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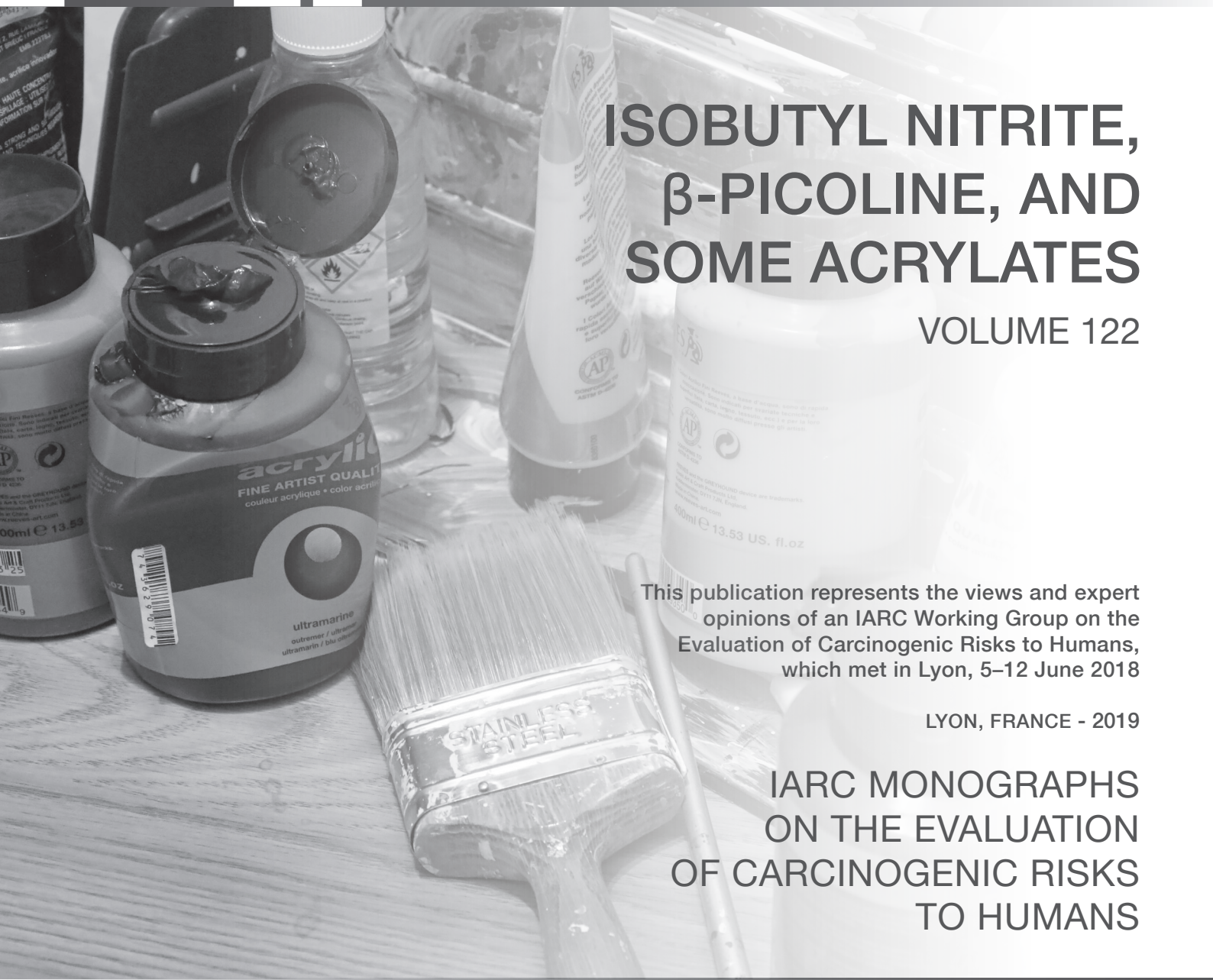


ISOBUTYL NITRITE, β-PICOLINE, AND SOME ACRYLATES

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

METHYL ACRYLATE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 96-33-3

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

IUPAC systematic name: methyl prop-2-enoate

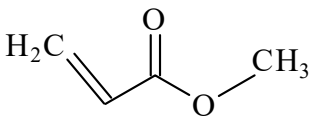
Synonym: methyl propenoate; acrylic acid methyl ester; methyl 2-propenoate; 2-propenoic acid; methyl ester; methoxycabonylethylene.

1.1.2 Structural and molecular formulae, and relative molecular mass

Chemical formula: $C_4H_6O_2$

Relative molecular mass: 86.09

Structural formula:



1.1.3 Chemical and physical properties

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

Boiling point: 80.7 °C at 1 atm (ACGIH, 2014)

Melting point: –76.5 °C (Budavari et al., 1996)

Solubility: slightly soluble in water; soluble in alcohol, ether, and other organic solvents (ACGIH, 2014)

Vapour pressure: 68.25 mm Hg [9.1 kPa] at 20 °C

Relative vapour density (air = 1): 2.97 (ACGIH, 2014)

Flash point: –2.8 °C, closed cup; 6.7 °C, open cup (ACGIH, 2014)

Explosive limits: upper, 25%; lower, 2.8% by volume in air (ACGIH, 2014)

Conversion factor: 1 ppm = 3.52 mg/m^3 at 25 °C and 1 atm.

