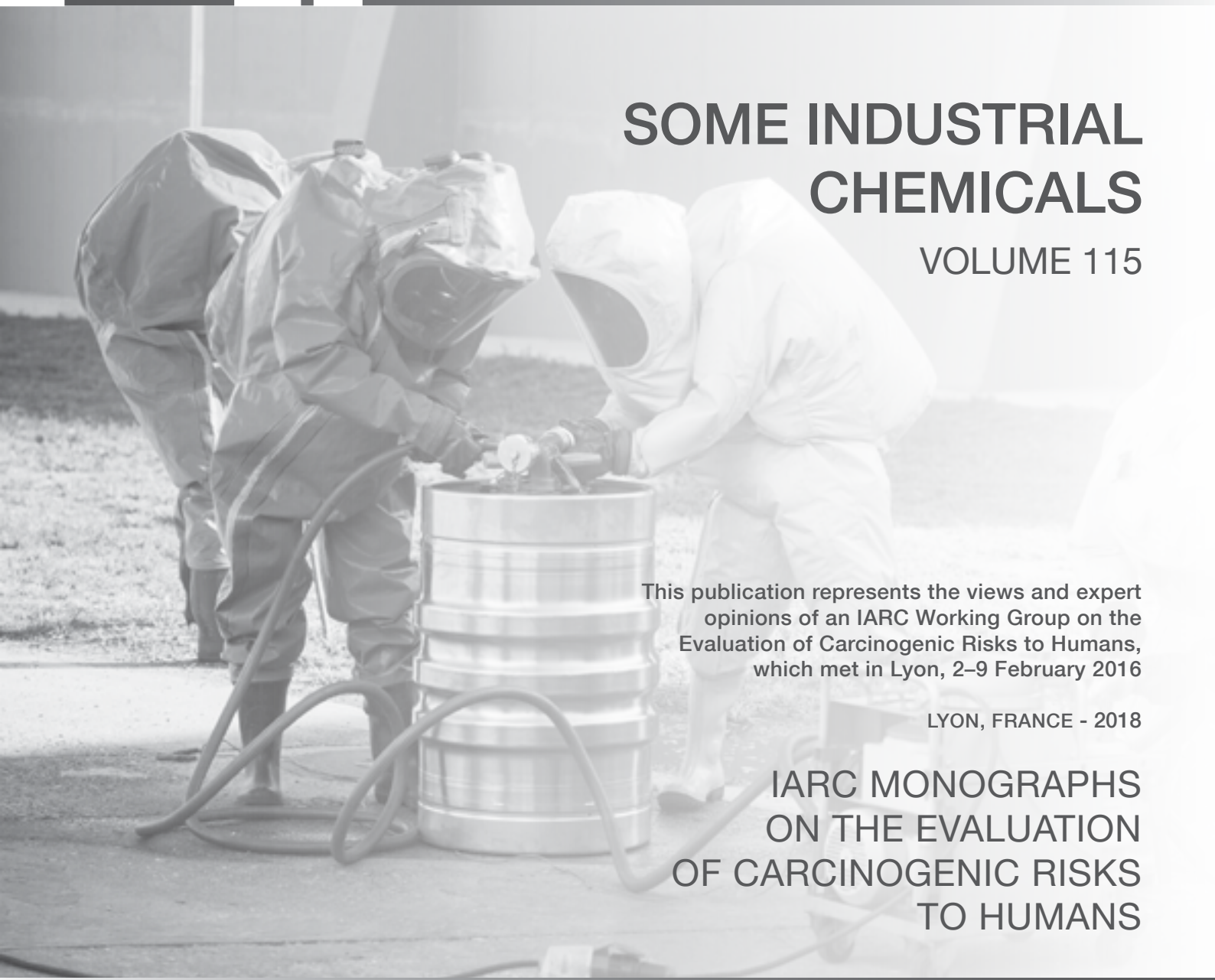
IARC MONOGRAPHS



SOME INDUSTRIAL CHEMICALS

VOLUME 115

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 2–9 February 2016

LYON, FRANCE - 2018

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1-BROMOPROPANE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 106-94-5

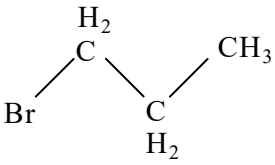
Chem. Abstr. Serv. Name: Propane, 1-bromo

IUPAC Systematic Name: 1-Bromopropane

Synonyms: 1-Propyl bromide; *n*-propyl bromide

Acronyms: 1BP; nPB.

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: C_3H_7Br

Relative molecular mass: 122.99

1.1.3 Chemical and physical properties of the pure substance

Description: Colourless to pale yellow liquid with a strong, characteristic sweet odour (Merck index, 2013)

Boiling point: 71 °C at 760 mm Hg (Merck index, 2013)

Melting point: –110 °C (Merck index, 2013)

Density: 1.353 at 20 °C (Merck index, 2013)

Vapour density: 4.25 (air = 1) (HSDB, 2016)

Solubility: Poorly soluble in water (2.45 mg/L at 20 °C) (HSDB, 2016); soluble in acetone, ethanol, ether, benzene, chloroform and carbon tetrachloride (HSDB, 2016)

Volatility: Vapour pressure, 110.8 mm Hg at 20 °C (HSDB, 2016)

Stability: Will not polymerize (HSDB, 2016)

Reactivity: Incompatible with strong oxidizing agents, acids and alkalis, alkali metals and finely powdered aluminium (GESTIS, 2015)

Flammability: Neat (pure) solvent, highly flammable liquid and vapour; hazardous when heated or exposed to flame or oxidizers (HSDB, 2016)

Flash point: –10 °C (GESTIS, 2015)

Auto-ignition temperature: 490 °C (HSDB, 2016)

Decomposition: Combustion by-product emits hydrogen bromide (HSDB, 2016)

Octanol/water partition coefficient: log K_{ow}, 2.10 (HSDB, 2016)

Conversion factor (at 25 °C, 760 mm Hg): 1 ppm = 5.03 mg/m^3.

1.1.4 Impurities

Production of commercial-grade 1-bromopropane produces low levels of a contaminant (0.1–0.2%), 2-bromopropane (i.e. isopropyl bromide; Chem. Abstr. Serv. Reg. No. 75-26-3). Contemporary manufacturing processes, however, result in < 0.1% 2-bromopropane contamination in neat 1-bromopropane solvents (Boekelheide et al., 2004; HSDB, 2016).

1.2 Production and use

1.2.1 Production

(a) Manufacturing process

1-Bromopropane is produced by treating *n*-propanol with bromide in the presence of sulfuric acid; once the propanol is unstable, hydrobromic acid is added and *n*-propyl bromide is flashed from the hot mixture. The resultant product is condensed, neutralized and fractionated. The procedure can be modified by using bromine (gas) together with a reducing agent such as sulfur, sulfur dioxide, phosphorus, or sodium borohydride (Kirk-Othmer, 1978).

(b) Production volume

In 2001, the United Nations Environment Programme (UNEP) projected that manufacture and use of 1-bromopropane would expand because it was being marketed to replace ozone-depleting solvents with high production volume for a range of applications in Asia (China, Japan, and the Republic of Korea), Europe (France, Germany, and the United Kingdom) and the USA (UNEP, 2001). Global production was estimated to be 20 000–30 000 tonnes in 2007 (UNEP, 2010), but specific volumes produced in each country were not available. The United States Environmental Protection Agency (EPA) reported in 2006 that national aggregate production was > 1–10 million pounds [> 450–4500 tonnes] (EPA, 2010). In 2011, the EPA listed the national production volume as > 15.3 million pounds [~7000 tonnes] (EPA, 2012).

1.2.2 Use

1-Bromopropane is a solvent for fats, waxes and resins and is primarily used as a chemical intermediate in the production of pesticides, quaternary ammonium compounds, flavours and fragrances, and pharmaceuticals in closed processes (NTP, 2013). In the mid-to-late 1990s, 1-bromopropane was introduced as a non-toxic, fast-drying solvent that does not leave surface residue for cleaning metals, plastics, and optical, electrical and electronic components (NTP, 2011; NIOSH, 2013). It was marketed as a substitute solvent for ozone-depleting and other solvents such as trichloroethylene, tetrachloroethylene (perchloroethylene) and methylene chloride. 1-Bromopropane is used for vapour degreasing and immersion cleaning, liquid and spray adhesive applications, fabric dry cleaning, and aerosol spray products (Blando et al., 2010; NTP, 2013).

1.3 Measurement and analysis

1.3.1 Detection and quantification

(a) Air monitoring

A few methods that are available for analysing 1-bromopropane in air are described in Table 1.1. In 2003, the United States National Institute for Occupational Safety and Health (NIOSH) issued a validated analytical method for 1-bromopropane in air (NIOSH, 2003a), which prescribes adsorption on activated charcoal, desorption with carbon disulfide (CS_2) and analysis by gas chromatography with flame ionization detection; the limit of detection for NIOSH method 1025 is 1 µg using a 12 L air sample. Occupational Safety and Health Administration (OSHA) method 1017 collects 1-bromopropane on activated charcoal but uses CS_2 (99%) and *N*,*N*-dimethylformamide for desorption and gas chromatography with electron capture detection; it is fully validated with a quantitative limit of 5.9 µg/m^3 for a 12 L air sample (OSHA, 2014).

Table 1.1 Selected methods of analysis for 1-bromopropane and biomarkers of exposure

Sample method	Sample preparation	Assay method	Limit of detection	Reference
1-Bromopropane in air				
NIOSH 1025	Active collection on activated charcoal; flow rate, 0.01–0.2 L/min (12 L); CS_2 desorption	GC/FID	1 µg	NIOSH (2003a)
OSHA 1017	Active collection on activated charcoal; flow rate, 0.05 L/min (12 L); CS_2/DMF, 99:1 (v/v) desorption	GC/ECD	5.9 µg/m^3	OSHA (2014)
OSHA PV2061	Active collection on activated charcoal; flow rate, 0.1 L/min (12 L); CS_2 desorption	GC/FID	37 µg/m^3	OSHA (1999)
IRSST 333-1	Active collection on activated charcoal; flow rate, 0.2 L/min (5 L); desorption NR	GC/FID	54 µg	IRSST (2015)
NR	Diffusive sampler; carbon cloth KF-1500; CS_2 desorption	GC	0.1 ppm	Kawai et al. (2001)
NR	Diffusive sampler; CS_2 desorption	GC/EID	0.13 ppm	Ichihara et al. (2004a)
1-Bromopropane in urine				
NR	Headspace collection; 5 mL urine into 20 mL vial; heated at 60 °C for 60 min	GC	2 µg/L	Kawai et al. (2001)
NR	Headspace collection; 5 mL urine into 20 mL vial; heated at 42 °C for 15 min; Tenax GC trap	GC/EID	0.5 ng/L	Ichihara et al. (2004a)
Bromide ion in urine				
NR	48 h, 7 interval composite specimens; nitric acid rinsed bottles; stored below −60 °C	ICP/MS	100 µg/L	Allain et al. (1990), Hanley et al. (2006, 2010)
AcPrCys in urine				
NR	Solid phase extraction (C18) column; methanol/water (40:60) wash; acetone elution	LC/ESI-MS	0.01 µg/L	Hanley et al. (2009) Cheever et al. (2009)
NR	1 mL urine in 1 mL ammonium formate buffer; pH adjusted to 2.4–2.6 with formic acid	LC/MS-MS	2 µg/L	Eckert & Göen (2014)
NR	Urine dissolved in NaOH; mixed in ethanol; acidified to pH 3 with H_3PO_4; ethyl acetate extraction; column chromatography with 2% methanol in ethyl acetate	LC/MS-MS	NR	Valentine et al. (2007)
GSPrCys adducts				
NR	Urine dissolved in NaOH; stirred with 1-bromopropane in ethanol; pH adjusted to 3 with HCl; washed with ice water and ethanol	LC/MS-MS	2.5 pmol	Valentine et al. (2007)

AcPrCys, *N*-acetyl-*S*-(*n*-propyl)-L-cysteine; CS_2, carbon disulfide; DMF, *N*,*N*-dimethylformamide; ECD, electron capture detection; EID, electron ionization detector; ESI, electrospray ionization; FID, flame ionization detector; GC, gas chromatography; GSPrCys, globin-*S*-propylcysteine; HCl, hydrochloric acid; H_3PO_4, phosphoric acid; ICP/MS, inductively coupled plasma/mass spectrometry; LC, liquid chromatography; LC/MS-MS, liquid chromatography-tandem mass spectrometry; MS, mass spectrometry; NaOH, sodium hydroxide; NR, not reported

(b) Biomarkers

Table 1.1 also contains details for laboratory methods of analysis of 1-bromopropane and biomarkers of exposure that include 1-bromopropane in urine, bromide ion in urine, and 1-bromopropane metabolites: *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys) and *S*-propylcysteine adducts on globin in urine.

