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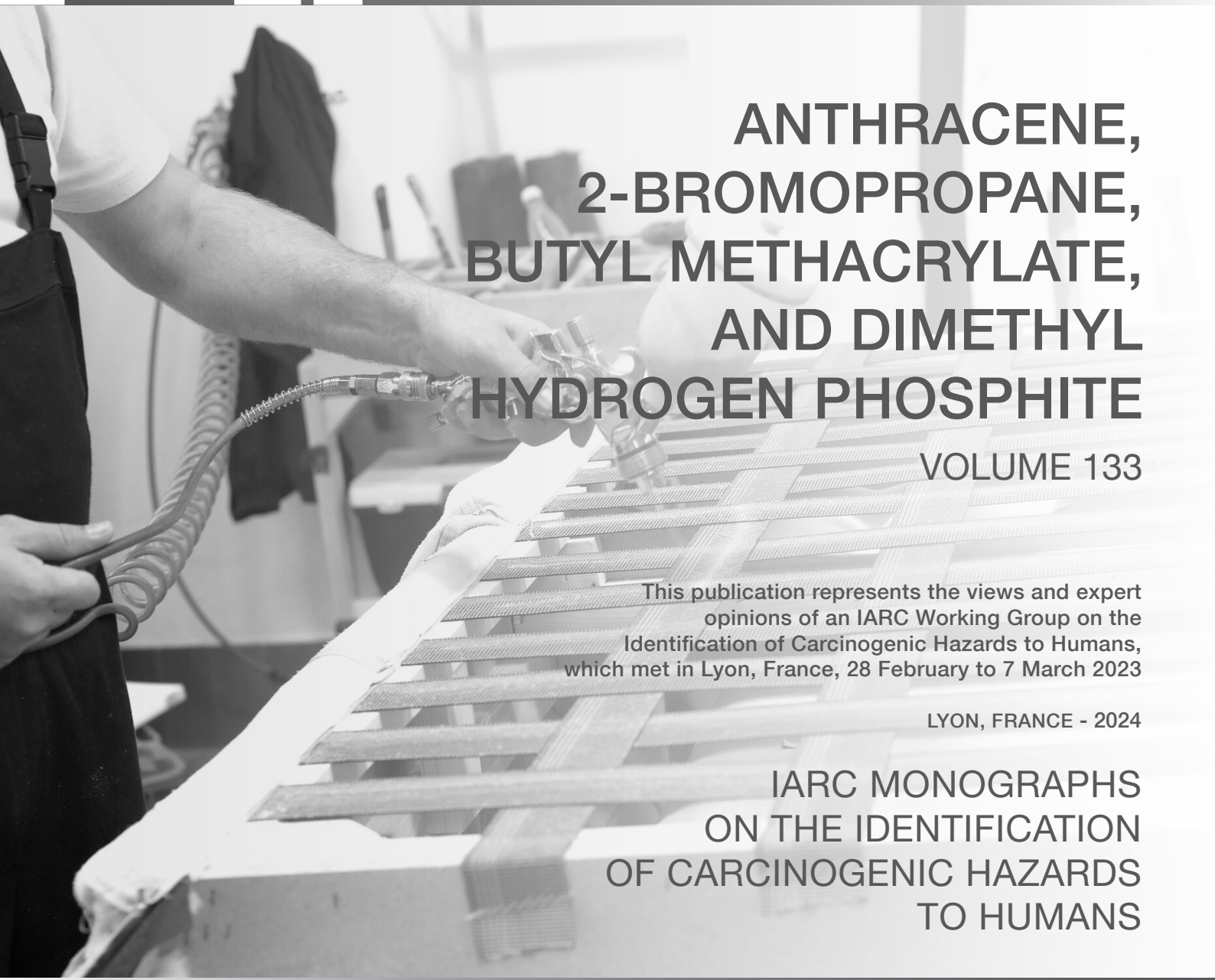

ANTHRACENE, 2-BROMOPROPANE, BUTYL METHACRYLATE, AND DIMETHYL HYDROGEN PHOSPHITE

VOLUME 133

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International Agency for Research on Cancer

World Health Organization

2-BROMOPROPANE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 75-26-3 (NCBI, 2022)

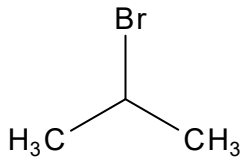
EC/List No.: 200-855-1 (NCBI, 2022)

IUPAC systematic name: 2-bromopropane (NCBI, 2022)

Synonyms: isopropyl bromide; propane, 2-bromo-; 1-bromo-1-methylethane; 2-BP (NCBI, 2022).

1.1.2 Structural and molecular information

Chemical structure:



Molecular formula: C_3H_7Br (NCBI, 2022)

Relative molecular mass: 122.99 (NCBI, 2022).

1.1.3 Chemical and physical properties

Description: clear colourless to slightly yellow liquid (NCBI, 2022)

Boiling-point: 59–60 °C (Royal Society of Chemistry, 2022; NCBI, 2022)

Melting-point: –89 to –92 °C (Royal Society of Chemistry, 2022; ECHA, 2022b; NCBI, 2022)

Flash-point: 19–20 °C at 101.3 kPa (Royal Society of Chemistry, 2022; ECHA, 2022b; NCBI, 2022)

Density: 1.31 g/mL at 20 °C (Royal Society of Chemistry, 2022; NCBI, 2022)

Vapour pressure: 26 kPa at 20 °C (ECHA, 2022b)

Solubility: 3.18 g/L at 20 °C in water; miscible with alcohol, benzene, chloroform, and ether (Royal Society of Chemistry, 2022; NCBI, 2022)

Octanol/water partition coefficient (P): log K_{ow} = 2.14 (Royal Society of Chemistry, 2022; NCBI, 2022)

Stability: 2-Bromopropane is not expected to undergo direct photolysis in the environment because it lacks functional groups that absorb light at wavelengths greater than 290 nm (NCBI, 2022).

[The Working Group used a conversion factor of 1 ppm ≈ 5.03 mg/m^3 at 25 °C (NTP, 2003).]

1.1.4 Impurities

2-Bromopropane of high purity (≥ 99%) is available commercially (NCBI, 2022).

Two studies in Asia reported on impurities associated with 2-bromopropane. In a plant in the Republic of Korea, the purity of 2-bromopropane used was 97.4% and impurities included *n*-heptane (0.33%), 1,2-dibromopropane (0.2%), and 1,1,1-trichloroethane (0.01%) (Park et al., 1997). In a plant in China, the reported purity of 2-bromopropane was 98.08% and impurities consisted of 2-propanol (isopropyl alcohol) (1.76%), dibromopropane (0.085%), benzene (0.055%), and trichloroethylene (0.010%) (Ichihara et al., 1999).

In the above-mentioned plant in the Republic of Korea, a mixture of two 2-bromopropane-containing solutions was used. SPG-6AR contained 60.7% of 2-bromopropane, 33% of *n*-heptane, and 1.55% of 1.1.1-trichloroethane; other chemicals, such as 1,2-dibromopropane and nitromethane, were detected at a level below 1%. Solvent 5200, used for cleaning, contained 99.1% of 2-bromopropane, 0.2% of 1,2-dibromopropane, and impurities at a level below 1% (Kim et al., 1996a; Park et al., 1997).

1.2 Production and use

1.2.1 Production process

2-Bromopropane is synthesized by heating 2-propanol together with hydrogen bromide (Ichihara et al., 1999; NCBI, 2022) and also occurs as an impurity of commercial-grade 1-bromopropane, historically at concentrations of 0.1–0.2% (IARC, 2018). In the American Society for Testing and Materials standards for 1-bromopropane used in vapour degreasing, 2-bromopropane is listed as an impurity at a maximum of 0.1% by weight (ASTM, 2000), but the standard was updated in 2018 to a maximum of 0.05% by weight (ASTM, 2018). [The Working Group noted that for other uses of 1-bromopropane, such as adhesives, no maximum level of 2-bromopropane impurity in 1-bromopropane has been set.]

1.2.2 Production volume

Production volumes for 2-bromopropane were reported to be < 1 000 000 pounds/year [< 450 tonnes/year] from 2016 to 2019 in the USA (US EPA, 2022). Manufactured and/or imported quantities of 2-bromopropane were 1 to < 1000 tonnes/year in Japan between 2012 and 2020, except for 1000–2000 tonnes in 2014 (NITE, 2023). [The Working Group could not identify any national production volume data outside of Japan and the USA. However, at least 13 manufacturers in China are known (ChemicalBook, 2023a), and one manufacturer in China reported a production volume of 2000 tonnes in 2015 (Jiangsu JiuLi Environmental Technology Co., Ltd, 2015).]

1.2.3 Uses

2-Bromopropane has been reported to be used in the synthesis of pharmaceuticals as an alkylating agent, and as an intermediate for dyes, pesticides, and other chemicals (Lewis, 2001; ChemicalBook, 2023b; ECHA 2023). [The Working Group was not able to identify for which specific pharmaceuticals 2-bromopropane is used in the synthesis.] Also, 2-bromopropane was used as a solvent to replace Freon 113 in an electronic component manufacturing factory in the Republic of Korea (Park et al., 1997). The average monthly use as a solvent was reported as 1301 kg (range, 750–2500 kg) from February 1994 to July 1995 (KOSHA, 1995). [The Working Group noted that no information was available on the locations of continuing use of 2-bromopropane.]

1.3 Detection and quantification

1.3.1 Air

2-Bromopropane can be determined in air samples using National Institute for Occupational Safety and Health (NIOSH) method 1025. The method uses a solid sorbent tube for sampling 2-bromopropane at 0.01–0.2 L/min, followed by quantitative analysis with gas chromatography-flame ionization detection (GC-FID). This method is linear over a wide range of concentrations (4.5–393 µg/sample), with a limit of detection (LOD) of 1 µg/sample (NIOSH, 2003a). The United States Occupational Safety and Health Administration (OSHA) published a validated method for analysis of 2-bromopropane in air samples using charcoal tubes and personal sampling pumps to collect 12 L air samples, followed by analysis with GC-electron capture detection (GC-ECD). The method's limit of quantification (LOQ) for 2-bromopropane is 1.8 ppb [9.2 µg/m^3] (OSHA, 2013).

1.3.2 Water

No data on 2-bromopropane analysis in water samples were available to the Working Group.

1.3.3 Consumer products

Because of its wide use in synthesis of pharmaceuticals, sensitive methods have been developed for analysis of 2-bromopropane impurities in bulk drugs. A GC-mass spectrometry (GC-MS) method was reported for determination of 2-bromopropane impurities in divalproex sodium (an anticonvulsant medication), with an LOQ of 5 ng/mL (Reddy et al., 2019). More recently, GC-MS/MS was applied to measure 2-bromopropane impurities in abiraterone acetate, which is used to treat prostate cancer, with an LOQ of 60 ng/mL (Zhong et al., 2022).

1.3.4 Human biomarkers

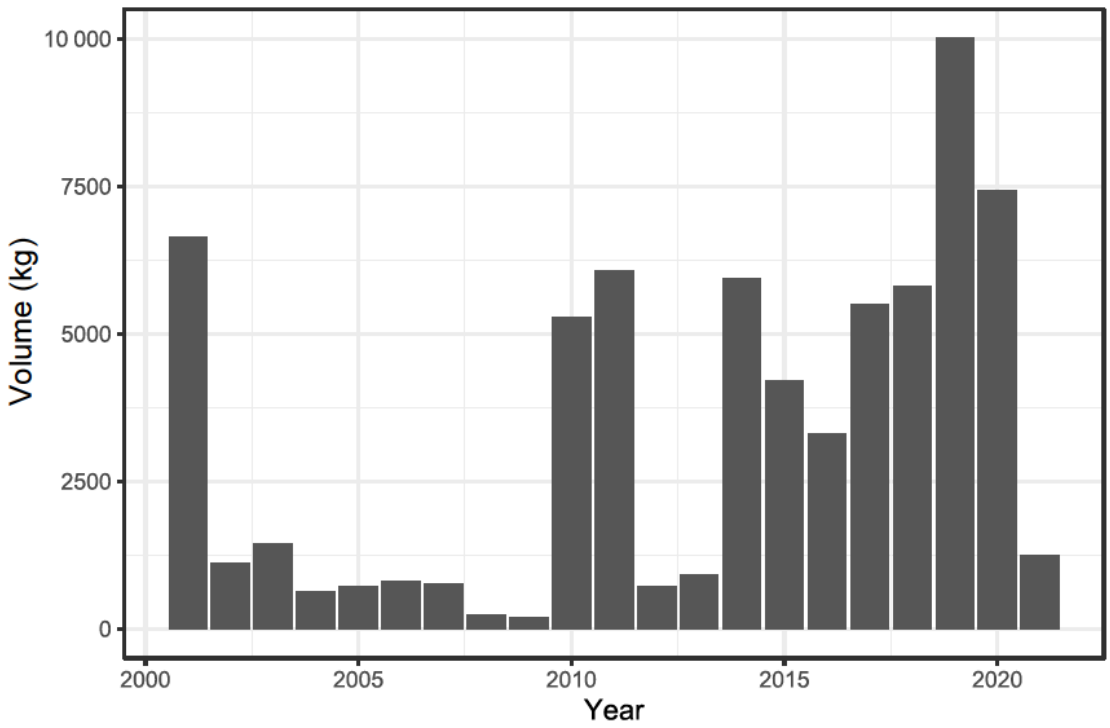
2-Bromopropane and its potential metabolites acetone and 2-propanol were determined in human and rat urine using a GC-FID method with LODs of 0.01, 0.05, and 0.10 µg/mL for 2-bromopropane, acetone, and 2-propanol, respectively (Kawai et al., 1997). A more sensitive method was reported for analysis of 2-bromopropane in human urine with headspace GC-ECD. The method was linear over a wide range of concentrations (0.03–12.5 µg/mL), with an LOD of 7 ng/mL (B'Hymer & Cheever, 2005). Column-switching liquid chromatography-tandem mass spectrometry (CSLC-MS/MS) was successfully applied for determination of isopropyl mercapturic acid, as a biomarker of 2-bromopropane exposure, in human urine samples. This rapid method was linear over a wide range of concentrations up to 2500 µg/L, with an LOD of 2.5 ng/mL (Eckert & Göen, 2014).

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

In Japan, the total release volume of 2-bromopropane into the environment was estimated to be 189–10 007 kg/year in 2001–2021 (Fig. 1.1). Almost all were air emissions (Japan Ministry of the Environment, 2023). In Japan, 2-bromopropane measurements in 13 and 19 air samples were below the LODs (0.17 and 0.20 µg/m^3, respectively) in 1998–1999 and 1997–1998, respectively. Measurements in six samples each from rivers and the sea were all below the LOD (0.01 µg/L) in 1997 (Japan Ministry of the Environment, 2005). No quantitative information on occurrence of 2-bromopropane in drinking-water, food, or consumer products was available to the Working Group.

Fig. 1.1 Release of 2-bromopropane into the environment in Japan between 2001 and 2021



Source: Japan Ministry of the Environment (2023).

1.4.2 Occupational exposure

The NIOSH National Occupational Exposure Survey (NOES) of 1981–1983 estimated that about 1582 chemists were potentially exposed to 2-bromopropane in the USA (NIOSH, 1983). [The Working Group estimated a confidence interval of 1029–2135 exposed workers. This estimate did not include workers potentially exposed to 2-bromopropane because of its presence as an impurity of 1-bromopropane.]

Occupational exposure to 2-bromopropane can occur via inhalation and/or dermal uptake (NCBI, 2022). Several studies have quantified 2-bromopropane in the air of workplace settings (Table 1.1). The geometric mean ambient concentration of 2-bromopropane in a workshop staffed with five workers in an integrated circuits parts factory in Japan was 3 mg/m^3. The workers were engaged in soldering of integrated circuits parts on the boards in which 2-bromopropane was applied by an automated process. There was no skin contact with liquid 2-bromopropane. One worker who was responsible for the operation of the machine for cleaning with 2-bromopropane, and checked the machine operation frequently, had the highest exposure. Personal air sampling was not carried out (Kawai et al., 1997).

After the reports of haematopoietic and reproductive disorders among workers using 2-bromopropane as a solvent in an electronics factory in the Republic of Korea (as detailed in Section 4.2), the use of 2-bromopropane was stopped. The mean duration of exposure was 10.1 months (range, 4–16 months) for the 15 women with primary ovarian failure. To characterize the workers' exposure, sampling was performed under simulated conditions. Stationary 3-hour

concentrations of 2-bromopropane ranged from 9.2 to 19.6 ppm [46.3–98.6 mg/m³]. Three short-term (23-minute) air monitoring measurements in the enclosure around the cleaning baths were performed at different heights above the cleaning solution and resulted in concentrations of 4359.5, 105.9, and 4140.9 ppm [21 928, 533, and 20 829 mg/m³] (details of the workers' tasks and exposures are described in Section 1.6) (KOSHA, 1995; Park et al., 1997). [The Working Group noted that the assessment under simulated conditions may have resulted in underestimated values of exposure.] Because of a lack of personal protective equipment and hand-dipping practices, dermal exposure to 2-bromopropane was likely but was not quantified (Kim et al., 1996b).