1.1.4 Technical products and impurities

Impurities reported in commercial-grade (technical) methyl acrylate (purity, 98.9–99.9%) include water (≤ 0.1% by weight), acrylic acid (0.01% by weight), and hydroquinone monomethyl ether (15, 200, or 1000 mg/kg) (HSDB, 2018).

1.2 Production and use

1.2.1 Production process

Methyl acrylate is produced by the oxidation of propylene to acrolein and then to acrylic acid; this is then reacted with methanol or, by a modification of the Reppe process, from acetylene and then reacted with methanol in the presence of acid and nickel carbonyl (ECETOC, 1998). Methyl acrylate can also be formed using organic carbonates as esterifying agents, isolating 2-halo-1-alkenes from hydrocarbon feedstocks, or by reacting formaldehyde with ketene to β-propiolactone, which is then reacted with methanol. To prevent spontaneous polymerization, methyl acrylate is stored with small amounts of hydroquinones (ECETOC, 1998).

1.2.2 Production volume

Methyl acrylate is a high production volume chemical (OECD, 2009), and is manufactured in and/or imported into the European Economic Area in quantities of 10–100 thousand metric tonnes per year (ECHA, 2018). The USA produced from more than 100 to 500 million pounds [> 45.4 to 227 thousand metric tonnes] in 2002 (HSDB, 2018). Production volumes for China ranged from 104 thousand metric tonnes in 2008 to 99 thousand metric tonnes in 2010 (Chinese Report, 2008, 2010). Recent figures for the first quarter of 2017 are 35.4 thousand metric tonnes (Chinese Report, 2017) [approximately 140 thousand metric tonnes in 2017, by extrapolation].

1.2.3 Use

The main uses of methyl acrylate are in the production of methyl acrylic polymers and, together with acrylonitrile, in the production of acrylic and modacrylic fibres. Methyl acrylic polymers are used in adhesives, resinous and polymeric coatings (including leather finish resins), paper, and paperboard that may come into contact with foods. Acrylic and modacrylic fibres are used in the clothing and home furnishing industries in fire-retardant fabrics, paint rollers, battery separators, and protective clothing (ECETOC, 1998; ACGIH, 2014). Methyl acrylate is also used to produce thermoplastic coatings, adhesives, sealants, amphoteric surfactants for shampoos, medical and dental prostheses, contact lenses, and speciality plastics including latex coatings, and floor and fabric finishes (ECETOC, 1998; ACGIH, 2014). It is also used in the synthesis of other organic molecules. The distribution of use in the 1990s was 38% for acrylic fibres, 15% for plastics additives, 12% for coatings and varnishes, 25% for the production of adhesives, detergents, flocculants, dispersion aids, and raw materials for organic synthesis, and 10% for other uses (ECETOC, 1998).

1.3 Analytical methods

Air sampling for methyl 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 1459 (NIOSH, 1994) and United States Occupational Safety and Health Administration (OSHA) Method 92 (OSHA, 2018). NIOSH Method 1459 has a detection limit of 10 μg per sample and OSHA Method 92 has a detection limit of 140 μg/m^3.

Methyl 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 technique 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 methyl acrylate was

not reported. Similar purge and trap methods are also reported for other aqueous, solid (including waste and soil), and tissue samples (NEMI, 1996).

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

Methyl acrylate may be released into the environment in fugitive and stack emissions or in wastewater during its production and use. Methyl acrylate is expected to volatize from water surfaces, and is not expected to persist or to bioaccumulate in the environment. The EPA Toxics Release Inventory reported methyl acrylate emissions in fugitive and stack air, as well as wastewater emissions, from 64 facilities in the USA in 2016, with similar numbers of facilities reporting emissions between 1990 and 2016 (EPA, 2017). These facilities were mostly classified as chemical (81%), hazardous waste (6%), chemical wholesalers (5%), and non-metallic mineral product (3%) industries, as well as other industries (3%) such as petroleum, plastics, and rubber. Median reported on- and offsite releases into the air were 500, 255, 223, and 72 pounds [227, 116, 101, and 33 kg] for the years 1990, 2000, 2010, and 2016, respectively (EPA, 2017). The Canadian National Pollutant Release Inventory reported a mean annual release of 2100 kg of methyl acrylate into the air from one facility in 1994 and no releases for the years 2000, 2010, and 2016; no releases onto land or into water were reported (Government of Canada, 2017). The Working Group found no reports of measured methyl acrylate concentrations in environmental media.

1.4.2 Exposure in the general population

Methyl acrylate exposure in the general population may occur through the use of products containing this chemical, such as adhesives and sealants; however, no quantitative information on exposure was available to the Working Group.

