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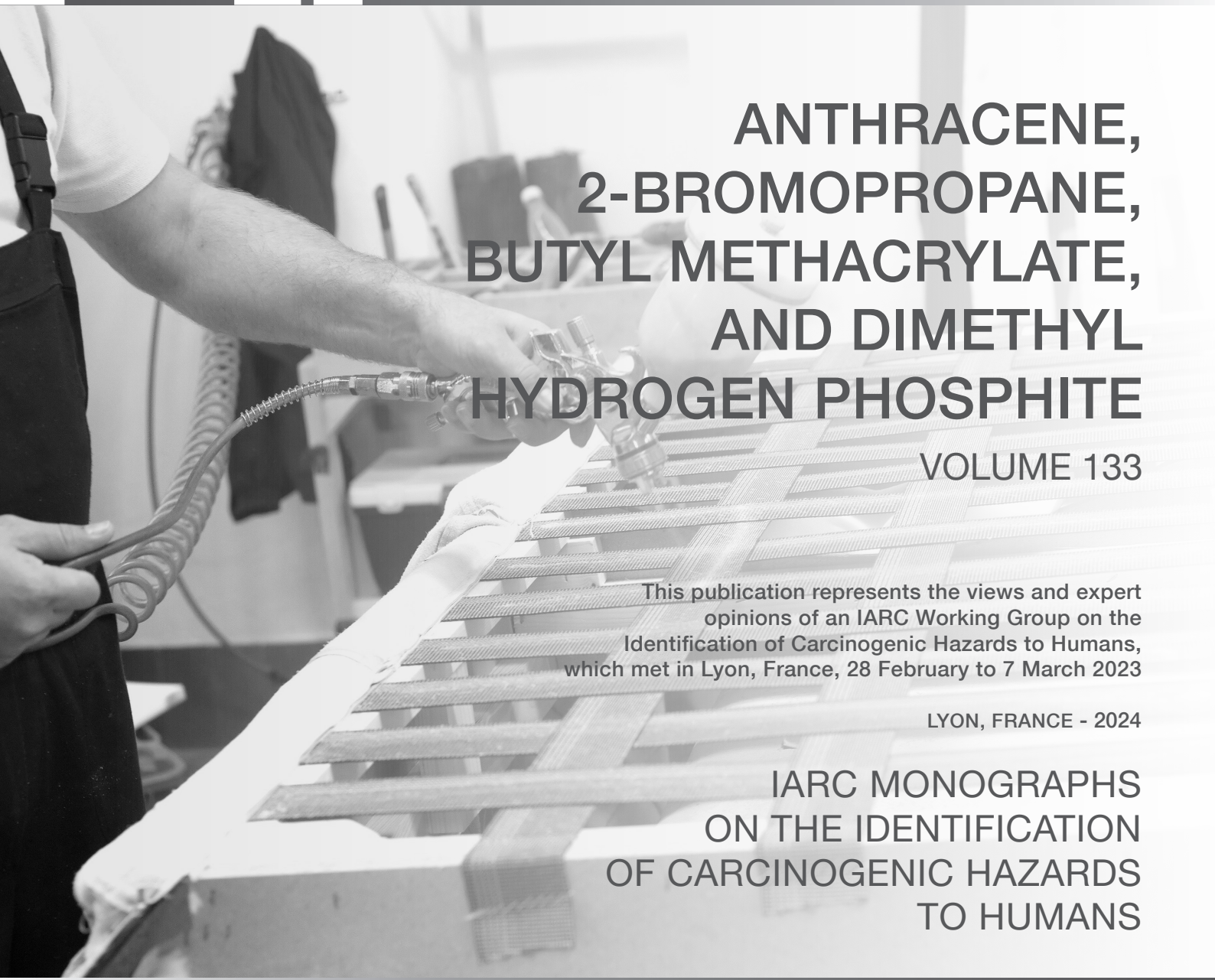

ANTHRACENE, 2-BROMOPROPANE, BUTYL METHACRYLATE, AND DIMETHYL HYDROGEN PHOSPHITE

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International Agency for Research on Cancer

World Health Organization

BUTYL METHACRYLATE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 97-88-1 (NCBI, 2022)

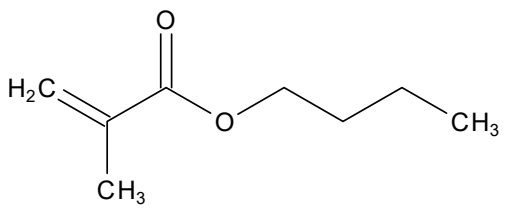
EC/List No.: 202-615-1 (NCBI, 2022)

IUPAC systematic name: butyl 2-methyl-prop-2-enoate (NCBI, 2022)

Synonyms: *n*-butyl methacrylate; butyl 2-methacrylate; 2-methyl-butylacrylate; butyl 2-methyl-2-propenoate; 2-propenoic acid, 2-methyl-, butyl ester; methacrylic acid, butyl ester; *n*BMA (NCBI, 2022).

1.1.2 Structural and molecular information

Chemical structure:



Molecular formula: $C_8H_{14}O_2$ (NCBI, 2022)

Relative molecular mass: 142.20 (NCBI, 2022).

1.1.3 Chemical and physical properties

Description: clear colourless liquid with faint characteristic odour of esters (NCBI, 2022)

Boiling point: 160–163 °C (NCBI, 2022; Royal Society of Chemistry, 2022)

Melting point: –50 to –75.0 °C (NCBI, 2022; Royal Society of Chemistry, 2022)

Flash point: 48.5–52 °C at 101.3 kPa (ECHA, 2022a, IFA, 202 (2)

Density: 0.894 g/mL at 20 °C (NCBI, 2022; Royal Society of Chemistry, 2022)

Vapour pressure: 3 hPa at 20 °C (IFA, 2022)

Solubility: 360 mg/L at 25 °C in water; soluble in ethyl ether and ethanol (ECHA, 2022a; NCBI, 2022)

Octanol/water partition coefficient (P): log K_{ow} = 2.88 (NCBI, 2022; Royal Society of Chemistry, 2022)

Stability: readily polymerized, which can be caused by heat, moisture, or oxidants (NCBI, 2022)

[The Working Group used a conversion factor of 1 ppm ≈ 5.91 mg/m^3 at 20 °C and 1.013 hPa (ECETOC, 1998).]

1.1.4 Technical grade and impurities

Butyl methacrylate of high purity (~99%) is available commercially from several vendors (ECETOC, 1997). Bulk methacrylates are subject to spontaneous polymerization unless a stabilizer is added. Polymerization inhibitors include hydroquinone, monomethyl ether of hydroquinone, or 2-(1,1-dimethylethyl)-4,6-dimethylphenol at 10–100 ppm or a total of < 0.1% by weight (ECETOC, 1998; OECD, 2007).

Typical impurities include methacrylic acid (CAS No. 79-41-4) or methyl methacrylate (CAS No. 80-62-6) (depending on the esterification route used for synthesis), the unreacted butanol, and water (ECETOC, 1998; NCBI, 2022).

1.2 Production and use

1.2.1 Production process

Butyl methacrylate can be manufactured in several ways. One method is via direct esterification of methacrylic acid or transesterification of methyl methacrylate with butanol (ECETOC, 1998; Bauer, 2000). Another method is the catalytic oxidation of isobutylene followed by esterification with butanol. Finally, acetone can be reacted with hydrocyanic acid and esterified in sulfuric acid with butanol (Bisesi, 1994).

1.2.2 Production volume

Butyl methacrylate has been classified by the Organisation for Economic Co-operation and Development as a High Production Volume chemical (OECD, 2007). Companies in China, Germany, Japan, the Republic of Korea, and the USA produce butyl methacrylate, although specific production amounts could not be pinpointed (OECD, 2007; Business Research Insights, 2021). Between 10 000 and 100 000 tonnes per year are manufactured in and/or imported to the European Economic Area (ECHA, 2022b). In the USA, 20 million to < 100 million pounds [~9100–45 000 tonnes] were produced or imported in 2019 (US EPA, 2020).

1.2.3 Uses

Butyl methacrylate is a monomer used to create acrylic polymers and is used in a variety of products worldwide. It is used in coatings, polyvinyl chloride plastics, polypropylene non-woven materials, glues, caulks or other sealants, inks and paints, pesticides, and healthcare materials, among others. The butyl group on the methacrylic ester adds flexibility to the resulting materials. Butyl methacrylate is also used in textile emulsions, leather creation, and paper finishing (ECETOC, 1998; Urban et al., 2006; Gantrade, 2018; Dow, 2020).