Using high-performance liquid chromatography with mass spectrometry, Cheever et al. (2009) isolated several mercapturic acid conjugates from highly exposed workers who used 1-bromopropane spray adhesives, the most abundant of which was propyl mercapturic acid (i.e. AcPrCys). AcPrCys was also associated with lower exposure to 1-bromoproopane among workers exposed to vapour degreasing solvents (Hanley et al., 2010). AcPrCys is more sensitive and specific than bromide because non-occupational exposure to bromide could occur from diet and medications (Hanley et al., 2009). Valentine et al. (2007) studied the utility of globin-*S*-propylcysteine (GSPrCys) and AcPrCys as biomarkers of exposure to 1-bromopropane in the urine of workers exposed at a factory producing 1-bromopropane. A significant increase in GSPrCys was found in workers exposed to 1-bromopropane compared with controls, and urinary AcPrCys levels increased with increased levels of exposure to 1-bromopropane in the air, supporting the hypothesis that these biomarkers can potentially be used to evaluate the exposure of humans to 1-bromopropane.

1.4 Occurrence and exposure

1.4.1 Natural occurrence

1-Bromopropane was detected qualitatively in six species of marine algae that produce it naturally (HSDB, 2016).

1.4.2 Environmental occurrence

Fugitive emissions of 1-bromopropane from industrial and commercial settings are possible from manufacturer, formulator and user sites and from aerosol products used by public consumers. No quantitative data for 1-bromopropane measured in the environment were available to the Working Group.

1.4.3 Occupational exposures

Several studies of occupational exposure were available in the literature that describes data on human exposure to 1-bromopropane reported from industrial and commercial facilities (Table 1.2). Occupational exposure may occur by inhalation and dermal absorption (NIOSH, 2009; Frasch et al., 2011a; NTP, 2013), particularly if the skin is occluded (Frasch et al., 2011b). Dermal exposure can be a significant source of 1-bromopropane absorption and most common glove and chemical protective materials do not provide adequate skin protection (Hanley et al., 2009, 2010; NIOSH, 2013). Facilities reported in the literature include: (a) chemical manufacturing; (b) spray adhesives in foam cushion fabricators; (c) vapour and immersion cleaning activities; (d) aerosol products; and (e) commercial dry cleaning.

(a) Chemical manufacturing

Using passive (diffusion) monitoring, exposure to 1-bromopropane ranging from non-detectable to 170 ppm were reported in chemical manufacturing facilities in China (Ichihara et al., 2004a, b, 2006).

In another chemical manufacturer in China, the exposures determined by passive air samplers (activated carbon cloth) ranged from 0.07 to 106 ppm for women, and from 0.06 to 115 ppm for men (Li et al., 2010).

In an adhesives manufacturing facility, Hanley et al. (2010) reported on urinary bromide and AcPrCys concentrations (mg/g creatinine)

Table 1.2 Occupational exposure to 1-bromopropane in industrial and commercial facilities

Industry, country, year	Job/process	Concentration, mean (range)			Comments[a]	Reference
		Air[a] (ppm)	Blood (mEq/L)[b]	Urine (mg/g creatinine)[b]		
Chemical synthesis						
China, NR	NR, women	NR (0.9–170.5)	NR	NR	*n* = 24; 1BP in air, BZ, passive (diffusion) monitoring	Ichihara et al. (2004a)
China, NR	NR, men	NR (ND–43.3)	NR	NR	*n* = 13; 1BP in air, BZ, passive (diffusion) monitoring	Ichihara et al. (2004a)
China, NR	NR, women	2.92 (0.34–49.19)	NR	NR	*n* = 23; 1BP in air, BZ, passive (diffusion) monitoring	Ichihara et al. (2004b)
China, NR	NR, women	NR (0.07–106.3)	NR	NR	*n* = 60; 1BP in air, BZ, passive (diffusion) monitoring	Li et al. (2010)
China, NR	NR, men	NR (0.06–114.8)	NR	NR	*n* = 26; 1BP in air, BZ, passive (diffusion) monitoring, 8–12-h TWA	Li et al. (2010)
China, NR	NR	15.3 (0.65–73.7)	NR	NR	*n* = 40; 1BP in air, BZ, passive (diffusion) monitoring, 8–12-h TWA	Ichihara et al. (2006)
Adhesive manufacture						
USA, 2004	Direct user	3.8 (0.26–19)	NR	Br: 4.51 (2.37) AcPrCys: 0.485 (2.30)	Air: *n* = 6, worker–days; urine: *n* = 3; 48-h urine specimens, GM (GSD)	Hanley et al. (2010)
	Non-user	0.33 (0.07–1.6)	NR	Br: 2.01 (1.42) AcPrCys: 0.128 (4.51)	Air: *n* = 16, worker–days; urine: *n* = 8; 48-h urine specimens; GM (GSD)	
Spray adhesives						
China, 2002	NR	133 (60–261)	NR	NR	*n* = 11; AM	Ichihara et al. (2002)
USA, 1998	Sprayers	193 (115.3–250.7)	NR	NR	*n* = 15; initial; AM	NIOSH (2002a)
USA, 1998	Saw	117.1 (85.1–159.2)	NR	NR	*n* = 12; initial; AM	
USA, 1998	Covers	197.0 (117.3–381.2)	NR	NR	*n* = 21; initial; AM	
USA, 1998	Assembly	169.8 (60.0–250.7)	NR	NR	*n* = 36; initial; AM	
USA, 1998	All departments	168.9 (60.0–381.2)	NR	NR	*n* = 69; initial; AM	
USA, 2000	Saw	1.8 (1.6–2.0)	NR	NR	*n* = 6; follow-up; AM	
USA, 2000	Covers	29.2 (2.8–58.0)	NR	NR	*n* = 12; follow-up; AM	
USA, 2000	Assembly	18.8 (6.1–32.0)	NR	NR	*n* = 11; follow-up; AM	
USA, 2000	All departments	19.0 (1.2–58)	NR	NR	*n* = 30; follow-up; AM	
USA, 2000	Sewing	1.2	NR	NR	*n* = 1; follow-up; AM	
USA, 2000	Sprayers	NR (12.3–95.8)	NR	NR	*n* = 12; follow-up; 15-min STEL	

Table 1.2 (continued)

Industry, country, year	Job/process	Concentration, mean (range)			Comments[a]	Reference
		Air[a] (ppm)	Blood (mEq/L)[b]	Urine (mg/g creatinine)[b]		
USA, 2000	Sprayers	65.9 (41.3–143.0)	NR	NR	*n* = 12; TWA; initial; GM	NIOSH (2002b)
USA, 2000	Sprayers	NR (33.7–173.9)	NR	NR	*n* = 9; 15-min STEL; initial; GM	
USA, 2000	Non-sprayers	NR (6.3–14.1)	NR	NR	*n* = 2; TWA; initial	
USA, 2001	Sprayers	16.6 (8.8–31.9)	NR	Br: 7.7 (2.5–38.0)	*n* = 12; TWA; follow-up; urine (mg/L); GM	
USA, 2001	Non-sprayers	NR (1.1–5.8)	NR	NR	*n* = 10; TWA; follow-up; GM	
USA, 1999	All exposed	81.2 (18.1–253.9)	NR	NR	*n* = 16; TWA; initial; GM	NIOSH (2003b)
USA, 1999	Sprayers	107.6 (57.7–253.9)	NR	NR	*n* = 12; TWA; initial; GM	
USA, 1999	Sprayers	101.4 (38.0–280.5)	NR	NR	*n* = 8; TWA; follow-up; GM	
USA, 2003 USA, 2007	Sprayers	130 (91–176) 108 (92–127)	Br: 107 (AM) (44–170) Reference (Br) = 0–40	NR	Air: TWA-actual; t = 7 h; blood: serum Br (mg/dL), *n* = 6 Air: 8-h TWA	Majersik et al. (2007)
USA, 2001	Sprayers	63.45 (4.3–271.4)	Br: 13.6 (0.62–43.5)	Br: 153 (ND–595.4)	*n* = 19; blood: serum Br (mg/dL); urinary Br (mg/dL); end-of-week specimens; AM	Toraason et al. (2006)
	Unexposed	1.7 (ND–10.4)	Br: 1.48 (ND–4.6)	Br: 16.6 (0.27–42.2)	*n* = 45; blood: serum Br (mg/dL); urinary Br (mg/dL); end-of-week specimens; AM	
USA, 2007	Sprayers All jobs	107 (58–254) 81 (18–254)	7.1 (AM) (3.0–12.5)	NR	Air: 9 months after hospital cases by NIOSH, *n* = 12 (sprayers), *n* = 16 (all jobs); blood: *n* = 4 patients	Raymond & Ford (2007)
USA, 2006	Sprayers	92 (45–200)	NR	Br: 195 (119–250) AcPrCys: 41.1 (22–127)	Air: *n* = 26, worker–days; urine: *n* = 13; 48-h urine specimens: GM	Hanley et al. (2006, 2009)
	Non-sprayers	11 (0.6–60)	NR	Br: 42.9 (5.5–149) AcPrCys: 10.2 (1.23–81.5)	Air: *n* = 34, worker–days; urine: *n* = 17; 48-h urine specimens	
	Controls	NR	NR	Br: 3.8 (2.6–5.9) AcPrCys: 0.024 (ND–0.318)	Air: *n* = 0; urine: *n* = 7 (Br), *n* = 21 (AcPrCys); single "spot" urine specimens	

Table 1.2 (continued)

Industry, country, year	Job/process	Concentration, mean (range)			Comments[a]	Reference
		Air[a] (ppm)	Blood (mEq/L)[b]	Urine (mg/g creatinine)[b]		
Vapour degreasing and immersion cleaning						
Painting workshop, Japan, NR	NR	1.42 NR (ND–27.8)	NR	NR	Air: *n* = 33	Kawai et al. (2001)
Electronic plant, Pennsylvania, USA, 2007	Direct user	178	Br: 48 mg/dL	NR	Air: *n* = 1 case hospitalized for symptoms of neurotoxic effects	CDC (2008)
USA, 2004	Near degreaser	2.6 (0.08–21)	NR	Br: 8.94 (1.69–115) AcPrCys: 1.7 (0.02–32.1)	Air: *n* = 44, worker–days; urine: *n* = 22; 48-h urine specimens: GM	Hanley et al. (2010)
	Away from degreasers	0.31 (0.08–1.7)	NR	Br: 3.74 (1.69–15.6) AcPrCys: 0.13 (0.007–1.88)	Air: *n* = 18, worker–days; urine: *n* = 9; 48-h urine specimens; GM	
	Controls	NR	NR	Br: 2.01 (0.90–3.55) AcPrCys: 0.024 (ND–0.318)	Urine: *n* = 21; single "spot" urine specimens; GM	
Golf club cleaning, Taiwan, China, 2013	NR	128.8 (97.3–188.6)	NR	AcPrCys: NR (0.171–2.71)	Air: *n* = 3, area samples – above wash tank, passive (diffusion) sampling; urine AcPrCys measured between 1–26 days after exposure, *n* = 6	Wang et al. (2015)
Unspecified metal cleaning, Japan, NR	NR	553 (353–663)	Br: 58 and 20 µg/mL	NR	1 case of severe neurotoxicity; air: *n* = NR; blood: serum Br measured 2 and 4 months after exposure, normal level, < 5 µg/mL, *n* = 1	Samukawa et al. (2012)
Aerosol products						
Textile manufacture, Canada, 2000	Cleaners	NR (8.5–23.5)	NR	NR	*n* = 4	Mirza et al. (2000)
Use, locations and dates NR	NR	NR (5.0–30.2)	NR	NR	*n* = 8; 8-h TWA; most sampling by passive (diffusion) badges	EPA (2002)
	NR	NR (45.1–254.0)	NR	NR	15-min STEL	

Table 1.2 (continued)

Industry, country, year	Job/process	Concentration, mean (range)			Comments[a]	Reference
		Air[a] (ppm)	Blood (mEq/L)[b]	Urine (mg/g creatinine)[b]		
Dry-cleaning fabrics						
USA, 2006	Facility 1, operator	40 (23–56)	NR	NR	*n* = 2	NIOSH (2008)
	Facility 1, cashier	17 (10–24)	NR	NR	*n* = 2	
	Facility 2, operator	7.2	NR	NR	*n* = 1; ~4-h TWA; t = 209 min	
	Facility 2, cashier	1.5	NR	NR	*n* = 1; ~4-h TWA; t = 212 min	
	Facility 3, operator	11	NR	NR	*n* = 1; ~4-h TWA; t = 163 min	
	Facility 4, operator	160	NR	NR	*n* = 1; ~4-h TWA; t = 241 min	
	Facility 4, cashier	2.4	NR	NR	*n* = 1; ~4-h TWA; t = 246 min	
USA, 2006	Shop A, operator	NR (12.7–54.55)	NR	NR	*n* = 4; 8-h TWA	Blando et al. (2010)
	Shop A, clerk	NR (8.31–21.85)	NR	NR	*n* = 4; 8-h TWA	
	Shop B, operator	41.65	NR	NR	*n* = 1; 8-h TWA	
	Shop B, clerk	0.65	NR	NR	*n* = 1; 8-h TWA	
	Shop C, operator	0.24 (ND–0.35)	NR	NR	*n* = 3; 8-h TWA	

[a] Reported as breathing zone, full-shift time-weighted average, and geometric mean unless otherwise noted.
[b] Unless indicated otherwise
1BP, 1-bromopropane; AcPrCys, *N*-acetyl-*S*-(*n*-propyl)-L-cysteine; AM, arithmetic mean; Br, bromide ion; BZ, breathing zone; GM, geometric mean; GSD, geometric mean standard deviation; ND, not detected; NR, not reported; STEL, short-term exposure level; t, sampling time; TWA, full-shift time-weighted average

among workers who directly used 1-bromopropane or were indirectly exposed by working in adjacent vicinities. Worker exposures ranged from 0.26 to 19 ppm for those employees directly using 1-bromopropane and from 0.07 to 1.6 ppm for those that did not use 1-bromopropane. The geometric mean (GM) for two consecutive days of air monitoring was 3.8 ppm and 0.33 ppm for users and non-users of 1-bromopropane, respectively.