1.4.3 Occupational exposure

Occupational exposure to methyl acrylate may occur through inhalation and dermal contact during its production and use as an intermediate in the production of fibres, resins, coatings, and other products. Average full-shift methyl acrylate concentrations in the air of 2 ppm [7 mg/m^3], with peaks of 12.6–30.0 ppm [44.4–106 mg/m^3] lasting 2–5 minutes and mean area concentrations of 5.4 ppm [19 mg/m^3] with a range of 0.6–17.2 ppm [2.1–60.5 mg/m^3], were reported for a chemical production facility in Texas, USA. The highest peak exposure was 122 ppm [429 mg/m^3] (ACGIH, 2014). [These concentrations were reported in American Conference of Governmental Industrial Hygienists threshold limit value documentation from unpublished data, where the measurements were presumably made before 1996.]

Residual methyl acrylate monomer (0.05%) has been found in the polymer powder used for dental resins (Davy & Braden, 1991).

1.5 Regulations and guidelines

Occupational exposure limits for methyl acrylate are in place in numerous countries (see Table 1.1). In the majority of these countries, the 8-hour time-weighted average (TWA) limit is either 7 or 18 mg/m^3, with a short-term limit of 14, 18, or 36 mg/m^3. In Australia, New Zealand, Singapore, and the USA (NIOSH and OSHA), the 8-hour TWA limit is 35 mg/m^3, with no short-term limit (IFA, 2018).

The United States Food and Drug Administration has established regulations for the use of monomers, polymers, and copolymers including methyl acrylate in food-contact materials. The proportion of the monomers should

Table 1.1 Occupational exposure limits for methyl acrylate

Country or region	Concentration (mg/m^3)	Interpretation	Comments
Australia	35	TWA	
Austria	18	TWA	
Belgium	36	STEL	
	7.2	TWA	
Canada, Ontario	7	TWA	
Canada, Quebec	7	TWA	
China	20	TWA	
Denmark	7	TWA	
	14	STEL	
European Union	18	TWA	Indicative OEL values
	36	STEL	
Finland	7	TWA	
	18	STEL	
France	18	TWA	Restrictive statutory limit values
	36	STEL	
Germany (AGS)	7.1	TWA	
	14.2	STEL	
Germany (DFG)	7.1	TWA	
	14.2	STEL	
Hungary	18	TWA	
	18	STEL	
Ireland	18	TWA	
	36	STEL	
Italy	7	TWA	Skin notation
	35	STEL	
Japan (JSOH)	7	TWA	
Latvia	20	TWA	
Netherlands	18	TWA	
	36	STEL	
New Zealand	35	TWA	
Poland	14	TWA	
	28	STEL	
Republic of Korea	7	TWA	
Romania	18	TWA	
	36	STEL	
Singapore	35	TWA	
Spain	7.2	TWA	Skin, sensitizer notation
Sweden	18	TWA	
	36	STEL	
Switzerland	18	TWA	
	18	STEL	
Turkey	18	TWA	
	36	STEL	

Table 1.1 (continued)

Country or region	Concentration (mg/m³)	Interpretation	Comments
UK	[36]	TWA	The UK Advisory Committee on Toxic Substances has expressed concern that, for the OEL shown in parentheses, health may not be adequately protected because of doubts that the limit was not soundly based; these OELs were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list
USA (ACGIH)	7.2	TWA	Eye, skin, upper respiratory tract irritation, eye damage
USA (NIOSH)	35	TWA	
USA (OSHA)	35	TWA	

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

not exceed 5% by weight of total polymer units (CFR, 2017).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

Methyl acrylate was previously reviewed by the Working Group in Volume 39 (IARC, 1986), Supplement 7 (IARC, 1987), and Volume 71 (IARC, 1999) of the *IARC Monographs*. The Volume 71 Working Group concluded that there was *inadequate evidence* in experimental animals for the carcinogenicity of methyl acrylate. This section provides an evaluation of the studies of carcinogenicity in experimental animals reviewed in the previous Monographs and Supplement, and of all studies published since then.

See Table 3.1

3.1 Mouse

Inhalation

Groups of 50 male and 50 female B6D2F1/Crlj mice (age, 6 weeks) were exposed to methyl acrylate (purity, 99.9%) at a concentration of 0 (control), 2.5, 10, or 40 ppm [0, 9, 35, or 141 mg/m^3] by whole-body inhalation for 6 hours per day, 5 days per week for 94 weeks (males) or 97 weeks (females) (Japan Bioassay Research Center, 2017). The study was originally designed for a 104-week exposure but, because the survival rates of the control groups of males and females were lower than 25% the later weeks of treatment (because of amyloidosis), the study was terminated at 94 weeks (males) and 97 weeks (females); the survival rate of males exposed at 40 ppm was significantly higher (27/50 vs 12/50 controls). Body weights in male and female mice exposed at 40 ppm were decreased in the early exposure periods, but were similar to controls by the end of the study. No significant increase in the incidence of any neoplastic lesions was found in the exposed male or female groups compared with controls (Japan Bioassay Research Center, 2017). [The Working Group noted that this was a well-conducted study that complied with good laboratory practice.]