A study of 2-bromopropane exposure was conducted at a factory manufacturing the chemical in Yixing City, Jiangsu Province, China, in 1996 (Ichihara et al., 1999). The factory had been producing 2-bromopropane at a rate of 5 tonnes/year since 1991. Production did not take place in the month of August every year, because of solvent evaporation at high summer temperatures. The study included 25 workers (11 male and 14 female) at the plant (employed for an average of ~2.5 years) who had time-weighted average (TWA) concentrations of 2-bromopropane exposure measured using personal passive samplers. Measurements were carried out in December; the room temperature was 10.5 °C, and the windows were half-open. [The Working Group noted that the exposures were probably lower at the time of the measurement compared with other times of the year.] Personal passive samplers were attached to each worker for one 8-hour daytime shift. Ambient concentrations of 2-bromopropane were also measured in the breathing zone of workers with detection tubes in four process-specific areas of the factory. Interviews with workers were also conducted to ascertain information on job tasks and exposure opportunities during work shifts. The TWA 2-bromopropane exposure concentration ranged from below the LOD (0.2 ppm [1.0 mg/m³]) to 5.84 ppm [29.4 mg/m³] among male workers and from below the LOD to 16.18 ppm [81.4 mg/m³] among female workers. The 10 female workers and one male worker with the job tasks of operator (n = 9) and mixer (n = 2) had the highest median 2-bromopropane concentrations [6.77 ppm; 34.1 mg/m³] and [6.30 ppm; 31.7 mg/m³], respectively and were reported to spend almost their entire shift inside the factory. All female workers at this factory were non-smokers. Workers in non-production jobs [71% male], such as boilers, accountants, salespeople, and managers, had non-detectable levels of exposure (except one accountant). The median instantaneous ambient concentrations of 2-bromopropane measured in the breathing zones of the process areas were 4.0 ppm [20.1 mg/m³] (range, 2.5–17.2 ppm [12.6–86.5 mg/m³]) for observing the temperature of reaction pots, 27.6 ppm [139 mg/m³] (range, 8.2–90.9 ppm [41.2–457 mg/m³]) for pouring distilled product into plastic containers, 38.8 ppm [195 mg/m³] (range, 17.6–57.6 ppm [88.5–290 mg/m³]) for mixing product with sodium hydrogen carbonate, and 88.6 ppm [446 mg/m³] (range, 19.8–110.8 ppm [99.6–557 mg/m³]) for pouring processed product into drums. The analysis of the 2-bromopropane produced showed 98.08% volume per volume (v/v) purity.

NIOSH performed 10 studies measuring exposure to 1-bromopropane, which also measured exposure to 2-bromopropane alongside 1-bromopropane, because of the presence of 2-bromopropane as an impurity in the material being used (Table 1.1). Exposures were evaluated among workers at furniture and adhesive manufacturing companies, where exposures originated from the adhesives being used or manufactured. Exposures were also evaluated at companies where 2-bromopropane exposure was being measured as a result of impurities in solvents used during degreasing operations. In 1998, at an aircraft cushion manufacturing plant

Table 1.1 Occupational exposure to 2-bromopropane measured in air samples

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
Machine operation/ machine cleaning with 2-BP, integrated circuits parts factory Japan, 1995	Ambient workplace air	5 (different sites in the workshop)	GC-FID (0.01 µg/mL)	3 mg/m³ (GM), 1.47 mg/m³ (GSD) (NR)	NR		Kawai et al. (1997)
Tactile switch assembly operation section, electronics factory Republic of Korea, 1995	Ambient workplace air (simulated setting)	14 (stationary samples near each cleaning bath, for 3 h) 3 short-term (15-min) samples inside the hood of each cleaning bath	GC-MS (NR)	Stationary samples: 12.4 ppm (9.2–12.6 ppm) [62.4 mg/m³ (46.3–98.6 mg/m³)] Short-term samples: 4140.7 ppm [20 828 mg/m³] (NR)	NR NR		KOSHA (1995); Park et al. (1997)
2-BP production factory China, 1996	Ambient workplace air, personal monitor	24	GC-EID (0.2 ppm [1.0 mg/m³] TWA)	Breathing zone samples (short-term): Observing the temperature of reaction pots: (2.5–17.2 ppm) [(12.6–86.5 mg/m³)] Pouring distilled product into plastic containers: (8.2–90.9 ppm) [(41.2–457 mg/m³)] Mixing product with sodium hydrogencarbonate: (17.6–57.6 ppm) [(88.5–290 mg/m³)]	4.0 ppm [20.1 mg/m³] 27.6 ppm [139 mg/m³] 38.8 ppm [195 mg/m³]	Duration of exposure: 5–69 months. Breathing zone sampling in ambient air was performed with detector tubes. Personal sampling was performed with passive samplers.	Ichihara et al. (1999)

Table 1.1 (continued)

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
2-BP production factory China, 1996 (cont.)				Pouring processed product into drums: (19.8–110.8 ppm) [(99.6–557 mg/m³)]	88.6 ppm [446 mg/m³]		Ichihara et al. (1999) (cont.)
				Personal samples (8-h TWA):			
				Operator (n = 9): (4.09–16.18 ppm) [(20.6–81.4 mg/m³)]	[6.77 ppm] [34.1 mg/m³]		
				Mixer (n = 2): (5.84–6.76 ppm) [(29.4–34.0 mg/m³)]	[6.30 ppm] [31.7 mg/m³]		
				Laboratory (n = 1): (NA)	[2.87 ppm] [14.4 mg/m³]		
				Repair (n = 2): (0.95–1.20 ppm) [(4.78–6.04 mg/m³)]	[1.08 ppm] [5.41 mg/m³]		
				Boiler (n = 2) : (< 0.2–0.80 ppm) [(< 1.0–4.02 mg/m³)]	[< 0.42 ppm] [< 2.1 mg/m³]		
				Other (white collar) (n = 7): (< 0.2–0.88 ppm) [(< 1.0–4.43 mg/m³)]	[< 0.2 ppm] [< 1.0 mg/m³]		

Table 1.1 (continued)

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
Adhesive use in aircraft cushion manufacturing plant North Carolina, USA, 1998	Personal monitoring (full-shift, short-term)	6930 full-shift TWA 11 area samples	GC-FID (1.0 µg/sample)	Overall: 0.14 ppm (< 0.01–0.55 ppm) [0.70 mg/m³ (< 0.05–2.77 mg/m³)]	NR	Adhesive containing low concentrations of 2-BP. Assembly sprayers and assemblers and covers workers worked directly with the adhesive formulations.	NIOSH (2002a)
				Assembly department: 0.30 ppm (0.10–0.55 ppm) [1.51 mg/m³ (0.50–2.77 mg/m³)]	NR		
				Covers department: 0.06 ppm (0.02–0.11 ppm) [0.30 mg/m³ (0.10–0.55 mg/m³)]	NR		
		12 short-term (15-min) samples among sprayers		Assembly department: [0.27 ppm] (0.2–0.4 ppm) [1.36 mg/m³ (1.0–2.0 mg/m³)] Covers department: NR (ND–0.1 ppm) [(ND–0.5 mg/m³)]	[1.26 mg/m³]		
Radio frequency and microwave communications component manufacturing plant, parts degreasing Indiana, USA, 2000	Personal air monitoring	20 full-shift TWA from 6 departments 2 short-term samples of several 1–5-min tasks for multiple workers	GC-FID (0.004 ppm [0.020 mg/m³] MDC for full-shift samples; 0.06 ppm [0.30 mg/m³] MDC for task-based samples)	Full-shift: all ND Task: all ND		Monitoring conducted after ventilation installation. Degreaser with possible 2-BP impurity. 20 workers sampled for 1 full shift each. Task samples combined 5 or 6 workers doing 1–5-minute tasks at degreaser.	NIOSH (2001)
	Stationary air monitoring	7	GC-FID (0.004 ppm [0.020 mg/m³] MDC)	1 sample 0.02 ppm [0.10 mg/m³], 6 samples ND			

Table 1.1 (continued)

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
Adhesive use in furniture cushion manufacturing company North Carolina, USA, 2000	Personal monitoring (full-shift/short-term (15-min)/ ceiling (5-min))	Personal monitoring (TWA) 12 (sprayers) 2 (floaters)	GC-FID (1 µg/sample)	Sprayers: 0.66 ppm (0.2–1.35 ppm) [3.32 mg/m³ (1.01–6.79 mg/m³)] Floaters: [0.15 ppm] (0.1–0.2 ppm) [0.75 mg/m³ (0.50–1.01 mg/m³)]	[2.77 mg/m³] [0.75 mg/m³]	Adhesive containing low concentrations of 2-BP.	NIOSH (2002b)
		Short-term (15-min) samples 9 (sprayers)	(0.06 ppm [0.30 mg/m³] MDC)	0.779 ppm (0.30–1.56 ppm) [3.92 mg/m³ (1.51–7.85 mg/m³)]	[3.12 mg/m³]		
		Ceiling measurements 11 (sprayers)	(0.12 ppm [0.60 mg/m³] MDC)	0.753 ppm (0.37–1.13 ppm) [3.79 mg/m³ (1.86–5.68 mg/m³)]	[3.47 mg/m³]		
Foam cushion manufacturing plant, adhesive spraying North Carolina, USA, 1999	Personal air monitoring (full-shift TWA)	Glue line: 7 (sprayers) 1 (cushion bundler) 1 (supervisor, setup) Springs line: 5 (sprayers) 1 (cushion bundler) 1 (setup)	GC-FID (2 µg/sample) (0.02 ppm) [0.10 mg/m³] MDC)	All positions: 0.24 ppm (GM) (0.08–0.68 ppm) [1.21 mg/m³ (0.40–3.42 mg/m³)] Glue line sprayers: 0.26 ppm (GM) (0.19–0.35 ppm) [1.31 mg/m³ (0.96–1.76 mg/m³)] Springs line sprayers: 0.38 ppm (GM) (0.24–0.68 ppm) [1.91 mg/m³ (1.21–3.42 mg/m³)]	NR [1.26 mg/m³] [1.76 mg/m³]	2-BP was measured in 2 bulk adhesive formulations at 0.135% and 0.0265%. Unclear whether measured in 1999 or 2001. Relationship between 2-BP exposure and semen quality and nerve conduction tests not assessed. End-of-week bromide ion (Br) in urine included in statistical analysis. Each worker sampled for 1 full shift.	NIOSH (2003b)

Table 1.1 (continued)

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
Foam cushion manufacturing plant, adhesive spraying North Carolina, USA, 1999 (cont.)				Single measures: Glue line doffer (cushion bundler): 0.16 ppm [0.80 mg/m³] Supervisor/ setup: 0.08 ppm [0.40 mg/m³] Springs line doffer (cushion bundler): 0.14 ppm [0.70 mg/m³] Foam setup: 0.11 ppm [0.53 mg/m³]			NIOSH (2003b) (cont.)
	Stationary monitoring			0.06 ppm[a] [0.30 mg/m³]			
Foam cushion manufacturing plant, adhesive spraying North Carolina, USA, 2001	Personal air monitoring (full-shift TWA)	Total: 40 Unexposed: 27 Exposed: 13 (including 8 sprayers and 5 non-sprayers)	GC-FID (0.8 µg/sample) (0.003 ppm [0.015 mg/m³] MDC)	Unexposed: NR (ND–< 0.01 ppm) [(ND–< 0.05 mg/m³)]	NR	Exposure designation based on job task review. Each worker sampled for 1 full shift.	NIOSH (2003b)
				Exposed: 0.066 ppm (GM) (ND–0.52 ppm) [0.33 mg/m³ (ND–2.62 mg/m³)]	NR		
Helicopter transmission manufacturing plant Texas, USA 2004	Personal breathing zone sampling on 2 consecutive days; pre-shift and post-shift exhaled breath sampling	5 in plating department (TWA calculations)	NIOSH method 1025. GC-FID (1 µg/sample) (0.016 ppm [0.08 mg/m³] MDC)	Day 1: 0.073 ppm (0.042–0.097 ppm) [0.37 mg/m³ (0.21–0.488) mg/m³)]	NR	2-BP was a contaminant of a 1-BP vapour degreasing solvent. Mentions ASTM standard of < 0.10% 2-BP.	NIOSH (2006a)
				Day 2: 0.022 ppm (0.017–0.031 ppm) [0.11 mg/m³ (0.086–0.156 mg/m³)]	NR		
Aerospace components manufacturing plant Illinois, USA, 2004	Personal air monitoring	11 using vapour degreasers on 2 consecutive days	GC-FID	ND (all samples)		2-BP was a contaminant of a 1-BP vapour degreasing solvent.	NIOSH (2006b)

Table 1.1 (continued)

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
Printed electronics circuit assembly manufacturing plant California, USA, 2004	Personal breathing zone air (full-shift TWA) and exhaled breath sampling	5 on 2 consecutive days	NIOSH method 1025. GC-FID (0.5 µg/sample) (0.0083 ppm [0.042 mg/m^3] MDC for air; 0.033 ppm [0.166 mg/m^3] MDC for exhaled breath)	ND (all personal breathing zone and exhaled breath samples)	NR	2-BP was a contaminant of a 1-BP cleaning solvent to remove oils and flux. Qualitatively examined skin contact.	NIOSH (2007a)
Dry cleaners New Jersey, USA, 2009	Personal samples (8-h TWA) Stationary samples	14 13	NIOSH method 1025. GC-FID (0.004 ppm [0.020 mg/m^3] TWA)	NR NR (ND–0.02 ppm) [(ND–0.10 mg/m^3)]	NR NR	The cleaning solvent contained 0.1% 2-BP. Area samples were collected in the front of the shop and in the back near the machine.	Blando et al. (2010)
Hydraulic power control component manufacturer, parts degreasing Arizona, USA, 2004	Personal air monitoring (full-shift TWA) Exhaled breath	2 full-shift samples each from 4 workers (n = 8) 25 exhaled breath samples from 5 workers	NIOSH method 1025. GC-FID (0.7 µg/sample) (0.012 ppm [0.060 mg/m^3] MDC for full-shift samples; 0.046 ppm [0.23 mg/m^3] MDC for exhaled breath samples)	Day 1: 0.0030 ppm (ND–0.0069 ppm) [0.016 mg/m^3 (ND–0.035 mg/m^3)] Day 2: 0.00038 ppm (ND–0.0015 ppm) [0.0019 mg/m^3 (ND–0.0075 mg/m^3)] Exhaled breath: all ND	NR	2-BP was not detected or was detected in trace quantities, between LOD and LOQ. The reported values are estimates, which could have considerable variability. 2-BP included in exposure assessment as assumed impurity in degreaser. Qualitative dermal exposure assessment done. Urine analysed for bromide ion and propyl mercapturic acid. Workers sampled on 2 consecutive days.	NIOSH (2007b)[b]

Table 1.1 (continued)

Occupational group/job type/ industry Location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median	Comments	Reference
Optical prism and assemblies manufacturer, using solvent to clean glass California, USA, 2004	Personal air monitoring (full-shift TWA) Exhaled breath (pre-shift and post-shift)	2 full-shift samples each from 7 workers (n = 14) Pre-shift and post-shift samples from 7 workers (n = 14)	NIOSH method 1025. GC-FID (0.5 µg/sample) (0.0083 ppm [0.042 mg/m^3] MDC for full-shift samples; 0.033 ppm [0.166 mg/m^3] MDC for exhaled breath samples)	Day 1: all ND Day 2: 0.026 ppm (ND–0.028 ppm) [0.131 mg/m^3 (ND–0.141 mg/m^3)] Exhaled breath: all ND	NR	Day 2 average was calculated only with detectable results (n = 3). 2-BP included in exposure assessment as assumed impurity in degreaser. Qualitative dermal exposure assessment done. Urine analysed for bromide ion and propyl mercapturic acid. Workers sampled on 2 consecutive days.	NIOSH (2007c)
Adhesives and coatings manufacturer, using solvent to produce adhesives Ohio, USA, 2004	Personal air monitoring (full-shift TWA) Exhaled breath (pre-shift and post-shift)	2 full-shift samples each from 11 workers (n = 22) Pre-shift and post-shift samples from 7 workers (n = 14)	NIOSH method 1025. GC-FID (0.5 µg/sample) (0.0083 ppm [0.042 mg/m^3] MDC for full-shift samples; 0.033 ppm [0.166 mg/m^3] MDC for exhaled breath samples)	Day 1: 0.19 ppm (ND–0.98 ppm) [0.96 mg/m^3 (ND–4.93 mg/m^3)] Day 2: 0.19 ppm (0.051–1.00 ppm) [0.96 mg/m^3 (0.26–5.03 mg/m^3)] Exhaled breath: all ND	NR	Day 1 average was calculated only with detectable results (n = 10). 2-BP included in exposure assessment as assumed impurity in adhesive. Highest 2-BP concentrations found in workers not near adhesive operations; may be interference or another source. Urine analysed for bromide ion and propyl mercapturic acid. Qualitative dermal exposure assessment done. Workers monitored for 2 full shifts.	NIOSH (2007d)

ASTM, American Society for Testing and Materials; 1-BP, 1-bromopropane; 2-BP, 2-bromopropane; GC-EID, gas chromatography-electron ionization detection; GC-FID, gas chromatography-flame ionization detection; GC-MS, gas chromatography-mass spectrometry; GM, geometric mean; GSD, geometric standard deviation; h, hour(s); LOD, limit of detection; LOQ, limit of quantification; MDC, minimum detectable concentration; min, minute; NR, not reported; ND, not detected; ppm, parts per million; TWA, time-weighted average.

[a] Single measurement, not the mean.

[b] The study was unclear on how censored (non-detect) data were used in calculating the average. The average was used instead of the geometric mean. Indicates that the 2-BP data are estimates.

in North Carolina, USA, full-shift exposures to 2-bromopropane ranged from < 0.01 to 0.55 ppm [< 0.05–2.77 mg/m³]; the highest full-shift exposures occurred in the assembly department (NIOSH, 2002a). In 2000, at a furniture cushion manufacturer in North Carolina, USA, full-shift personal exposures ranged from 0.19 to 1.35 ppm [0.96–6.79 mg/m³]; the highest mean exposure occurred among adhesive sprayers (0.66 ppm [3.32 mg/m³]) (NIOSH, 2002b). In 1999, at a furniture cushion manufacturer in North Carolina, USA, full-shift exposures ranged from 0.08 to 0.68 ppm [0.40–3.42 mg/m³]; the highest mean exposures occurred among adhesive sprayers (0.31 ppm [1.56 mg/m³]) (NIOSH, 2003b). In 2001, at the same plant in North Carolina, USA, full-shift exposures ranged from non-detected to < 0.01 ppm [< 0.05 mg/m³] (minimum quantifiable concentration) among workers determined to be "unexposed" on the basis of job task review, and from non-detected to 0.52 ppm [2.62 mg/m³] among exposed workers. The geometric mean exposures remained highest among adhesive sprayers: 0.18 ppm [0.91 mg/m³] (range, 0.06–0.52 ppm [0.30–2.62 mg/m³]) (NIOSH, 2003b). In 2004, at an adhesive manufacturer in Ohio, USA, full-shift exposures ranged from non-detected to 1.0 ppm [5.0 mg/m³], and all pre-shift and post-shift exhaled breath samples were below the LOD (NIOSH, 2007d). The highest 2-bromopropane exposures measured at the adhesive manufacturing facility occurred among workers not working at the adhesive line, and the authors suggested that there may have been analytical interference or an unrecognized additional source of 2-bromopropane exposure (NIOSH, 2007d). [The Working Group noted that the authors reported possible analytical challenges that may make the reported exposure data less reliable.]