(b) Spray adhesives in foam cushions

Several publications were available for 1-bromopropane spray adhesives used in foam-fabricating plants where seat cushions were assembled. Adhesive is applied to foam and cloth using compressed air spray guns. Once the foam parts are glued, the workers used bare hands to align and press the pieces together and shape edges; hence skin contact contributed to the absorbed dose for sprayers.

At a foam cushion plant where 1-bromopropane spray adhesives were used, 1-bromopropane exposure concentrations ranged from 60 to 261 ppm, as estimated by passive sampling; the mean exposure was 133 ppm (Ichihara et al., 2002).

The NIOSH conducted health hazard evaluation (HHE) site investigations at three independent foam fabricating facilities (NIOSH, 2002a, b, 2003b) which included initial and follow-up site surveys. At the first plant (NIOSH, 2003b), the initial mean concentration of 1-bromopropane was 81 ppm for sprayers and other workers in spraying areas (range, 18–254 ppm); the mean for sprayers was 108 ppm. Some minor maintenance was performed on the general ventilation system before the return survey. Although the GM exposure to 1-bromopropane was lowered for all exposed jobs combined (GM, 46 ppm; 7.2–281 ppm), the exposures of sprayers remained essentially the same (mean, 101 ppm; range, 38–280 ppm) because no local exhaust ventilation was installed at their work stations.

The initial exposure levels to 1-bromopropane at the second plant (NIOSH, 2002a) were 170 ppm (GM) and ranged from 60 to 381 ppm. Differences in mean exposure were found between departments (i.e. covers, 197 ppm; assembly, 170 ppm; saw, 117 ppm). After implementing engineering controls (i.e. spray booth enclosures, local and general ventilation improvements), the follow-up evaluation showed a substantial reduction in the exposures of workers to 1-bromopropane with a mean of 19 ppm (range, 1.2–58 ppm).

The initial exposures of sprayers to 1-bromopropane at the third foam cushion factory (NIOSH, 2002b) ranged from 41 to 143 ppm, with a GM of 66 ppm. This facility also made modifications to local and general exhaust ventilation and exposures to 1-bromopropane were substantially reduced at the follow-up survey (mean, 16.6 ppm; range, 8.8–32 ppm).

Start-of- and end-of-work week blood and urine samples were collected from 41 and 22 workers at two facilities where 1-bromopropane spray adhesives were used for foam cushion fabrication (Toraason et al., 2006). Bromide was measured in the blood and urine as a biomarker of exposure. Overall, the air concentrations of 1-bromopropane ranged from 0.2 to 271 ppm at facility A and from 4 to 27 ppm at facility B, and the highest exposures were measured in workers classified as sprayers. 1-Bromopropane concentrations were statistically significantly correlated with individual blood and urine bromide concentrations. Serum and urine bromide levels of up to 43.5 and 595.4 mg/dL, respectively, were measured for sprayers.

Majersik et al. (2007) published a case study of six patients who worked at a foam cushion factory where glue containing 1-bromopropane was sprayed. The mean exposure to 1-bromopropane at this plant was 130 ppm (range, 91–176 ppm) collected over a 7-hour sampling period. Serum bromide levels were elevated

(107 mg/dL), ranging from 44 to 170 mg/dL (reference, 0–40 mg/dL).

Hanley et al. (2006, 2009) conducted an exposure assessment study using air sampling and measurement of urinary metabolites at two facilities using 1-bromopropane adhesives to construct polyurethane foam seat cushions. Complete 48-hour urine specimens were obtained from 30 workers on two consecutive days and were collected into composite samples representing three time intervals: at work, after work, but before bedtime, and upon awakening. GM breathing zone concentrations of 1-bromopropane were 92 ppm for adhesive sprayers and 11 ppm for other jobs. For sprayers, urinary bromide concentrations ranged from 77 to 542 mg/g creatinine at work, from 58 to 308 mg/g creatinine after work and from 46 to 672 mg/g creatinine in wake-up samples. Pre-week urinary bromide concentrations for sprayers were substantially higher than those for the non-sprayers and controls, with GMs of 102, 31, and 3.8 mg mg/g creatinine, respectively. Correlation of 48-hour urinary bromide with exposure to 1-bromopropane was statistically significant ($r^2 = 0.89$) for all jobs combined. The GM AcPrCys concentrations were 41 mg/g creatinine ($P < 0.05$) for sprayers, 10 mg/g creatinine ($P < 0.01$) for non-sprayers and 0.024 mg/g creatinine for controls.

(c) Vapour degreasing and immersion cleaning

In a Japanese painting workshop that used 1-bromopropane to clean parts, Kawai et al. (2001) evaluated the concentrations of 1-bromopropane in the air using passive samplers. The GM was 1.42 ppm with a maximum concentration of 27.8 ppm.

Hanley et al. (2010) measured the levels of 1-bromopropane in the air and those of bromide and AcPrCys in the urine and found GM breathing zone concentrations of 2.6 and 0.31 ppm for workers near degreasers and those furthest from degreasers, respectively. Urinary metabolites (mg/g creatinine) showed the same trend, with higher levels observed in workers near degreasers (48-hour GM bromide, 8.9 versus 3.7; 48-hour GM AcPrCys, 1.7 versus 0.13, respectively).

In a metal-cleaning facility, 1-bromopropane concentrations ranged from 353 to 663 ppm, with a mean of 553 ppm, and an elevated level of 58 µg/mL serum bromide was found in one worker (normal level, < 5 µg/mL) (Samukawa et al., 2012).

The mean 1-bromopropane concentration above a degreasing tank used for cleaning golf clubs was 129 ppm (range, 97–189 ppm). Levels of AcPrCys, collected 1–26 days after exposure were reported to range from 0.17 to 2.7 mg/g when normalized with creatinine (Wang et al., 2015).

(d) Aerosol products

Aerosol spray products are typically used intermittently for short periods and spray emissions often are not regulated by engineering controls (NTP, 2013). In a study to assess exposures from aerosol cleaning, 1-bromopropane concentrations ranged from 8.5 to 23.5 ppm (Mirza et al., 2000).

In aerosol samples from eight exposed workers, the full-shift concentration of 1-bromopropane ranged from 5 to 30 ppm (EPA, 2002).

(e) Dry cleaning

NIOSH (2008) conducted an evaluation at four dry-cleaning shops in the USA. At one facility, exposure to 1-bromopropane was 40 ppm for the machine operator and 17 ppm for the cashier clerk. At the other dry-cleaning shops, partial shift exposures to 1-bromopropane were 7.2 (209 minutes), 11 (163 minutes) and 160 (241 minutes) ppm for the operators typically working in the laundry room, and 1.5 (212 minutes) and 2.4 (246 minutes) ppm for cashiers working in the front of the store.

Blando et al. (2010) conducted follow-up investigations at the same four dry-cleaning laundries. The concentrations of 1-bromopropane were in the range of non-detectable to 55 ppm for operators in the laundries and 0.6–22 ppm for cashier clerks.

1.4.4 Exposure of the general population

No data were available to the Working Group.

1.5 Regulations and guidelines

The State of California Department of Industrial Relations has promulgated an 8-hour time-weighted average (TWA) permissible exposure limit for 1-bromopropane of 5 ppm [25 mg/m^3] with a skin notation (CA DIR, 2009). The state of California has also listed 1-bromopropane as a developmental hazard under proposition 65 of the California Clean Water Act (CA EPA, 2008). The Canadian Ministry of Health issued an 8-hour TWA occupational exposure limit for 1-bromopropane of 10 ppm [~50 mg/m^3] (GESTIS, 2015). In 2012, the Japan Society for Occupational Health proposed to set an occupational exposure limit for 1-bromopropane of 0.5 ppm (2.5 mg/m^3) (JSOH, 2015). In 2013, the American Conference of Governmental Industrial Hygienists adopted a TWA threshold limit value of 0.1 ppm short-term exposure limit with an A3 note "known animal carcinogen with unknown relevance to humans" (HSDB, 2016). In the 13th Report on Carcinogens, the United States National Toxicology Program (NTP) classified 1-bromopropane as "reasonably anticipated to be a human carcinogen" (NTP, 2013).

In November 2012, in accordance with Article 57 and 59 of the European Committee regulation 1907/2006, the European Chemical Agency identified 1-bromopropane as a substance of very high concern due to the risk of reproductive toxicity (ECHA, 2012). The European Chemical Bureau has labelled 1-bromopropane as H360FD "may damage fertility or the unborn child", H319 "causes serious eye irritation", H315 "causes skin irritation", H373 "may cause damage to organs from prolonged and repeated exposures", H335 "may cause irritation" and H336 "may cause drowsiness or dizziness" (ECHA, 2016).

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

One well-conducted good laboratory practice study evaluated the carcinogenicity of 1-bromopropane (NTP, 2011). Groups of 50 male and 50 female B6C3F$_1$ mice (age, 5–6 weeks) were exposed by inhalation to 1-bromopropane (purity, > 99.9%) at a dose of 0, 62.5, 125, or 250 ppm for 6 hours and 10 minutes per day on 5 days per week for 105 weeks. No effect on survival or body weights was observed.

In females, treatment with 1-bromopropane resulted in a significant increase in the incidence of lung alveolar/bronchiolar adenoma or carcinoma (combined) at all doses: 1/50 controls, 9/50 at 62.5 ppm ($P = 0.010$ by the pairwise Poly-3 test), 8/50 at 125 ppm ($P = 0.016$ by the pairwise Poly-3 test), and 14/50 at 250 ppm ($P < 0.001$ by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend in the incidence of lung alveolar/bronchiolar adenoma or carcinoma (combined) using the Poly-3 test ($P < 0.001$). Treatment with 1-bromopropane at a dose of 250 ppm also significantly increased the incidence of lung alveolar/bronchiolar adenoma:

Table 3.1 Studies of carcinogenicity with 1-bromopropane in experimental animals exposed by inhalation

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals/group No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, $B6C3F_1$ (F) 5–6 wks 105 wks NTP (2011)	Purity, > 99.9% 0, 62.5, 125 or 250 ppm, 6 h and 10 min/day, 5 days/wk 50/group 36, 40, 37, 42	*Lung, alveolar/bronchiolar* Adenoma: 1/50, 6/50, 4/50, 10/50 Carcinoma: 0/50, 7/50, 5/50, 4/50 Adenoma or carcinoma (combined): 1/50, 9/50, 8/50, 14/50	 Trend test: $P = 0.007$ (Poly-3 test) Pairwise: $P = 0.006$ for 250 ppm (one-sided Poly-3 test) Pairwise: $P = 0.009$ and $P = 0.031$ for 62.5 and 125 ppm, respectively (one-sided Poly-3 test) Trend test: $P < 0.001$ (Poly-3 test) Pairwise: $P = 0.010$, $P = 0.016$, $P < 0.001$ for 62.5, 125, 250 ppm, respectively (one-sided Poly-3 test)	Principal strengths of the study: covered most of the lifespan, multiple dose study; large numbers of animals per group and GLP
Mouse, $B6C3F_1$ (M) 5–6 wks 105 wks NTP (2011)	Purity, > 99.9% 0, 62.5, 125 or 250 ppm, 6 h and 10 min/day, 5 days/wk 50/group 37, 33, 32, 36	*All organs, all sites* None	 NS	Principal strengths of the study: covered most of the lifespan, multiple dose study; large numbers of animals per group and GLP No neoplastic effects
Rat, F344 (M) 5–6 wks 105 wks NTP (2011)	Purity, > 99.9% 0, 125, 250, or 500 ppm, 6 h and 10 min/day, 5 days/wk 50/group 23, 26, 18, 13	*Large intestine (rectum or colon)* Adenoma: 0/50, 0/50, 2/50, 1/50 *Skin* Keratoacanthoma: 0/50, 3/50, 6/50, 6/50 Keratoacanthoma or squamous cell carcinoma (combined): 1/50, 4/50, 6/50, 8/50 Keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (combined): 1/50, 7/50, 9/50, 10/50	 NS Trend test: $P = 0.008$ (Poly-3 test) Pairwise: $P = 0.012$, $P = 0.010$ for 250, 500 ppm, respectively (one-sided Poly-3 test) Trend test: $P = 0.006$ (Poly-3 test) Pairwise: $P = 0.044$, $P = 0.009$ for 250, 500 ppm, respectively (one-sided Poly-3 test) Trend test: $P = 0.003$ (Poly-3 test) Pairwise: $P = 0.028$, $P = 0.006$, $P = 0.002$ for 125, 250, 500 ppm, respectively (one-sided Poly-3 test)	Principal strengths of the study: covered most of the lifespan, multiple dose study; large number of animals per group, and GLP Incidence of adenoma of the large intestine (rectum or colon) in historical controls: 0/349 (inhalation); 2/1398 (all routes)