3.2 Rat

Inhalation

In a study by Reininghaus et al. (1991), groups of 86 male and 86 female Sprague-Dawley rats (age, 35 days) were exposed to methyl acrylate (purity, > 99.8%; main impurities, methyl propionate and ethyl acrylate) at a concentration of 0, 15, 45, or 135 ppm [0, 53, 158, or 475 mg/m^3] by whole-body inhalation for 6 hours per day, 5 days per week, for 24 months. During weeks 1–13, the rats were exposed to one third of the final test substance concentration. Interim kills were carried out after 12 months (10 males and 10 females per group) and 18 months (15 male and 15 females per group). No significant sex-specific differences in mortality were observed. From week 15 to the end of the exposure period, the body weights of male and female rats exposed at the highest dose (135 ppm) were significantly lower (~4%) than those of other groups.

The incidence of sarcoma of the soft tissue (skin or subcutis) [not otherwise specified] in exposed males was increased compared with controls, with a significant positive trend [P = 0.014, Cochran–Armitage trend test]: 0/86, 4/86 (5%), 0/86, and 6/86 (7%), respectively [P = 0.029 at 135 ppm, Fisher exact test]. The incidence of "malignant leukaemic tumours" (leukaemia, lymphoma, and lymphosarcoma) in exposed males was increased compared with controls, with a significant positive trend [P = 0.003, Cochran–Armitage trend

Table 3.1 Studies of carcinogenicity with methyl 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, B6D2F$_1$/Crlj (M) 6 wk 94 wk JBRC (2017)	Inhalation (whole-body exposure) Methyl acrylate, 99.9% None 0, 2.5, 10, 40 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 12, 16, 12, 27	*Any tumour type* No significant increase in the incidence of any neoplastic lesion	NS	Principal strengths: study covered most of lifespan; well-conducted GLP study Principal limitations: survival rate of control group was < 25% in later weeks of the treatment period (due to amyloidosis); study therefore terminated at wk 94 Survival of mice exposed at 40 ppm was significantly higher
Full carcinogenicity Mouse, B6D2F$_1$/Crlj (F) 6 wk 97 wk JBRC (2017)	Inhalation (whole-body exposure) Methyl acrylate, 99.9% None 0, 2.5, 10, 40 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 12, 12, 12, 20	*Any tumour type* No significant increase in the incidence of any neoplastic lesion	NS	Principal strengths: study covered most of lifespan; well-conducted GLP study Principal limitations: survival rate of control group was < 25% in later weeks of the treatment period (due to amyloidosis); study therefore terminated at wk 97 No significant difference in survival between control and treated groups
Full carcinogenicity Rat, Sprague-Dawley (M) 35 d 24 mo Reininghaus et al. (1991)	Inhalation (whole-body exposure) Methyl acrylate, > 99.8% None 0, 15, 45, 135 ppm for 6 h/d, 5 d/wk 86, 86, 86, 86 NR, NR, NR, NR	*Soft tissues*: sarcoma [not otherwise specified] 0/86*, 4/86 (5%), 0/86, 6/86 (7%)** *Haematopoietic and lymphoid tissues*: "malignant leukaemic tumours" (leukaemia, lymphoma, and lymphosarcoma) 0/86*, 3/86 (3%), 7/86 (8%)**, 0/86	*[P = 0.014, Cochran–Armitage trend test]; **[P = 0.029, Fisher exact test] *[P = 0.003, Cochran–Armitage trend test]; **[P = 0.014, Fisher exact test]	Principal strengths: well-conducted study From week 1 to week 13, the rats were exposed to one third of the final test substance concentrations; survival similar between groups

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, Sprague-Dawley (F) 35 d 24 mo Reininghaus et al. (1991)	Inhalation (whole-body exposure) Methyl acrylate, > 99.8% None 0, 15, 45, 135 ppm for 6 h/d, 5 d/wk 86, 86, 86, 86 NR, NR, NR, NR	*Pituitary gland*: adenoma 10/86 (12%)*, 21/86 (24%)**, 23/86 (27%)***, 9/86 (10%)	*[$P = 0.006$, Cochran–Armitage trend test]; **[$P = 0.046$, Fisher exact test]; ***[$P = 0.019$, Fisher exact test]	Principal strengths: well-conducted study From wk 1 to wk 13, the rats were exposed to one third of the final test substance concentrations; survival similar between groups
Full carcinogenicity Rat, F344/DuCrlCrlj (M) 6 wk 104 wk JBRC (2017)	Inhalation (whole-body exposure) Methyl acrylate, 99.9% None 0, 10, 40, 160 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 38, 42, 35, 39	*Nasal cavity*: squamous cell carcinoma 0/50*, 0/50, 1/50, 6/50**	*$P \leq 0.0002$, Cochran–Armitage trend test, Peto trend test; **$P = 0.0133$, Fisher exact test	Principal strengths: study covered most of lifespan; well-conducted GLP study Survival in exposed groups similar to controls; historical control incidence: nasal cavity squamous cell carcinoma, 0/649
Full carcinogenicity Rat, F344/DuCrlCrlj (F) 6 wk 104 wk JBRC (2017)	Inhalation (whole-body exposure) Methyl acrylate, 99.9% None 0, 10, 40, 160 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 40, 39, 43, 41	*Nasal cavity*: squamous cell carcinoma 0/50, 0/50, 0/50, 2/50	NS	Principal strengths: study covered most of lifespan; well-conducted GLP study Survival in exposed groups similar to controls Historical control incidence: nasal cavity squamous cell carcinoma, 0/650; adrenal gland pheochromocytoma (benign or malignant, combined), 18/650 (range, 0–8%); adrenal gland pheochromocytoma (benign), 11/650 (range, 0–8%); adrenal gland pheochromocytoma (malignant), 7/650 (range, 0–4%)
		Adrenal gland Pheochromocytoma (benign or malignant, combined) 1/50*, 1/50, 1/50, 4/50 (8%)	*$P = 0.0420$, Peto trend test	
		Pheochromocytoma (benign) 1/50, 0/50, 1/50, 2/50 (4%)	NS	
		Pheochromocytoma (malignant) 0/50, 1/50, 0/50, 2/50 (4%)	NS	