These materials are used in a variety of industries. In Denmark, Finland, Norway, and Sweden in 2011–2020, butyl methacrylate was used most frequently in wholesale trade and repair of motor vehicles; the manufacture of other transport equipment, furniture, and non-furniture wood and cork products; and the repair and installation of machinery and equipment (SPIN, 2023). The highest-volume uses in these countries in 2000–2020 were in the manufacture of chemicals and chemical preparations (such as paints, lacquers, varnishes, adhesives, and binders), specialized construction activities, furniture manufacture, repair of machinery and equipment, and wholesale and retail trade and repair of motor vehicles (SPIN, 2023).

Butyl methacrylate monomer has been used to create monolithic columns for gas chromatographic analysis of parabens (Carrasco-Correa et al., 2015). The monomer is used directly in only a few consumer products; it has been included in nail polish, and possibly in nail extension and nail hardener products (Kanerva et al., 1996; Sainio et al., 1997; Cosmetic Ingredient Review Expert Panel, 2005; Ceballos et al., 2019), and in fragrances at an estimated worldwide use of < 1 tonne per year in 2015 (Api et al., 2020). In

addition, some dental products and joint replacement cement may include butyl methacrylate monomer (Cautilli and Hozack, 1994; Urban et al., 2006). Food-grade plastics can contain butyl methacrylate (ECETOC, 1998).

1.3 Detection and quantification

Methodologies for the collection, detection, and quantification of butyl methacrylate in air, water, and consumer products have been developed and used in research. [The Working Group did not identify butyl methacrylate sample collection and analytical methods that have undergone validation by authoritative bodies or consensus organizations.] The characteristic self-polymerization of acrylates, particularly at high temperatures, poses challenges when developing sampling and analysis methods.

1.3.1 Air

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) suggested that National Institute for Occupational Safety and Health (NIOSH) method 1450 (esters I) can be adopted to sample for butyl methacrylate using activated carbon media followed by gas chromatography-flame ionization detection (GC-FID) (ECETOC, 1998).

A few documents and studies describe practical sample collection and analysis of butyl methacrylate. Two older reports described dosing a cartridge with Tenax GC sorbent material for thermal desorption and analysis via GC (US EPA, 1984; ECETOC, 1997). Another report described active sample collection from air using activated charcoal media (NIOSH, 1981). Butyl methacrylate can be analysed in these media via GC or high-performance liquid chromatography (HPLC) and mass spectrometry (MS).

One study evaluated a methodology for sampling and analysis of four methacrylate compounds using activated carbon media, desorbed using carbon bisulfide and analysed using GC-FID; the minimum quantifiable concentration in a 3 L air sample was 0.07 mg/m^3, and samples were stable at room temperatures for at least a week (Rong et al., 2019).

1.3.2 Water

Butyl methacrylate has been measured in aqueous solutions via direct GC or HPLC. Ultraviolet detection has been used after chromatographic separation (ECETOC, 1997). If polymer is present, solvent extraction or headspace analysis should be undertaken first (ECETOC, 1997). The limit of detection (LOD) with a GC-C18 reversed-phase column was reported to be 0.05 mg/L in ecotoxicological tests, although the detector was not reported by ECETOC (1997).

1.3.3 Soil, sediment, and consumer products

Although the Working Group did not identify validated methods for measuring butyl methacrylate in soil, sediments, biosolids, or consumer products, several methods have been developed and used for specific applications. ECETOC suggested that residual monomer in products, aqueous polymer emulsions, or other materials can be analysed using headspace analysis after extraction using a low-volatility solvent (ECETOC, 1997). Residual butyl methacrylate has been measured in water-based polymer emulsions using headspace GC-MS, with an LOD of 1.4 mg/kg (Petha et al., 2017), in dental acrylic resins (LOD, 0.295 µg/mL; Urban et al., 2006), and in food-contact plastics using HPLC after methanol extraction (LOD, 0.03 mg/kg; Qiu et al., 2021). A nail hardener consumer product was analysed for the presence of monomer via GC-MS (Kanerva et al., 1996).

1.3.4 Human biomarkers

The Working Group was not able to identify human biomarkers that have been validated for exposure to butyl methacrylate. HPLC and GC methods have reportedly been used to analyse for the presence of monomer in biological media (in blood, urine, amniotic fluids, liver, and lung tissue) (ECETOC, 1998). [The Working Group noted that specific methodological details were not found in the report from ECETOC (1998).]

HPLC with ultraviolet detection has been used to measure butyl methacrylate and the metabolite methacrylic acid in biological samples (blood, liver) after butyl acetate extraction (Jones, 2002).

1.4 Occurrence and exposure

1.4.1 Occurrence

(a) Air, water, and soil

In 2010–2020 in Japan, estimated releases of butyl methacrylate into the air averaged [5204 kg] and ranged from 9383 kg in 2014 to 2011 kg in 2020 (Japan Ministry of the Environment, 2023). The chemical and warehousing industries reported the largest releases to the atmosphere, and only the chemical industry reported releases to water systems (Japan Ministry of the Environment, 2021). ECETOC reported estimates of environmental releases in 1994 in the European Union (< 0.3 tonnes to air and < 0.15 tonnes to water), but more recent estimates were not identified (ECETOC, 1998). Unreacted butyl methacrylate monomer is not expected to accumulate in environmental media, because of its short half-life in air and water (ECETOC, 1997). In 2011, a Japanese nationwide survey found butyl methacrylate in air samples from 2 of the valid 14 sites, at levels up to 37 ng/m^3 (LOD, 8.7 ng/m^3) (Japan Ministry of the Environment, 2012). Butyl methacrylate was not detected in the surface water of 14 sampled sites (7 rivers, 5 coastal and 2 offshore sites; LOD, 12 ng/m^3). In Japan in 2007, a total of 68 facilities reported butyl methacrylate releases: 67 reported releases in air (total, 4645 kg) and 5 in water (total, 1907 kg) (Japan Ministry of the Environment. 2007). In 2009, the corresponding values for a total of 62 facilities were 62 (total, 3125 kg) and 3 (total, 1703 kg), reporting releases in air and water, respectively (Japan Ministry of the Environment, 2009).

(b) Consumer products and food

Migration of unreacted butyl methacrylate into food from packaging is expected to be low (ECETOC, 1998). One study analysed food-grade plastics for the presence of butyl methacrylate, which was not found above the LOD (0.03 mg/kg) (Qiu et al., 2021).

In a method-development study, residual butyl methacrylate monomer was extracted from acrylic resins used in dental applications using 2 mL of methanol; the mean concentration of extracted monomer from a 100 mg specimen ranged from 160.56 µg/mL to 277.87 µg/mL (Urban et al., 2006).

In 1995 in Finland, butyl methacrylate was detected in small amounts in 6 of 42 [25%] nail polish samples tested; concentrations ranged from 0.014% to 0.067% (Sainio et al., 1997).

1.4.2 Occupational exposure

The exposure routes for butyl methacrylate are via inhalation, dermal exposure, and ingestion. Although the vapour pressure of butyl methacrylate is lower than that of other methacrylates, inhalation is likely to be the primary route of exposure in the workplace, with contributions from dermal exposure and accidental ingestion in some settings. Dermal absorption is likely if skin exposure occurs (ECETOC, 1998).

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 (NIOSH, 1988), workers in

the USA who were potentially exposed to butyl methacrylate were represented in the following industries, from most to least: miscellaneous manufacturing, chemicals and allied products, instruments and related products, machinery, rubber and miscellaneous plastic products, printing and publishing, wholesale trade and durable goods, paper and allied products, special trade contractors, health services, fabricated metal products, and trucking and warehousing (NIOSH, 1983) [10 001 exposed workers were reported; the Working Group estimated a confidence interval of 5400–14 600].

Occupational exposure in air in different jobs and industries is summarized in Table 1.1.

In France, the Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles (INRS) provided butyl methacrylate exposure data for 2000–2020 by industry and occupation (INRS, 2022). The data for the three most studied occupations for butyl methacrylate sampling in these data are included in Table 1.1. The highest single personal exposure measurement (90 mg/m^3) was among equipment operators in the chemical industry in the manufacture of adhesives (INRS, 2022). By industry, the chemical manufacturing industry had the highest mean exposure (n = 26; 14 mg/m^3) (INRS, 2022).

The highest measured concentrations reported were measured in a paint-manufacturing plant in China in 2017, where mean concentrations ranged from 6.7 mg/m^3 in a warehouse to 57.3 mg/m^3 on a reaction line and in inspection (Ding, 2019).

In 1981, stationary measurements were taken while a facsimile machine was running (about 1 hour daily) in an office space where administrative staff worked; concentrations ranged from 0.13 mg/m^3 to 0.29 mg/m^3 and were considered low by the authors of the report (NIOSH, 1981). Exposures to butyl methacrylate have occurred among office and machine repair technicians because of its presence in facsimile machine paper. [The Working Group noted that it is not clear to what extent paper containing butyl methacrylate continues to be used.]