In 2000, at a communications component manufacturing plant in Indiana, USA, where exposures occurred during degreasing in a ventilated area, all measured exposures were below the minimum detectable concentration (0.004 ppm [0.020 mg/m³] for full-shift samples; 0.06 ppm [0.30 mg/m³] for task-based samples) (NIOSH, 2001). In 2004, at an optical prism manufacturer in California, USA, where full-shift exposures occurred during degreasing operations, exposures ranged from non-detectable to 0.028 ppm [0.141 mg/m³], and no 2-bromopropane was detected in exhaled breath samples (NIOSH, 2007c). [The Working Group noted that the minimum detectable concentration was calculated using sampling and analytical method information, rather than the achieved laboratory LOD for NIOSH (2007b, c, d), and that censored (non-detected) data were excluded from the average in NIOSH (2007c). Given that measurement of 2-bromopropane was not the primary aim of these studies, because of potential censored data issues the range should be treated as the most reliable data of these 2-bromopropane measurements.] In 2004, at a hydraulic power control component manufacturer in Arizona, USA, where exposures occurred during degreasing, full-shift exposures ranged from non-detected (minimum detectable concentration, 0.012 ppm [0.060 mg/m³] for full-shift samples) to 0.0069 ppm [0.035 mg/m³] (NIOSH, 2007b). [The Working Group noted that these measurements are below the given minimum detectable concentration and may not be accurate.] In 2004 at a helicopter transmission manufacturer in Texas, USA, where 2-bromopropane exposures occurred during degreasing operations, full-shift exposures ranged from 0.017 to 0.097 ppm [0.086 to 0.488 mg/m³] (NIOSH, 2006a). In 2004 at an aerospace component manufacturing plant, where 2-bromopropane exposures were expected to occur during degreasing operations, none of the full-shift samples were above the LOD (NIOSH, 2006b). It was noted in several of the evaluations that dermal exposures were likely but were only evaluated qualitatively (NIOSH 2007a, b, c, d).

In 2009, four dry-cleaning shops in New Jersey, USA, using a dry-cleaning solvent containing 1-bromopropane consented to air sampling. The dry-cleaning solvent used in one of the shops contained approximately 0.1% 2-bromopropane. The highest 2-bromopropane measurement of the 12 stationary air samples (2–5 samples per shop) was 0.02 ppm [0.10 mg/m^3], but 2-bromopropane was not detected in 14 personal air samples (Blando et al., 2010).

In 2011, 3 workers with protective masks in one 2-bromopropane manufacturing plant in Japan had a mean full-shift personal measurement of 2.64 ppm [13.3 mg/m^3] TWA for 8 hours. One worker was exposed to 32 ppm [161 mg/m^3] of 2-bromopropane while filling drums in a 2-bromopropane manufacturing plant. In the filling area, 96 ppm [483 mg/m^3] of 2-bromopropane were measured in one 45-minute stationary monitoring sample. Four workers in two factories using 2-bromopropane had a mean full shift personal measurement of 0.067 ppm [0.34 mg/m^3] TWA of 2-bromopropane (Ministry of Health, Labour and Welfare, Japan, 2016). [The Working Group noted that there was no information about the tasks in which 2-bromopropane was used in these factories.]

1.4.3 Exposure of the general population

No quantitative data on exposure of the general population were available to the Working Group.

1.5 Regulations and guidelines

An occupational exposure level (OEL) for 2-bromopropane was established at 1 ppm [5 mg/m^3] in the Republic of Korea in 1998 (Yu et al., 1999) and in Finland since 2002 (Ministry of Social Affairs and Health, 2020). An OEL for 2-bromopropane was recommended at 1.0 ppm by the Japan Society for Occupational Health in 1999 and revised at 0.5 ppm [2.5 mg/m^3] in 2021 (Nomiyama, 2021). 2-Bromopropane was restricted for use by pregnant workers, workers who have recently given birth or are breast-feeding, and young people (aged < 18 years) on the basis of a reproductive toxicity classification 1A (ECHA, 2022a). 2-Bromopropane is classified as a reproductive toxicant class 1A in the Republic of Korea (Ministry of Employment and Labor notification 2018-62) (Park, 2020) and as group 1 in Japan by the Japan Society for Occupational Health (Nomiyama, 2021).

For the European Union, the European Chemicals Agency banned the use of 2-bromopropane for cosmetics.

1.6 Quality of exposure assessment in key mechanistic studies in humans

The Working Group reviewed two cross-sectional studies (Kim et al., 1996b; Ichihara et al., 1999) that contributed to mechanistic evidence on immunosuppression after exposure to 2-bromopropane. The studies focused on relatively small groups of workers in an electronics plant in the Republic of Korea, who were exposed to 2-bromopropane used in cleaning baths during the production of electronic switches, and workers in a 2-bromopropane production plant in China. The study in the Republic of Korea involved 25 female workers and 8 male workers, all exposed to 2-bromopropane. The study in China involved a total of 25 workers, of whom operators, mixers, boilers, and a laboratory worker were exposed to 2-bromopropane. The study also included salespeople and accountants who were not exposed to 2-bromopropane.

Details on the exposure assessment methods used in the studies are summarized in Table S1.2 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/631).

1.6.1 Exposure assessment methods

Air concentrations of various chemicals used in the tactile switch assembly operation section of the electronics factory in the Republic of Korea were assessed under simulated conditions, as detailed in Section 1.4.2. Fourteen stationary air samples were collected to obtain background levels near each cleaning bath and a few automatic assembly machines for 3 hours. Three short-term (15-minute) air samples were collected in the enclosure around the cleaning baths (KOSHA, 1995; Kim et al., 1996b). Personal breathing zone measurements were not conducted, and there was also no quantification of the dermal exposure that had been reported by the involved workers. The compositions of the different chemical mixtures used in the production process were assessed by chemical analyses of bulk samples. The solvent used in the cleaning baths contained 97.4% 2-bromopropane.

In the 2-bromopropane manufacturing plant in China, air concentrations of 2-bromopropane and 2-propanol were measured with passive samplers for all workers during an entire working day, which lasted 8 hours (Ichihara et al., 1999). The production workers worked in three shifts, and the office workers worked in day shifts. Ambient air sampling of 2-bromopropane with indicator tubes in the breathing zone of the workers was also performed. The authors estimated cumulative exposure by multiplying the result of each worker's single 8-hour TWA measurement of exposure to 2-bromopropane by the duration of employment.

1.6.2 Critical review of exposure assessment methods

The exposure assessment methods used in the study of the workers in the Republic of Korea provided anecdotal evidence of background concentrations of 2-bromopropane and a few co-exposures around the cleaning baths and the automatic assembly machines (Kim et al., 1996b). They also provided estimates of short-term levels in the enclosures around the cleaning baths, where workers had to perform tasks irregularly. From interviews with the workers, it was apparent that dermal exposure of 2-bromopropane was likely as well, because of hand-dipping and not using dermal hand protection. The authors convincingly showed that the personal exposures of the workers involved had been very high (> 10 ppm [> 50 mg/m^3]) and that dermal exposure would have also contributed.

The exposure assessment methods used in the study of the workers in China entailed personal shift-long (8-hour) measurements, which indicated high exposures (> 10–100 ppm [> 50–500 mg/m^3]) for most of the workers in the production area (Ichihara et al., 1999). Clear differences in exposure were seen between the different stages in the production process, with 20-fold higher exposures at the end of the process compared with the beginning of the process. The estimation of cumulative exposure based on a single measurement (with the implicit assumption that it is representative of the whole employment period, which varied between 5 and 69 months) will have led to non-differential misclassification and attenuation of the exposure–outcome associations. A group-based strategy (assigning exposure based on job-specific average exposure) would have prevented bias towards the null of exposure–outcome associations. Also, in this study dermal exposure to 2-bromopropane was not taken into account.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

Inhalation

In a subchronic study that used a genetically modified mouse strain and complied with Good Laboratory Practice (GLP), groups of 25 male and 25 female Jic:CB6F1-Tg rasH2@Jcl (rasH2) mice (age, 7–8 weeks) were treated with 2-bromopropane (purity, 99.9%) by inhalation with whole-body exposure for 6 hours per day, 5 days per week, for 26 weeks (JBRC, 2019a, b; also reported by Goto et al., 2023). The concentration in the exposure chambers was set to 0 (clean air; control), 67, 200, or 600 ppm for the control group and the groups at the lowest, intermediate, and highest concentrations, respectively, for males and females and was monitored every 15 minutes. The mean air concentrations (± SD) for these groups were 0.0 ± 0.0, 66.8 ± 1.2, 200.6 ± 3.6, and 599.2 ± 10.0 ppm, respectively. For males, the survival rate of the group at 200 ppm was lower than that of controls starting at week 15. For females, the survival rate in the group at 600 ppm was lower than that of controls starting at week 19 and continued to decrease until study termination. At 26 weeks, survival was 25/25, 25/25, 21/25, and 24/25 for males, and 23/25, 24/25, 24/25, and 19/25 for females, for 0 (control), 67, 200, and 600 ppm, respectively. Male mice at 200 and 600 ppm showed a suppression of body-weight gain throughout the exposure period, whereas male mice at 67 ppm showed a decrease of body-weight gain until week 23. The relative final body weight in males was 98%, 91%, and 91% of the control value for the groups at 67, 200, and 600 ppm, respectively. Female mice at 600 ppm showed a small suppression of body-weight gain throughout the exposure period. The relative final body weight in females was 102%, 96%, and 94% of the control value for the groups at 67, 200, and 600 ppm, respectively. All mice underwent complete necropsy, and all organs and tissues were examined microscopically.

In male mice, there were significant positive trends in the incidence of bronchioloalveolar carcinoma of the lung (P = 0.0226, Peto trend test, prevalence method; P = 0.0347, Cochran–Armitage trend test) and in the incidence of bronchioloalveolar adenoma or carcinoma (combined) of the lung (P = 0.0312, Peto trend test, prevalence method). There was a significant positive trend in the incidence of haemangioma or haemangiosarcoma (combined) of the subcutis (P = 0.0466, Peto trend test, combined analysis).

In female mice, there was a significant positive trend in the incidence of bronchioloalveolar adenoma or carcinoma (combined) of the lung (P = 0.0415, Peto trend test, prevalence method). There were significant positive trends in the incidence of malignant lymphoma of the lymph nodes (P = 0.0144, Peto trend test, standard method and combined analysis; P = 0.0186, Cochran–Armitage trend test) and in the incidence of malignant lymphoma of all sites (lymph nodes and thymus) (P = 0.0296, Peto trend test, standard method; P = 0.0073, Peto trend test, combined analysis; P = 0.0094, Cochran–Armitage trend test).

[The Working Group noted that this was a well-described and well-conducted subchronic study that complied with GLP, used multiple concentrations, used both sexes (with respective control groups), and used a genetically modified mouse strain that is highly susceptible to carcinogenesis.]

Table 3.1 Studies of carcinogenicity in rats and transgenic mice exposed to 2-bromopropane

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, Jic:CB6F1-Tg rasH2@Jcl (rasH2) (M) 7–8 wk 26 wk JBRC (2019d)	Inhalation (whole-body exposure) Purity, 99.9% Air 0, 67, 200, 600 ppm 6 h/day, 5 days/wk 25, 25, 25, 25 25, 25, 21, 24	*Lung* Bronchioloalveolar carcinoma 0/25, 1/25, 3/25, 4/25	*P* = 0.0226, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis *P* = 0.0347, Cochran–Armitage trend test	*Principal strengths*: well-conducted GLP study; males and females used; multiple concentrations used.
		Bronchioloalveolar adenoma or carcinoma (combined) 3/25, 4/25, 5/25, 8/25	*P* = 0.0312, 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	
		Subcutis Haemangioma or haemangiosarcoma (combined) 0/25, 0/25, 1/25, 2/25	*P* = 0.0466, Peto trend test, combined analysis NS, Peto trend test, standard method and 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, Jic:CB6F1-Tg rasH2@Jcl (rasH2) (F) 7–8 wk 26 wk JBRC (2019d)	Inhalation (whole-body exposure) Purity, 99.9% Air 0, 67, 200, 600 ppm 6 h/day, 5 days/wk 25, 25, 25, 25 23, 24, 24, 19	*Lung* Bronchioloalveolar adenoma or carcinoma (combined) 4/25, 3/25, 7/25, 8/25 *Lymph nodes* Malignant lymphoma 0/25, 0/25, 0/25, 2/25 *All sites* Malignant lymphoma 1/25, 0/25, 0/25, 4/25	*P* = 0.0415, 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 *P* = 0.0144, Peto trend test, standard method *P* = 0.0144, Peto trend test, combined analysis Data not applicable for Peto trend test, prevalence method *P* = 0.0186, Cochran–Armitage trend test *P* = 0.0073, Peto trend test, combined analysis *P* = 0.0296, Peto trend test, standard method NS, Peto trend test, prevalence method *P* = 0.0094, Cochran–Armitage trend test	*Principal strengths*: well-conducted GLP study; males and females used; multiple concentrations used.

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 (2019a)	Inhalation (whole-body exposure) Purity, ≥ 99.7% Air 0, 67, 200, 600 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 31, 19, 0	*Zymbal gland* Malignant tumours 0/50, 5/50*, 6/50**, 23/50***	$P < 0.0001$, Peto trend test, standard method $P = 0.0010$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0281$, **$P = 0.0133$, ***$P < 0.0001$, Fisher exact test	*Principal strengths*: well-conducted GLP study; multiple concentrations used; males and females used; covered most of the lifespan; adequate number of animals per group; adequate duration of exposure and observation. *Other comments*: lower survival in all treated groups. Historical controls reported by Takanobu et al. (2015): benign tumours of the Zymbal gland, 2/699 (0.3%; range, 0–2.0%); malignant tumours of the Zymbal gland, 2/699 (0.3%; range, 0–2.0%); bronchioloalveolar adenoma, 40/699 (5.7%; range, 2.0–12.0%); basal cell epithelioma of the skin/appendage, 1/699 (0.1%; range, 0–2.0%); keratoacanthoma of the skin/appendage, 25/699 (3.6%; range, 0–14.0%); sebaceous adenoma of the skin/appendage, 1/699 (0.1%; range, 0–2.0%); squamous cell papilloma of the skin/appendage, 8/699 (1.1%; range, 0–4.0%); squamous cell carcinoma of the skin/appendage, 1/699 (0.1%; range, 0–2.0%); adenoma of the large intestine, 1/699 (0.1%; range, 0–2.0%); mucinous adenocarcinoma of the large intestine, 0/699; malignant lymphoma, 1/699 (0.1%; range, 0–2.0%); squamous cell papilloma of the stomach, 1/699 (0.1%; range, 0–2.0%); squamous cell carcinoma of the stomach, 3/699 (0.4%; range, 0–2.0%); adenoma of the preputial gland, 11/699 (1.6%; range, 0–6.0%); fibroma of the subcutis, 68/699 (9.7%; range, 2.0–16.3%); fibrosarcoma of the subcutis, 4/699 (0.6%; range, 0–4.0%); haemangioma of the subcutis, 1/699 (0.1%; range, 0–2.0%); follicular adenoma of the thyroid gland, 8/698 (1.1%; range, 0–4.1%); follicular adenocarcinoma of the thyroid gland, 2/698 (0.3%; range, 0–2.0%); bronchioloalveolar carcinoma, 7/699 (1.0%; range, 0–4.0%); haemangioma (all sites), 1/699 (0.1%; range, 0–2.0%); brain glioma, 4/699 (0.6%; range, 0–4.0%); mononuclear cell leukaemia, 81/699 (11.6%; range, 6.0–20.0%).
		Benign or malignant tumours (combined) 0/50, 5/50*, 7/50**, 25/50***	$P < 0.0001$, Peto trend test, standard method $P = 0.0002$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0281$, **$P = 0.0062$, ***$P < 0.0001$, Fisher exact 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Skin/appendage* Basal cell epithelioma 0/50, 0/50, 2/50, 3/50	$P = 0.0103$, Peto trend test, standard method $P = 0.0025$, Peto trend test, prevalence method $P = 0.0001$, Peto trend test, combined analysis $P = 0.0298$, Cochran–Armitage trend test	
		Keratoacanthoma 4/50, 5/50, 7/50, 6/50	$P = 0.005$, 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	
		Sebaceous adenoma 0/50, 1/50, 2/50, 10/50*	$P < 0.0001$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0006$, Fisher exact 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		Basal cell carcinoma		
		0/50, 0/50, 0/50, 12/50*	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0001$, Fisher exact test	
		Squamous cell carcinoma or basal cell carcinoma (combined)		
		0/50, 1/50, 0/50, 13/50*	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P < 0.0001$, Fisher exact test	
		Squamous cell papilloma, basal cell epithelioma, sebaceous adenoma, keratoacanthoma, squamous cell carcinoma, or basal cell carcinoma (combined)		
		5/50, 6/50, 9/50, 22/50*	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0001$, Fisher exact 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Large intestine* Adenoma 0/50, 0/50, 1/50, 3/50	$P = 0.0059$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P = 0.0139$, Cochran–Armitage trend test	
		Adenocarcinoma 0/50, 1/50, 6/50*, 8/50**	$P = 0.0002$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P = 0.0012$, Cochran–Armitage trend test *$P = 0.0133$, **$P = 0.0029$, Fisher exact test	
		Adenoma or adenocarcinoma (combined) 0/50, 1/50, 7/50*, 11/50**	$P < 0.0001$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0062$, **$P = 0.0003$, Fisher exact 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Small intestine* Adenocarcinoma 0/50, 0/50, 2/50, 7/50*	$P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P = 0.0435$, Peto trend test, standard method $P = 0.0001$, Cochran–Armitage trend test *$P = 0.0062$, Fisher exact test	
		Lymph nodes Malignant lymphoma 1/50, 0/50, 3/50, 7/50*	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, combined analysis $P = 0.0470$, Peto trend test, prevalence method $P = 0.0013$, Cochran–Armitage trend test *$P = 0.0297$, Fisher exact test	
		Stomach Squamous cell papilloma 0/50, 0/50, 1/50, 4/50	$P < 0.0001$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P = 0.0032$, 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		Squamous cell papilloma or carcinoma (combined)		
		0/50, 0/50, 1/50, 5/50*	$P < 0.0001$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P = 0.0007$, Cochran–Armitage trend test *$P = 0.0281$, Fisher exact test	
		Preputial gland		
		Adenoma		
		0/50, 0/50, 1/50, 4/50	$P = 0.0032$, Peto trend test, standard method $P = 0.0213$, Peto trend test, prevalence method $P = 0.0003$, Peto trend test, combined analysis $P = 0.0032$, Cochran–Armitage trend test	
		Adenoma or squamous cell papilloma (combined)		
		0/50, 0/50, 1/50, 4/50	$P = 0.0032$, Peto trend test, standard method $P = 0.0213$, Peto trend test, prevalence method $P = 0.0003$, Peto trend test, combined analysis $P = 0.0032$, 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		Adenocarcinoma, adenoma, or squamous cell papilloma (combined)		
		0/50, 1/50, 1/50, 4/50	$P = 0.0217$, Peto trend test, prevalence method $P = 0.0068$, Peto trend test, standard method $P = 0.0005$, Peto trend test, combined analysis $P = 0.0149$, Cochran–Armitage trend test	
		Subcutis		
		Haemangioma		
		0/50, 0/50, 3/50, 1/50	$P = 0.0001$, 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	
		Fibroma		
		7/50, 5/50, 15/50*, 5/50	$P = 0.0005$, Peto trend test, standard method $P = 0.0003$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis NS, Cochran–Armitage trend test *$P = 0.0448$, Fisher exact 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		Fibroma or fibrosarcoma (combined)		
		7/50, 5/50, 16/50*, 5/50	$P = 0.0005$, Peto trend test, standard method $P = 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis NS, Cochran–Armitage trend test *$P = 0.0279$, Fisher exact test	
		Thyroid		
		Follicular adenoma		
		0/50, 1/50, 5/50*, 2/50	$P = 0.0007$, 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 *$P = 0.0281$, Fisher exact test	
		Follicular adenocarcinoma		
		0/50, 3/50, 1/50, 0/50	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	