d, day; F, female; GLP, good laboratory practice; M, male; mo, month; NR, not reported; NS, not significant; ppm, parts per million; wk, week

test]: 0/86, 3/86 (3%), 7/86 (8%), and 0/86, respectively [$P = 0.014$ at 45 ppm, Fisher exact test]. The incidence of adenoma of the pituitary gland in exposed females was increased compared with controls, with a significant positive trend [$P = 0.006$, Cochran-Armitage trend test]: 10/86 (12%), 21/86 (24%), 23/86 (27%), and 9/86 (10%), respectively [$P = 0.046$ at 15 ppm, $P = 0.019$ at 45 ppm; Fisher exact test] (Reininghaus et al., 1991). [The Working Group noted this was a well-conducted study and that the exposure schedule was unusual.]

Groups of 50 male and 50 female Fischer 344/DuCrlCrlj rats (age, 6 weeks) were exposed to methyl acrylate (purity, 99.9%) at a concentration of 0 (control), 10, 40, or 160 ppm [0, 35, 141, or 563 mg/m^3] by whole-body inhalation for 6 hours per day, 5 days per week, for 104 weeks. No significant difference in mortality was observed between the groups. Body weights in male and female rats exposed to methyl acrylate at 160 ppm were decreased. At 104 weeks, there was a statistically significant increase in the incidence of squamous cell carcinoma of the nasal cavity in male rats at the highest dose ($P = 0.0133$, Fisher exact test) compared with controls, with a significant positive trend (0/50, 0/50, 1/50, and 6/50 (12%); $P \leq 0.0002$, Cochran–Armitage trend test); no squamous cell carcinomas of the nasal cavity were observed in 649 male historical controls from the laboratory. There were 2 cases (2/50, 4%) of squamous cell carcinoma of the nasal cavity in females exposed at 160 ppm (and none in the other groups), which was not a statistically significantly increase; however, this is a rare tumour that was not observed in 650 female historical controls from the laboratory. There was a significant positive trend in the incidence of pheochromocytoma (benign or malignant, combined) of the adrenal gland in females (1/50, 1/50, 1/50, and 4/50; $P = 0.0420$, Peto trend test) [the incidence in females exposed at 160 ppm (8%) equalled the upper limit of the range observed in female historical controls from the laboratory (0–8%) (Japan Bioassay Research Center (2017)]. [The Working Group noted that this was a well-conducted study that complied with good laboratory practice.]

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 methyl acrylate in humans were not available to the Working Group.

4.1.2 Experimental systems

Methyl acrylate has been shown to be readily absorbed in rats (Sapota, 1988, 1993) and guinea-pigs (Seutter & Rijntjes, 1981) after the radiolabelled compound was given by intraperitoneal injection or orally. Dermal absorption has also been demonstrated in guinea-pigs; radiolabelled methyl acrylate had fully penetrated the dermis after 16 hours and was spread throughout the body (Seutter & Rijntjes, 1981).

Methyl acrylate was distributed to all major tissues after oral exposure or intraperitoneal injection in rats (Sapota 1988, 1993) and guinea-pigs (Seutter & Rijntjes, 1981). In rats, the highest concentration of radiolabel was detected in the liver and kidney 1 and 2 hours after intraperitoneal or oral exposure, respectively (Sapota, 1988, 1993). The highest concentrations of radiolabelled methyl acrylate detected using whole-body autoradiography of guinea-pigs were observed in the liver, bladder, and brain, or in the peritoneum and liver, 1 hour after oral exposure or intraperitoneal injection, respectively. Radiolabel quickly disappeared from all tissues, but at a slightly

slower rate after intraperitoneal injection than after oral exposure (Seutter & Rijntjes, 1981).

In rats, the major route of excretion of methyl acrylate is via expiration (as carbon dioxide, CO_2, > 50%) and urine (10–50%), and, to smaller extent, faeces (1–3%) (Sapota, 1988, 1993). The total radiolabel excreted after oral exposure or intraperitoneal injection of radiolabelled methyl acrylate within 72 hours was approximately 97% and 91% of the administered dose, respectively (Sapota, 1988). A similar excretion pattern was observed in guinea-pigs (Seutter & Rijntjes, 1981).