The cross-sectional portion of one study (group B, Raymond, 1996) evaluated butyl methacrylate exposure among facsimile machine repair workers by measuring breathing-zone total particulate; this sampling methodology is not a standard approach and measures a surrogate rather than the specific agent (for analytical methods, see Section 1.3.1). [The Working Group noted that the authors included conflicting data about the composition of facsimile machine fumes; unpublished data indicated that two thirds of machine particulate emitted is butyl methacrylate, but data in an appendix indicated that butyl methacrylate comprises one third of machine particulate. Vapour (gas) exposures were not measured, but the article also provided conflicting information about the butyl methacrylate content of emitted gases. Sales and administrative workers were classified as not exposed, because the machine tasks were not performed in their workplace; it is not clear whether they participated in air monitoring.] In a case series with seven technicians (group A), employees were determined to be exposed given their work as a machine repair technician combined with use of butyl methacrylate-containing paper. In a follow-up with 32 employees (group C), the workers were classified as not exposed (or less exposed), given their work doing some repair tasks (less frequently than technicians in group A and group B) and the gradual discontinuation of acrylate-containing paper. No quantitative exposure assessment was done for group A or group C (Raymond, 1996).

For shipbuilding work in Finland, Engström et al. (1990) measured personal exposures of up to 0.14 mg/m^3 during outfitting work using an epoxyester-based primer.

An ECETOC report contained butyl methacrylate exposure data for full and partial shifts for several tasks at a monomer production facility

Table 1.1 Occupational exposure to butyl methacrylate measured in air samples

Occupational group/job type Location and date	Monitoring method	No. of samples Type of sampling	Analytical method (LOD)	Mean (range) mg/m³	Median (IQR)	Comments	Reference
Monomer production and/or handling							
Monomer production/laboratory City unknown, 1992–1993	NR	NR NR/area	NR (NR)	0.06 (NR)	–	4–8 h	ECETOC (1998)
	NR	NR NR/area	NR (NR)	NR (< 0.5–0.14)	–	5 min to 1 h	
Monomer production/task NR City unknown, 1992	NR	NR Area	NR (NR)	0.4 (NR)	–	4–8 h	ECETOC (1998)
Monomer production/filling City unknown, 1992–1993	NR	NR	NR (NR)	0.05 (NR)	–	4–8 h	ECETOC (1998)
	NR	NR	NR (NR)	NR (ND to < 0.11)	–	5 min to 1 h	
Monomer production/other operations City unknown, 1992–1994	NR	NR	NR (NR)	0.02 (NR)	–	4–8 h	ECETOC (1998)
Polymerization/storage and distribution City unknown, 1992–1994	NR	NR	NR (NR)	0.32 (NR)	–	4–8 h	ECETOC (1998)
Polymerization/block City unknown, 1992–1994	NR	NR	NR (NR)	0.29 (NR)	–	4–8 h	ECETOC (1998)
Polymerization/block City unknown, 1992–1994	NR	NR	NR (NR)	1.49 (NR)	–	5 min to 1 h	ECETOC (1998)
Paint manufacturer/MG[c] reaction line Guangzhou, China, 2017	NR	3 NR	GC (0.1 mg/m³)	34.7 (NR)	–	Duration, NR	Ding (2019)
Paint manufacturer/replacement kettle Guangzhou, China, 2017	NR	3 NR	GC (0.1 mg/m³)	23.8 (NR)	–	Duration, NR	Ding (2019)
Paint manufacturer/emulsification Guangzhou, China, 2017	NR	3 NR	GC (0.1 mg/m³)	43.2 (NR)	–	Duration, NR	Ding (2019)
Paint manufacturer/AC[c] reaction line Guangzhou, China, 2017	NR	3 NR	GC (0.1 mg/m³)	57.3 (NR)	–	Duration, NR	Ding (2019)
Paint manufacturer/inspection Guangzhou, China, 2017	NR	3 NR	GC (0.1 mg/m³)	57.3 (NR)	–	Duration, NR	Ding (2019)
Paint manufacturer/warehouse Guangzhou, China, 2017	NR	3 NR	GC (0.1 mg/m³)	6.7 (NR)	–	Duration, NR	Ding (2019)
Operator of chemical industry devices France, 2010–2020	NR	22 PBZ	NR (NR)	15 (< LOQ[b]–90)	2.0 (< LOQ–23)	Duration, NR	INRS (2022)

Table 1.1 (continued)

Occupational group/job type Location and date	Monitoring method	No. of samples Type of sampling	Analytical method (LOD)	Mean (range) mg/m³	Median (IQR)	Comments	Reference
Non-production workplaces or unknown							
Facsimile machine operation Jamaica, New York, USA, 1981	Activated charcoal tube	5 Area	NR (NR)	0.21 (0.13–0.29)	0.21 (NR)	Partial shift (6 h in total)	NIOSH (1981)
Shipbuilding hull construction City unknown, 1990 or earlier	Amberlite XAD-2 tubes	1 PBZ	GC with FID	0.020	NA	30–60 min	Engström et al. (1990)
Shipbuilding outfitting work City unknown, 1990 or earlier	Amberlite XAD-2 tubes	9 PBZ	GC with FID	NR (NR–0.14)	0.030 (NR)	30–60 min	Engström et al. (1990)
Facsimile machine repair New York, New York, USA, before 1996	NR	1 PBZ	NR (NR)	0.60[a]	NA	6 h	Raymond (1996)
Facsimile machine repair Dallas, Texas, USA, before 1996	NR	NR PBZ	NR (NR)	NR (0.14–0.40)[a]	NR (NR)	128–420 min	Raymond (1996)
Moulder/laminator France, 2000–2020	NR	28 PBZ	NR (NR)	1.6 (< LOQ[b]–37)	0.20 (0.098–0.30)	Duration, NR	INRS (2022)
Operator of an adhesives application device France, 2010–2020	NR	11 PBZ	NR (NR)	3.9 (< LOQ[b]–37)	< LOQ (< LOQ to < LOQ)	Duration, NR	INRS (2022)

FID, flame ionization detection; GC, gas chromatography; h, hour(s); IQR, interquartile range; LOD, limit of detection; LOQ, limit of quantification; min, minute(s); NA, not applicable; ND, not detectable; NR, not reported; PBZ, personal breathing zone.

[a] This measurement was for total particulate, used as a surrogate for butyl methacrylate exposure.

[b] LOQ was not reported for Institut national de recherche et de sécurité (INRS) data.

[c] The meaning of the abbreviations "AC" and "MG" was not available to the Working Group.

and at a polymerization facility. The highest short-term (5 minutes to 1 hour) exposure at the monomer production facility (0.14 mg/m^3) was recorded in a laboratory, and the highest short-term (5 minutes to 1 hour) exposure at the polymerization facility (1.49 mg/m^3) was during block polymerization (ECETOC, 1998).

Peak levels of butyl methacrylate were detected but not quantified during joint implant cement removal during a hip surgery revision and were below the LOD of the method used (0.01 mg/sample) (Cautilli & Hozack, 1994).

[The Working Group noted that exposure assessment data were not found for workers in several industries with known use of butyl methacrylate, such as furniture manufacturing and repair, construction, vehicle repair and manufacturing, and dental care.]

1.4.3 Exposure of the general population

One government report from Japan published estimated exposures for the general population based on butyl methacrylate releases and environmental sampling data in air and water. The report estimated a maximum exposure of 0.32 µg/m^3 based on a plume–puff model and reported releases in 2010 (Japan Ministry of the Environment, 2021). The same report estimated maximum ingestion exposures of 0.00048 µg/kg per day using data for public freshwater sources and 0.0088 µg/kg per day using water discharge data (Japan Ministry of the Environment, 2021).

The general population may be exposed to residual monomer from new dental fillings, food packaging, and cosmetic products (see Section 1.4.1b).

In 2016 and 2017, 18 air samples (personal and static) were collected in 7 nail salons in Boston (USA). Butyl methacrylate was not detected, but ethyl methacrylate and methyl methacrylate were detected with median values of 24 µ/m^3 and 190 µ/m^3, respectively (Ceballos et al., 2019). In a similar study in 17 nail salons in Michigan (USA), butyl methacrylate was not detected in the 68 air samples analysed, but ethyl methacrylate and methyl methacrylate were detected with mean values of 75 µ/m^3 and 4820 µ/m^3, respectively (Zhong et al., 2019).

The Working Group did not identify published data on biomonitoring of butyl methacrylate.

1.5 Regulations and guidelines

1.5.1 Occupational exposure limits

Governments in the following seven countries have established 8-hour time-weighted average occupational exposure limits for butyl methacrylate: Canada, Denmark, Latvia, Norway, Poland, Romania, and Sweden (see Table 1.2). The limits for time-weighted average for an 8-hour workday or a 40-hour workweek range from 30 mg/m^3 in Latvia to 300 mg/m^3 in Sweden. Four of these countries also have short-term exposure limits (for 15 minutes), which range from 250 mg/m^3 to 450 mg/m^3. Under the European Union directive to protect young people, workers younger than 18 years may not be exposed to butyl methacrylate in the workplace, because of the potential for sensitization (ECHA, 2022c).