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 (2019a) (cont.)		Follicular adenoma or adenocarcinoma (combined)		
		0/50, 4/50, 6/50*, 2/50	$P = 0.0026$, 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 *$P = 0.0133$, Fisher exact test	
		Lung		
		Bronchioloalveolar adenoma		
		3/50, 7/50, 5/50, 7/50	$P = 0.0011$, 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	
		Bronchioloalveolar carcinoma		
		1/50, 3/50, 1/50, 2/50	NS, Peto trend test, standard method, Peto trend test, prevalence method, Peto trend test, combined analysis NS, Cochran–Armitage trend test	
		Bronchioloalveolar adenoma, squamous cell carcinoma, or bronchioloalveolar carcinoma (combined)		
		4/50, 8/50, 6/50, 9/50	$P = 0.0094$, Peto trend test, standard method $P = 0.0003$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		*All sites* Haemangioma (subcutis and spleen) 0/50, 1/50, 3/50, 2/50	$P < 0.0001$, 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	
		Brain Glioma 0/50, 2/50, 4/50, 2/50	$P = 0.0040$, Peto trend test, standard method $P = 0.0046$, Peto trend test, combined analysis NS, Peto trend test, prevalence method NS, Cochran–Armitage trend test	
		Spleen Mononuclear cell leukaemia 10/50, 7/50, 16/50, 4/50	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, combined analysis $P = 0.0297$, 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 Rat, F344/DuCrlCrlj (M) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Pancreas* Islet cell adenoma 3/50, 2/50, 5/50, 1/50	$P = 0.0193$, 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	
		Islet cell adenoma or islet cell adenocarcinoma (combined) 3/50, 3/50, 7/50, 1/50	$P = 0.0030$, Peto trend test, prevalence method $P = 0.0087$, Peto trend test, combined analysis NS, Peto trend test, standard 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a)	Inhalation (whole-body exposure) Purity, ≥ 99.7% Air 0, 67, 200, 600 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 43, 36, 25, 0	*Mammary gland* Adenoma 1/50, 0/50, 5/50, 0/50	$P = 0.0056$, 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	*Principal strengths*: well-conducted GLP study; multiple concentrations used; males and females used; covered most of the lifespan; adequate number of animals per group; adequate duration of exposure and observation. *Other comments*: lower survival in all treated groups. Historical controls reported by Takanobu et al. (2015): adenoma of the mammary gland, 1/550 (0.2%; range, 0–2.0%); adenocarcinoma of the mammary gland, 3/550 (0.5%; range, 0–2.0%); mononuclear cell leukaemia, 66/550 (12.0%; range, 4.0–18.0%); fibroadenoma of the mammary gland, 60/550 (10.9%; range, 4.0–16.0%); adenoma of the large intestine, 0/550; mucinous adenocarcinoma of the large intestine, 0/550; benign tumours of the Zymbal gland, 0/550; malignant tumours of the Zymbal gland, 2/550 (0.4%; range, 0–2.0%); adenoma of the clitoral gland, 11/550 (2.0%; range, 0–4.0%); basal cell epithelioma of the skin/appendage, 0/550; keratoacanthoma of the skin/appendage, 1/550 (0.2%; range, 0–2.0%); sebaceous adenoma of the skin/appendage, 0/550; squamous cell papilloma of the skin/appendage, 2/550 (0.4%; range, 0–2.0%); squamous cell carcinoma of the skin/appendage, 3/550 (0.5%; range, 0–2.0%); trichoepithelioma of the skin/appendage, 1/550 (0.2%; range, 0–2.0%); fibroma of the subcutis, 6/550 (1.1%; range, 0–2.0%); fibrosarcoma of the subcutis, 0/550; adenoma of the uterus, 1/550 (0.2%; range, 0–2.0%); adenocarcinoma of the uterus, 4/550 (0.7%; range, 0–4.0%).
		Adenocarcinoma 0/50, 2/50, 5/50*, 48/50**	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0281$, **$P < 0.0001$, Fisher exact test	
		Fibroadenoma 2/50, 4/50, 13/50*, 1/50	$P = 0.0051$, Peto trend test, standard method $P = 0.0002$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis NS, Cochran–Armitage trend test *$P = 0.0019$, Fisher exact 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		Adenoma or fibroadenoma (combined)		
		3/50, 4/50, 16/50*, 1/50	$P = 0.0051$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis NS, Cochran–Armitage trend test *$P = 0.0008$, Fisher exact test	
		Adenocarcinoma or adenosquamous carcinoma (combined)		
		0/50, 2/50, 6/50*, 48/50**	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P = 0.0133$, **$P < 0.0001$, Fisher exact test	
		Adenoma, fibroadenoma, adenocarcinoma, or adenosquamous carcinoma (combined)		
		3/50, 6/50, 21/50*, 48/50*	$P < 0.0001$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P < 0.0001$, Cochran–Armitage trend test *$P < 0.0001$, Fisher exact 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Spleen* Mononuclear cell leukaemia 2/50, 6/50, 10/50*, 1/50	*P* = 0.0042, Peto trend test, standard method *P* = 0.0407, Peto trend test, prevalence method *P* = 0.0008, Peto trend test, combined analysis NS, Cochran–Armitage trend test **P* = 0.0139, Fisher exact test	
		Vagina Squamous cell papilloma 1/50, 2/50, 7/50*, 4/50	*P* = 0.0007, 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 **P* = 0.0297, Fisher exact test	
		Squamous cell papilloma or carcinoma (combined) 1/50, 2/50, 8/50*, 4/50	*P* = 0.0005, 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 **P* = 0.0154, Fisher exact 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Large intestine* Adenoma or adenocarcinoma (combined) 0/50, 0/50, 2/50, 4/50	$P = 0.0001$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P = 0.0076$, Cochran–Armitage trend test	
		Zymbal gland Malignant tumours 0/50, 1/50, 1/50, 4/50	$P = 0.0096$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P = 0.0149$, Cochran–Armitage trend test	
		Benign or malignant tumours (combined) 0/50, 1/50, 1/50, 4/50	$P = 0.0096$, Peto trend test, standard method $P < 0.0001$, Peto trend test, prevalence method $P < 0.0001$, Peto trend test, combined analysis $P = 0.0149$, 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Clitoral gland* Adenoma 1/50, 1/50, 4/50, 4/50	*P* = 0.0421, Peto trend test, prevalence method *P* = 0.0297, Peto trend test, combined analysis NS, Peto trend test, standard method NS, Cochran–Armitage trend test	
		Squamous cell papilloma or adenoma (combined) 1/50, 1/50, 4/50, 5/50	*P* = 0.0154, Peto trend test, prevalence method *P* = 0.0104, Peto trend test, combined analysis NS, Peto trend test, standard method *P* = 0.0481, Cochran–Armitage trend test	
		Squamous cell papilloma, adenoma, or adenocarcinoma (combined) 1/50, 1/50, 5/50, 6/50	*P* = 0.0069, Peto trend test, prevalence method *P* = 0.0046, Peto trend test, combined analysis NS, Peto trend test, standard method *P* = 0.0226, 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Skin/appendage* Squamous cell papilloma 2/50, 0/50, 0/50, 4/50	$P = 0.0055$, Peto trend test, prevalence method Data not applicable for Peto trend test, standard method or Peto trend test, combined analysis $P = 0.0501$, Cochran–Armitage trend test	
		Squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or sebaceous adenoma (combined) 4/50, 0/50, 0/50, 5/50	$P = 0.0106$, 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	
		Squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or squamous cell carcinoma (combined) 4/50, 0/50, 1/50, 5/50	$P = 0.0107$, Peto trend test, prevalence method $P = 0068$, Peto trend test, combined analysis NS, Peto trend test, standard 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 Rat, F344/DuCrlCrlj (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Subcutis* Fibroma 2/50, 1/50, 4/50, 0/50	$P = 0.0407$, 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	
		Fibroma or fibrosarcoma (combined) 2/50, 1/50, 5/50, 2/50	$P = 0.0258$, Peto trend test, standard method $P = 0.0045$, Peto trend test, prevalence method $P = 0.0003$, Peto trend test, combined analysis NS, Cochran–Armitage trend test	
		Uterus Endometrial stromal polyp 9/50, 4/50, 11/50, 8/50	$P = 0.0154$, Peto trend test, prevalence method $P = 0.0111$, Peto trend test, combined analysis NS, Peto trend test, standard method NS, Cochran–Armitage trend test	
		Adenoma or adenocarcinoma (combined) 2/50, 0/50, 1/50, 4/50	$P = 0.0003$, 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	

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 (F) 6–7 wk 104 wk JBRC (2019a) (cont.)		*Pancreas* Islet cell adenoma 1/50, 0/50, 4/50, 0/50	$P = 0.0163$, 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	
		Islet cell adenoma or islet cell adenocarcinoma (combined) 1/50, 1/50, 4/50, 0/50	$P = 0.0290$, 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).

3.2 Rat

Inhalation

In a well-conducted chronic toxicity and carcinogenicity study that complied with Good Laboratory Practice (GLP), groups of 50 male and 50 female F344/DuCrlCrlj rats (age, 6–7 weeks) were treated with 2-bromopropane (purity, ≥ 99.7%) by inhalation with whole-body exposure for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2019c, d; also reported by Senoh et al., 2023). The concentration in the exposure chambers was set to 0 (clean air; control), 67, 200, or 600 ppm for males and females and was monitored every 15 minutes. The mean air concentrations (± standard deviation, SD) for these groups were measured as 0.0 ± 0.0, 67.2 ± 0.3, 200.2 ± 0.6, and 600.9 ± 1.5 ppm, respectively. The survival rates of males and females in the 67 and 200 ppm groups were lower than those in the control group, and none of the males in the 600-ppm group were alive by week 85. At study termination, survival was 38/50, 31/50, 19/50, and 0/50 in males, and 43/50, 36/50, 25/50, and 0/50 in females, for 0 (control), 67, 200, and 600 ppm, respectively. The body weights of males and females in the groups at 67 and 200 ppm remained similar to those of their respective controls. In the groups at 600 ppm, males and females did not survive beyond week 84 and showed a decrease in body-weight gain starting from week 4 for males and from week 5 for females and continuing throughout the exposure period for both males and females. In males, the relative final body weight (except for the 600-ppm group, which was measured at week 82) at 67, 200, and 600 ppm was 101%, 99%, and 69% of the control value, respectively. In females, the relative final body weight (except for the 600-ppm group, which was measured at week 82) at 67, 200, and 600 ppm was 99%, 103%, and 72% of the control value, respectively. All rats underwent complete necropsy, and all organs and tissues were examined microscopically.

In male rats, there were significant increases in tumour incidence for many different tissue types. There was a significant positive trend ($P < 0.0001$, Peto trend test, standard method and combined analysis; $P = 0.0010$, Peto trend test, prevalence method; $P < 0.0001$, Cochran–Armitage trend test) in the incidence of malignant tumours of the Zymbal gland: 0/50, 5/50 (10%), 6/50 (12%), and 23/50 (46%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of malignant tumours of the Zymbal gland was significantly increased in each of the treated groups ($P = 0.0281$, $P = 0.0133$, and $P < 0.0001$ at 67, 200, and 600 ppm, respectively; Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 2/699 (0.3%; range, 0–2.0%). [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 data reported by Takanobu et al. (2015) are from control male F344/DuCrlCrlj rats in inhalation studies by the Japan Bioassay Research Center, but these studies were started in 2000–2009, in contrast to the 2-bromopropane study, which started in 2016.]

There was a significant positive trend ($P < 0.0001$, Peto trend test, standard method and combined analysis; $P = 0.0002$, Peto trend test, prevalence method; $P < 0.0001$, Cochran–Armitage trend test) in the incidence of benign or malignant tumours (combined) of the Zymbal gland: 0/50, 5/50 (10%), 7/50 (14%), and 25/50 (50%) for the groups at 0 (control), 67, 200, and

600 ppm, respectively. The incidence of benign or malignant tumours (combined) of the Zymbal gland was significantly increased in each of the treated groups (P = 0.0281, P = 0.0062, and P < 0.0001 at 67, 200, and 600 ppm, respectively; Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 2/699 (0.3%; range, 0–2.0%).

There were significant positive trends in the incidence of tumours of the skin/appendage. Specifically, there was a significant positive trend in the incidence of basal cell epithelioma (P = 0.0103, Peto trend test, standard method; P = 0.0025, Peto trend test, prevalence method; P = 0.0001, Peto trend test, combined analysis; P = 0.0298, Cochran–Armitage trend test). There was a significant positive trend in the incidence of keratoacanthoma (P = 0.005, Peto trend test, prevalence method). There was a significant positive trend (P < 0.0001, Peto trend test, prevalence method; P < 0.0001, Cochran–Armitage trend test) in the incidence of sebaceous adenoma: 0/50, 1/50 (2%), 2/50 (4%), and 10/50 (20%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of sebaceous adenoma was significantly increased at the highest concentration (P = 0.0006, Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 1/699 (0.1%; range, 0–2.0%). There was a significant positive trend (P < 0.0001, Peto trend test, standard method, prevalence method, and combined analysis; P < 0.0001, Cochran–Armitage trend test) in the incidence of basal cell carcinoma: 0/50, 0/50, 0/50, and 12/50 (24%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of basal cell carcinoma was significantly increased at the highest concentration (P = 0.0001, Fisher exact test). There was a significant positive trend (P < 0.0001, Peto trend test, standard method, prevalence method, and combined analysis; P < 0.0001, Cochran–Armitage trend test) in the incidence of squamous cell carcinoma or basal cell carcinoma (combined): 0/50, 1/50 (2%), 0/50, and 13/50 (26%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell carcinoma or basal cell carcinoma (combined) was significantly increased at the highest concentration (P < 0.0001, Fisher exact test). The incidence of basal cell epithelioma, sebaceous adenoma, and squamous cell carcinoma of the skin/appendage in historical controls reported by Takanobu et al. (2015) was 1/699 (0.1%; range, 0–2.0%), 1/699 (0.1%; range, 0–2.0%), and 1/699 (0.1%; range, 0–2.0%), respectively. There was a significant positive trend (P < 0.0001, Peto trend test, standard method, prevalence method, and combined analysis; P < 0.0001, Cochran–Armitage trend test) in the incidence of squamous cell papilloma, basal cell epithelioma, sebaceous adenoma, keratoacanthoma, squamous cell carcinoma, or basal cell carcinoma (combined): 5/50 (10%), 6/50 (12%), 9/50 (18%), and 22/50 (44%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell papilloma, basal cell epithelioma, sebaceous adenoma, keratoacanthoma, squamous cell carcinoma, or basal cell carcinoma (combined) was significantly increased at the highest concentration (P = 0.0001, Fisher exact test). There was a significant positive trend in the incidence of adenoma of the large intestine (P = 0.0059, Peto trend test, prevalence method; P = 0.0139, Cochran–Armitage trend test). There was a significant positive trend (P = 0.0002, Peto trend test, prevalence method; P = 0.0012, Cochran–Armitage trend test) in the incidence of adenocarcinoma of the large intestine: 0/50, 1/50 (2%), 6/50 (12%), and 8/50 (16%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenocarcinoma of the large intestine was significantly increased at 200 and 600 ppm (P = 0.0133 and P = 0.0029, respectively, both Fisher exact test). There was a significant positive trend (P < 0.0001, Peto trend test, prevalence method; P < 0.0001, Cochran–