There are two suggested detoxification pathways for methyl acrylate (Sapota, 1993) (see Fig. 4.1): (i) hydrolysis by carboxylesterases to acrylic acid and methanol, with further hydration of the double bond of acrylic acid to form 3-hydroxypropionic acid that can then be oxidized to malonic acid and further to CO_2; and (ii) conjugation with endogenous glutathione and subsequent excretion as mercapturic acid in urine.

These two metabolic pathways are supported by several findings in the literature (Delbressine et al., 1981; Miller et al., 1981; Seutter & Rijntjes, 1981; Vodička et al., 1990; Black et al., 1993; Sapota, 1993). For instance, methyl acrylate has been shown to be hydrolysed by rat tissue carboxylesterases to acrylic acid (Miller et al., 1981). An increase in the amount of excreted mercapturic acid derivatives of methyl acrylate, more specifically thioethers, was also observed in rats and guinea-pigs after intraperitoneal injection, and in guinea-pigs after oral and dermal exposure to methyl acrylate. In rats, the thioethers were identified as *N*-acetyl-(2-carboxyethyl)-L-cysteine and the corresponding monomethyl ester at a ratio of 20:1 (Delbressine et al., 1981; Seutter & Rijntjes, 1981). This is consistent with the observed chemical reactivity of methyl acrylate with glutathione in vitro, with an estimated half-life of 18.4 minutes (Miller et al., 1981; Vodička et al., 1990).

4.1.3 Modulation of metabolic enzymes

At doses of up to 160 μM, methyl acrylate did not induce mRNA of the endogenous human NAD(P)H:quinone oxidoreductase (*HQOR1*) gene in the human hepatocarcinoma cell line (HepG2) (Winner et al., 1997). However, at 20 μM, it caused a twofold induction of quinone reductase in the mouse Hepa 1c1c7 cell line (Talalay, 1989).

4.2 Mechanisms of carcinogenesis

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016). Data were available only for the key characteristic "is genotoxic".

4.2.1 Genetic and related effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.1

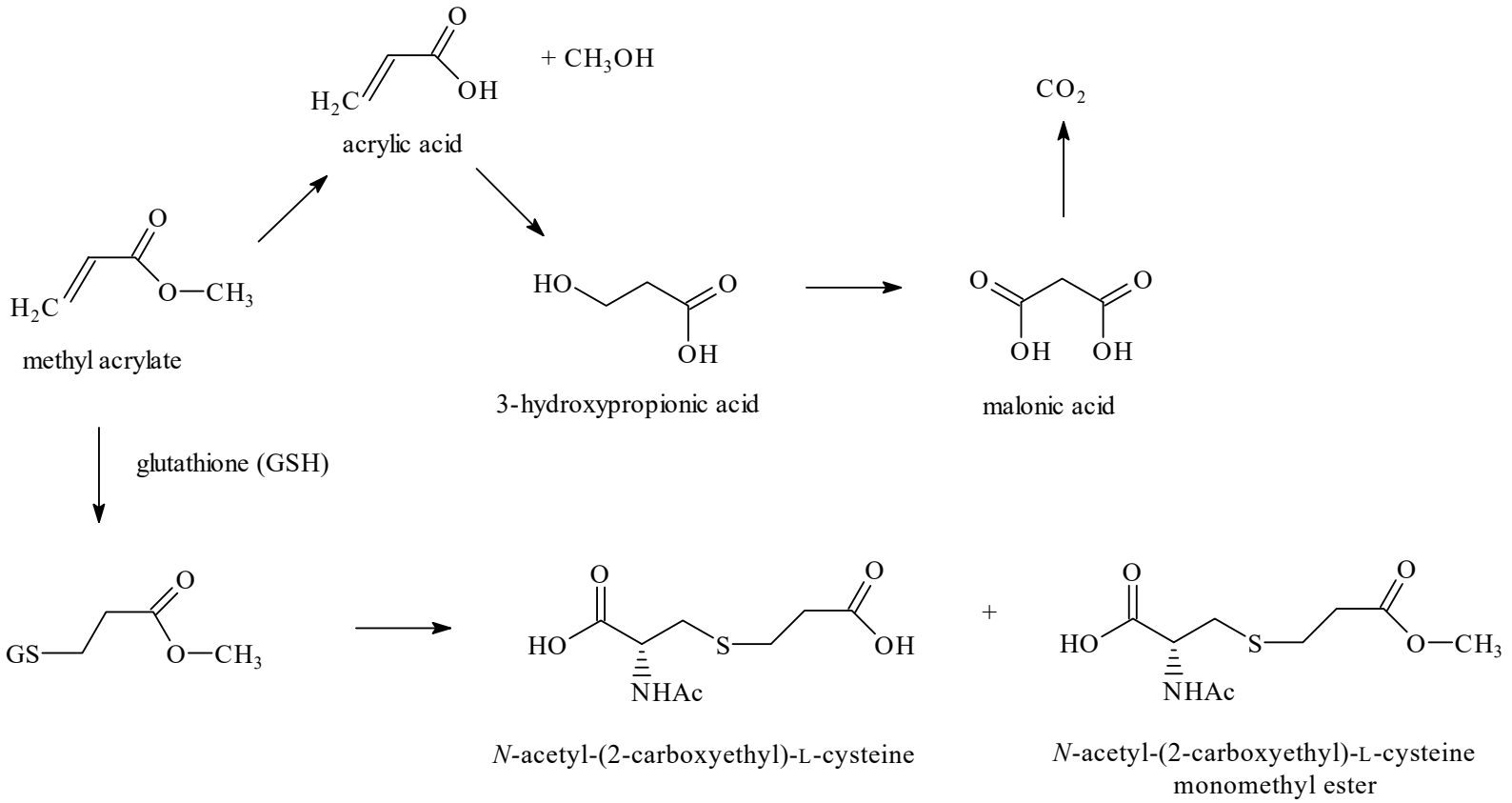
There was an increase in the frequency of micronucleated cells in the bone marrow of male BALB/c mice exposed to methyl acrylate by two intraperitoneal injections given 24 hours apart (Przybojewska et al., 1984). However, in ddY outbred mice, methyl acrylate gave negative results in assays for micronucleus formation after oral exposure (a single dose of 250 mg/kg bw) or by inhalation (2100 ppm for 3 hours) (Hachiya et al., 1982; Sofuni et al., 1984).