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals/group No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344 (M) 5–6 wks 105 wks NTP (2011) (cont.)		*Multiple organs* Malignant mesothelioma: 0/50, 2/50, 2/50, 4/50	Trend test: $P = 0.031$ (Poly-3 test) Pairwise: $P = 0.046$ for 500 ppm (one-sided Poly-3 test)	Malignant mesothelioma was found in the epididymis in all affected animals, with other tissues variably affected; rate in historical controls: 5/349 (inhalation); 35/1398 (all routes)
		Pancreas Islet cell adenoma: 0/50, 5/50, 4/50, 5/50	Trend test: $P = 0.043$ (Poly-3 test) Pairwise: $P = 0.029$, $P = 0.050$, $P = 0.019$ for 125, 250, 500 ppm, respectively (one-sided Poly-3 test)	
		Islet cell carcinoma: 3/50, 7/50, 5/50, 3/50	NS	
		Islet cell adenoma or carcinoma (combined): 3/50, 10/50, 9/50, 8/50	Pairwise: $P = 0.031$, $P = 0.043$ for 125, 250 ppm, respectively (one-sided Poly-3 test)	
Rat, F344/N (F) 5–6 wks 105 wks NTP (2011)	Purity, > 99% 0, 125, 250, or 500 ppm, 6 h and 10 min/day, 5 days/wk 50/group 34, 33, 30, 24	*Large intestine (rectum or colon)* Adenoma: 0/50, 1/50, 2/50, 5/50	Trend test: $P = 0.004$ (Poly-3 test) Pairwise: $P = 0.018$ for 500 ppm (one-sided Poly-3 test)	Principal strengths of the study: covered most of the lifespan, multiple dose study; large number of animals per group, and GLP Incidence of large intestine (rectum or colon) adenoma in historical controls: 2/350 (inhalation); 16/1350 (all routes)
		Skin Squamous cell papilloma, keratocacanthoma, basal cell adenoma or basal cell carcinoma (combined): 1/50, 1/50, 1/50, 4/50	Trend test: $P = 0.050$ (Poly-3 test)	
		Basal cell carcinoma: 0/50, 0/50, 0/50, 1/50	NS	

F, female; GLP, good laboratory practice; M, male; NS, not significant; wk, week

1/50 controls, 6/50 at 62.5 ppm, 4/50 at 125 ppm and 10/50 at 250 ppm (P = 0.006 by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend using the Poly-3 test (P = 0.007). At doses of 62.5 and 125 ppm, 1-bromopropane significantly increased the incidence of lung alveolar/bronchiolar carcinoma: 0/50 controls, 7/50 at 62.5 ppm (P = 0.009 by the pairwise Poly-3 test), 5/50 at 125 ppm (P = 0.031 by the pairwise Poly-3 test) and 4/50 at 250 ppm.

Treatment with 1-bromopropane did not result in significant increases in tumour incidence, unusual tumours, or early-onset tumours in males. [The strengths of this study included the large numbers of animals, compliance with good laboratory practice, the evaluation of multiple dose levels and a duration of exposure that involved most of the lifespan.]

3.2 Rat

Inhalation

One well-conducted good laboratory practice study evaluated the carcinogenicity of 1-bromopropane (NTP, 2011). Groups of 50 male and 50 female Fischer 344/N rats (age, 5–6 weeks) were exposed by inhalation to 1-bromopropane (purity, > 99.9%) at a dose of 0, 125, 250, or 500 ppm for 6 hours and 10 minutes per day on 5 days per week for 105 weeks. Survival was significantly decreased in male rats exposed to 500 ppm. No effect on body weights was observed.

In males, treatment with 1-bromopropane significantly increased the incidence of skin tumours (keratoacanthoma, basal cell adenoma, basal cell carcinoma and squamous cell carcinoma combined) at all doses: 1/50 controls, 7/50 at 125 ppm (P = 0.028 by the pairwise Poly-3 test), 9/50 at 250 ppm (P = 0.006 by the pairwise Poly-3 test), and 10/50 at 500 ppm (P = 0.002 by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend using the Poly-3 test (P = 0.003). The incidence of this combination of skin tumours in historical controls was 19/349 (range, 0–10%) in inhalation studies and 97/1398 (range, 0–20%) in all studies. At doses of 250 and 500 ppm, 1-bromopropane significantly increased the incidence of skin keratoacanthoma: 0/50 controls, 3/50 at 125 ppm, 6/50 at 250 ppm (P = 0.012 by the pairwise Poly-3 test), and 6/50 at 500 ppm (P = 0.010 by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend using the Poly-3 test (P = 0.008). The incidence of skin keratoacanthoma in historical controls was 10/349 (range, 0–8%) in inhalation studies and 66/1398 (range, 0–16%) in all studies. At doses of 250 and 500 ppm, 1-bromopropane significantly increased the incidence of skin keratoacanthoma or squamous cell carcinoma (combined): 1/50 controls, 4/50 at 125 ppm, 6/50 at 250 ppm (P = 0.044 by the pairwise Poly-3 test) and 8/50 at 500 ppm (P = 0.009 by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend using the Poly-3 test (P = 0.006). The incidence of this combination of skin tumours in historical controls was 11/349 (range, 0–8%) in inhalation studies and 74/1398 (range, 0–16%) in all studies. The incidence of basal cell carcinoma was 0/50 controls, 2/50 at 125 ppm, 1/50 at 250 ppm and 2/50 at 500 ppm; that of squamous cell carcinoma was 1/50 controls, 1/50 at 125 ppm, 0/50 at 250 ppm, and 2/50 at 500 ppm. 1-Bromopropane also induced a non-significant increase in the incidence of large intestine (rectum or colon) adenoma: 0/50 controls, 0/50 at 125 ppm, 2/50 at 250 ppm, and 1/50 at 500 ppm. Although not statistically significant, this increase equalled or exceeded that observed in male historical controls (0/349 in inhalation studies and 2/1398 in all studies; range, 0–2%). Statistical analysis did not detect a positive dose-related trend. A significant increase in the incidence of malignant mesothelioma of the epididymis was also observed: 0/50 controls, 2/50 at 125 ppm, 2/50 at 250 ppm, and 4/50 at 500 ppm (P = 0.046 by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend using the Poly-3 test

(P = 0.031). The incidence of malignant mesothelioma in historical controls was 5/349 (range, 0–6%) in inhalation studies, and 35/1398 (range, 0–6%) in all studies. The incidence of pancreatic islet cell adenoma or carcinoma (combined) was also significantly increased: 3/50 controls, 10/50 at 125 ppm (P = 0.031 by the pairwise Poly-3 test), 9/50 at 250 ppm (P = 0.043 by the pairwise Poly-3 test), and 8/50 at 500 ppm. Statistical analysis did not detect a positive dose-related trend. The incidence of this combination of pancreatic islet cell tumours in historical controls was 37/349 (range, 6–18%) in inhalation studies, and 119/1394 (range, 0–18%) in all studies. A significant increase in the incidence of pancreatic islet cell adenoma was also observed at all doses: 0/50 controls, 5/50 at 125 ppm (P = 0.029 by the pairwise Poly-3 test), 4/50 at 250 ppm (P = 0.050 by the pairwise Poly-3 test), and 5/50 at 500 ppm (P = 0.019 by the pairwise Poly-3 test). Statistical analysis detected a positive dose-related trend using the Poly-3 test (P = 0.043). The incidence of pancreatic islet cell adenoma in historical controls was 20/349 (range, 0–12%) in inhalation studies, and 90/1394 (range, 0–14%) in all studies.

In females, treatment with 1-bromopropane resulted in an increase in the incidence of large intestine (rectum or colon) adenoma at all doses: 0/50 controls, 1/50 at 125 ppm, 2/50 at 250 ppm, and 5/50 at 500 ppm (P = 0.018 by the pairwise Poly-3 test). Although statistically significant only at 500 ppm, this increase equalled or exceeded that observed in female historical controls (0/350 in inhalation studies; 3/1350 (range, 0–2%) in all studies). Statistical analysis detected a positive dose-related trend in the incidence of large intestine (rectum or colon) adenoma using the Poly-3 test (P = 0.004). 1-Bromopropane also resulted in a non-significant positive trend (P = 0.050) in the incidence of skin tumours (squamous cell papilloma, keratoacanthoma, basal cell adenoma and basal cell carcinoma combined): 1/50 controls, 1/50 at 125 ppm, 1/50 at 250 ppm, and 4/50 at 500 ppm. Although not statistically significant, the incidence in the high-dose group exceeded that observed in historical controls (2/350 (range, 0–2%) in inhalation studies; 16/1350 (range, 0–6%) in all studies). The incidence of basal cell carcinoma was 0/50 controls, 0/50 at 125 ppm, 0/50 at 250 ppm, and 1/50 at 500 ppm. [The strengths of this study included the large numbers of animals, compliance with good laboratory practice, the evaluation of multiple dose levels and a duration of exposure that involved most of the lifespan.]

4. Mechanistic and Other Relevant Data

Data on the toxicokinetics and genotoxicity of 1-bromopropane in humans and experimental animals have been reviewed (NTP, 2013). Sections 4.1 and 4.2 present a summary of the most relevant information.

4.1 Absorption, distribution, metabolism, excretion

4.1.1 Humans

(a) Absorption, distribution, and excretion

Exposure to 1-bromopropane in humans is liable to occur by inhalation or dermal contact, and it has been demonstrated that 1-bromopropane undergoes absorption by both routes in humans (Hanley et al., 2006; Cheever et al., 2009).

In a study addressing the absorption characteristics of 1-bromopropane, human epidermal membranes (collected from Caucasian female donors undergoing elective surgical procedures) were subjected in vitro to different exposure scenarios using neat 1-bromopropane or a saturated aqueous solution. The compound was readily absorbed, although the absorption potential depended upon the type and duration

of exposure. Losses due to evaporation were approximately two orders of magnitude greater than dermal absorption (Frasch et al., 2011a).

No data on the distribution of 1-bromopropane in humans were available to the Working Group.

Limited information was available regarding the excretion of 1-bromopropane in humans. Studies of exposed workers have reported the presence of non-metabolized 1-bromopropane in the urine (Kawai et al., 2001; Ichihara et al., 2004a). These studies found a significant correlation between the levels of 1-bromopropane in the urine and the levels of exposure to 1-bromopropane in the air. Bromide ion was also excreted but the high background levels from dietary and pharmaceutical sources represent a confounding factor.

(b) Metabolism

1-Bromopropane metabolites have been detected in the urine of occupationally exposed humans. The major metabolite is AcPrCys, the concentration of which increases with increasing ambient exposure levels (Hanley et al., 2009, 2010). Several other mercapturate conjugates have been identified, including *N*-acetyl-*S*-(*n*-propyl)-L-cysteine-*S*-oxide, *N*-acetyl-*S*-(2-carboxyethyl)-L-cysteine, and *N*-acetyl-*S*-(3-hydroxy-*n*-propyl)-L-cysteine (Cheever et al., 2009; Hanley et al., 2009). A proposed phase I metabolite is 3-bromopropanoic acid (B'Hymer & Cheever, 2004; Mathias et al., 2012).

Conjugates of oxidative metabolites identified in experimental animals (see Section 4.1.2b) do not appear to have been reported in humans.

4.1.2 Experimental systems

(a) Absorption, distribution, and excretion

Studies in rats and mice have demonstrated that 1-bromopropane is well absorbed after inhalation (Ishidao et al., 2002; Garner et al., 2006), intraperitoneal administration (Jones & Walsh, 1979) or oral exposure (Lee et al., 2010). When male Wistar rats were exposed to 1-bromopropane vapour at doses of either 700 ppm (for 6 hours per day for 1 day or 4 or 12 weeks) or 1500 ppm (for 6 hours per day on 5 days per week for 3 or 4 weeks), the blood concentration of the compound decreased linearly in a time-dependent manner and was below the limit of detection 0.7 hours after the end of the exposure (Ishidao et al., 2002).