As of 1998, companies that produce butyl methacrylate have adopted internal occupational exposure limits at or near 50 ppm [296 mg/m^3], with a short-term exposure limit of 75 ppm [443 mg/m^3] (ECETOC, 1998). [The Working Group noted that there are no details available on how the private limits were derived.]

Derived no-effect levels (DNELs) are available for butyl methacrylate and are already used as part of the chemical safety assessment in registration dossiers prepared by registrants under the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation (ECHA, 2022d).

Table 1.2 Occupational exposure limits for butyl methacrylate

Country	8-hour TWA[a] (mg/m³)	Short-term, 15 minutes (mg/m³)	Reference
Latvia	30	Not available	Republic of Latvia (2007)
Norway	59	Not available	Ministry of Labour and Social Inclusion (2022)
Poland	100	300	Central Institute for Labour Protection - National Research Institute (2023)
Denmark	145	290	Labour Supervision (2007)
Romania	150	250	Ministry of Labour and Social Protection (2002)
Canada	290	Not available	WorkSafeBC (2023)
Sweden	300	450	Swedish Work Environment Authority (2018)

TWA, time-weighted average.
[a] Some limits were issued in parts per million. They were converted to mg/m³ using normal temperature and pressure: 20 °C and 101 325 Pa.

1.5.2 Consumer products

In the USA, butyl methacrylate has been identified as an indirect food additive (Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces) as a component of polymeric adhesives, paper, paperboard, and plastics in contact with food; the monomer itself has not been identified as an additive directly to food (US FDA, 2022). The European Food Safety Authority panel on food contact materials, enzymes, flavourings, and processing aids concluded that the intended use of a (butyl acrylate, butyl methacrylate, methyl methacrylate) copolymer in rigid polyvinyl chloride at a maximum level of 1% weight per weight (w/w) and in polylactic acid at a maximum level of 5% w/w is not of safety concern for the consumer (EFSA, 2011). Based on this, the European Commission established that copolymers containing butyl methacrylate, when intended to be used on plastic materials and articles intended to come into contact with food, are limited to be used in rigid polyvinyl chloride at a maximum level of 1% or 2%, depending on the copolymer (European Commission, 2011).

1.6 Quality of exposure assessment in key mechanistic studies in humans

The Working Group reviewed one study in exposed humans. It contained a case series (group A, $n = 7$), a cross-sectional study (group B, $n = 18$), and a follow-up of workers after the product of concern was mostly discontinued, meaning that the butyl methacrylate was eliminated from the facsimile transceiver process (group C, $n = 32$). The small cross-sectional study (group B, $n = 18$) was dedicated to the identification of pulmonary and immunological changes among a subset of facsimile machine repair workers (group A) (Raymond, 1996). Details on the exposure assessment are summarized in Table S1.3 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/631), and exposure levels are described in Section 1.4.2 and Table 1.1.

1.6.1 Exposure assessment methods

Group A: Exposure was determined by job role as a facsimile machine repair technician concurrent with use of acrylate-containing paper and reported exposure to facsimile machine fumes during testing. The facsimile paper used

was made with butyl methacrylate polymer and emitted butyl methacrylate when it was "burned" during facsimile receipt or testing. No specific information about the paper and ingredients was provided. The duration and number of repairs was described to be proportional to symptom intensity, according to informal, non-systematic reporting from patients.

Group B: In this study, workers were identified as exposed ($n = 6$) if they worked as facsimile machine repair technicians and unexposed ($n = 12$) if they worked as administration or sales personnel for the same company in a separate building 2 miles [3.2 km] away.

For the repair technicians, a surrogate for butyl methacrylate exposure was measured through breathing-zone sampling of particulate in air during machine repair and testing. Particle sampling and analysis by gravimetry was used as a surrogate for butyl methacrylate exposure. The particles were sampled during 2.4–7 hours in the breathing zone during machine repair and testing. The results were presented as a time-weighted average. The article cited unpublished data suggesting that fresh facsimile particulate emissions contained about two thirds butyl methacrylate and vapour emissions contained about one third butyl methacrylate. However, a table in the appendix presented data showing the opposite (that emitted particulate contained one third butyl methacrylate and emitted vapours contained two thirds butyl methacrylate). [The Working Group noted that this inconsistency adds further difficulty to interpreting the non-specific air measurements.] Emitted fumes and vapours also contain smaller amounts of ethane, propane, butane, and other unidentified compounds (called "miscellaneous" by the authors). Vapour phase was not sampled in this study, probably resulting in exposure underestimation. A questionnaire was presented to workers to ask about symptoms, age, and smoking status, but it did not cover work-related information (e.g. machine repair and testing performed) or non-occupational exposure sources. The authors did not report demographics for the exposed and unexposed groups separately but reported that they had similar age and smoking status. Mechanical ventilation conditions available were listed (e.g. ventilation rate and availability of local exhaust ventilation) but were not considered or discussed further.

For the unexposed control group, it is unclear whether they were included in the air monitoring campaign (reported as background monitoring) or whether exposure was assumed to be zero. They worked in a building 2 miles [3.2 km] from the machine repair site, and the workers reported having little contact with those activities, so they were likely to be correctly classified as unexposed.

Group C: This group had less-frequent exposure to machine emissions, because their duties were broader than machine repair and testing. In addition, workers' exposures to emissions containing butyl methacrylate decreased in frequency as use of acrylate-containing paper was discontinued and phased out as machines came in for repair. However, residual exposure to low levels still occurred during the testing of machines because some contained the discontinued paper.

1.6.2 Quality of exposure assessment methods

The quality of exposure assessment for butyl methacrylate in this study was only moderate for the workers in group B and was poor for group A and group C. The primary limitation is the use of particle sampling and analysis by gravimetry as a surrogate for butyl methacrylate exposure, rather than characterization and measurement of butyl methacrylate directly in both fume and vapour fractions. In Section 1.3, several possible methods for measuring butyl methacrylate are described. Although butyl methacrylate had been found in air samples in previous studies where facsimile machine operation occurred, the

approach followed in this study does not enable an evaluation of the exposure to butyl methacrylate or an identification of other fume and vapour emission components (NIOSH, 1981). No exposure measurements were taken after the acrylate-containing paper had been discontinued, although residual butyl methacrylate exposure may have occurred because of the use of older machines and residual acrylate-containing paper stock. Another limitation was the lack of information about the variability of exposures within and between workers across shifts and/or job tasks. A single measurement was taken for each worker and was used in subsequent linear regression.

Exposures for group C were the least detailed, because the description was anecdotal and exposure was changing during this follow-up. No details were provided about the frequency or the magnitude of exposures, so the workers cannot be classified as exposed or unexposed.

Overall, the exposure assessment was useful to understand that there was likely to be butyl methacrylate exposure during facsimile machine repair (particularly for group A and group B), but with high uncertainties about the magnitude of exposures (in particulate and vapour forms) and the mixtures of chemicals present in the emissions.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

Studies of carcinogenicity in mice and rats exposed to butyl methacrylate were limited to inhalation studies conducted by the Japan Bioassay Research Center (JBRC, 2018a, b, c, d; also reported by Furukawa et al., 2023). The results of these studies are summarized in Table 3.1.