(ii) Non-human mammalian cells in vitro

See Table 4.2

In Chinese hamster ovary (CHO) AS52 cells, methyl acrylate was not mutagenic in the xanthine-guanine phosphoribosyl transferase (*Xprt*) assay (Oberly et al., 1993). In addition, no mutagenic effect was reported in the

Fig. 4.1 Proposed metabolic pathways for methyl acrylate, based on identification of acrylic acid, carbon dioxide, and mercapturic acid conjugates



The *N*-acetyl-(2-carboxyethyl)-L-cysteine conjugate may also stem from glutathione addition to acrylic acid
Compiled by the Working Group

Table 4.1 Genetic and related effects of methyl acrylate in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration	Reference
Micronucleus formation	Mouse, ddY (M)	Bone marrow	–	250 mg/kg bw	Oral	Hachiya et al. 1982
Micronucleus formation	Mouse, BALB/c (M)	Bone marrow	+	37.5 mg/kg bw	Intraperitoneal injection, ×2	Przybojewska et al. (1984)
Micronucleus formation	Mouse, ddY (NR)	Bone marrow	–	2100 ppm	Inhalation, 3 h	Sofuni et al. (1984)

bw, body weight; h, hour; HID, highest ineffective dose; LED, lowest effective dose; M, male; NR, not reported; ppm, parts per million

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

Table 4.2 Genetic and related effects of methyl acrylate in non-human mammalian cells in vitro

End-point	Species, cell line	Results[a]		Concentration (LEC or HIC) (μg/mL)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Mutation (*Tk*)	Mouse, L5178Y lymphoma cells	(+)	NT	14	Only positive at cytotoxic concentrations	Moore et al. (1988)
Mutation (*Xprt*)	Chinese hamster ovary, CHO-AS52	–	NT	25		Oberly et al. (1993)
Mutation (*Hgprt*)	Chinese hamster ovary, CHO	–	NT	80		Moore et al. (1991)
Mutation (*Hgprt*)	Chinese hamster ovary, CHO	–	NT	18		Moore et al. (1989)
Chromosomal aberrations	Mouse, L5178Y lymphoma cells	(+)	NT	16	Only positive at cytotoxic concentrations	Moore et al. (1988)
Chromosomal aberrations	Chinese hamster ovary, CHO	(+)	NT	14	Only positive at cytotoxic concentrations	Moore et al. (1989)
Micronucleus formation	Chinese hamster ovary, CHO	–	(+)	2109	Only positive at cytotoxic concentrations	Kirpnick et al. (2005)

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

[a] –, negative; (+), positive result in a study of limited quality; the level of significance was set at $P < 0.05$ in all cases

Table 4.3 Genetic and related effects of methyl acrylate in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation (Ames test)	–	–	3 µmol/plate		Florin et al. (1980)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation (Ames test)	–	–	1250 µg/plate		Waegemaekers & Bensink (1984)
Saccharomyces cerevisiae RS112	DEL recombination	(+)	–	500 µg/mL	Significant toxicity (< 5% survival)	Kirpnick et al. (2005)

DEL, deletion; HIC, highest ineffective concentration; LEC, lowest effective concentration

[a] –, negative; (+), positive result in a study of limited quality; the level of significance was set at $P < 0.05$ in all cases

hypoxanthine-guanine phosphoribosyl transferase (*Hgprt*) assay in CHO cells exposed to methyl acrylate (Moore et al., 1989, 1991). At cytotoxic test concentrations with less than 50% cell survival, methyl acrylate induced mutations at the thymidine kinase ($Tk^{+/-}$) locus in L5178Y mouse lymphoma cells without metabolic activation (Moore et al., 1988), and increased the frequency of chromosomal aberrations in CHO cells and L5178Y mouse lymphoma cells in the absence of metabolic activation (Moore et al., 1988, 1989). In CHO cells, methyl acrylate increased the frequency of micronucleus formation at cytotoxic concentrations in the presence but not absence of S9 (Kirpnick et al., 2005).