Armitage trend test) in the incidence of adenoma or adenocarcinoma (combined) of the large intestine: 0/50, 1/50 (2%), 7/50 (14%), and 11/50 (22%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenoma or adenocarcinoma (combined) of the large intestine was significantly increased at 200 and 600 ppm ($P = 0.0062$ and $P = 0.0003$, respectively, both Fisher exact test). The incidence of adenoma and of mucinous adenocarcinoma of the large intestine in historical controls reported by Takanobu et al. (2015) was 1/699 (0.1%; range, 0–2.0%) and 0/699, respectively. There was a significant positive trend ($P = 0.0435$, Peto trend test, standard method; $P < 0.0001$, Peto trend test, prevalence method and combined analysis; $P = 0.0001$, Cochran–Armitage trend test) in the incidence of adenocarcinoma of the small intestine: 0/50, 0/50, 2/50 (4%), and 7/50 (14%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenocarcinoma of the small intestine was significantly increased at the highest concentration ($P = 0.0062$, Fisher exact test). There was a significant positive trend ($P = 0.0470$, Peto trend test, prevalence method; $P < 0.0001$, Peto trend test, standard method and combined analysis; $P = 0.0013$, Cochran–Armitage trend test) in the incidence of malignant lymphoma of the lymph nodes: 1/50 (2%), 0/50, 3/50 (6%), and 7/50 (14%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of malignant lymphoma of the lymph nodes was significantly increased at the highest concentration ($P = 0.0297$, Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 1/699 (0.1%; range, 0–2.0%). There was a significant positive trend ($P < 0.0001$, Peto trend test, prevalence method; $P = 0.0032$, Cochran–Armitage trend test) in the incidence of squamous cell papilloma of the stomach: 0/50, 0/50, 1/50 (2%), and 4/50 (8%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell papilloma of the stomach at the highest concentration exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 1/699 (0.1%; range, 0–2.0%). There was a significant positive trend ($P < 0.0001$, Peto trend test, prevalence method; $P = 0.0007$, Cochran–Armitage trend test) in the incidence of squamous cell papilloma or carcinoma (combined) of the stomach: 0/50, 0/50, 1/50 (2%), and 5/50 (10%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell papilloma or carcinoma (combined) of the stomach was significantly increased at the highest concentration ($P = 0.0281$, Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 3/699 (0.4%; range, 0–2.0%). There were significant positive trends in the incidence of tumours of the preputial gland. Specifically, there were significant positive trends in the incidence of adenoma ($P = 0.0032$, Peto trend test, standard method; $P = 0.0213$, Peto trend test, prevalence method; $P = 0.0003$, Peto trend test, combined analysis; $P = 0.0032$, Cochran–Armitage trend test), in the incidence of adenoma or squamous cell papilloma (combined) ($P = 0.0032$, Peto trend test, standard method; $P = 0.0213$, Peto trend test, prevalence method; $P = 0.0003$, Peto trend test, combined analysis; $P = 0.0032$, Cochran–Armitage trend test), and in the incidence of adenocarcinoma, adenoma, or squamous cell papilloma (combined) ($P = 0.0068$, Peto trend test, standard method; $P = 0.0217$, Peto trend test, prevalence method; $P = 0.0005$, Peto trend test, combined analysis; $P = 0.0149$, Cochran–Armitage trend test). There was a significant positive trend ($P = 0.0005$, Peto trend test, standard method; $P = 0.0003$, Peto trend test, prevalence method; $P < 0.0001$, Peto trend test, combined analysis) in the incidence of fibroma of the subcutis: 7/50 (14%), 5/50 (10%), 15/50 (30%), and 5/50 (10%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of fibroma of the subcutis was

significantly increased at 200 ppm (P = 0.0448, Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 68/699 (9.7%; range, 2.0–16.3%). There was a significant positive trend (P = 0.0005, Peto trend test, standard method; P = 0.0001, Peto trend test, prevalence method; P < 0.0001, Peto trend test, combined analysis) in the incidence of fibroma or fibrosarcoma (combined) of the subcutis: 7/50 (14%), 5/50 (10%), 16/50 (32%), and 5/50 (10%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of fibroma or fibrosarcoma (combined) of the subcutis was significantly increased at 200 ppm (P = 0.0279, Fisher exact test). The incidence in the control group and all treated groups exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 4/699 (0.6%; range, 0–4.0%). There was a significant positive trend (P = 0.0001, Peto trend test, prevalence method) in the incidence of haemangioma of the subcutis: 0/50, 0/50, 3/50 (6%), and 1/50 (2%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of haemangioma of the subcutis at 200 ppm exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 1/699 (0.1%; range, 0–2.0%). There was a significant positive trend (P = 0.0007, Peto trend test, prevalence method) in the incidence of follicular adenoma of the thyroid gland: 0/50, 1/50 (2%), 5/50 (10%), and 2/50 (4%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of follicular adenoma of the thyroid gland was significantly increased at 200 ppm (P = 0.0281, Fisher exact test). There was a significant positive trend (P = 0.0026, Peto trend test, prevalence method) in the incidence of follicular adenoma or adenocarcinoma (combined) of the thyroid gland: 0/50, 4/50 (8%), 6/50 (12%), and 2/50 (4%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of follicular adenoma or adenocarcinoma (combined) of the thyroid gland was significantly increased at 200 ppm (P = 0.0133, Fisher exact test), and the incidence in all treated groups exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 2/698 (0.3%; range, 0–2.0%). There were significant positive trends in the incidence of bronchioloalveolar adenoma of the lung (P = 0.0011, Peto trend test, prevalence method) and in the incidence of bronchioloalveolar adenoma, squamous cell carcinoma, or bronchioloalveolar carcinoma (combined) of the lung (P = 0.0094, Peto trend test, standard method; P = 0.0003, Peto trend test, prevalence method; P < 0.0001, Peto trend test, combined analysis). [The Working Group noted that bronchioloalveolar neoplasms and squamous cell neoplasms of the lung should not be combined (see Brix et al., 2010, and General Remarks). Therefore, the Working Group did not consider combination of bronchioloalveolar neoplasms of the lung and squamous cell carcinoma of the lung to be appropriate for detection of increase in tumour incidence.] There was a significant positive trend (P < 0.001, Peto trend test, prevalence method) in the incidence of haemangioma of all sites (subcutis and spleen): 0/50, 1/50 (2%), 3/50 (6%), and 2/50 (4%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of haemangioma of all sites (subcutis and spleen) at 200 and 600 ppm exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 1/699 (0.1%; range, 0–2.0%). There was a significant positive trend (P = 0.0040, Peto trend test, standard method; P = 0.0046, Peto trend test, combined analysis) in the incidence of glioma of the brain: 0/50, 2/50 (4%), 4/50 (8%), and 2/50 (4%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of glioma at 200 ppm exceeded the upper bound of the range observed in historical controls reported by Takanobu et al. (2015): 4/699 (0.6%; range, 0–4.0%). There was a significant positive trend (P < 0.001, Peto trend test, standard method and

combined analysis; $P = 0.0297$, Peto trend test, prevalence method) in the incidence of mononuclear cell leukaemia of the spleen: 10/50 (20%), 7/50 (14%), 16/50 (32%), and 4/50 (8%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of mononuclear cell leukaemia of the spleen at 200 ppm exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 81/699 (11.6%; range, 6.0–20.0%). There were significant positive trends in the incidence of islet cell adenoma of the pancreas ($P = 0.0193$, Peto trend test, prevalence method) and in the incidence of islet cell adenoma or islet cell adenocarcinoma (combined) of the pancreas ($P = 0.0030$, Peto trend test, prevalence method; $P = 0.0087$, Peto trend test, combined analysis).

In female rats, there was a significant positive trend ($P = 0.0056$, Peto trend test, prevalence method) in the incidence of adenoma of the mammary gland: 1/50 (2%), 0/50, 5/50 (10%), and 0/50 for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenoma of the mammary gland at 200 ppm exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 1/550 (0.2%; range, 0–2.0%). [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 data reported by Takanobu et al. (2015) are from control female F344/DuCrlCrlj rats in inhalation studies by the Japan Bioassay Research Center, but these studies were started in 2000–2009, in contrast to the 2-bromopropane study, which started in 2016.]

There was a significant positive trend ($P < 0.0001$, Peto trend test, standard method, prevalence method, and combined analysis; $P < 0.0001$, Cochran–Armitage trend test) in the incidence of adenocarcinoma of the mammary gland: 0/50, 2/50 (4%), 5/50 (10%), and 48/50 (96%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenocarcinoma of the mammary gland was significantly increased at 200 and 600 ppm ($P = 0.0281$ and $P < 0.0001$, respectively, both Fisher exact test), and the incidence in all treated groups exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 3/550 (0.5%; range, 0–2.0%). There was a significant positive trend ($P = 0.0051$, Peto trend test, standard method; $P = 0.0002$, Peto trend test, prevalence method; $P < 0.0001$, Peto trend test, combined analysis) in the incidence of fibroadenoma of the mammary gland: 2/50 (4%), 4/50 (8%), 13/50 (26%), and 1/50 (2%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of fibroadenoma of the mammary gland was significantly increased at 200 ppm ($P = 0.0019$, Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 60/550 (10.9%; range, 4–16.0%). There was a significant positive trend ($P = 0.0051$, Peto trend test, standard method; $P < 0.0001$, Peto trend test, prevalence method and combined analysis) in the incidence of adenoma or fibroadenoma (combined) of the mammary gland: 3/50 (6%), 4/50 (8%), 16/50 (32%), and 1/50 (2%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenoma or fibroadenoma (combined) of the mammary gland was significantly increased at 200 ppm ($P = 0.0008$, Fisher exact test). There was a significant positive trend ($P < 0.0001$, Peto trend test, standard method, prevalence method, and combined analysis; $P < 0.0001$, Cochran–Armitage trend test) in the incidence of adenocarcinoma or adenosquamous carcinoma (combined) of the

mammary gland: 0/50, 2/50 (4%), 6/50 (12%), and 48/50 (96%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenocarcinoma or adenosquamous carcinoma (combined) of the mammary gland was significantly increased at 200 and 600 ppm (P = 0.0133 and P < 0.0001, respectively, both Fisher exact test). There was a significant positive trend (P < 0.0001, Peto trend test, standard method, prevalence method, and combined analysis; P < 0.0001, Cochran–Armitage trend test) in the incidence of adenoma, fibroadenoma, adenocarcinoma, or adenosquamous carcinoma (combined) of the mammary gland: 3/50 (6%), 6/50 (12%), 21/50 (42%), and 48/50 (96%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenoma, fibroadenoma, adenocarcinoma, or adenosquamous carcinoma (combined) of the mammary gland was significantly increased at 200 and 600 ppm (P < 0.0001, Fisher exact test). [The Working Group noted that mammary gland adenoma and mammary gland fibroadenoma should not be combined, because they are thought to arise from different parts of the mammary gland (see Brix et al., 2010). The only exception may occur when an adenoma or a carcinoma arises from a fibroadenoma, and then it should be combined with other adenomas and carcinomas of the mammary gland. The conditions for this exception were not reported for the current study by JBRC (2019c, d). Therefore, the Working Group did not consider combination of mammary gland adenoma and mammary gland fibroadenoma, or combination of mammary gland adenoma, fibroadenoma, adenocarcinoma, and adenosquamous carcinoma, to be appropriate for detection of increase in tumour incidence.]

There was a significant positive trend (P = 0.0042, Peto trend test, standard method; P = 0.0407, Peto trend test, prevalence method; P = 0.0008, Peto trend test, combined analysis) in the incidence of mononuclear cell leukaemia of the spleen: 2/50 (4%), 6/50 (12%), 10/50 (20%), and 1/50 (2%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of mononuclear cell leukaemia of the spleen was significantly increased at 200 ppm (P = 0.0139, Fisher exact test) and exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 66/550 (12%; range, 4–18.0%).

There was a significant positive trend (P = 0.0007, Peto trend test, prevalence method) in the incidence of squamous cell papilloma of the vagina: 1/50 (2%), 2/50 (4%), 7/50 (14%), and 4/50 (8%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell papilloma of the vagina was significantly increased at 200 ppm (P = 0.0297, Fisher exact test). There was a significant positive trend (P = 0.0005, Peto trend test, prevalence method) in the incidence of squamous cell papilloma or carcinoma (combined) of the vagina: 1/50 (2%), 2/50 (4%), 8/50 (16%), and 4/50 (8%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell papilloma or carcinoma (combined) of the vagina was significantly increased at 200 ppm (P = 0.0154, Fisher exact test).

There was a significant positive trend (P = 0.0001, Peto trend test, prevalence method; P = 0.0076, Cochran–Armitage trend test) in the incidence of adenoma or adenocarcinoma (combined) of the large intestine. The incidence of adenoma and of mucinous adenocarcinoma of the large intestine in historical controls reported by Takanobu et al. (2015) was 0/550 for both.

There was a significant positive trend (P = 0.0096, Peto trend test, standard method; P < 0.0001, Peto trend test, prevalence method and combined analysis; P = 0.0149, Cochran–Armitage trend test) in the incidence of malignant tumours of the Zymbal gland. There was a significant positive trend (P = 0.0096, Peto trend test, standard method; P < 0.0001, Peto trend test, prevalence method and combined analysis; P = 0.0149, Cochran–Armitage trend test) in

the incidence of benign or malignant tumours (combined) of the Zymbal gland. The incidence of benign or malignant tumours (combined) of the Zymbal gland at the highest concentration (4/50; 8%) exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 2/550 (0.4%; range, 0–2.0%).

There were significant positive trends in the incidence of tumours of the clitoral gland. Specifically, there were significant positive trends in the incidence of adenoma (P = 0.0421, Peto trend test, prevalence method; P = 0.0297, Peto trend test, combined analysis), in the incidence of squamous cell papilloma or adenoma (combined) (P = 0.0154, Peto trend test, prevalence method; P = 0.0104, Peto trend test, combined analysis; P = 0.0481, Cochran–Armitage trend test), and in the incidence of squamous cell papilloma, adenoma, or adenocarcinoma (combined) (P = 0.0069, Peto trend test, prevalence method; P = 0.0046, Peto trend test, combined analysis; P = 0.0226, Cochran–Armitage trend test). There was a significant positive trend (P = 0.0055, Peto trend test, prevalence method) in the incidence of squamous cell papilloma of the skin/appendage: 2/50 (4%), 0/50, 0/50, and 4/50 (8%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of squamous cell papilloma of the skin/appendage at the highest concentration exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 2/550 (0.4%; range, 0–2.0%). There was a significant positive trend in the incidence of squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or sebaceous adenoma (combined) of the skin/appendage (P = 0.0106, Peto trend test, prevalence method). There was a significant positive trend in the incidence of squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or squamous cell carcinoma (combined) of the skin/appendage (P = 0.0107, Peto trend test, prevalence method; P = 0.0068, Peto trend test, combined analysis). There was a significant positive trend (P = 0.0407, Peto trend test, prevalence method) in the incidence of fibroma of the subcutis: 2/50 (4%), 1/50 (2%), 4/50 (8%), and 0/50 for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of fibroma of the subcutis at 200 ppm exceeded the upper bound of the range observed in historical controls as reported by Takanobu et al. (2015): 6/550 (1.1%; range, 0–2.0%). There was a significant positive trend in the incidence of fibroma or fibrosarcoma (combined) of the subcutis (P = 0.0258, Peto trend test, standard method; P = 0.0045, Peto trend test, prevalence method; P = 0.0003, Peto trend test, combined analysis). There was a significant positive trend in the incidence of endometrial stromal polyps of the uterus (P = 0.0154, Peto trend test, prevalence method; P = 0.0111, Peto trend test, combined analysis). There was a significant positive trend (P = 0.0003, Peto trend test, prevalence method) in the incidence of adenoma or adenocarcinoma (combined) of the uterus: 2/50 (4%), 0/50, 1/50 (2%), and 4/50 (8%) for the groups at 0 (control), 67, 200, and 600 ppm, respectively. The incidence of adenoma and of adenocarcinoma of the uterus in historical controls reported by Takanobu et al. (2015) was 1/550 (0.2%; range, 0–2.0%) and 4/550 (0.7%; range, 0–4.0%), respectively. There were significant positive trends in the incidence of islet cell adenoma of the pancreas (P = 0.0163, Peto trend test, prevalence method) and in the incidence of islet cell adenoma or islet cell adenocarcinoma (combined) of the pancreas (P = 0.0290, Peto trend test, prevalence method).

Regarding non-neoplastic lesions, in male rats, there were increases in the incidence of bronchioloalveolar epithelial hyperplasia of the lung and of extramedullary haematopoiesis in the spleen at the highest concentration. In female rats, there were increases in the incidence and/or severity of the following non-neoplastic lesions: extramedullary haematopoiesis in the spleen (at the intermediate and highest concentrations),

ulcers of the forestomach (at the intermediate and highest concentrations), and hyperplasia of the vagina (at the intermediate concentration).

[The Working Group noted that this was a well-described and well-conducted study that complied with GLP, used multiple concentrations, used both sexes (with respective control groups), had an adequate duration of exposure and observation, and had an adequate number of animals per group. The Working Group also noted that an unusually high degree of carcinogenic activity with regard to incidence, site, and types of tumours was observed in both males and females.]

3.3 Evidence synthesis for cancer in experimental animals

The carcinogenicity of 2-bromopropane has been assessed in one well-conducted subchronic study that complied with GLP in genetically modified male and female Jic:CB6F1-Tg rasH2@Jcl (rasH2) mice treated by inhalation (JBRC, 2019a, b; also reported by Goto et al., 2023) and in one well-conducted GLP study in male and female F344/DuCrlCrlj rats treated by inhalation (JBRC, 2019c, d; also reported by Senoh et al., 2023).