3.1 Mouse

In a well-conducted study of chronic toxicity and carcinogenicity that complied with Good Laboratory Practice (GLP), groups of 50 male and 50 female B6D2F$_1$/Crl mice (age, 6–7 weeks) were treated with butyl methacrylate (purity, > 99.8%) by inhalation with whole-body exposure for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2018a, b; also reported by Furukawa et al., 2023). The concentration in the exposure chambers was set to 0 (clean air, control), 8, 30, or 125 ppm for males and females and was monitored every 15 minutes. The mean air concentrations were the target values, and the coefficients of variation were within 1.3%. At week 104, the survival rates of males at 8 and 125 ppm were lower than those of the control group. Survival at study termination was 45/50, 35/50, 41/50, and 37/50 for males and 36/50, 32/50, 33/50, and 33/50 for females at 0 (control), 8, 30, and 125 ppm, respectively. Body-weight gain of male mice at the highest concentration was significantly decreased from week 3 of exposure until week 82, compared with controls. The relative final body weight in males was 102%, 103%, and 100% of the control value at 8, 30, and 125 ppm, respectively. Food consumption of male mice at the highest concentration was significantly decreased from week 3 of exposure until week 102, compared with the control value. Body-weight gain of female mice at the highest concentration was significantly decreased from week 3 of exposure until week 70, compared with controls. The relative final body weight in females was 102%, 101%, and 100% of the control value at 8, 30, and 125 ppm, respectively. Food consumption of female mice at the highest concentration was significantly decreased from week 1 of exposure until week 70, compared with the control value. All mice underwent complete

Table 3.1 Studies of carcinogenicity in mice and rats exposed to butyl methacrylate

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence (%)	Significance	Comments
Full carcinogenicity Mouse, B6D2F$_1$/Crl (M) 6–7 wk 104 wk JBRC (2018a)	Inhalation (whole-body exposure) Purity, ≥ 99.8% Air 0, 8, 30, 125 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 45, 35, 41, 37	*Liver* Hepatocellular adenoma 23/50 (46%), 27/50 (54%), 30/50 (60%), 24/50 (48%)	$P = 0.0255$, Peto trend test, standard method NS, Peto trend test, prevalence method NS, Peto trend test, combined analysis NS, Cochran–Armitage trend test	*Principal strengths*: well-conducted GLP study; covered most of lifespan; males and females used; multiple concentrations used; adequate number of animals per group. *Other comments*: lower survival in low-dose and high-dose group. *Historical controls*: hepatocellular adenoma, 20.1% (range, 8–36%); histiocytic sarcoma (all sites), 7.8% (2–12%) (reported by Furukawa et al., 2023).
		Hepatocellular carcinoma 12/50 (24%), 13/50 (26%), 16/50 (32%), 10/50 (20%)	NS	
		Hepatocellular adenoma or carcinoma (combined) 32/50 (64%), 33/50 (66%), 41/50 (82%)*, 31/50 (62%)	*$P = 0.0352$, Fisher exact test NS, Peto trend test, standard method NS, Peto trend test, prevalence method NS, Peto trend test, combined analysis NS, Cochran–Armitage trend test	
		All sites Histiocytic sarcoma 0/50, 1/50 (2%), 1/50 (2%), 3/50 (6%)	$P = 0.0219$, Peto trend test, standard method $P = 0.0393$, Peto trend test, combined analysis NS, Peto trend test, prevalence method NS, Cochran–Armitage trend test	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence (%)	Significance	Comments
Full carcinogenicity Mouse, B6D2F$_1$/Crl (F) 6–7 wk 104 wk JBRC (2018a)	Inhalation (whole-body exposure) Purity, ≥ 99.8% Air 0, 8, 30, 125 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 36, 32, 33, 33	*Pituitary gland* Adenoma: anterior lobe 3/50 (6%), 1/50 (2%), 4/50 (8%), 6/50 (12%) *All sites* Haemangiosarcoma 1/50 (2%), 2/50 (4%), 2/50 (4%), 4/50 (8%)	P = 0.0439, Peto trend test, combined analysis NS, Peto trend test, standard method NS, Peto trend test, prevalence method NS, Cochran–Armitage trend test P = 0.0318, Peto trend test, prevalence method NS, Peto trend test, standard method NS, Peto trend test, combined analysis NS, Cochran–Armitage trend test	*Principal strengths*: well-conducted GLP study; covered most of lifespan; males and females used; multiple concentrations used; adequate number of animals per group. *Historical controls*: adenoma of the anterior lobe of the pituitary gland, 12.8% (range, 4–20%); haemangiosarcoma (all sites), 3% (range, 0–6%) (reported by Furukawa et al. (2023).
Full carcinogenicity Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2018d)	Inhalation (whole-body exposure) Purity, ≥ 99.8% Air 0, 30, 125, 500 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 41, 36, 28	*Spleen* Mononuclear cell leukaemia 8/50 (16%), 8/50 (16%), 11/50 (22%), 14/50 (28%) *Subcutis* Fibroma 4/50 (8%), 5/50 (10%), 3/50 (6%), 6/50 (12%)	P = 0.0050, Peto trend test, standard method P = 0.0146, Peto trend test, combined analysis NS, Peto trend test, prevalence method NS, Cochran–Armitage trend test P = 0.0264, Peto trend test, standard method NS, Peto trend test, prevalence method NS, Peto trend test, combined analysis NS, Cochran–Armitage trend test	*Principal strengths*: well-conducted GLP study; covered most of lifespan; males and females used; multiple concentrations used; adequate number of animals per group. *Other comments*: lower survival in high-dose group. *Historical controls*: mononuclear cell leukaemia of the spleen, 61/649 (9.4%; range, 4–14%); fibroma of the subcutis, 75/649 (11.6%; range, 6–16%); interstitial cell tumour of the testis, 531/649 (81.8%; range, 72–98%).

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence (%)	Significance	Comments
Full carcinogenicity Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2018d) (cont.)		*Testis* Interstitial cell tumour, benign 43/50 (86%), 48/50 (96%), 44/50 (88%), 48/50 (96%)	*P* = 0.0316, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis; NS, Cochran–Armitage trend test	
Full carcinogenicity Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2018d)	Inhalation (whole-body exposure) Purity, ≥ 99.8% Air 0, 30, 125, 500 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 39, 38, 37, 37	*Mammary gland* Fibroadenoma 6/50 (12%), 4/50 (8%), 6/50 (12%), 9/50 (18%)	*P* = 0.0349, Peto trend test, prevalence method NS, Peto trend test, standard method NS, Peto trend test, combined analysis NS, Cochran-Armitage trend test	*Principal strengths*: well-conducted GLP study; covered most of lifespan; males and females used; multiple concentrations used; adequate number of animals per group. *Historical controls*: fibroadenoma of the mammary gland, 75/650 (11.5%; range, 6–20%); C-cell adenoma or C-cell carcinoma (combined) of the thyroid gland, 84/650 (12.9%; range, 2–26%).
		Thyroid C-cell adenoma 4/50 (8%), 3/50 (6%), 9/50 (18%), 6/50 (12%)	NS	
		C-cell carcinoma 0/50, 0/50, 2/50 (4%), 2/50 (4%)	NS	
		C-cell adenoma or carcinoma (combined) 4/50 (8%), 3/50 (6%), 11/50 (22%)*, 8/50 (16%)	**P* = 0.0453, Fisher exact test NS, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis NS, Cochran–Armitage trend test	

F, female; GLP, Good Laboratory Practice; h, hour(s); M, male; NS, not significant; ppm, parts per million; wk, week(s).

necropsy, and all organs and tissues were examined microscopically.

In male mice, there was a significant positive trend in the incidence of hepatocellular adenoma of the liver (P = 0.0255, Peto trend test, standard method); the incidence of 23/50 (46%), 27/50 (54%), 30/50 (60%), and 24/50 (48%) for the groups at 0 (control), 8, 30, and 125 ppm, respectively, exceeded the upper bound of the range observed in historical controls (average, 20.1%; range, 8–36%) from this laboratory at all doses. [The Working Group noted that several Peto trend tests were conducted in this study; the Peto test standard method was referred to as death analysis, the Peto test prevalence method was referred to as incidental tumour test, and the Peto test combined analysis was referred to as death analysis plus incidental tumour test. A significant P value in any Peto test was considered relevant for the detection of treatment-related increases in tumour incidence. The Working Group also noted that the mouse strain and the diet used in this study were different from those in historical controls. In this study, the laboratory changed the mouse strain from the previous strain ($B6D2F_1$/Crlj) to $B6D2F_1$/Crl, using a new production system (International Genetic Standardization), even though the two strains are similar. In addition, a low-protein diet was used instead of the diet previously used in the studies comprising historical controls.] The incidence of hepatocellular adenoma or carcinoma (combined) of the liver of 32/50 (64%), 33/50 (66%), 41/50 (82%), and 31/50 (62%) for the groups at 0 (control), 8, 30, and 125 ppm, respectively, was significantly increased (P = 0.0352, Fisher exact test) in the group at 30 ppm compared with controls. [The Working Group considered that the lack of a significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) at the highest concentration may be due to the suppression of body-weight gain during the experimental period.] There was a significant positive trend in the incidence of histiocytic sarcoma of all sites (including the subcutis, liver, epididymis, or peritoneum) (P = 0.0219, Peto trend test, standard method; P = 0.0393, Peto trend test, combined analysis); the incidence of 0/50, 1/50 (2%), 1/50 (2%), and 3/50 (6%) for the groups at 0 (control), 8, 30, and 125 ppm, respectively, was within the range observed in historical controls (average, 7.8%; range, 2–12%) from this laboratory.