One study reported the distribution of [^{14}C]1-bromopropane in rats and mice in exhaled air, urine and faeces that were collected at various time points following intravenous administration. The radioactivity recovered totalled 83–103%, with the largest fractions accounting for volatile organic compounds (25–71%), carbon dioxide (10–31%) and urine (13–23%). The radioactivity recovered from the total carcass (2–6%) and the faeces (< 1–4%) was comparatively negligible. Data for recovery from individual tissues were not presented, with the exception of some limited information for the liver. The liver/blood radioactivity ratios (approximately 3) were similar in both species, regardless of the dose (Garner et al., 2006).

After intraperitoneal administration of a single dose of 200 mg/kg bw of [^{14}C]1-bromopropane in rats, 60% was exhaled unchanged within 4 hours, and only trace amounts were detected in the exhaled air after that time-point. Exhaled carbon dioxide accounted for only 1.4% of the total dose and approximately 45% of the metabolized dose was excreted in the urine after 100 hours (Jones & Walsh, 1979).

In contrast to humans, the urinary excretion of non-metabolized 1-bromopropane does not appear to have been reported in rodents.

(b) Metabolism

The metabolism of 1-bromopropane has been investigated in several studies in experimental animals.

In-vivo studies have been conducted in rats and mice exposed by inhalation and oral, subcutaneous or intraperitoneal administration (Jones & Walsh, 1979; Garner et al., 2006, 2007; Valentine et al., 2007). The four urinary mercapturates identified in exposed humans were also found in experimental animals and additional urinary metabolites were detected in animals, although differences in the metabolite profile were noted. This may result from differences in the routes of administration, species specificities or detection methodologies. Figure 4.1 presents an overview of the metabolite structures that have been identified following inhalation and oral administration and include brominated and debrominated phase I metabolites, and phase II conjugates.

Some of the reactive species that have been identified in vivo or have been postulated, including 2,3-epoxy-1-propanol (glycidol), α-bromohydrin, and 1,2-epoxypropane (propylene oxide), are genotoxic (see Section 4.2.3).

Several debrominated metabolites of 1-bromopropane were identified in studies in vitro with rat liver microsomes, but were not detected in vivo (reviewed in NTP, 2013).

Most of the 1-bromopropane metabolites that have been identified are formed from oxidation reactions and glutathione (GSH) conjugation. Evidence that cytochrome P450 (CYP) 2E1 contributes significantly to the metabolism of 1-bromopropane was presented in a study in which *Cyp2e1*$^{-/-}$ (knockout) and wildtype mice were exposed to the compound by inhalation for 6 hours (Garner et al., 2007). Compared with their wildtype counterparts, the elimination half-life was much longer in the knockout mice (3.2 versus 1.3 hours), the ratio of GSH conjugation to 2-hydroxylation increased fivefold and the urinary concentration of *N*-acetyl-*S*-(2-hydroxypropyl)cysteine was reduced by approximately 50%. A study in which rats were exposed to 1-bromopropane by inhalation and intravenous injection confirmed that the clearance of 1-bromopropane is saturable and that elimination is not only highly dependent on CYP but also on GSH-dependent metabolism (Garner & Yu, 2014).

4.2 Mechanisms of carcinogenesis

The evidence on the "key characteristics" of carcinogens (Smith et al., 2016) – concerning whether 1-bromopropane induces oxidative stress and chronic inflammation, is immunosuppressive, is genotoxic, and modulates receptor-mediated effects – is summarized below.

4.2.1 Oxidative stress

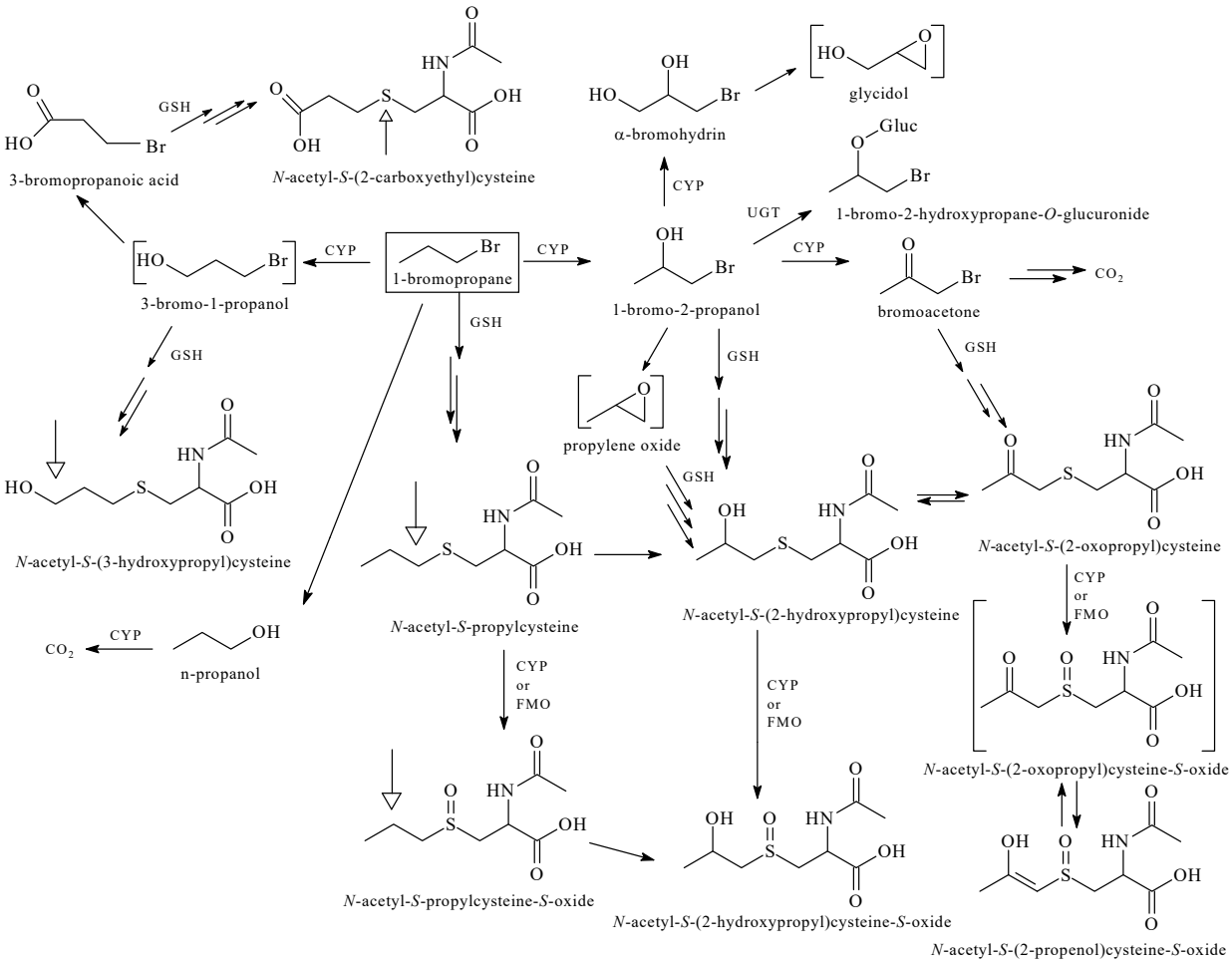
(a) Humans

The detection of urinary *N*-acetyl-*S*-propylcysteine indicated that 1-bromopropane induced GSH conjugation (Valentine et al., 2007; Hanley et al., 2009, 2010; Mathias et al., 2012), but did not directly signify the induction of oxidative stress.

(b) Experimental systems

Studies of urinary metabolites in experimental animals have revealed mercapturates derived from 1-bromopropane conjugated with GSH (Grenby & Young, 1959, 1960; Barnsley, 1966; Barnsley et al., 1966; Jones & Walsh 1979; Garner et al., 2006). An in-vitro study showed that 1-bromopropane is oxidized by liver microsomes, resulting in the production of metabolites including propene, 1,2-epoxypropane, and 1,2-propanediol (Tachizawa et al., 1982). The addition of GSH to the incubation mixture yielded *S*-propyl GSH, and *S*-hydroxyl propyl GSH. [The Working Group noted that the above studies showed that 1-bromopropane or its oxidized metabolites can be conjugated with GSH, which might result in an increase in oxidative stress through the depletion of GSH.]

Fig. 4.1 Metabolism of 1-bromopropane in rodents and humans



Structures in square brackets represent postulated intermediates. The white arrows indicate the urinary metabolites that have been identified in humans

CYP, cytochrome P450; FMO, flavin-containing monooxygenase; Gluc, glucuronide; GSH, glutathione; UGT, uridine 5′-diphospho (UDP)-glucuronosyltransferase

Compiled by the Working Group using data from Jones & Walsh (1979) and Garner et al. (2006, 2007)

A decrease in GSH was observed in the liver of mice 12 hours after a single oral dose of 200–1000 mg/kg body weight (bw) of 1-bromopropane (Lee et al., 2005, 2007), in the spleen of the mice after a single oral dose of 1000 mg/kg bw of 1-bromopropane (Lee et al., 2007), in the cerebral cortex of rats after daily oral administration of 200–800 mg/kg bw of 1-bromopropane for 12 days (Zhong et al., 2013; Guo et al., 2015), and in the cerebrum, cerebellum, and brainstem of rats after inhalation exposure to 800 ppm of 1-bromopropane for 7 days or 12 weeks (Wang et al., 2002, 2003). In contrast, an increase in GSH was observed in the spinal cord of rats after inhalation exposure to 200–800 ppm of 1-bromopropane for 7 days or 12 weeks (Wang et al., 2002, 2003).

The ratio of GSH to oxidized GSH was decreased in the liver after inhalation exposure for 28 days of C57BL/6J or BALB/cA mice to 50 ppm of 1-bromopropane and BALB/cA mice to 110 ppm of 1-bromopropane (Liu et al., 2009), and in the cerebral cortex of rats following oral administration of 100–800 mg/kg bw of

1-bromopropane for 12 days (Zhong et al., 2013; Guo et al., 2015). The level of oxidized GSH did not change in the cerebrum, cerebellum or spinal cord of rats exposed by inhalation to 200–800 ppm of 1-bromopropane for 7 days (Wang et al., 2002), but was increased in the cerebrum of rats after 12 weeks of inhalation exposure to 800 ppm of 1-bromopropane (Wang et al., 2003).

Several studies have indicated lipid peroxidation, protein affected by lipid peroxidation and protein carbonylation induced by exposure to 1-bromopropane. Malondialdehyde (MDA) levels were significantly increased in the liver of mice after a single oral administration of 1-bromopropane at a dose of 500 and 1000 mg/kg bw (Lee et al., 2005), or after inhalation exposure to 300 ppm of 1-bromopropane for 28 days in *Nrf2*-null mice (Liu et al., 2010). Thiobarbituric acid-reactive substances were significantly increased in the liver of mice after a single oral dose of 1-bromopropane at 1000 mg/kg bw, and this increase was enhanced significantly by pretreatment with phenobarbital (Lee et al., 2010). The level of lipid peroxide in the liver microsomes was significantly increased after 8 weeks of exposure by inhalation to 1-bromopropane at doses of 300 and 1800 ppm in female rats, and at 1800 ppm in male rats (Kim et al., 1999a). Exposure by inhalation for 4 weeks to 1-bromopropane increased thiobarbituric acid-reactive substances at doses of 400–1000 ppm, and protein carbonyl and reactive oxygens species at doses of 800–1000 ppm in the cerebellum of rats (Subramanian et al., 2012). The levels of MDA (at a dose of 800 mg/kg bw), MDA-modified proteins (at a dose of 800 mg/kg bw) and 4-hydroxy-2-nonenal-modified proteins (at doses of 200–800 mg/kg bw) (Zhong et al., 2013) and those of *N*-epsilon-hexanoyl-lysin-modified proteins (at doses of 200–800 mg/kg bw), and 4-hydroxy-2-nonenal-modified proteins (at doses of 100–800 mg/kg bw) (Guo et al., 2015) were increased in the cerebral cortex of rats after oral administration of 1-bromopropane for 12 days. Male Fischer 344 rats were exposed by inhalation to 1-bromopropane at doses of 0, 400, or 1000 ppm for 8 hours per day, on 7 days per week for 4 weeks (Huang et al., 2012). Hippocampal reactive oxygen species and protein carbonyl were increased significantly. Matrix-assisted laser-desorption ionization time-of-flight mass spectrometry identified 10 individual proteins with increased carbonyl modification.

