One cohort study found no increased risk of mortality from multiple cancer types in acrylic sheet manufacturing workers where ethyl acrylate exposure may have occurred. A general-population case–control study found an increased risk of cancer of the rectum and no increased risk of cancer of the colon for occupational exposure to aliphatic esters. However, exposure assessment in all three studies was not specific to ethyl acrylate.

5.3 Cancer in experimental animals

Ethyl acrylate was tested for carcinogenicity in one well-conducted gavage study and one well-conducted inhalation study in male and female mice. Ethyl acrylate was tested for carcinogenicity in one gavage study and one well-conducted inhalation study in male and female rats, and one gavage study in male rats.

In male mice, exposure to ethyl acrylate by gavage caused a significant increase in the

incidence and a positive trend in the incidence of squamous cell papilloma, squamous cell carcinoma, and squamous cell papilloma or carcinoma (combined) of the forestomach. In female mice, exposure to ethyl acrylate by gavage caused a significant increase in the incidence and a positive trend in the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach. In male mice, exposure to ethyl acrylate by inhalation caused a significant increase in the incidence of follicular cell adenoma of the thyroid. There was no significant increase in the incidence of any tumours in female mice exposed to ethyl acrylate by inhalation.

In male rats, exposure to ethyl acrylate by gavage caused a significant increase in the incidence and a positive trend in the incidence of squamous cell papilloma, squamous cell carcinoma, and squamous cell papilloma or carcinoma (combined) of the forestomach. In female rats, exposure to ethyl acrylate by gavage caused a significant increase in the incidence and a positive trend in the incidence of squamous cell papilloma and squamous cell papilloma or carcinoma (combined) of the forestomach. In the other gavage study in male rats, ethyl acrylate caused a significant increase in the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach. In male rats, exposure to ethyl acrylate by inhalation caused a significant increase in the incidence of follicular cell adenoma or carcinoma (combined) of the thyroid. There was no significant increase in the incidence of any tumours in female rats exposed to ethyl acrylate by inhalation.

5.4 Mechanistic and other relevant data

No data on absorption, distribution, metabolism, or excretion in exposed humans were available. In rats, ethyl acrylate is rapidly absorbed from the gastrointestinal tract and widely distributed. Ethyl acrylate-derived radiolabel was retained to a greater extent in the rat forestomach than in other organs 24 hours after exposure by oral gavage. In rats, there are two major metabolic pathways: (i) enzymatic hydrolysis of ethyl acrylate to acrylic acid and ethanol catalysed by carboxylesterases, with a subsequent high-efficiency conversion of both metabolites to CO_2; and (ii) binding of ethyl acrylate and acrylic acid to glutathione and proteins. Ethyl acrylate is excreted primarily as CO_2 in rats exposed orally; approximately 10% is excreted as urinary mercapturates, with 4% excreted in the faeces.

Regarding the key characteristics of carcinogens, ethyl acrylate has demonstrable genotoxicity; positive results without cytotoxicity have been observed in some assays in studies conducted in vivo and in studies conducted in vitro in non-human mammalian cell lines. However, the findings are equivocal because of inconsistencies and lack of reproducibility, meaning that the evidence is not strong. In human cells in vitro, results for micronucleus formation were equivocal across multiple studies, although positive findings were reported below the predefined cytotoxicity cut-off. In rats and mice, ethyl acrylate did not induce DNA strand breaks, and mutations were not induced in *gpt* transgenic mice. In the mouse assay for micronucleus formation, ethyl acrylate gave positive results in the BALB/c strain in one study, positive results in one of two trials in another study of BALB/c mice, and negative results in the C57BL/6 strain. Results were consistently positive in mammalian cells in vitro for several end-points (including strand breaks, mutation, and chromosomal aberrations), in some cases with an increase in the frequency of micronucleus formation without cytotoxicity in a dose-dependent manner. In non-mammalian tests including the Ames assay, results were negative.

There is *strong* evidence that ethyl acrylate alters cell proliferation, cell death, or nutrient supply, based primarily on experimental animal

studies in vivo, with some evidence of cytotoxicity in various human cells in vitro. No data were available in exposed humans. Exposure to ethyl acrylate by oral gavage for 2 years resulted in hyperplasia in the forestomach of Fischer 344/N rats and B6C3F$_1$ mice, but the glandular stomach was not examined. In Fischer 344 rats given a single oral dose, cell proliferation was increased in both the forestomach and glandular stomach but did not persist in the glandular stomach. Hyperplasia was seen in the forestomach, but not in the glandular stomach, in 2-week oral gavage studies. In a 13-week study in Fischer 344 rats, hyperplasia in the forestomach was seen when ethyl acrylate was given by oral gavage or by drinking-water, but was not sustained after cessation of exposure. Reversibility was dependent on duration of treatment; rats exposed for 12 months had sustained hyperplasia in the forestomach.

There is *strong* evidence that ethyl acrylate induces chronic inflammation, based on studies in experimental animals. No data were available in exposed humans. In male and female Fischer 344/N rats and B6C3F$_1$ mice exposed to ethyl acrylate by oral gavage for 2 years, inflammation of the forestomach was induced. Exposure of Fischer 344 rats to ethyl acrylate for 2 weeks by oral gavage, but not by drinking-water, induced inflammation of the forestomach; the incidence of inflammation in the glandular stomach was lower than in the forestomach. In rats, exposure to ethyl acrylate by a single oral dose consistently induced inflammation in the forestomach in two studies. Exposure of *gpt* delta transgenic mice to ethyl acrylate by oral gavage for 28 days resulted in inflammatory cell infiltration in the forestomach.

Several studies reported depletion of glutathione, the principal cellular non-protein thiol, induced by exposure to ethyl acrylate in human cells in vitro and in rodent studies.

In humans, irritant and allergic contact dermatitis has been reported, with similar results in some studies in rodents.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of ethyl acrylate.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

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

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