In female mice, there was a significant positive trend in the incidence of adenoma of the anterior lobe of the pituitary gland (P = 0.0439, Peto trend test, combined analysis); the incidence of 3/50 (6%), 1/50 (2%), 4/50 (8%), and 6/50 (12%) for the groups at 0 (control), 8, 30, and 125 ppm, respectively, was within the range observed in historical controls (average, 12.8%; range, 4–20%) from this laboratory for the intermediate and highest dose. [The Working Group noted that neither the incidence of carcinoma nor the incidence of hyperplasia in the anterior lobe of the pituitary gland was significantly increased.] There was a significant positive trend in the incidence of haemangiosarcoma of all sites (including the spleen, subcutis, liver, uterus, bone marrow, peritoneum, or retroperitoneum) (P = 0.0318, Peto trend test, prevalence method); the incidence of 1/50 (2%), 2/50 (4%), 2/50 (4%), and 4/50 (8%) for the groups at 0 (control), 8, 30, and 125 ppm, respectively, exceeded the upper bound of the range observed in historical controls (average, 3.0%; range, 0–6%) from this laboratory at the highest concentration.

There were no increases in the incidence of the non-neoplastic lesions in sites where tumour incidence was considered increased. [The Working Group noted this was a well-described and well-conducted study that complied with GLP, used multiple concentrations, used both sexes, used an adequate number of animals per group, and had an adequate duration of exposure and observation.]

3.2 Rat

In a well-conducted study of chronic toxicity and carcinogenicity that complied with GLP, groups of 50 male and 50 female F344/DuCrlCrlj rats (age, 6–7 weeks) were treated with butyl methacrylate (purity, > 99.8%) by inhalation with whole-body exposure for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2018c, d; also reported by Furukawa et al., 2023). The concentration in the exposure chambers was set to 0 (clean air, control), 30, 125, or 500 ppm for males and females and was monitored every 15 minutes. The mean air concentrations were the target values, and the coefficients of variation were within 1.0%. At 104 weeks, the survival rate of males at the highest concentration was lower than that of the control group. Survival at study termination was 38/50, 41/50, 36/50, and 28/50 for males and 39/50, 38/50, 37/50, and 37/50 for females at 0 (control), 30, 125, and 500 ppm, respectively. Body-weight gain of male rats at the highest concentration was significantly decreased in the early exposure period and from week 70 to the end of the study, compared with controls. The relative final body weight in males was 99%, 99%, and 94% of the control value for 30, 125, and 500 ppm, respectively. Food consumption of male rats at the highest concentration was significantly decreased from week 78 of exposure until week 98, compared with the control value. Body-weight gain of female rats at the highest concentration was significantly decreased in the early exposure period and from week 42 to the end of the study, compared with controls. The relative final body weight in females was 98%, 104%, and 92% of the control value at 30, 125, and 500 ppm, respectively. Food consumption of female rats at the highest concentration was significantly decreased from week 62 of exposure until week 102, compared with the control value. All rats underwent complete necropsy, and all organs and tissues were examined microscopically.

In male rats, there was a significant positive trend in the incidence of mononuclear cell leukaemia of the spleen (P = 0.0050, Peto trend test, standard method; P = 0.0146, Peto trend test, combined analysis); the incidence of 8/50 (16%), 8/50 (16%), 11/50 (22%), and 14/50 (28%) for the groups at 0 (control), 30, 125, and 500 ppm, respectively, exceeded the upper bound of the range observed in historical controls (average, 9.4%; range, 4–14%) from this laboratory at all doses. [The Working Group noted that several Peto trend tests were conducted in this study; the Peto test standard method was referred to as death analysis, the Peto test prevalence method was referred to as incidental tumour test, and the Peto test combined analysis was referred to as death analysis plus incidental tumour test. A significant P value in any Peto test was considered relevant for the detection of treatment-related increases in tumour incidence.] There was a significant positive trend in the incidence of fibroma of the subcutis (P = 0.0264, Peto trend test, standard method); the incidence of 4/50 (8%), 5/50 (10%), 3/50 (6%), and 6/50 (12%) for the groups at 0 (control), 30, 125, and 500 ppm, respectively, was within the range observed in historical controls (average, 11.6%; range, 6–16%) from this laboratory. There was a significant positive trend in the incidence of benign interstitial cell tumour of the testis (P = 0.0316, Peto trend test, prevalence method); the incidence of 43/50 (86%), 48/50 (96%), 44/50 (88%), and 48/50 (96%) for the groups at 0 (control), 30, 125, and 500 ppm, respectively, was within the range observed in historical controls (average, 81.8%; range, 72–98%) from this laboratory. [The Working Group noted that interstitial cell tumour is a common spontaneous tumour with a high incidence in Fischer 344 rats.]

In female rats, there was a significant positive trend in the incidence of fibroadenoma of the mammary gland (P = 0.0349, Peto trend test, prevalence method); the incidence of 6/50 (12%), 4/50 (8%), 6/50 (12%), and 9/50 (18%) for

the groups at 0 (control), 30, 125, and 500 ppm, respectively, was within the range observed in historical controls (average, 11.5%; range, 6–20%) from this laboratory. The incidence of C-cell adenoma or carcinoma (combined) of the thyroid gland of 4/50 (8%), 3/50 (6%), 11/50 (22%), and 8/50 (16%) for the groups at 0 (control), 30, 125, and 500 ppm, respectively, was significantly increased (P = 0.0453, Fisher exact test) in the group at 125 ppm compared with controls. The incidence of C-cell adenoma or carcinoma (combined) of the thyroid gland was within the range observed in historical controls (average, 12.9%; range, 2–26%) from this laboratory.

For both male and female mice, there were no increases in the incidence of non-neoplastic lesions at sites at which tumour incidence was considered to be increased. [The Working Group noted that this was a well-described and well-conducted study that complied with GLP, used multiple concentrations, used both sexes, used an adequate number of animals per group, and had an adequate duration of exposure and observation.]

3.3 Evidence synthesis for cancer in experimental animals

The carcinogenicity of butyl methacrylate has been assessed in one well-conducted inhalation study that complied with GLP in male and female B6D2F$_1$/Crl mice (JBRC, 2018a, b; also reported by Furukawa et al., 2023) and in one well-conducted inhalation study that complied with GLP in male and female F344/DuCrlCrlj rats (JBRC, 2018c, d; also reported by Furukawa et al., 2023).

In the inhalation study that complied with GLP in male and female B6D2F$_1$/Crl mice, there was a significant positive trend in the incidence of hepatocellular adenoma of the liver in males. The incidence of hepatocellular adenoma or carcinoma (combined) of the liver was significantly increased in males at 30 ppm. There was a significant positive trend in the incidence of histiocytic sarcoma of all sites. In female mice, there was a significant positive trend in the incidence of adenoma of the anterior lobe of the pituitary gland. There was a significant positive trend in the incidence of haemangiosarcoma of all sites (JBRC, 2018a, b; also reported by Furukawa et al., 2023).

In the inhalation study that complied with GLP in male and female F344/DuCrlCrlj rats, there was a significant positive trend in the incidence of mononuclear cell leukaemia of the spleen in males. There was a significant positive trend in the incidence of fibroma of the subcutis and of benign interstitial cell tumour of the testis. In female rats, there was a significant positive trend in the incidence of fibroadenoma of the mammary gland. The incidence of C-cell adenoma or carcinoma (combined) of the thyroid gland was significantly increased in the group at 125 ppm compared with controls (JBRC, 2018c, d; also reported by Furukawa et al., 2023).

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

Data on absorption of butyl methacrylate in humans were limited to one study that used human epidermis samples in an in vitro system (Jones, 2002). *n*-Butyl methacrylate (100 µL/cm^2) was absorbed through the epidermis, with a mean rate of absorption of 76.7 µg/cm^2 per hour and a total amount absorbed of 2% over a 24-hour period. Data on distribution, metabolism, and excretion of butyl methacrylate in humans were not available to the Working Group.

4.1.2 Experimental systems

(a) Absorption

An in vitro system using Wistar rat epidermis and whole (viable) Fischer 344 rat skin was used to evaluate absorption of *n*-butyl methacrylate [butyl methacrylate] in the skin (Jones, 2002). *n*-Butyl methacrylate (100 µL/cm^2) was absorbed through the skin. The rat epidermis was about 20 times as permeable as the human epidermis. The mean rate of absorption and the total amount absorbed were 1540 µg/cm^2 per hour and 18% over 24 hours, respectively, for Wistar rat epidermis and 40.9 µg/cm^2 per hour and 0.4% over 10 hours, respectively, for Fischer 344 rat skin. [Based on the study by Jones (2002), the difference in absorption between whole rat skin and epidermis may be attributable to first-pass hydrolysis of butyl methacrylate in the dermis, which was excised from the epidermis in the other absorption tests (rat and human). First-pass hydrolysis could be expected to be lower in human skin than in rat skin. The study reported that for whole rat skin absorption, methacrylic acid but not butyl methacrylate was detected in the receptor chamber and suggested that all the compound absorbed underwent first-pass metabolism in the skin. However, the Working Group considered that this hypothesis was not corroborated by enough evidence. In addition, the Working Group noted that the exact dose applied on the epidermis in the rat study was not clearly reported.]