In the inhalation study that complied with GLP in genetically modified male and female Jic:CB6F1-Tg rasH2@Jcl (rasH2) mice (JBRC, 2019a, b; also reported by Goto et al., 2023), there were significant positive trends in the incidence of bronchioloalveolar carcinoma of the lung and in the incidence of bronchioloalveolar adenoma or carcinoma (combined) of the lung in male mice. There was a significant positive trend in the incidence of haemangioma or haemangiosarcoma (combined) of the subcutis in male mice. In female mice, there was a significant positive trend in the incidence of bronchioloalveolar adenoma or carcinoma (combined) of the lung. There were significant positive trends in the incidence of malignant lymphoma of the lymph nodes and in the incidence of malignant lymphoma of all sites.

In the inhalation study that complied with GLP in male and female F344/DuCrlCrlj rats (JBRC, 2019c, d; also reported by Senoh et al., 2023), there were significant increases in tumour incidence for many different tissue types.

In male rats, there was a significant positive trend in the incidence of malignant tumours of the Zymbal gland, and the incidence was significantly increased in all treated groups. There was a significant positive trend in the incidence of benign or malignant tumours (combined) of the Zymbal gland, and the incidence was significantly increased in all treated groups. There were significant positive trends in the incidence of basal cell epithelioma of the skin/appendage and in the incidence of keratoacanthoma of the skin/appendage. There was a significant positive trend in the incidence of sebaceous adenoma of the skin/appendage, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of basal cell carcinoma of the skin/appendage, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of squamous cell carcinoma or basal cell carcinoma (combined) of the skin/appendage, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of squamous cell papilloma, basal cell epithelioma, sebaceous adenoma, keratoacanthoma, squamous cell carcinoma, or basal cell carcinoma (combined) of the skin/appendage, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of adenoma of the large intestine. There was a significant positive trend in the incidence of adenocarcinoma of the large intestine, and the incidence was significantly increased at 200 and 600 ppm. There was a significant positive

trend in the incidence of adenoma or adenocarcinoma (combined) of the large intestine, and the incidence was significantly increased at 200 and 600 ppm. There was a significant positive trend in incidence of adenocarcinoma of the small intestine, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of malignant lymphoma of the lymph nodes, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of squamous cell papilloma of the stomach. There was a significant positive trend in the incidence of squamous cell papilloma or carcinoma (combined) of the stomach, and the incidence was significantly increased at the highest concentration. There was a significant positive trend in the incidence of adenoma of the preputial gland, of adenoma or squamous cell papilloma (combined) of the preputial gland, and of adenocarcinoma, adenoma, or squamous cell papilloma (combined) of the preputial gland. There was a significant positive trend in the incidence of fibroma of the subcutis, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of fibroma or fibrosarcoma (combined) of the subcutis, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of haemangioma of the subcutis. There was a significant positive trend in the incidence of follicular adenoma of the thyroid gland, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of follicular adenoma or adenocarcinoma (combined) of the thyroid gland, and the incidence was significantly increased at 200 ppm. In addition, there was a significant positive trend in the incidence of bronchioloalveolar adenoma of the lung. There was a significant positive trend in the incidence of haemangioma of all sites. There was a significant positive trend in the incidence of glioma of the brain. There was a significant positive trend in the incidence of mononuclear cell leukaemia of the spleen. There were significant positive trends in the incidence of islet cell adenoma of the pancreas and in the incidence of islet cell adenoma or islet cell adenocarcinoma (combined) of the pancreas.

In female rats, there was a significant positive trend in the incidence of adenoma of the mammary gland. There was a significant positive trend in the incidence of adenocarcinoma of the mammary gland, and the incidence was significantly increased at 200 and 600 ppm. There was a significant positive trend in the incidence of fibroadenoma of the mammary gland, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of adenocarcinoma or adenosquamous carcinoma (combined) of the mammary gland, and the incidence was significantly increased at 200 and 600 ppm. There was a significant positive trend in the incidence of mononuclear cell leukaemia of the spleen, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of squamous cell papilloma of the vagina, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of squamous cell papilloma or carcinoma (combined) of the vagina, and the incidence was significantly increased at 200 ppm. There was a significant positive trend in the incidence of adenoma or adenocarcinoma (combined) of the large intestine. There were significant positive trends in the incidence of malignant tumours of the Zymbal gland and in the incidence of benign or malignant tumours (combined) of the Zymbal gland. There were significant positive trends in the incidence of tumours of the clitoral gland. Specifically, there were significant positive trends in the incidence of adenoma, in the incidence of squamous cell papilloma or adenoma (combined), and in the incidence of squamous cell papilloma, adenoma, or adenocarcinoma (combined). There was a significant positive trend in the incidence of

squamous cell papilloma of the skin/appendage. There was a significant positive trend in the incidence of squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or sebaceous adenoma (combined) of the skin/appendage. There was a significant positive trend in the incidence of squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or squamous cell carcinoma (combined) of the skin/appendage. There were significant positive trends in the incidence of fibroma of the subcutis and in the incidence of fibroma or fibrosarcoma (combined) of the subcutis. There were significant positive trends in the incidence of endometrial stromal polyps of the uterus and in the incidence of adenoma or adenocarcinoma (combined) of the uterus. There were significant positive trends in the incidence of islet cell adenoma of the pancreas and in the incidence of islet cell adenoma or islet cell adenocarcinoma (combined) of the pancreas.

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

Two studies that investigated the toxicokinetics of 2-bromopropane in exposed humans, both in occupational settings, were available to the Working Group (Kawai et al., 1997, 2002).

Kawai et al. (1997) measured urinary metabolites of 2-bromopropane in 5 male workers exposed to 2-bromopropane at a geometric mean concentration of 3 mg/m^3 (geometric SD, 1.47 mg/m^3) and 20 unexposed male workers. The concentration of 2-bromopropane was measured by stationary air sampling at five sites in the workshop, following a grid sampling strategy. End-of-shift urinary concentrations of 2-bromopropane, 2-propanol (isopropyl alcohol), and acetone were measured with headspace GC-FID, and the end-of-shift urinary concentration of bromide ion was measured with GC-ECD after methylation using dimethyl sulfate. No 2-bromopropane or 2-propanol was detected in end-of-shift urine samples. The urinary concentrations of acetone and bromide ion for four exposed workers were within the ranges found for unexposed workers, but for one worker were higher than the upper limits of the ranges for unexposed workers. The worker with the highest urinary concentration was also likely to have the highest exposure because he was in charge of maintenance and frequent checking of a machine that used 2-bromopropane. [The Working Group noted that this study suggests that 2-bromopropane undergoes hydrolysis to produce bromide ion and 2-propanol, which oxidizes to acetone, in the urine of humans. The exposures at this plant (3 mg/m^3 [0.6 ppm]) were lower than the one government OEL of 1 ppm.]

Kawai et al. (2002) investigated the metabolism and excretion of 2-bromopropane with GC-ECD in urine samples from 10 groups (23–54 per group) in China, Japan, and the Republic of Korea. Derived data indicated that the mean metabolic bromide ion concentrations were 5.4 and 6.5 mg/mL in the urine of men and women, respectively, in Japan and ranged from 1.8 to 2.8 mg/mL for four groups in China and from 8 to 12 mg/mL for four groups of women in the Republic of Korea. Regression analyses showed that the urinary bromide concentration was positively associated with intake of marine products and negatively associated with intake of cereals or potato. [The Working Group noted that urinary bromide can be derived from intake of marine products in humans; therefore, it does not necessarily indicate exposure to a brominated compound that includes 2-bromopropane. The Working Group noted that acetone is also not specific as a biomarker for 2-bromopropane exposure.]

4.1.2 Experimental systems

(a) Absorption

Kim et al. (1997) reported that the penetration speeds of 2-bromopropane into the skin of male Crl:SKH-hrBr hairless mice were 4.165 mg/cm^2 per hour as measured with in vitro diffusion cell methods and 3.12 mg/cm^2 per hour as measured with in vivo methods.

(b) Metabolism

In the urine of rats exposed to 2-bromopropane at 0, 500, 1000, or 1500 mg/m^3 for 4 hours, concentrations of acetone and bromide ion increased in a dose-dependent manner (Kawai et al., 1997). Urinary metabolites were analysed in two rats that were fed a diet containing ^{35}S-labelled yeast and then dosed with 2-bromopropane. Traces of radioactive material, with the same R_F value (retention factor; describing migration in the solvent) as isopropyl mercapturic acid, were detected in the ethyl acetate extract of acidified urine excreted in the first 24 hours (Barnsley et al., 1966).

Kaneko et al. (1997) assessed the metabolism of 2-bromopropane by measuring the rate of disappearance of the substrate (2-bromopropane) and the rate of formation of the product (2-propanol). The reaction mixture contained rat hepatic microsomes, nicotinamide adenine dinucleotide phosphate (NADP), glucose 6-phosphate, and 2-bromopropane at 0.025–6.4 mM. The double reciprocal plot of the rate of metabolism against the concentration of the substrate indicated at least two sets of the metabolic constants V_{max} (maximal velocity) and K_m (Michaelis constant) in the metabolism of 2-bromopropane: V_{max1} = 0.38 mmol/mg protein per minute, V_{max2} = 1.30 mmol/mg protein per minute, K_{m1} = 0.07 mM, and K_{m2} = 0.32 mM. Calculations based on the formation of the product 2-propanol showed a lower V_{max2} of 1.02 nmol/mg protein per minute and a higher K_{m2} of 0.58 mM.

[The Working Group noted that the difference between the rate of disappearance of the substrate and the rate of formation of the product suggests the presence of metabolic pathways other than the pathway from 2-bromopropane to 2-propanol.]

A study on aerobic degradation of 2-bromopropane by a tropical marine yeast, *Yarrowia lipolytica* NCIM 3589, showed that the first product was 2-propanol, which was further metabolized to 2-propionic acid, eventually leading to the formation of carbon dioxide (Vatsal et al., 2015).

[The Working Group noted that, on the basis of the available data, 2-bromopropane is likely to be hydrolysed to bromide ion and 2-propanol, which is expected to be further oxidized to acetone, as well as being partially conjugated with glutathione.]

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 2-bromopropane is electrophilic or can be metabolically activated to electrophiles; is genotoxic; induces oxidative stress; is immunosuppressive; modulates receptor-mediated effects; or causes immortalization. No data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is electrophilic or can be metabolically activated to electrophiles

One study investigating the potential of 2-bromopropane to be electrophilic was available to the Working Group. An excess amount (0.3 mL) of 2-bromopropane was incubated with 2.0 mg of 2′-deoxyguanosine, dissolved in 1.0 mL of phosphate-buffered saline at pH 7.4, and incubated at 37 °C for 16 hours. After removal of the unreacted 2-bromopropane by extraction with diethyl ether, the remaining aqueous

solution was heated at 100 °C for 30 minutes. The high-performance liquid chromatography (HPLC) chromatogram identified one peak corresponding to N^7-isopropyl guanine (Zhao et al., 2002). [Given that the specific gravity of 2-bromopropane is 1.306 g/mL (20/4 °C), the concentration of 2-bromopropane in the reaction solution is 16.3 mM. The Working Group noted that the study showed qualitatively the potential of DNA adduct formation by 2-bromopropane in a cell-free system, although the experimental conditions were not appropriate.]

4.2.2 Is genotoxic

(a) Humans

(i) Exposed humans

No data in humans exposed to 2-bromopropane were available to the Working Group.

(ii) Human primary cells

Toraason et al. (2006) reported that exposure to 2-bromopropane at 1 mM for 4 and 8 hours, but not at 0.01 or 0.1 mM for 8 hours, significantly increased the comet tail moment, as measured with the alkaline electrophoresis (comet) assay, in primary human leukocytes from an unexposed non-smoking adult male volunteer (Toraason et al., 2006). [The Working Group noted that the comet tail moment was increased by exposure to 2-bromopropane only at the highest dose of 1 mM.]

(b) Experimental systems

(i) Non-human mammals in vivo

Pregnant ICR mice were exposed to 2-bromopropane by intraperitoneal injection with a single dose of 300, 600, 900, or 1800 mg/kg bw on day 0 of gestation. The frequency of micronuclei was evaluated in the embryos removed after cervical dislocation of the mothers on day 3 of gestation (Ishikawa et al., 2001). The exposure to 2-bromopropane increased the number of micronuclei per embryo in a dose-dependent manner. The percentage of embryos with micronuclei increased significantly at 900 and 1800 mg/kg bw. [The Working Group noted that the dose of 2-bromopropane was according to the Organisation for Economic Co-operation and Development (OECD) guideline (OECD, 2016) and that the micronucleus assay was performed as described in Titenko-Holland et al. (1998).]

The frequency of micronuclei did not increase in bone marrow polychromatic erythrocytes of Sprague-Dawley rats exposed to 2-bromopropane by intraperitoneal injection at 125, 250, or 500 mg/kg bw for 6 days per week for 28 days. However, the ratio (percentage) of polychromatic erythrocytes to the total number of erythrocytes was decreased in both male and female rats, suggesting bone marrow depression (Maeng & Yu, 1997). In contrast, the frequency of micronucleated hepatocytes (per 1000 hepatocytes) increased significantly in the liver of partially hepatectomized male Sprague-Dawley rats exposed intraperitoneally to 2-bromopropane at 200, 400, 800, or 1600 mg/kg bw (two injections), compared with the control group (olive oil, 4 mg/kg bw) (Maeng et al., 1996).

(ii) Non-human mammalian cells in vitro

In primary Leydig cells derived from Sprague-Dawley rats and exposed to 2-bromopropane at 0.01, 0.10, or 1 mM for 24 hours, the proportion of cells with undamaged DNA decreased significantly and the proportion with different grades of damaged DNA increased significantly, as measured with the single-cell gel electrophoresis (comet) assay. A total of 450 cells were evaluated in each dose group. Specifically, the percentage of cells with 5–20% and 20–40% of DNA damage was observed starting at 0.01 mM 2-bromopropane, the percentage with 40–90% of DNA damage was observed at concentrations above 0.10 mM, and the percentage with > 90% of DNA damage was observed at 1 mM (Wu et al., 2002).

Chromosomal aberrations were not observed in Chinese hamster lung cells exposed to 2-bromopropane at six different concentrations ranging from 0.077 to 2.46 mg/mL for 6 hours with metabolic activation (with the S9 microsomal mixture) and for 24 hours without metabolic activation (Maeng & Yu, 1997).

(iii) Non-mammalian experimental systems

Exposure to 2-bromopropane, tested at five concentrations (50, 100, 500, 1000, and 5000 µg/plate) in a preliminary assay and at five concentrations (313, 625, 1250, 2500, and 5000 µg/plate) in a second assay, induced mutagenicity in the *Salmonella typhimurium* strain TA100 with metabolic activation with the S9 microsomal mixture in a dose-dependent manner, and in the strain TA1535 with or without metabolic activation. In contrast, mutagenicity was not observed in the *S. typhimurium* strains TA98 or TA1537 or in *Escherichia coli* WP2 *uvrA*, indicating that 2-bromopropane induced mainly base-pair substitution mutations in *S. typhimurium* strains (Maeng & Yu, 1997).

4.2.3 Induces oxidative stress

(a) Humans

(i) Exposed humans

No data in humans exposed to 2-bromopropane were available to the Working Group.

(ii) Human cells in vitro

Flow cytometry-based analysis showed that exposure to 2-bromopropane at 100 µM for 24 hours increased the number of reactive oxygen species (ROS)-positive cells, as indicated by elevated levels of dihydroethidium, in spermatogenic cultures differentiated from human male embryonic stem cells for 10 days (Easley et al., 2015). Induction of oxidative stress was also confirmed by the elevation of ROS levels as observed with live-cell 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) imaging, and by the translocation of nuclear factor erythroid 2-related factor 2 (NRF2), a master regulator of oxidative stress, into the nucleus after exposure to 2-bromopropane at the same concentration [100 µM] for 24 hours. Annexin V flow cytometry-based analysis showed that pretreatment with the antioxidant l-sulforaphane at 1.0 µM significantly improved cell viability in cultures treated with 2-bromopropane at 100 µM for 24 hours (Easley et al., 2015). [The Working Group noted that the DCFH-DA method is known to produce ROS, and that the imaging of vehicle- or H_2O_2-exposed human spermatogenic cells showed the absence or presence of DCFH-DA-positive cells, respectively. In addition, the Working Group noted that the study was correctly performed and well controlled, because the percentage of cell viability was improved by pretreatment with the antioxidant l-sulforaphane.]

(b) Experimental systems

(i) Non-human mammals in vivo

Huang et al. (2009) showed that exposure of male Sprague-Dawley rats to 2-bromopropane by intraperitoneal injection at 1 g/kg bw per day for 7 days induced lipid peroxidation. There were significantly increased levels of 2-thiobarbituric acid-reactive substances (TBARS) in plasma and the epididymis, expressed as nmol/mL of plasma and nmol/mg protein of the epididymis, but not in the testis. 2-Bromopropane also induced a decrease in glutathione-*S*-transferase activity, as measured by the conjugation of 1-chloro-2,4-dinitrobenzene with reduced glutathione, in the testis and the epididymis. Glutathione-*S*-transferase activity was expressed as µmol/minute per mL of plasma and µmol/minute per mg protein of the testis and the epididymis. However, apoptosis, as measured by increased terminal deoxynucleotidyl transferase deoxyuridine phosphate (dUTP) nick end labelling (TUNEL)-positive or caspase-3-positive spermatogenic cells, was observed in the testis.

Pretreatment with 5 mg/kg of the antioxidant melatonin was able to attenuate the 2-bromopropane-induced oxidative damage and apoptosis in the various compartments investigated (Huang et al., 2009).

(ii) Non-human mammalian cells in vitro

Chan (2011) showed that exposure of mouse blastocyst cells to 2-bromopropane at 5 μM increased the fluorescence intensity of DCFH-DA, which indicates the generation of ROS. Pretreatment with 20 μM resveratrol blocked the generation of ROS.