Two studies have investigated the role of GSH depletion and lipid peroxidation in the mechanism of hepatotoxicity. Male ICR mice that received a single oral dose of 200, 500, or 1000 mg/kg bw of 1-bromopropane had increased serum alanine amino transferase and aspartate amino transferase activities, decreased GSH content and increased levels of *S*-propyl GSH conjugate in the liver 12 hours after the treatment. The GSH conjugate was maximally increased 6 hours after treatment with 1000 mg/kg bw of 1-bromopropane in parallel with the decrease in GSH content. MDA increased dose-dependently 12 hours after the treatment (Lee et al., 2005). Groups of 24 male *Nrf2*-null mice and 24 wildtype mice were exposed by inhalation to 1-bromopropane at doses of 0, 100, or 300 ppm for 8 hours per day for 28 days (Liu et al., 2010). *Nrf2*-null mice had higher levels of MDA, a higher ratio of oxidized GSH to the reduced form of GSH and lower total GSH content than wildtype mice. The constitutive level and the increase in the ratio per exposure level of GSH *S*-transferase (GST) activity were lower in the liver of *Nrf2*-null mice than that of wildtype mice. *Nrf2*-null mice showed greater areas of necrosis in the liver compared with wildtype mice. The level of MDA in the liver was only increased by the dose of 300 ppm in *Nrf2*-null mice, but did not change in wildtype mice at any exposure level. [The Working Group noted that these two studies suggested that treatment with 1-bromopropane induced hepatotoxicity and lipid peroxidation through GSH depletion due to the formation of GSH conjugates in the liver of mice.]

A proteomic study suggested a change in the expression levels of proteins related to immunity in the brain hippocampus of rats. Male Fischer 344 rats were exposed by inhalation to 1-bromopropane at doses of 0, 400, or 1000 ppm for 8 hours per day for 1 or 4 weeks (Huang et al., 2011). Changes in the expression level of proteins related to immunity and the response to stress, including the upregulation of glucose-regulated protein 78, heatshock protein 60, GSTA3 and GSTP1 and the downregulation of protein DJ-1 (also known as Parkinson disease protein 7), were observed. [The Working Group interpreted the results to be consistent with effects on oxidative stress.]

4.2.2 Chronic inflammation and immunosuppression

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) In vivo

Male and female Fischer 344/N rats exposed by inhalation to 1-bromopropane (at doses of 125, 250, or 500 ppm) for 2 years demonstrated chronic inflammation in the nose and larynx at several doses (Morgan et al., 2011; NTP, 2011). Chronic inflammation of the lung was also observed in females exposed to 500 ppm. In the trachea, an increased incidence of chronic active inflammation was observed in all exposed groups of females, and in males exposed to 500 ppm. Inflammatory lesions with Splendore-Hoeppli material were present primarily in the nose and skin of male and female rats, indicating that 1-bromopropane caused immunosuppression.

Significant decreases in the spleen immunoglobulin M response to sheep erythrocytes were observed in mice (at doses of 125–500 ppm) and rats (at a dose of 1000 ppm) after exposure to 1-bromopropane for 10 weeks. Total spleen cells and T cells were significantly decreased after 4 weeks of exposure in mice and rats (Anderson et al., 2010).

A single oral administration of 1-bromopropane to female mice suppressed the immune response, including the number of antibody-forming cells per spleen (at doses of 200–1000 mg/kg bw), antibody-forming cells per spleen cell (at doses of 500–1000 mg/kg bw), and $CD4^+$ $IL\text{-}2^+$ cells per spleen (at doses of 200–1000 mg/kg bw) in response to concanavalin A (Lee et al., 2007).

(ii) In vitro

Serial studies have shown that exposure to 1-bromopropane at doses of 1–10 μM produced inducible nitric oxide synthases, interleukin-1β, interleukin-6 and tumour necrosis factor-α (Han et al., 2008) and upregulated cyclooxygenase-2 (Han et al., 2012) through nuclear factor-κB in a murine macrophage cell line. In contrast, exposure to 1-bromopropane inhibited the DNA-binding activity of nuclear factor-κB (Yoshida et al., 2007) and decreased brain-derived neurotrophic factor mRNA expression in murine astrocytes (Yoshida et al., 2009) [but these data on astrocytes should be interpreted carefully because the concentration of 1-bromopropane was very high (0.1 or 1 mM)].

4.2.3 Genetic and related effects

See Table 4.1 and Table 4.2

(a) Humans

S-Propylcysteine haemoglobin adducts were measured in 26 Chinese female factory workers exposed to 1-bromopropane by inhalation and possibly by skin contact. The controls were age-matched workers (n = 32) from a Chinese beer factory. Exposure levels ranged from 0.34 to 49.2 ppm for the workers who gave blood samples and from 0 to 170.54 ppm for the workers who gave urine samples. A significant increase in

Table 4.1 Genetic and related effects of 1-bromopropane in humans

Tissue, cell type	End-point	Test	Results without metabolic activation	Dose (LED or HID)	Comments	Reference
Venous blood, leukocytes; 64 workers occupationally exposed at two facilities in the USA (18 men and 46 women); one group with low exposure and one group with high exposure (sprayers); no controls	DNA damage	DNA strand breaks (comet assay)	± (not significant)	Up to 5 ± 1 ppm in the low-exposure group; up to 83 ± 85 ppm in the high-exposure group	Higher tail moments (non-sprayers) and dispersion coefficients (sprayers) at the end of the week in the same individuals ($P < 0.05$)	Toraason et al. (2006)
Venous blood, leukocytes (in vitro)	DNA damage	DNA strand breaks (comet assay)	+	1 mM	Increased DNA damage (tail moments) at ≥ 4 h	Toraason et al. (2006)

+, positive; ±, equivocal; h, hour; HID, highest ineffective dose; LED, lowest effective dose; wk, week

Table 4.2 Genetic and related effects of 1-bromopropane in experimental systems

Species, strain, sex	End-point	Test	Results		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Mouse, B6C3F$_1$, M/F (peripheral blood erythrocytes)	Chromosomal damage	Micronuclei	–	–	Inhalation, 500 ppm, 3 h/day on 5 days/wk for 3 mo		NTP (2011)
Rat, Sprague-Dawley, M	Mutation	Dominant lethal test	–	NA	Gastric intubation, 400 mg/kg bw once daily for 5 days		Saito-Suzuki et al. (1982)
Mouse, ICR, M	Mutation	Dominant lethal test	–	NA	Gavage, 600 mg/kg bw once daily for 10 days		Yu et al. (2008)
Salmonella typhimurium TA98	Mutation	Reverse mutation	–	–	20.3 µmol/plate [2497 µg/plate]	Closed system incubation	Barber et al. (1981)
Salmonella typhimurium TA100, TA1535	Mutation	Reverse mutation	+	+	4.9 µmol/plate [603 µg/plate]	Closed system incubation	Barber et al. (1981)
Salmonella typhimurium TA97, TA98, TA100, TA1535	Mutation	Reverse mutation	–	–	10 000 µg/plate	Mutagenicity at ≥ 3333 µg/plate, not reliable due to high toxicity	NTP (2011)
Salmonella typhimurium TA98, TA100	Mutation	Reverse mutation	–	–	5000 (10 000 with metabolic activation) µg/plate		NTP (2011)
Escherichia coli WP2uvrA/pKM101	Mutation	Reverse mutation	–	–	5000 (10 000 with metabolic activation) µg/plate		NTP (2011)

+, positive; –, negative; bw, body weight; F, female; HID, highest ineffective dose; LED, lowest effective dose; M, male; mo, month, NA, not applicable; wk, week

S-propylcysteine adducts was observed in the haemoglobin of exposed workers (1.52 pmol/mg globin) compared with the controls (0.11 pmol/mg globin). In addition, the level of urinary AcPrCys increased with increasing exposure concentrations (Valentine et al., 2007).

The comet assay was used to assess DNA damage (strand breaks) in the peripheral blood leukocytes from 64 workers (18 men and 46 women) exposed occupationally to 1-bromopropane at two facilities in the USA that used spray adhesives containing 1-bromopropane. Because no unexposed population was available, the workers were divided into groups with higher exposure (sprayer) and lower exposure (non-sprayers). Overall, the exposures ranged from 0.2 to 271 ppm in one facility and from 4 to 27 ppm in the other facility, with workers classified as sprayers having the highest exposures. The TWA concentrations of 1-bromopropane were significantly correlated with blood and urine bromide concentrations. No significant differences in DNA damage in leukocytes were observed between the workers with high exposure (sprayers) and low exposure (no-sprayers). At the facility with the higher exposures, a paired analysis between the end- and start-of-the-week values indicated that non-sprayers had significantly increased comet tail moments and sprayers had significantly increased comet tail moment dispersion coefficients. Although not statistically significant, all of the other associations between the 1-bromopropane exposure indices and DNA damage were positive, with the exception of the end-of-work-week urinary bromide. A marginal correlation was found between DNA damage and *GSTM1*-positive genotypes (Toraason et al., 2006). [The Working Group noted the small number of subjects and the lack of controls. This study provided some evidence that exposure to 1-bromopropane induces DNA damage in humans.]

When assessed in vitro, DNA damage (comet assay) was significantly increased in human leukocytes exposed to 1 mM 1-bromopropane for 8 hours. Under the same conditions, apoptosis was significantly induced at 10-fold lower concentrations of 1-bromopropane (Toraason et al., 2006).

(b) Experimental systems

In rodents exposed in vivo, 1-bromopropane did not increase micronucleus formation in peripheral blood erythrocytes (NTP, 2011) or cause dominant lethal mutations (Saito-Suzuki et al., 1982; Yu et al., 2008). [However, the dominant lethal mutation assay is generally regarded as relatively insensitive for the detection of mutagenic agents.]

Although 1-bromopropane did not induce mutations in bacteria under standard assay conditions (NTP, 2011), it did induce mutations in bacteria in both the presence and absence of exogenous mammalian metabolic activation in the only reported study, the design of which was appropriate for testing a highly volatile chemical (Barber et al., 1981).

Reactive metabolites cause genotoxic effects in vitro, including DNA adduct formation, mutations and DNA or chromosome damage. Glycidol and propylene oxide cause cytogenetic effects in vivo and are carcinogenic in experimental animals (Stolzenberg & Hine, 1979, 1980; IARC, 1994, 2000).

4.2.4 Receptor-mediated effects

(a) Humans

One epidemiological study suggested that exposure to 1-bromopropane affected thyroid-stimulating hormone or follicular-stimulating hormone in female workers. A significant increasing trend in thyroid-stimulating hormone with exposure levels from 0.07 to 106.4 ppm and a significant increasing trend in thyroid-stimulating hormone and follicular-stimulating hormone with cumulative exposure levels from 2 to 3618 ppm × months were shown in 60 female

workers exposed to 1-bromopropane (Li et al., 2010).

(b) Experimental systems

Two studies investigated the reproductive toxicity and endocrine effects of 1-bromopropane in male and female rats (Ichihara et al., 2000a; Yamada et al., 2003). Exposure to 1-bromopropane (200, 400 and 800 ppm for 12 weeks) significantly decreased the weight of seminal vesicles, which is known to reflect blood testosterone levels, in male rats. The weight of the pituitary glands was decreased by 400 and 800 ppm and failure of spermiation, shown by an increase in retained sperm at post-spermiation stages, also suggested endocrine effects (Ichihara et al., 2000a). In female rats, 1-bromopropane increased the disruption of estrous cycles and also decreased antral and growing follicles in the ovary but not primordial follicles. The levels of luteinizing hormone and follicle-stimulating hormone were not altered in females exposed to 1-bromopropane at a dose of 800 ppm for 7 weeks or at doses of 200 and 400 ppm for 12 weeks (Yamada et al., 2003).

4.2.5 Altered cell proliferation or death

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling-positive granular cells (Subramanian et al., 2012) and pyknotic shrinkage in the cytoplasm of Purkinje cells (Ohnishi et al., 1999; Mohideen et al., 2013) and nuclei of granular cells (Mohideen et al., 2013) in the cerebellum have been reported in rats exposed to 1-bromopropane by inhalation at high doses of 1000–1500 ppm. Exposure of rats to 1-bromopropane at doses of 800–1000 ppm also suppressed neurogenesis in the dentate gyrus (Zhang et al., 2013). Exposure of rats to 1-bromopropane by inhalation increased phosphorylation of 14-3-3-θ protein in the hippocampus (at a dose of 1000 ppm for 4 weeks), which is related to apoptosis signalling, increased mitochondrial Bax (at a dose of 1000 ppm for 1 week or doses of 400–1000 ppm for 4 weeks), decreased cytosolic Bax (at doses of 400–800 ppm for 4 weeks), decreased mitochondrial cytochrome c and increased cytosolic cytochrome c (at a dose of 1000 ppm for 1 week or doses of 400–1000 ppm for 4 weeks) (Huang et al., 2015).