(b) Distribution

White outbred male rats intraperitoneally injected with 6.7 mmol/kg body weight of radiolabelled butyl methacrylate ([1-^{14}C-butyl] methacrylate) showed radioactivity in the liver, kidney, heart, brain, and plasma, with the highest levels in the liver and kidney and the lowest levels in the brain (Svetlakov et al., 1989). The highest levels of radioactivity were reached in 2 hours and were sustained for 12 hours. [The Working Group noted that the strain of rat was not given.]

(c) Metabolism

ECHA (2022b) reported that *n*-butyl methacrylate [butyl methacrylate] is rapidly hydrolysed by carboxylesterases found in tissues. The half-life of *n*-butyl methacrylate was about 8 minutes, and 99.7% was removed by first-pass metabolism in the rat liver. Butyl methacrylate was completely metabolized to methacrylic acid in the rat skin (Jones, 2002). [The Working Group noted that it is unclear which reference(s) in ECHA (2022b) were used for these data.]

Kotlovskiĭ et al. (1985, 1987, 1988) conducted a series of studies investigating the effects of butyl methacrylate on liver microsomes from rats. Butyl methacrylate interacted with the haemoprotein of liver microsomes obtained from white outbred male rats, with an absorption maximum at 388 nm and minimum at 421–425 nm. [The Working Group noted that the rat strains were not reported.] Butyl methacrylate also stimulated oxygen consumption by liver microsomes (Kotlovskiĭ et al., 1985). In liver microsomes obtained from phenobarbital-induced rats, cytochrome P450 was inactivated only in the presence of butyl methacrylate and NADPH (nicotinamide adenine dinucleotide phosphate, reduced form), but butyl methacrylate alone did not inactivate cytochrome P450. Inactivation of P450 did not occur in vivo. [The Working Group noted that the rat strains were not reported.] A minor subfraction (48 kD) of microsomal protein was reduced by butyl methacrylate (Kotlovskiĭ et al., 1987). [The Working Group noted that the molecular weight standard was used, but no positive control was mentioned and no western blot images were shown.] In liver microsomes isolated from control Wistar rats, butyl methacrylate was hydrolysed to butanol at a rate of 55 ± 11 nmol butanol/1 mg protein per minute (Kotlovskiĭ et al., 1988). [The Working Group noted that sex was not mentioned.] The enzymatic nature of

the alcohol formation reaction was confirmed by the fact that preliminary incubation of rat liver microsomes at 100 °C for 3 minutes prevented the appearance of butanol. [The Working Group noted that the strain of rat was mentioned only in the 1988 study.]

[The Working Group acknowledged that methacrylic acid is a possible metabolite of butyl methacrylate; however, there is not enough evidence to show the metabolic pathway of methacrylic acid in mammalian species in vivo.]

4.2. Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether butyl methacrylate is genotoxic; induces oxidative stress; or induces chronic inflammation. No data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is genotoxic

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Three studies in experimental systems were available to the Working Group (Waegemaekers & Bensink, 1984; Zeiger et al., 1987; Fediukovich et al., 1988).

Waegemaekers & Bensink (1984) assessed the mutagenicity of 27 acrylate esters, including butyl methacrylate, in the *Salmonella* microsome assay. None of these acrylate esters were mutagenic in the standard Ames assay with TA1535, TA1537, TA1538, TA98, and TA100, both with and without Aroclor 1254-induced or phenobarbital-induced S9 microsomes mix.

Zeiger et al. (1987) reported the results and data from the testing of 255 chemicals for their ability to induce mutations in *Salmonella*. All chemicals were tested, in the presence or absence of liver S9 microsomes from Aroclor-induced male Sprague-Dawley rats and Syrian hamsters, in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and/or TA97. The test result for butyl methacrylate was negative.

Fediukovich et al. (1988) reported that butyl methacrylate failed to induce chromosomal aberrations in rat bone marrow cells. The lack of chromosomal aberrations in vivo suggests that butyl methacrylate does not induce changes in chromosome structure or number.

In the European Chemicals Agency (ECHA) brief profile (ECHA, 2022a), butyl methacrylate is listed as negative regarding genetic toxicity because no adverse effects were observed in vitro or in vivo. [The Working Group had no access to original studies from the profile summary, only to the ECHA conclusion. Overall, the Working Group concluded that the studies available do not support the genotoxicity of butyl methacrylate.]

4.2.2 Induces oxidative stress

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

One study in vitro was available to the Working Group (McCarthy et al., 1994). In this study, the reactivity of several acrylates with glutathione was investigated (reactivity with deoxyribonucleosides was tested only for ethyl acrylate) using glutathione or rat erythrocytes followed by the measurement of free thiol. In the cell-free system, butyl methacrylate did not react with glutathione. Butyl methacrylate was not tested in erythrocytes. [The Working Group noted that the decreased reactivity of methacrylates may be due to a combination of electronic and steric factors introduced by the α-methyl group. The

quality of the study was considered acceptable. This study did not support the hypothesis that butyl methacrylate induces oxidative stress.]

4.2.3 Induces chronic inflammation

(a) Humans

One original study in exposed humans (Raymond, 1996) and one review article on methyl methacrylate and respiratory sensitization (Borak et al., 2011), which also mentioned butyl methacrylate, were available to the Working Group.

Raymond (1996) reported results of a case-series study and a cross-sectional study in technicians repeatedly exposed to facsimile machine fumes and suggested a link between exposure to butyl methacrylate-bearing facsimile fumes and inflammation. In the cross-sectional study, all technicians who had daily contact with facsimile machine fumes (0.14–0.40 mg/m^3 of air) had increased serum immunoglobulin E (IgE) levels (mean ± standard error of the mean, 202 ± 69 U/mL; normal, < 41 U/mL) compared with administrative and sales staff members. IgE and fume levels were positively correlated (r = 0.83). In addition, exposure to fumes caused lung crackles in four of six technicians who were evaluated, whereas the technicians who were not exposed had no crackles. [The Working Group noted that the crackles suggested that butyl methacrylate fumes may have caused inflammation in terminal airway units.] In the case-series study, respiratory reactions and increased levels of blood immunoglobulins (IgE, IgM) among workers with repeated exposure to such airborne emissions of facsimile machine fumes were reported. Exposed workers reported sore throat, fever, lymphadenopathy, chest tightness, dry cough, and dyspnoea, which improved after reassignment. Although chest radiographs were normal, some workers had lung crackles and spirometric abnormalities. Reassignment away from the exposure was followed by improvement of most abnormalities. In a follow-up observation after withdrawal of butyl methacrylate-containing paper, 15 of 32 technicians had increased serum concentrations of total IgE at the time of their initial evaluation. A full set of four serial IgE determinations was available in 10 of these 15 technicians; the final mean value after 21 months of follow-up was lower than both the initial mean and the maximal value ($P < 0.05$).

[The Working Group noted that, because of its limited volatility, butyl methacrylate was associated with a low inhalation toxicity to the lung; however, when it is used as a component of electrosensitive paper, as in the facsimile process, butyl methacrylate could be given off as a fume.] Fume concentrations were evaluated gravimetrically; however, the levels of butyl methacrylate were not evaluated. [The Working Group noted that the authors referred to a previous, unpublished analysis of these emissions from the facsimile machines, which had shown that butyl methacrylate comprised about one third of the vapour phase and more than two thirds of the particulate phase of freshly generated fumes. However, this was considered insufficient to determine exposure variability, because no exposure monitoring specific to butyl methacrylate was performed (see also the exposure assessment review and critique in Section 1, Table S1.3, in Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/631). The Working Group also noted that the study by Raymond (1996) had several limitations, as also discussed by the authors, including a small number of exposed subjects and no pre-exposure physical examinations.]

Methyl methacrylate is a respiratory irritant and dermal sensitizer, whereas its respiratory sensitization potential remains controversial; occupational asthma has been reported in a small number of case reports (Borak et al., 2011). Concerning butyl methacrylate, in the review of Borak et al. (2011), a case study of occupational

asthma and allergic rhinitis due to xerographic toner was reported (Wittczak et al., 2003). The case involved a female secretary aged 44 years who had a 2-year history of rhinorrhoea, dyspnoea, and coughing attacks that occurred 15–20 minutes after making photocopies using xerographic toner containing "polystyrene-*n*-butyl methacrylate, polystyrene-*n*-butyl acrylate, etc.".

[The Working Group noted that these studies may suggest the involvement of butyl methacrylate in the chronic lung inflammatory response under certain circumstances, because health conditions improved after workers were reassigned. However, no evidence of unresolved inflammation supporting persistence of the effect was reported.]

(b) Experimental systems

The Japan Bioassay Research Center conducted 13-week dose-finding inhalation toxicity studies (JBRC, 2015a, b, c, d) of butyl methacrylate in mice and rats for a 104-week carcinogenicity study.