In addition, Wu et al. (2002) showed that exposure of primary Leydig cells derived from Sprague-Dawley rats to 2-bromopropane at 0.1 or 1 mM not only induced DNA damage (as reported in Section 4.2.2(b)(ii)) but also significantly increased malondialdehyde levels (expressed in μmol/mL) and glutathione peroxidase enzymatic activity (expressed in U/mL) and decreased superoxide dismutase enzymatic activity (expressed in U/mL).

4.2.4 Is immunosuppressive

(a) Humans

Several studies reported signs of haematotoxicity (depletion of immune cells), which can be associated with immunosuppression (Smith et al., 2020). In a case-series study in an electronics factory in the Republic of Korea, alterations in haematopoiesis, and hence myelotoxicity, were reported in workers who were highly exposed to 2-bromopropane while working in the tactile switch assembly operation section, where 2-bromopropane was used as a solvent (Kim et al., 1996b; Park et al., 1997). The investigation started after the reporting of amenorrhoea among 16 of the 25 female workers employed in the tactile switch assembly operation section. [Exposure characterizations of the studies, including critical appraisals, are provided in Sections 1.4 and 1.6.] The mean stationary concentration of 2-bromopropane under simulated conditions in the factory was calculated as 12.4 ppm (SD, 3.13 ppm; range, 9.2–19.6 ppm). In contrast, the short-term stationary concentration of 2-bromopropane inside the hood of the cleaning baths was calculated as 4140.7 ppm. The employees performed work there irregularly (with unknown frequency and duration). Workers were suspected to have significant dermal exposures, because they reported unprotected hand-dipping of parts into the 2-bromopropane cleaning solvent. [The Working Group considered that the calculated exposure was probably underestimated, because the assessment was performed only under simulated conditions.]

Kim et al. (1996b) described clinical findings in the exposed workers. Blood samples were collected from 25 female workers and 8 male workers. The measurements comprised blood count, haemoglobin, and a test for bleeding tendency. Among the female workers, 11 women had leukocyte levels (range, 1910–3980 cells/μL) lower than the normal range (4800–10 800 cells/μL), 8 women had erythrocyte levels lower than the normal range (range, 2.8–3.7 × 10^6 cells/μL; lower reference normal value, 4.2 × 10^6 cells/μL), and 9 women had platelet levels lower than the normal range (range, 1.5–10.9 × 10^4 cells/μL; lower reference normal value, 13 × 10^4 cells/μL). All the women who reported amenorrhoea had pancytopenia. Two women with signs of marked pancytopenia (erythrocytes, 2.28–2.57 × 10^6 cells/μL; leukocytes, 1650–1910 cells/μL; platelets, 1.5–1.7 × 10^4 cells/μL) had bone marrow biopsy findings that showed marked hypoplastic marrow (with cellularity of 15% and 25%, respectively). Among the male workers, 3 men had leukocyte levels lower than the normal range (range, 4340–4680 cells/μL) and, among them, one had mild pancytopenia (erythrocytes, 3.53 × 10^6 cells/μL; leukocytes, 4680 cells/μL; platelets, 6.8 × 10^4 cells/μL) (Kim et al., 1996b).

Additional comparative analyses were performed between highly exposed workers and "unexposed worker" groups: (i) workers in a section other than the tactile switch assembly operation section, and (ii) workers who quit the job before 2-bromopropane was introduced as a solvent (Park et al., 1997).

Park et al. (1997) did not report any findings of pancytopenia in the "unexposed worker" groups among 77 workers in the tactile switch processing operation section and the general switch processing operation section, or among the 6 employees who worked in the tactile switch assembly operation section before 2-bromopropane was introduced as a solvent. [Although the exposure assessment had limitations, i.e. the stationary measurement was performed in a simulated exposure setting and no dermal exposure was measured, the Working Group noted that all the workers were clearly exposed to high levels of 2-bromopropane (see Section 1.6) and considered the study particularly informative because it provided evidence of immunosuppressive effects in humans, on the basis of findings of leukopenia and evidence of bone marrow suppression.]

Haematological effects in workers exposed to 2-bromopropane were also studied in a 2-bromopropane production facility in China (Ichihara et al., 1999). A cross-sectional study was performed in 25 workers (11 men and 14 women) employed in December 1996. Exposures to 2-bromopropane were measured in workers directly involved in the production (operators and mixers), those in areas adjacent to production (laboratory worker, repairperson, boiler), and "unexposed" workers (accountants, salespeople, engineer, assistant manager). Median exposures for workers directly involved in production and transfer were 6.77 ppm (for operators) and 6.30 ppm (for mixers). Workers in areas adjacent to production (laboratory worker, repairperson, boiler) were exposed at lower levels. One accountant had a full-shift exposure of 0.88 ppm above the LOD of 0.02 ppm; the exposures in other non-factory-related workers (accountants, salespeople, engineer, assistant manager) were below the LOD on the sampling day. Instantaneous stationary air samples, although they were collected using imprecise detection and measurement methods, indicated median area concentrations for specific production areas, ranging between 4.0 ppm and 88.6 ppm. The medical examination included interviews, blood sample collections, hormone levels, and sperm samples (see also Section 4.2.5). Leukocytes, erythrocytes, haemoglobin, and haematocrit were measured. No workers showed signs of leukocytopenia or pancytopenia, including the 4 women with amenorrhoea or polymenorrhoea. Among the female workers with normal menstruation, leukocyte counts were lower in the 5 female operators (who were exposed to 2-bromopropane) than in the unexposed female workers (3 accountants and 1 analyst) ($P < 0.05$). Leukocyte counts decreased with increasing TWA of 2-bromopropane exposure, although this inverse association was weak. Erythrocyte counts also decreased with increasing TWA of 2-bromopropane exposure ($P < 0.05$). [The exposure assessment method used by the authors (individual-based assessment of exposure based on a single 8-hour TWA personal measurement) will have led to attenuation of the exposure–outcome associations. A group-based approach (in which each worker would have been assigned the median exposure of the job they performed) would have resulted in a stronger and unbiased estimate of the exposure–outcome associations. The Working Group therefore re-analysed the association between exposure to 2-bromopropane and the outcomes leukocyte count and erythrocyte count. For the association between 2-bromopropane and leukocyte count, the group-based exposure assessment would have resulted in an almost 2-fold stronger inverse association ($\beta = -0.1369$, group-based, versus $\beta = -0.0784$, individual-based) with a slightly

stronger statistical significance (P = 0.1294 versus P = 0.2597). For the association between 2-bromopropane and erythrocyte count, the group-based exposure assessment would have resulted in a 2-fold stronger inverse association (β = −0.0796, group-based, versus β = −0.0384, individual-based) with a stronger statistical significance (P = 0.0042 versus P = 0.0874) (Fig. 4.1).]

(b) Experimental systems

Sprague-Dawley rats were exposed orally to 2-bromopropane at 100, 330, or 1000 mg/kg bw per day for 28 consecutive days (Jeong et al., 2002). The rats were immunized intravenously with sheep erythrocytes 4 days before necropsy. Exposure to 2-bromopropane at 1000 mg/kg bw per day significantly reduced body weight, thymus weight, leukocyte count, and platelet count in peripheral blood, and the number of different subpopulations of splenic lymphocytes. In addition, there were dose-dependent decreases in the number of thymocyte subpopulation cells per thymus and in the number of $CD4^+CD8^+$ cells in the thymus, with statistically significant changes at 330 and 1000 mg/kg bw per day. Exposure to 2-bromopropane also induced decreases in the numbers of $CD4^-CD8^+$, $CD4^+CD8^-$, and $CD4^-CD8^-$ cells in the thymus and in the numbers of total cells per spleen, antibody-forming cells per spleen, antibody-forming cells per spleen cell, T cells per spleen, T helper cells per spleen, cytotoxic T cells per spleen, and B cells per spleen, with statistically significant changes at 1000 mg/kg bw per day. [The Working Group noted that the study suggested an immunotoxic potential of 2-bromopropane in rats.]

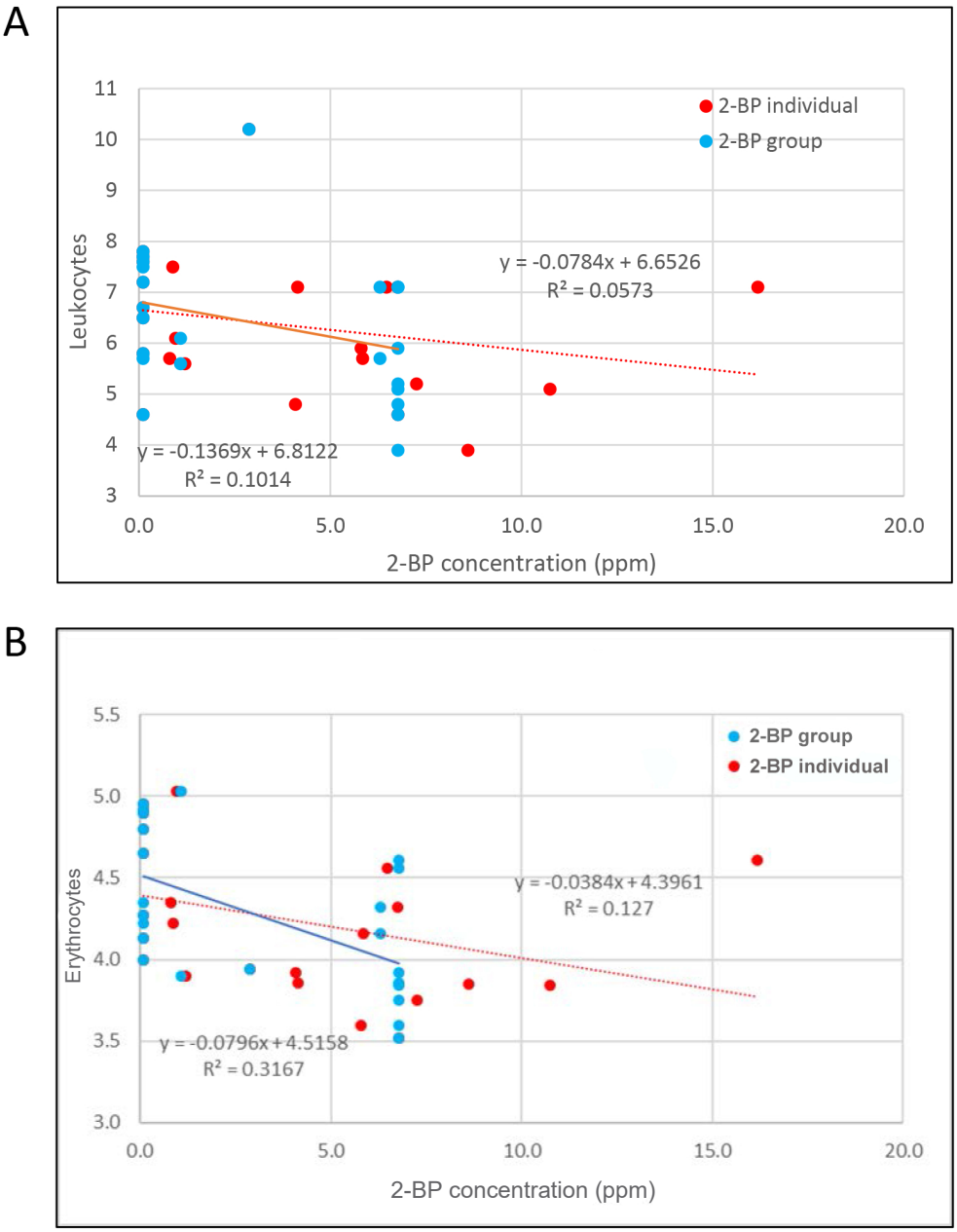
Exposure of CD3-stimulated splenocytes derived from C3H male mice to 2-bromopropane at 10 μM for 24 hours downregulated the expression of the tumour necrosis factor alpha (TNFα) gene but did not alter the expression of the pro-inflammatory cytokines interleukin 6 (IL-6), IL-1, and interferon gamma (IFNγ) (Kim et al., 2002). Similarly, serum IL-6 levels did not increase after single or repeated intraperitoneal injections of 2-bromopropane at 3.5 g/kg bw in C3H male mice. No effect was observed after 24 or 48 hours of 2-bromopropane treatment of CD3-stimulated mice splenocytes (Kim et al., 2003).

Exposure of male Wistar rats to 2-bromopropane by inhalation at 1000 ppm for 9 weeks or at 3000 ppm for 9–11 days significantly decreased the erythrocyte, platelet, and leukocyte counts, and levels of haemoglobin and haematocrit in the peripheral blood (Ichihara et al., 1997). In the same experimental setting, exposure to 2-bromopropane significantly decreased the erythrocyte count at 300 ppm and higher, platelet count at 300 and 1000 ppm, and leukocyte count at 1000 ppm. The highest concentration induced a hypoplastic profile in the bone marrow, causing replacement of fatty spaces, and a decrease in the number of megakaryocytes, but it did not change the ratio of granulocytes to erythrocytes in the bone marrow (Nakajima et al., 1997).

Oral exposure of male Sprague-Dawley rats to 2-bromopropane at 1000 mg/kg bw per day significantly decreased the weight of the spleen after 2 and 4 weeks of exposure and the weight of the thymus after 2, 3, and 4 weeks of exposure, and reduced the peripheral leukocyte count after 3 weeks of exposure. The weight of the spleen did not recover 8 weeks after the end of exposure (Lee et al., 1998).

In a dose-finding study for a carcinogenicity test that complied with GLP, groups of 10 male and 10 female F344/DuCrlCrlj rats (age, 6–7 weeks) were treated with 2-bromopropane (purity, 99.7%) 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), 100, 300, 1000, 2000, and 3000 ppm (JBRC, 2016a, b). In the haematology results, there were significant decreases in the erythrocyte count, haemoglobin, haematocrit, platelet count, and leukocyte count, and increases in

Fig. 4.1 Leukopenia and pancytopenia in workers exposed to 2-bromopropane



Regression analysis of 2-bromopropane (2-BP) exposure levels (ppm) and (A) leukocyte and (B) erythrocyte counts ($\times 10^6$/mL) in workers at a production plant in Yixing City, Jiangsu Province, China, as per a group-based approach (blue dots), compared with an individual-based approach (red dots). Data from Ichihara et al. (1999) were re-analysed by the Working Group with the group-based approach. A group-based approach (in which each worker would have been assigned the median exposure of the job they performed) would have resulted in a stronger and unbiased estimate of the exposure–outcome associations. For the association between 2-BP and leukocyte count, the group-based exposure assessment would have resulted in an almost 2-fold stronger inverse association ($\beta = -0.1369$, group-based, versus $\beta = -0.0784$, individual-based). For the association between 2-BP and erythrocyte count, the group-based exposure assessment would have resulted in a 2-fold stronger inverse association ($\beta = -0.0796$, group-based, versus $\beta = -0.0384$, individual-based).
Created by the Working Group.

mean corpuscular volume and mean corpuscular haemoglobin in the male and female groups at 1000 ppm and higher. In addition, there was a significant dose-dependent increase in reticulocyte counts in the male groups at 2000 ppm and higher and in the female groups at 1000 ppm and higher. There was a significant decrease in the absolute and relative weights of the thymus in the male and female groups at 1000 ppm and higher. In addition, there were significant decreases in the absolute and relative weights of the testis and the epididymis in the male groups at 300 ppm and higher. In the histopathology results, there were significant increases in the incidence of decreased haematopoiesis of the bone marrow in the male and female groups at 2000 ppm and higher and in the incidence of atrophy of the thymus and extramedullary haematopoiesis in the spleen in the male and female groups at 1000 ppm and higher. In addition, there were significant increases in the incidence of oedema and tubular atrophy in the testis in the groups at 300 ppm and higher, decreased sperm count in the epididymis in the groups at 1000 ppm and higher, and debris of spermatic elements in the epididymis in all treated groups (JBRC, 2016a, b).

4.2.5 Modulates receptor-mediated effects

(a) Humans

Alterations in hormone levels and myelotoxicity were reported in the two cross-sectional studies that investigated the effects of 2-bromopropane exposure in workers in an electronics factory in the Republic of Korea (Kim et al., 1996b) and in a 2-bromopropane production factory in China (Ichihara et al., 1999). Both studies are also described in Section 4.2.4, and their exposure assessment is reported in Section 1.6. More details on the alterations in hormone levels are given below.

Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and testosterone were measured in the population of workers, including 25 women and 8 men, employed in the electronics factory in the Republic of Korea (Kim et al., 1996b). Female workers were followed up at 2 and 7 years after the first investigation (Koh et al., 1998; Yun et al., 2002), and male workers were followed up at 2–3 months (Hong et al., 2002). In the 16 women who reported amenorrhoea (lasting 2–14 months), FSH levels were elevated (range, 27.8–136.7 mIU/mL) compared with reference normal values (1.9–11.9 mIU/mL); this is indicative of ovarian failure. In 14 of the 16 women, LH levels were also elevated (range, 12.9–48.7 mIU/mL) above normal values (1.9–11.9 mIU/mL). Prolactin levels were within the normal range, and estradiol levels were lower (< 13.6 pg/mL) than normal values (30–120 pg/mL). Koh et al. (1998) reported the results of ovarian biopsy in 6 of the women with amenorrhoea and confirmed the diagnosis of ovarian failure. Two of the 16 women with amenorrhoea recovered their ovarian function after 24 months from the last exposure (Koh et al., 1998). At the 7-year follow-up of these 16 women, 10 women recovered from the amenorrhoea only after hormone replacement therapy (Yun et al., 2002). Serum levels of FSH and LH decreased but remained elevated above the normal ranges both in women who recovered from amenorrhoea (FSH mean, 88.29; SD, 24.69 mIU/mL; LH mean, 26.45; SD, 11.79) and in those who did not recover from amenorrhoea (FSH mean, 76.68; SD, 27.98; LH mean, 26.45; SD, 11.79). Among the 8 male workers, FSH levels (13.5–19 mIU/mL) were towards the upper end of the normal range, and LH, prolactin, and testosterone levels were within the normal range (Kim et al., 1996b). Signs of oligospermia, azoospermia, and reduced sperm motility were also reported in 4, 2, and 5 men, respectively.