4.3 Data relevant to comparisons across agents and end-points

High-throughput screening data generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast™) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013) were considered in the assessment of the seven chemicals reviewed in the present volume of *IARC Monographs* (1-bromopropane, 2-mercaptobenzothiazole, 3-chloro-2-methylpropene, *N*,*N*-di-methylformamide, *N*,*N*-dimethyl-*p*-toluidine, hydrazine and tetrabromobisphenol A). The EPA has systematically analysed concentration–response sample-assay pairs from ToxCast and Tox21. The resulting concentration–response models and bioactivity determination have been publicly released via the interactive Chemical Safety for Sustainability ToxCast Dashboard (EPA, 2015a, b). Summary matrix files, the ToxCast data analysis pipeline R package and a connected database (invitrodb_v1) are also available (EPA, 2015c). The ToxCast data analysis pipeline R package and the associated database enable access to all of the underlying concentration–response data, the analysis decision logic and methods, concentration–response model outputs, bioactivity determination, and bioactivity caution flags.

The Tox21 and ToxCast research programmes have tested more than 8000 and 1800 chemicals,

respectively. ToxCast specifically has tested 1000 chemicals across the full assay battery in conjunction with ToxCast Phase I and II. The remaining 800 chemicals were tested as part of an endocrine profiling effort that resulted in a subset of assays being tested. For the seven chemicals in the current Volume, no testing data were available for two, one was tested only in Tox21 assay components and the remaining four chemicals were tested in both ToxCast and Tox21 assays.

Data on the current publicly released ToxCast assay battery, including the Tox21 assays run at the National Institutes of Health, comprise 821 assay end-points derived from 558 assay components (i.e. readouts) and 342 assays (i.e. experiments). The 342 assays were sourced from seven vendors or collaborators spanning diverse technological and biological space, including over 300 gene targets. Approximately half of the final assay end-points were analysed from biochemical (cell-free) assay formats and the remainder from cell-based or zebrafish larvae. The biochemical assays have no xenobiotic metabolism capacity, while the cell-based assays have a variable biotransformation capability varying from very limited to moderate. Chemical effects requiring biotransformation to active metabolites may be missed in some or all of the in-vitro assays. Relatively uniform testing concentration ranges were used, from low nanomolar up to approximately 100–200 µM. Compounds with a very low relative molecular mass generally have only low affinity for biomolecular interactions due to limited free energy for binding (Hopkins et al., 2004). Hence in-vitro screening at the concentrations used in ToxCast and Tox21 may be insufficient to detect molecular receptor-type interactions. These compounds with a very low relative molecular mass may also have high vapour pressure, which could lead to loss of the sample during testing and thus a failure to reach effective active concentrations.

The Tox21 and ToxCast in-vitro assays were selected to cover a broad range of potential toxicity mechanisms and are not specifically focused on carcinogenesis. Therefore, the Working Group of the *IARC Monographs* Volume 112 mapped the 821 assay end-points available at that time to the key characteristics of known human carcinogens (IARC, 2014). The consensus assignments resulted in 263 assay end-points mapped to seven of 10 key characteristics (IARC, 2017). Additional assay end-points have been included in Tox21 and ToxCast data since that determination. These were reviewed and 18 further assay end-points were added to the mapped key characteristics resulting in a total of 281. The assay end-points used, the bioactivity determination, and the mapping to key characteristics is included as supplementary material to *IARC Monographs* Volume 115 (IARC, 2018). The key characteristics listing and the number of assays included are briefly described below.

1. *Is electrophilic or can be metabolically activated* – 81 assay end-points consisting of CYP biochemical activity assays including aromatase;
2. *Is genotoxic* – 14 assay end-points consisting of cellular TP53 induction and DNA repair-sensitive cellular assays;
3. *Alters DNA repair or causes genomic instability* – 0 assay end-points;
4. *Induces epigenetic alterations* – 18 assay end-points including biochemical assays targeting histone deacetylases and other enzymes that modify chromatin as well as cellular transcription factor assays involved in epigenetic regulation;
5. *Induces oxidative stress* – 34 assay end-points, all cellular assays, targeting nuclear erythroid-related factor 2/antioxidant response element (NRF2/ARE), other stress-related transcription factors and protein upregulation in response to reactive oxygen species;

6. *Induces chronic inflammation* – 48 assay end-points measuring protein expression levels in primary human cells in complex environments;
7. *Is immunosuppressive* – 0 assay end-points;
8. *Modulates receptor-mediated effects* – 143 assay end-points targeting nuclear receptors (including aromatic hydrocarbon receptor, AhR) in cellular assays for transactivation, receptor dimerization and nuclear translocation as well as biochemical radioligand-binding assays and coregulatory recruitment assays;
9. *Causes immortalization* – 0 assay end-points;
10. *Alters cell proliferation, cell death or nutrient supply* – 157 assay end-points measuring cytotoxicity by a wide variety of assay formats in cell lines, primary human cells and developing zebrafish larvae.

The assay end-point groupings were not intended to serve as definitive linkages to carcinogenic outcomes but to provide insight into the bioactivity profile of a chemical highlighting its potential to interact with or disrupt targets biologically associated with cancer. The specific assays tested, the mapping to the key characteristics of carcinogens and the bioactivity determination can be found in the Supplementary Material (IARC, 2018). A summary of potentially significant outcomes for 1-bromopropane and other chemicals evaluated in the present volume are outlined below.

4.3.1 Specific effects across the "key characteristics" based on data from high-throughput screening in vitro

(a) 3-Chloro-2-methylpropene

This compound was not tested.

(b) N,N-Dimethyl-p-toluidine

This compound was not tested.

(c) 1-Bromopropane

This compound was tested as part of the Tox21 programme, but not in ToxCast assays, and was inactive in all 179 bioassays with the exception of a single testing in an assay for *TP53* activation. However, a parallel cell viability test was positive, confounding the results, and four other tests of the *TP53* activation assay gave negative results for 1-bromopropane. No chemical quality control information was available for the tested sample due to the current unavailability of appropriate detection methods for this structure. [The Working Group noted that the chemical has a fairly low relative molecular mass (122.99). In addition, 1-bromopropane has a vapour pressure of 13.3 kPa at 18 °C (ILO, 2004), which may be sufficiently high to allow vaporization during testing and loss of the sample. Thus, the ability to detect bioactivity in the Tox21 assays may have been limited.]

(d) 2-Mercaptobenzothiazole

Analysis of 2-mercaptobenzothiazole included bioactivity data from high-throughput screening assays from Tox21 and ToxCast. It was tested across the full assay suite of ToxCast and Tox21 with data for 887 assay end-points. The analytical quality control of the tested sample showed the intended structure was present and purity was > 90%.

1. Is electrophilic or can be metabolically activated: 2-mercaptobenzothiazole was tested in 11 assay end-points and found active in six, all of which were CYP inhibition assays. This activity does not necessarily demonstrate that the chemical generates electrophilic products upon CYP-mediated metabolism, but does support that 2-mercaptobenzothiazole can be a promiscuous CYP substrate and/or inhibitor.

2. Is genotoxic: 2-mercaptobenzothiazole was tested in nine assay end-points related to genotoxicity and was found to be active in none.

4. *Induces epigenetic alterations*: 2-mercaptobenzothiazole was active in two of

10 assay end-points, both of which were transcription factor assays (DNA binding) that lacked high confidence in epigenetic activity due to lack of validity with reference chemicals.

5. *Induces oxidative stress*: 2-mercaptobenzothiazole was active in three of 16 assay end-points mapped to oxidative stress, two assays for NRF2/ARE activation and one for nuclear respiratory factor 1.

6. *Induces chronic inflammation*: 2-mercaptobenzothiazole was tested in 45 assay end-points mapped to chronic inflammation and was active in none.

8. *Modulates receptor-mediated effects*: 2-mercaptobenzothiazole was active in 13 of 93 assay end-points mapped to receptor-mediated effects. It had the most pronounced activity towards the peroxisome proliferator-activated receptors (PPARs), in particular PPARγ, and AhR.

10. *Alters cell proliferation, cell death or nutrient supply*: 2-mercaptobenzothiazole was active in 7 of 67 assay end-points.

Overall, 2-mercaptobenzothiazole was very weakly cytotoxic, did not show evidence of genotoxicity but did inhibit CYP activities and show signs of inducing oxidative stress. It was notably active as a modulator of nuclear receptor activity, in particular AhR and PPARs, and was active in 47 of 636 assays not mapped to cancer end-points. Notably, it induced developmental abnormalities in zebrafish larvae in two different assays including morphological effects linked to AhR activity, jaw and snout malformations (Prasch et al., 2003). It also modulated steroid biosynthesis pathways in H295R human adrenocortical carcinoma cells.

(e) N,N-*Dimethylformamide*

N,*N*-Dimethylformamide was tested in 36 Tox21 and 865 ToxCast assay end-points and had no bioactivity. Although one sample showed bioactivity for four ToxCast end-points (retinoid X receptor α, retinoid X receptor β, nuclear receptor-related factor-1, and peroxisome proliferation response element γ), a second sample of *N*,*N*-dimethylformamide showed no bioactivity in these assays. No analytical quality control of the tested sample for ToxCast and Tox21 was presented because no structure detection method was available at the time of analysis. [The Working Group noted that the low relative molecular mass of *N*,*N*-dimethylformamide (73.1) as well as the limited biotransformation capacity of the assays may have made the detection of activity in the ToxCast and Tox21 assays unlikely.]

(f) Hydrazine sulfate

Hydrazine sulfate was tested in 182 Tox21 bioassays and the multiplexed transcription factor activation assays in ToxCast (135 end-points). It was marginally active in the Tox21 AHR reporter gene assay (concentration at half-maximal activity, AC_{50}, 48 μM), but was inactive in the ToxCast AhR end-point in the Attagene transcription factor assay platform. [The Working Group interpreted this as only very weak evidence of possible AhR activity.] The only other ToxCast active call was a very marginal activity (AC_{50}, 58 μM) in downregulation of NRF2, an assay end-point of undetermined significance in the downregulation direction. No analytical quality control of the tested sample for ToxCast and Tox21 was presented because no structure detection method was available at the time. [The Working Group noted that the molecular weight of hydrazine is low (32 g/mol) and that minimal biotransformation was present in the assays, probably limiting the ability to detect any potential activity of hydrazine.]

(g) Tetrabromobisphenol A

Tetrabromobisphenol A was tested across the full assay suite of ToxCast and Tox21 with data available for 836 assay end-points. The analytical quality control of the tested sample showed the intended structure was present and purity was greater than 90%.

Specific effects across seven of the 10 key characteristics based on data from high-throughput screening in vitro were:

1. *Is electrophilic or can undergo metabolic activation*: tetrabromobisphenol A was tested in 31 assay end-points and was found to be active in three – the inhibition of CYP2C9, CYP2C19 and CYP19 (aromatase), the latter of which regulates the conversion of androgens to estrogens. This activity is consistent with the inhibition of enzyme activity, possibly by acting as a substrate of the CYPs, but is not necessarily indicative of activation.

2. *Is genotoxic*: tetrabromobisphenol A was tested in nine assay end-points related to genotoxicity and was found to be active in six (five were repeated testing over time of the same assay end-point, the other was from a different assay technology), all of which were related to the activation of *TP53* in human hepatoma HepG2 cells. [The Working Group noted that *TP53* activation can occur in response to a variety of cell stress in addition to DNA damage.]

4. *Induces epigenetic alterations*: tetrabromobisphenol A was active in four of 11 assay end-points, all of which were transcription factor activation end-points mapped to the DNA-binding subcategory. [The Working Group noted that these end-points have not been validated extensively with reference compounds for epigenetic alterations.]

5. *Induces oxidative stress*: tetrabromobisphenol A was active in eight of 18 assay end-points mapped to oxidative stress. The eight active assay end-points were all stress-related genes, in particular the NRF2/ARE pathway together with the heatshock response factor, metal response factor and the endoplasmic reticulum stress response.

6. *Induces chronic inflammation*: tetrabromobisphenol A was tested in 45 assay end-points mapped to chronic inflammation and was active in none. Most of these assays used primary human cell lines with clear evidence of cytotoxicity, potentially confounding the results for inflammatory responses.

8. *Modulates receptor-mediated effects*: tetrabromobisphenol A was active in 24 of 93 assay end-points mapped to receptor-mediated effects. Strong evidence of activity was found for the PPARγ receptor as well as activity for the androgen receptor, glucocorticoid receptor, farnesyl X receptor and the xenobiotic receptor PXR. Tetrabromobisphenol A was determined to be inactive as an estrogen receptor agonist or antagonist using a model combining results from 18 estrogen receptor pathway assay end-points (Judson et al., 2015).

10. *Alters cell proliferation, cell death or nutrient supply*: tetrabromobisphenol A was active in 37 of 73 assay end-points mapped to this category and was the highest-ranked chemical among all chemicals evaluated in the *IARC Monographs* with ToxCast data (195 total). The majority of the active end-points were for cytotoxicity in cell lines and primary human cells. It was also active in several end-points mapped to cell cycle as well as those mapped to mitochondrial toxicity by loss of mitochondria membrane potential.