(iii) Non-mammalian systems

See Table 4.3

In *Saccharomyces cerevisiae*, methyl acrylate significantly increased the frequency of DNA deletions detected in the deletion (DEL) assay in the absence but not the presence of S9, but only at concentrations at which there was less than 5% cell viability (Kirpnick et al., 2005).

Methyl acrylate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538, without or with metabolic activation (Florin et al., 1980; Waegemaekers & Bensink, 1984).

4.2.2 Other mechanisms

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Dose-related atrophy of the neurogenic epithelial cells and hyperplasia were observed in the nasal mucosa of all male and female Sprague-Dawley rats exposed to methyl acrylate by inhalation at concentrations of 0, 15, 45, and 135 ppm for 6 hours per day, 5 days per week, for 24 months (Reininghaus et al., 1991).

4.3 Other adverse effects

4.3.1 Irritancy and sensitization

(a) Humans

Irritation and sensitization after exposure to methyl acrylate have been described, in some cases with complex exposures; positive patch-test responses to methyl acrylate have also been reported (Cavelier et al., 1981; Kanerva et al., 1994; Lammintausta et al., 2010).

(b) Experimental systems

The immunogenicity of methyl acrylate was investigated by determining the induction of immunoglobulin G antibodies in female Hartley guinea-pigs in vivo (Bull et al., 1987). The injection of 0.25 mL of an emulsion of equal volumes of a 20 mM solution of methyl acrylate and Freund's complete adjuvant resulted in the induction of antigen-specific antibodies reactive with methyl acrylate.

Methyl acrylate was determined to be a weak sensitizer (effective concentration required to produce a threefold increase in proliferation of draining lymph node cells compared with control values), EC3, 19.6) in a local lymph node assay in female CBA/Ca mice (Dearman et al., 2007).

5. Summary of Data Reported

5.1 Exposure data

Methyl acrylate is a chemical with a high production volume that is produced worldwide. It is used in the production of acrylic fibres, fire-retardant fabrics, resinous and polymeric coatings and varnishes, adhesives, sealants, and medical and dental prostheses, and as an intermediate in the synthesis of other compounds. Occupational exposure occurs primarily through inhalation and dermal contact during its production and use as an intermediate. One study in a chemical production facility reported concentrations at and above occupational exposure limits. Methyl acrylate may be released into the air and water during its production and use. However, information on concentrations in environmental media and exposure in the general population was not available.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Methyl acrylate was tested for carcinogenicity in one inhalation study in male and female mice, and two inhalation studies in male and female rats.

In one well-conducted inhalation study in rats, the incidence of sarcoma of the soft tissue (of the skin or subcutis, not otherwise specified) and "malignant leukaemic tumours" (leukaemia, lymphoma, and lymphosarcoma) in males was significantly increased with a significant positive trend, and the incidence of adenoma of the pituitary gland in females was significantly increased with a significant positive trend.

In one well-conducted good laboratory practice (GLP) inhalation study in rats, a statistically significant increase in the incidence of squamous cell carcinoma of the nasal cavity in male rats (with a significant positive trend) and in the incidence of squamous cell carcinoma of the nasal cavity in female rats was observed (2/50 treated females compared with 0/650 in female historical controls). In addition, a significant positive trend in the incidence of pheochromocytoma of the adrenal gland (benign or malignant tumours combined) was observed in female rats.

In a well-conducted GLP inhalation study in mice, there was no significant increase in the incidence of any neoplastic lesions in the treated

groups of males and females compared with controls.

5.4 Mechanistic and other relevant data

No data on absorption, distribution, metabolism, or excretion in exposed humans were available. In rodents, methyl acrylate is readily absorbed via all routes of exposure, widely distributed in the body, and excreted mainly as CO_2 in expired air and as mercapturic acid conjugates in the urine. Methyl acrylate is metabolized via hydrolysis by carboxylesterases to acrylic acid and methanol, and subsequent formation of CO_2, as well as via conjugation with glutathione.

With respect to the key characteristics of human carcinogens, adequate data to evaluate methyl acrylate were only available for genetic and related effects. There is *weak* evidence that methyl acrylate is genotoxic. No data were available in exposed humans or human cells in vitro. Methyl acrylate increased the frequency of micronucleus formation in BALB/c mice after intraperitoneal exposure, but not in ddY outbred mice treated by inhalation or oral exposure. In rodent cells in vitro, methyl acrylate did not induce mutations in several studies. Some positive findings were reported for mutation, micronucleus formation, and chromosomal aberrations, but only at cytotoxic concentrations. Similarly, methyl acrylate gave positive results in the yeast DNA deletion assay at cytotoxic concentrations. Further, methyl acrylate gave negative results in the Ames test, both with and without metabolic activation.

In humans, the development of allergic contact dermatitis has been described. Immunogenicity was also shown in studies in rodents.

In the chronic bioassay, nasal toxicity was reported.

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

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

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