Hong et al. (2002) followed up these men at 2–3 months after the initial examination and found that FSH and LH levels remained towards the upper end of the normal range (FSH range

in men, 9.6–74.4 mIU/mL; LH range in men, 40.6–4.8 mIU/mL).

Serum levels of FSH and LH were also measured in workers in the 2-bromopropane factory in China (Ichihara et al., 1999). In addition, estradiol was measured in women and testosterone was measured in men. In men, levels of FSH and LH were towards the upper end of the normal range, and testosterone levels were within the normal range. In women, FSH, LH, and estradiol levels were within the normal range. In a regression analysis, LH, FSH, estradiol, and testosterone levels were not associated with values of individual TWA 2-bromopropane concentration. [The Working Group noted that almost all female workers with amenorrhoea had higher FSH and LH levels and lower estradiol levels, and that male workers with severely decreased sperm indices had higher FSH levels and lower testosterone levels, suggesting that an increase in FSH or LH levels results from reduced sex hormone production in the ovary or the testis.]

(b) Experimental systems

(i) Non-human mammals in vivo

Wu et al. (1999a) investigated the male reproductive toxicity of 2-bromopropane in sexually mature and immature male Sprague-Dawley rats. Mature and immature rats treated for 5 days per week for 5–7 weeks with subcutaneous injection of 2-bromopropane at 600 and 1800 mg/kg bw had significantly reduced serum testosterone levels. At the highest dose of 1800 mg/kg bw, there was a significant increase in *β-LH* gene expression in the pituitary gland. [The Working Group interpreted the increased gene expression of *β-LH* as being a result of positive feedback due to decreased serum testosterone level.]

Male Wistar rats were exposed to 2-bromopropane by inhalation for 8 hours per day for 7 days per week at 0, 300, or 1000 ppm for 9 weeks or at 3000 ppm for 9–11 days (Ichihara et al., 1997). Exposure to 2-bromopropane decreased in a dose-dependent manner the epididymal sperm count and motility and the number of erythrocytes and platelets at 300 ppm or higher. Histopathological examination showed a decrease in spermatogenic cells at 300 ppm and depletion of spermatogenic cells at 1000 and 3000 ppm, but Sertoli cells remained. In female Wistar rats exposed to 2-bromopropane by inhalation at 100, 300, or 1000 ppm for 8 hours per day, 7 days per week, for 9 weeks, the vaginal smear test showed that the number of normal estrous cycles decreased at 300 and 1000 ppm, and the histopathological study showed dose-dependent atresia of ovarian follicle accompanied by decreased numbers of normal atresia and growing follicles at 300 and 1000 ppm (Kamijima et al., 1997).

Four groups of 5 female ICR mice each were exposed to 2-bromopropane at 0, 500, 1000, or 2000 mg/kg bw by intraperitoneal injection, 8 times at intervals of 2 or 3 days for 17 days (Sekiguchi & Honma, 1998). Pregnant mare's serum gonadotropin and human chorionic gonadotropin were injected on day 15 and day 17 of 2-bromopropane injection to induce superovulation, and the liver, uterus, and oviduct were removed on autopsy. Exposure to 2-bromopropane at 2000 mg/kg bw did not change the body weight or liver weight but decreased the weight of the uterus. However, 2-bromopropane decreased the numbers of ovulated ova in a dose-dependent manner, with a significant change at 1000 and 2000 mg/kg bw.

Omura et al. (1999) investigated target cells of 2-bromopropane in the testis of Wistar rats by intraperitoneal injection of 2-bromopropane at 1335 mg/kg bw for 1–5 days and found that 2-bromopropane targets spermatogonia. Takeuchi et al. (2004) investigated the developmental effects of exposure to 2-bromopropane by inhalation on pups of Sprague-Dawley rats. Adult female rats were exposed to 2-bromopropane at 0, 125, 250, 500, or 1000 ppm for 6 hours per day, 7 days per

week, during 2 weeks of the pre-mating period, during the mating period until copulation, and during days 0–19 of gestation. After parturition, the dams were allowed to breastfeed their pups until postnatal day 4. No signs indicating maternal toxicity, such as abnormal clinical signs or body-weight loss, were observed. Exposure to 2-bromopropane at 1000 ppm significantly decreased the number of pups, although the number of implantations was not decreased. The weight or survival of pups was not affected by exposure to 2-bromopropane until postnatal day 4. The study showed that exposure to 2-bromopropane induced fetal lethality in the post-implantation period (Takeuchi et al., 2004).

Kim et al. (2004a) investigated the effects on embryo-fetal development of maternal exposure to 2-bromopropane in pregnant ICR mice treated by subcutaneous injection at 0, 500, 1000, or 1500 mg/kg per day on days 6–17 of gestation. Caesarean sections were carried out on all dams on day 18 of gestation, and the fetuses were examined for external, visceral, and skeletal abnormalities. A dose-dependent decrease in fetal body weight and an increase in the incidence of fetal malformations and of ossification delay were found.

Kim et al. (2004b) investigated the effects on embryo-fetal development of maternal exposure to 2-bromopropane in pregnant Sprague-Dawley rats treated by subcutaneous injection at 0, 250, 500, or 1000 mg/kg bw per day on days 6–19 of gestation. An increase in the number of fetal deaths, a decrease in litter size, a decrease in fetal body weight, and an increase in the incidence of fetal malformations were observed at 1000 mg/kg bw per day, which induced maternal toxicity such as an increase in the incidence of abnormal signs, a suppression of body weight and body-weight gain, and a decrease in food intake. Minimal developmental toxicity, including decreased fetal body weight and increased fetal ossification delay, was observed at 500 mg/kg bw per day, but no adverse effects on dams or fetal development were observed at 250 mg/kg bw per day (Kim et al., 2004b).

[The Working Group noted that developmental effects were observed at the level that induced maternal toxicity in mice and rats.]

(ii) Non-human mammalian cells in vitro

Exposure of primary Leydig cells derived from male Sprague-Dawley rats to 2-bromopropane at 0.01 or 0.1 mM did not induce a detectable change in the secretion of testosterone during 24 hours of treatment, but exposure at 1 mM decreased the secretion of testosterone after 12 hours of treatment (Wu et al., 1999b). [The Working Group noted that the 1 mM concentration of 2-bromopropane induced cytotoxicity.]

[The Working Group acknowledged that several of the effects observed after exposure to 2-bromopropane and reported in this section were also consistent with reproductive toxicity mediated through receptor modulation. However, the Working Group deemed it relevant to include evidence reporting on measured changes in blood levels of hormones, i.e. LH, estradiol, and testosterone, including studies in experimental systems in vivo, in line with the evidence on cancers in experimental animals (see Section 3) in relevant target organs (e.g. the uterus, mammary gland, and thyroid).]

4.2.6 Causes immortalization

Human cells in vitro

Exposure to 2-bromopropane significantly increased spheroid formation in various human colorectal adenocarcinoma cells at non-cytotoxic concentrations: 0.01–1 μM in CSC221 cells, 0.05–1 μM in DLD1 cells, 0.01–5 μM in Caco2 cells, and 0.1–1 μM in HT29 cells (Cho et al., 2017). After 72 hours of exposure to 2-bromopropane, the cancer stem cell markers *ALDH-1*, *CD133*, *LGR-5*, and *MSI-1* increased at the mRNA and protein levels, and *CD44* and *BMI-1* increased at the mRNA levels in CSC221 cells.

In addition, 2-bromopropane enhanced the activation of promoters associated with cancer stem cell markers, such as TOPflash and glioma-associated oncogene homologue zinc finger protein (Gli). 2-Bromopropane increased the mRNA expression of signalling molecules such as Gli-1, Gli-2, Smoothened (SMO), and β-catenin. [The Working Group noted that 2-bromopropane increased the stemness of cancer cells. However, the Working Group questioned the relevance of the test system and the markers.]

4.3 Evaluation of high-throughput in vitro toxicity screening data

2-Bromopropane 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 2-bromopropane high-throughput toxicity testing 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, 2022a). 2-Bromopropane was inactive in all but 2 of the 111 assays. The active hit calls were in two viability assays mapped to the key characteristic "alters cell proliferation, cell death, or nutrient supply", but both results were flagged for low efficacy and activity only at the highest testing concentration of 79.2 μM. [The Working Group considered this as weak evidence of activity for this key characteristic.]

The chemical analysis of a dimethyl sulfoxide stock solution used in testing was graded "Fns", indicating that no 2-bromopropane was detected (NIH, 2022). 2-Bromopropane has an experimental vapour pressure of 216 mm Hg [at 25 °C] (US EPA, 2022b). [The Working Group concluded that this high volatility may have led to little or no presence of the chemical in the biological assays.]

5. Summary of Data Reported

5.1 Exposure characterization

2-Bromopropane is synthesized by heating 2-propanol (isopropyl alcohol) together with hydrogen bromide. It also occurs as an impurity of commercial-grade 1-bromopropane used in vapour degreasing, historically at concentrations of 0.1–0.2% but nowadays to a maximum of

0.05%. For other uses of 1-bromopropane, such as adhesives, no maximum level of 2-bromopropane impurity in 1-bromopropane has been set. Historically the production volume for 2-bromopropane has been low. It was originally produced in Japan and the USA. Currently at least 13 manufacturers in China are known, but production volumes are unknown.

Occupational exposure to 2-bromopropane can occur via the respiratory and/or dermal route during its production and use as a cleaning or dry-cleaning agent or solvent, and in the production and application of adhesives. Historical evidence of very high personal exposure comes from studies in a plant producing 2-bromopropane and in an electronics plant where it has been used as a cleaning agent. Occupational exposure to 2-bromopropane has also occurred because of its presence as an impurity of 1-bromopropane, which since the 1990s has been used as a substitute for ozone-depleting and other solvents.

There are no available data on exposure of the general population to 2-bromopropane.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Treatment with 2-bromopropane caused an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in males and females of a single species (rat) in one study that complied with Good Laboratory Practice (GLP).

2-Bromopropane was administered by inhalation in one study that complied with GLP, in male and female F344/DuCrlCrlj rats. In male rats, 2-bromopropane caused an increase in the incidence of the following tumours: malignant tumours of the Zymbal gland and benign or malignant tumours (combined) of the Zymbal gland; malignant tumours and appropriate combinations of malignant or benign tumours of the skin/appendage: specifically, basal cell carcinoma of the skin/appendage, squamous cell carcinoma or basal cell carcinoma (combined) of the skin/appendage, and squamous cell papilloma, basal cell epithelioma, sebaceous adenoma, keratoacanthoma, squamous cell carcinoma, or basal cell carcinoma (combined) of the skin/appendage; adenocarcinoma of the large intestine and adenoma or adenocarcinoma (combined) of the large intestine; adenocarcinoma of the small intestine; malignant lymphoma of the lymph nodes; squamous cell papilloma or carcinoma (combined) of the stomach; adenocarcinoma, adenoma, or squamous cell papilloma (combined) of the preputial gland; fibroma or fibrosarcoma (combined) of the subcutis; follicular adenoma or adenocarcinoma (combined) of the thyroid gland; glioma of the brain; mononuclear cell leukaemia of the spleen; and islet cell adenoma or islet cell adenocarcinoma (combined) of the pancreas.

In female rats, 2-bromopropane caused an increase in the incidence of the following tumours: adenocarcinoma of the mammary gland and adenocarcinoma or adenosquamous carcinoma (combined) of the mammary gland; mononuclear cell leukaemia of the spleen; squamous cell papilloma or carcinoma (combined) of the vagina; adenoma or adenocarcinoma (combined) of the large intestine; malignant tumours of the Zymbal gland and benign or malignant tumours (combined) of the Zymbal gland; squamous cell papilloma, adenoma, or adenocarcinoma (combined) of the clitoral gland; squamous cell papilloma, trichoepithelioma, basal cell epithelioma, keratoacanthoma, or squamous cell carcinoma (combined) of the skin/appendage; fibroma or fibrosarcoma (combined) of the subcutis; adenoma or adenocarcinoma (combined) of the uterus; and islet cell adenoma or islet cell adenocarcinoma (combined) of the pancreas.

5.4 Mechanistic evidence

The only evidence of absorption, distribution, metabolism, and excretion in humans and rats in vivo comes from concentrations of acetone and bromide ion in the urine after inhalation exposure to 2-bromopropane; however, these markers are unreliable.

One experimental study showed skin penetration of 2-bromopropane in hairless mice in vivo and in vitro. Data on the metabolism of 2-bromopropane are available from acellular systems with rat hepatic microsomes, suggesting that 2-bromopropane is hydrolysed to bromide ion and 2-propanol, which is expected to be further oxidized to acetone, as well as the presence of other metabolic pathways. Urinary excretion of isopropyl mercapturic acid in rats dosed with 2-bromopropane suggests that 2-bromopropane is partially conjugated with glutathione.

Data were available for 2-bromopropane for the following key characteristics of carcinogens: "is genotoxic", "induces oxidative stress", "is immunosuppressive", and "modulates receptor-mediated effects".

There is consistent and coherent evidence that 2-bromopropane exhibits key characteristics of carcinogens.

2-Bromopropane is genotoxic. No data were available in humans exposed to 2-bromopropane. There is consistent and coherent evidence for the genotoxicity of 2-bromopropane in experimental systems. In one study using the comet assay in primary human leukocytes, 2-bromopropane induced DNA damage. 2-Bromopropane caused a dose-dependent increase in micronucleus formation in mouse embryos and in rat liver, but not in polychromatic erythrocytes in rat bone marrow. 2-Bromopropane increased the frequency of DNA damage in primary Leydig cells derived from rats but did not cause chromosomal aberrations in Chinese hamster lung cells with or without metabolic activation. 2-Bromopropane was mutagenic in the *Salmonella typhimurium* strain TA100 with metabolic activation in a dose-dependent manner and in the strain TA1535 with or without metabolic activation but did not induce mutagenicity in *S. typhimurium* strains TA98 or TA1537 or in *Escherichia coli* WP2 *uvrA*, indicating that 2-bromopropane induced base-pair substitution mutations in *Salmonella* strains.

2-Bromopropane induces oxidative stress. No data were available in humans or in human primary cells exposed to 2-bromopropane. There is consistent and coherent evidence for induction of oxidative stress by 2-bromopropane in experimental systems. In one study in spermatogenic cells differentiated from human embryonic stem cells, 2-bromopropane increased levels of reactive oxygen species and translocation of NRF2 into the nucleus. In rats, 2-bromopropane increased levels of 2-thiobarbituric acid-reactive substances in plasma and the epididymis and decreased glutathione levels in the testis and the epididymis. Exposure to 2-bromopropane increased the generation of reactive oxygen species in mouse blastocyst cells, and increased malondialdehyde levels and glutathione peroxidase activity and decreased superoxide dismutase activity in Leydig cells derived from rats.

2-Bromopropane is immunosuppressive. The evidence in exposed humans is suggestive. One study among workers at an electronics factory who were exposed to solvents containing 2-bromopropane showed that 2-bromopropane induced pancytopenia in blood and hypoplastic bone marrow. Another study, among workers manufacturing 2-bromopropane, showed an inverse association between 2-bromopropane exposure level and both leukocyte and erythrocyte cell counts. The evidence is consistent and coherent in experimental systems. In rats, exposure to 2-bromopropane caused dose-dependent decreases in thymus weight and cellularity, leukocyte count, and various subpopulations of lymphocytes in the spleen and the thymus, haematotoxicity, and significant evidence of

decreased haematopoiesis of the bone marrow. In addition, a decrease in the T-cell-dependent antibody response was observed.

There is suggestive evidence that 2-bromopropane modulates receptor-mediated effects. In one study among workers at an electronics factory who were exposed to 2-bromopropane-containing solvents, amenorrhoea was seen in female workers with high levels of follicle-stimulating hormone and luteinizing hormone and low levels of estradiol. In the same electronics factory, azoospermia or oligospermia was observed in male workers. In a second study, among workers manufacturing 2-bromopropane, findings for modulation of receptor-mediated effects were largely negative. In rats, exposure to 2-bromopropane resulted in reduced serum testosterone levels and significantly increased expression of the β-luteinizing hormone (β-LH) gene in the pituitary gland.

For the key characteristics "is electrophilic or can be metabolically activated to electrophiles", "induces chronic inflammation", and "causes immortalization", there was a paucity of available data.

2-Bromopropane 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 2-bromopropane 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 2-bromopropane.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-bromopropane.

6.3 Mechanistic evidence

There is *strong evidence* that 2-bromopropane exhibits key characteristics of carcinogens in experimental systems.

6.4 Overall evaluation

2-Bromopropane is *probably carcinogenic to humans (Group 2A).*

6.5 Rationale

The Group 2A evaluation for 2-bromopropane is based on *sufficient evidence* for cancer in experimental animals and *strong mechanistic evidence* in experimental systems, supported by suggestive mechanistic evidence in exposed humans. The *sufficient evidence* for cancer in experimental animals is based on an increase in the incidence of malignant neoplasms in males and females of a single species (rat) in one study that complied with Good Laboratory Practice. In addition, an increase in the incidence of appropriate combinations of benign and malignant neoplasms was observed in males and females in this study. Also, an unusually high degree of carcinogenic activity with regard to incidence, site, and types of tumours was observed in both males and females. The evidence regarding cancer in humans was *inadequate* because no studies were available.

There was *strong* mechanistic evidence of several key characteristics of carcinogens (genotoxicity, induction of oxidative stress, and immunosuppression) in experimental systems. There was suggestive evidence of immunosuppression

and of modulation of receptor-mediated effects in two studies of small numbers of workers exposed to 2-bromopropane. Although no experimental studies were available in human primary cells or tissues, the Working Group concluded that a Group 2A evaluation was appropriate, given the unusually high degree of carcinogenic activity observed in the animal bioassays and the consistent and coherent evidence that 2-bromopropane exhibits key characteristics of carcinogens, in particular immunosuppression, across mammalian species and in vitro systems, supported by suggestive evidence of immunosuppression and of modulation of receptor-mediated effects in exposed humans.

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