In a dose-finding study for a carcinogenicity test, groups of 10 male and 10 female B6D2F$_1$/Crlj mice (age, 6–7 weeks) were treated with butyl methacrylate (purity, 99.8%) by inhalation with whole-body exposure for 6 hours per day, 5 days per week, for 13 weeks, at concentrations of 0 (clean air, control), 31, 63, 125, 250, and 500 ppm (JBRC, 2015a, b).

After a 13-week exposure period, one male mouse exposed to 31 ppm accidently died. In histopathology, there was no significant increase in findings suggesting chronic inflammation, whereas regeneration, atrophy, necrosis and eosinophilic change of olfactory epithelium, respiratory metaplasia of gland, and eosinophilic change of respiratory epithelium of nasal cavity were observed in male and female mice exposed to 500 ppm. Similar alterations were found to decrease in male mice exposed to 63 ppm and female mice exposed to 31 ppm.

In a dose-finding study for a carcinogenicity test, groups of 10 male and 10 female F344/DuCrlCrlj rats (age, 6–7 weeks) were treated with butyl methacrylate (purity, 99.8%) by inhalation with whole-body exposure for 6 hours per day, 5 days per week, for 13 weeks, at concentrations of 0 (clean air, control), 63, 125, 250, 500, and 1000 ppm (JBRC, 2015c, d). There was a significant decrease in absolute and relative weights of the thymus in the group of male rats exposed to 1000 ppm. In histopathology, there was no significant increase in findings suggesting chronic inflammation, whereas epithelial cell degeneration and regeneration in response to stimulation of the nasal cavity were observed. Inflammation of the nasal cavity was observed in a small number of females, but it was not statistically significant compared with controls. [The Working Group noted that in well-conducted studies in experimental animals, butyl methacrylate has shown some nasal irritation (eosinophilic change) and alterations of nasal epithelium, which, however, did not result in a tumour in the nasal cavity in 104-week carcinogenicity studies of mice and rats. See also Sections 3.1 and 3.2.]

4.3 Evaluation of high-throughput in vitro toxicity screening data

Butyl methacrylate was tested in high-throughput toxicity screening assays under the Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Thomas et al., 2019). Chemical samples were procured at high purity, prepared in dimethyl sulfoxide stock solutions at a concentration of about 20 mM, and tested over a period of several years in biochemical and cellular bioassays measuring a wide variety of biological end-points. In addition, chemical analysis of the samples was done in high-throughput fashion at an early and a late stage of the sample testing lifetime, as

described in Tice et al. (2013). Data on testing results from the concentration–response testing design for all end-points were analysed for significant activity, and an active/inactive "hit call" was made for each response, together with a potency value (Filer et al., 2017). For all active calls, individual concentration–response curves were examined to ensure that biologically meaningful activity was detected. Bioassay end-points were mapped, where possible, to the key characteristics of carcinogens using the "kc-hits" software (the key characteristics of carcinogens – high-throughput screening discovery tool, available from https://gitlab.com/i1650/kc-hits; Reisfeld et al., 2022) to aid in providing mechanistic insights (Chiu et al., 2018). The detailed results are available in the supplementary material for this volume (Annex 2, Supplementary material for Section 4, Evaluation of high-throughput in vitro toxicity screening data, online only, available from: https://publications.iarc.who.int/631) and are briefly summarized below.

The testing results for butyl methacrylate high-throughput toxicity in the CompTox Chemicals Dashboard encompassed 235 assay end-points, of which 111 were mapped to the key characteristics of carcinogens. The cytotoxicity limit based on a panel of cellular cytotoxicity and viability assays was estimated to be > 1 mM (US EPA, 2022). Only 4 of the mapped end-points indicated positive results, and all were flagged with multiple curve-fitting warnings. [The Working Group did not consider these to be biologically relevant responses.]

The analysis of a stock solution of butyl methacrylate in dimethyl sulfoxide showed the presence of the parent compound at both an early and a late time point in the solution lifetime, although the concentration was listed as 5–30% of expected (NIH, 2022).

5. Summary of Data Reported

5.1 Exposure characterization

Butyl methacrylate is a High Production Volume chemical that is used to create polymers in a variety of products worldwide. It is used in coatings, polyvinyl chloride plastics, polypropylene non-woven materials, glues, caulks or other sealants, inks and paints, pesticides, and health-care materials, among others.

Occupational exposures may occur in the manufacture of chemicals (including butyl methacrylate); the manufacture of paints, coatings, adhesives, and plastics; construction; furniture manufacturing; textile manufacturing; printing and publishing; maritime vessel repair; health and dental care; and personal-care services. The highest exposures were found in paint and adhesive manufacturing. Exposure can occur via all routes, but inhalation is considered the most significant. Seven countries have established limits for occupational exposure to butyl methacrylate in air. Exposure of workers younger than 18 years is restricted in the European Union. Biomonitoring methodologies have not been established.

For the general population, exposure can occur via contaminated air and water, via food contained in butyl methacrylate-containing plastics, and in personal-care and health-care products. Butyl methacrylate has been measured in nail polishes and lacquers and in dental and joint replacement polymers. However, few exposure measurement data for the general population were available. A limit on the migration of methacrylate acids into food from plastic containers has been set by the European Commission.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Treatment with butyl methacrylate caused an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in two species (mouse and rat).

Butyl methacrylate was administered by inhalation in one study that complied with Good Laboratory Practice in male and female B6D2F_1/Crl mice. In males, butyl methacrylate caused an increase in the incidence of hepatocellular adenoma or carcinoma (combined) of the liver and histiocytic sarcoma of all sites. In females, butyl methacrylate caused an increase in the incidence of haemangiosarcoma of all sites.

Butyl methacrylate was administered by inhalation in one study that complied with Good Laboratory Practice in male and female F344/DuCrlCrlj rats. In males, butyl methacrylate caused an increase in the incidence of mononuclear cell leukaemia of the spleen. In females, butyl methacrylate caused an increase in the incidence of C-cell adenoma or carcinoma (combined) of the thyroid gland.

5.4 Mechanistic evidence

The available data on absorption, metabolism, and excretion of butyl methacrylate in humans are scarce. Only one study on the absorption of butyl methacrylate in humans was available; this study demonstrated dermal absorption in human epidermis samples in an in vitro system. Skin absorption was shown in one in vitro study using epidermis and whole skin of rats. Butyl methacrylate was distributed to the liver, kidney, heart, brain, and plasma of rats. Butyl methacrylate was shown to be hydrolysed to butanol in rat liver microsomes in one study and to methacrylic acid in a second study in rat skin in vitro. No studies on the excretion of butyl methacrylate in rodents were available.

Few mechanistic data were available for butyl methacrylate regarding the key characteristics of carcinogens "is genotoxic", "induces oxidative stress", and "induces chronic inflammation".

There were no mechanistic studies in humans with exposure specifically attributable to butyl methacrylate only.

Regarding genotoxicity, butyl methacrylate did not induce chromosomal aberrations in rat bone marrow cells. In addition, butyl methacrylate gave negative results for gene mutagenicity in the presence and absence of metabolic activation in two well-conducted studies using the Ames assay with various *Salmonella typhimurium* strains.

Butyl methacrylate did not induce oxidative stress in one study in a cell-free system in which butyl methacrylate did not react with glutathione.

There was one study in workers repeatedly exposed for up to 18 months to facsimile machine fumes containing butyl methacrylate; it showed increased levels of blood immunoglobulins (IgE, IgM) and respiratory symptoms (sore throat, chest tightness, dry cough, and dyspnoea). After task reassignment or substitution of butyl methacrylate-free paper, the levels of IgE decreased but remained higher than normal levels. In addition, there was evidence of inflammation in one report of occupational asthma and rhinitis after exposure to facsimile machine fumes. These data could indicate the involvement of butyl methacrylate in chronic lung inflammation.

No data were available regarding butyl methacrylate and the other key characteristics of carcinogens.

Butyl methacrylate was found to be mostly without effects relevant to the key characteristics of carcinogens in the assay battery of the Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA,

although the butyl methacrylate testing solution was considered problematic for use in high-throughput assays.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of butyl methacrylate.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of butyl methacrylate.

6.3 Mechanistic evidence

There is *inadequate* mechanistic evidence.

6.4 Overall evaluation

Butyl methacrylate is *possibly carcinogenic to humans (Group 2B).*

6.5 Rationale

The Group 2B evaluation for butyl methacrylate is based on *sufficient evidence* for cancer in experimental animals. The *sufficient evidence* for cancer in experimental animals is based on an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in males and females of two species (rat and mouse) in two studies that complied with Good Laboratory Practice. The evidence regarding cancer in humans was *inadequate*, because no studies were available. There was also *inadequate* mechanistic evidence.

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