Overall, tetrabromobisphenol A demonstrated strong cytotoxic effects that may have confounded the results from other end-points. It activated several stress pathways, in particular the oxidative stress pathway. It was also a promiscuous nuclear receptor modulator with higher potency towards PPARγ than other receptors, but also active for steroid hormone receptors and the xenobiotic receptor PXR. In assay end-points not currently mapped to the key characteristics of carcinogens, tetrabromobisphenol A disrupted steroidogenesis in H295R human adrenal corticocarcinoma cells through the upregulation of progesterone and hydroxyprogesterone.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Neurotoxicity

(a) Humans

The major adverse effect of 1-bromopropane identified in humans is neurotoxicity, which affects the peripheral nerves and the central nervous system. After repetitive exposure to 1-bromopropane at levels of up to several hundred parts per million, workers showed a disability in walking and reported paresthesia or anaesthesia mainly in the lower limbs. Sensory and motor conduction velocity decreased and elongation of distal latency in lower extremities was also reported. Intoxicated cases also showed aggressive behaviour during exposure to 1-bromopropane but cognitive dysfunction and depressive mood after exposure (Sclar, 1999; Ichihara et al., 2002; Majersik et al., 2007; Wang et al., 2015). Epidemiological studies of workers producing 1-bromopropane showed dose-dependent changes including an increase in tibial motor distal latency, a decrease in sural nerve conduction velocity, a decrease in scores in the Benton cognitive test and an increase in the threshold for vibration sense in the toes (Li et al., 2010).

(b) Experimental systems

Numerous animal studies have demonstrated the neurotoxicity of 1-bromopropane (e.g. Ichihara et al., 2000b; Mohideen et al., 2011; Subramanian et al., 2012). Wistar rats exposed to 1-bromopropane at doses of 200, 400, or 800 ppm for 8 hours per day on 7 days per week for 12 weeks showed degeneration of the myelin sheath in the posterior tibial nerve or tibial nerve and decreased cerebrum weight (Ichihara et al., 2000b). Exposure to 1-bromopropane induced DNA fragmentation (terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling-positive cells) (Subramanian et al., 2012) and decreased myelin basic protein (Mohideen et al., 2013) in the cerebellum.

4.5.2 Other types of toxicity

(a) Humans

No clinical case reports have indicated the haematotoxicity of 1-bromopropane. Epidemiological studies showed lower leukocyte counts compared with age-matched controls (Ichihara et al., 2004b) and a significant trend in the decrease in erythrocytes or haematocrit with exposure level or cumulative exposure level (Li et al., 2010).

There are no clinical case reports showing liver injury after exposure to 1-bromopropane (Sclar, 1999; Samukawa et al., 2012). An epidemiological study showed a positive trend in the increase in lactate dehydrogenase with exposure to 1-bromopropane in female workers, but did not show any trend in the change in alanine aminotransferase or aspartate aminotransferase. The same study showed significant trend in the increase in blood urea nitrogen with exposure in male workers (Li et al., 2010).

(b) Experimental systems

In mice, necrotic changes were observed in the liver at a low exposure level of 50 ppm (Liu et al., 2009) compared with the subtle changes in the liver of rats exposed to 1-bromopropane at a higher level of 800 ppm (Ichihara et al., 2000b). Oxidation of 1-bromopropane by CYP, GSH depletion and oxidative stress may be involved in 1-bromopropane-induced hepatotoxicity (Lee et al., 2005, 2007, 2010; Liu et al., 2010). Female rats exposed to 1-bromopropane at concentrations of 800 or 1590 ppm showed increased absolute kidney weight (Yamada et al., 2003; Ichihara, 2005). Another study identified tubular casts in the kidney after exposure to 1800 ppm (Kim et al., 1999b).

Exposure to 1-bromopropane reduced the motility of epididymal sperm in rats (Ichihara et al., 2000a; Banu et al., 2007) and mice (Liu et al., 2009). The effects of 1-bromopropane on sperm motility were less marked in

CYP2E1-null mice, suggesting a contribution of CYP2E1 to the reduction in sperm motility (Garner et al., 2007).

5. Summary of Data Reported

5.1 Exposure data

1-Bromopropane is a solvent that is used in spray adhesives to fabricate polyurethane foam cushions, as a vapour degreasing agent and as a cleaning solvent for metals, plastics, optical and electronic components, and for dry cleaning fabrics. 1-Bromopropane is also used as a chemical intermediate in the manufacture of pesticides, flavours and fragrances, and pharmaceuticals. Occupational exposures to 1-bromopropane through inhalation and dermal uptake have been reported in the production of chemicals, the manufacture of adhesives, in the production and use of spray adhesives, vapour degreasing and in dry cleaning fabrics. 1-Bromopropane has been measured in the air, urine and serum of workers, but exposures of the general population have not been reported.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1-Bromopropane was tested for carcinogenicity by inhalation in one good laboratory practice (GLP) study in male and female mice, and in one GLP study in male and female rats.

In the study in mice, inhalation of 1-bromopropane was associated with a significantly increased incidence of alveolar/bronchiolar carcinoma of the lung, and a significantly increased incidence (with a significant positive trend) of alveolar/bronchiolar adenoma or carcinoma (combined) and alveolar/bronchiolar adenoma of the lung in females, but no significant increase in tumour incidence in males.

In the study in male rats, inhalation of 1-bromopropane caused a significantly increased incidence (with a significant positive trend) of tumours of the skin (keratoacanthoma, basal cell adenoma, basal cell carcinoma and squamous cell carcinoma combined), and of keratoacanthoma and keratoacanthoma or squamous cell carcinoma (combined). It also caused a significant increase in the incidence of malignant mesothelioma of the epididymis (with a significant positive trend). It was associated with a significantly increased incidence of pancreatic islet cell adenoma (with a significant positive trend) and of pancreatic islet cell adenoma or carcinoma (combined), and was associated with a non-significant increase in the incidence of adenoma of the large intestine (colon or rectum), a tumour never observed in historical controls for inhalation studies.

In the study in female rats, inhalation of 1-bromopropane caused a significantly increased incidence (with a significant positive trend) of adenoma of the large intestine (colon or rectum) and was associated with a non-significant positive trend in the incidence of tumours of the skin (squamous cell papilloma, keratoacanthoma, basal cell adenoma and basal cell carcinoma combined).

5.4 Mechanistic and other relevant data

In humans, metabolites of 1-bromopropane have been detected in the urine of workers after occupational exposure. The concentration of the major metabolite identified, *N*-acetyl-*S*-propylcysteine, increased with increasing levels of ambient exposure. 3-Bromopropanoic acid identified in rats exposed to 1-bromopropane has been postulated as a phase I metabolite.

With respect to the key characteristics of human carcinogens, there is *strong* evidence that 1-bromopropane is electrophilic or can be metabolically activated. No reports in humans were available on the conjugates of oxidative metabolites identified in experimental animals. *N*-Acetyl-*S*-propylcysteine was detected in the urine of exposed workers and *S*-propylcysteine haemoglobin adducts were measured in the blood of Chinese factory workers exposed to 1-bromopropane.

There is *strong* evidence that 1-bromoproane induces oxidative stress, induces chronic inflammation and is immunosuppressive, based on studies in rodents exposed in vivo. Inflammation was seen in the nose, larynx, trachea and lung in exposed rodents. 1-Bromopropane blocked the activation of nuclear factor-κB in murine astrocytes in vitro and suppressed neurogenesis in rats.

There is *moderate* evidence that 1-bromoproane modulates receptor-mediated effects and is genotoxic. In exposed humans, some evidence of DNA damage in leukocytes was available from a small study of workers exposed to 1-bromopropane. In rodents in vivo, 1-bromopropane did not induce micronucleus formation in peripheral blood erythrocytes or cause dominant lethal mutations.

There were few data on other key characteristics of carcinogens (alters DNA repair or causes genomic instability, induces epigenetic alterations, causes immortalization, or alters cell proliferation, cell death, or nutrient supply).

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of 1-bromopropane.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-bromopropane.

6.3 Overall evaluation

1-Bromopropane is *possibly carcinogenic to humans (Group 2B)*.

References

Allain P, Mauras Y, Dougé C, Jaunault L, Delaporte T, Beaugrand C (1990). Determination of iodine and bromine in plasma and urine by inductively coupled plasma mass spectrometry. *Analyst*, 115(6):813–5. PMID:2393085

Anderson SE, Munson AE, Butterworth LF, Germolec D, Morgan DL, Roycroft JA et al. (2010). Whole-body inhalation exposure to 1-bromopropane suppresses the IgM response to sheep red blood cells in female B6C3F1 mice and Fisher 344/N rats. *Inhal Toxicol*, 22(2):125–32. doi:10.3109/08958370902953910 PMID:20041805

B'Hymer C, Cheever KL (2004). Development of a gas chromatographic test for the quantification of the biomarker 3-bromopropionic acid in human urine. *J Chromatogr B Analyt Technol Biomed Life Sci*, 802(2):361–6. doi:10.1016/j.jchromb.2003.12.004 PMID:15018799

Banu S, Ichihara S, Huang F, Ito H, Inaguma Y, Furuhashi K et al. (2007). Reversibility of the adverse effects of 1-bromopropane exposure in rats. *Toxicol Sci*, 100(2):504–12. doi:10.1093/toxsci/kfm245 PMID:17890766

Barber ED, Donish WH, Mueller KR (1981). A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay. *Mutat Res*, 90(1):31–48. doi:10.1016/0165-1218(81)90048-3 PMID:7029269

Barnsley EA (1966). The formation of 2-hydroxypropylmercapturic acid from 1-halogenopropanes in the rat. *Biochem J*, 100(2):362–72. doi:10.1042/bj1000362 PMID:5968536

Barnsley EA, Grenby TH, Young L (1966). Biochemical studies of toxic agents. The metabolism of 1- and 2-bromopropane in rats. *Biochem J*, 100(1):282–8. doi:10.1042/bj1000282 PMID:5965256

Blando JD, Schill DP, De La Cruz MP, Zhang L, Zhang J (2010). Preliminary study of propyl bromide exposure

among New Jersey dry cleaners as a result of a pending ban on perchloroethylene. *J Air Waste Manag Assoc*, 60(9):1049–56. doi:10.3155/1047-3289.60.9.1049 PMID:20863050

Boekelheide K, Darney SP, Daston GP, David RM, Luderer U, Olshan AF et al.; NTP Center for the Evaluation of Risks to Human Reproduction Bromopropanes Expert Panel (2004). NTP-CERHR Expert Panel Report on the reproductive and developmental toxicity of 2-bromopropane. *Reprod Toxicol*, 18(2):189–217. doi:10.1016/j.reprotox.2003.10.003 PMID:15019719

CA DIR (California Department of Industrial Relations) (2009). California code of regulations. Airborne contaminants. California, USA: State of California Department of Industrial Relations. Available from: http://www.dir.ca.gov/oshsb/airborne_contaminants09.html.

CA EPA (2008). Chemicals known to the state to cause cancer or reproductive toxicity. July 15 2016. Safe Drinking Water and Toxic Enforcement Act of 1986. California, USA: Office of Environmental Health Hazard Assessment, State of California Environmental Protection Agency. Available from: http://oehha.ca.gov/media/downloads/crnr/p65list071516.pdf.

CDC (2008). Neurologic illness associated with occupational exposure to the solvent 1-bromopropane–New Jersey and Pennsylvania, 2007–2008. Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep*, 57(48):1300–2. PMID:19052528

Cheever KL, Marlow KL, B'hymer C, Hanley KW, Lynch DW (2009). Development of an HPLC-MS procedure for the quantification of N-acetyl-S-(n-propyl)-l-cysteine, the major urinary metabolite of 1-bromopropane in human urine. *J Chromatogr B Analyt Technol Biomed Life Sci*, 877(8-9):827–32. doi:10.1016/j.jchromb.2009.02.010 PMID:19237326

ECHA (2012). Agreement of the member state committee on the identification of 1-bromopropane [n-propyl bromide] as a substance of very high concern. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/documents/10162/7183371/agreement_1-bromopropane_en.pdf.

ECHA (2016). 1-Bromopropane. Brief profile. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu//fr/brief-profile/-/briefprofile/100.003.133.

Eckert E, Göen T (2014). Rapid determination of four short-chain alkyl mercapturic acids in human urine by column-switching liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*, 965:54–60. doi:10.1016/j.jchromb.2014.06.009 PMID:24997437

EPA (2002). Summary of data on workplace exposure to n-propyl bromide. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OAR-2002-0064-0347&disposition=attachment&contentType=pdf.

EPA (2010). Non-confidential IUR production volume information. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/chemical-data-reporting/downloadable-2006-iur-public-database, search by CAS No. 106-94-5.

EPA (2012). Chemical Data Access Tool (CDAT) [online database]. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://java.epa.gov/oppt_chemical_search/.

EPA (2015a). Interactive Chemical Safety for Sustainability (iCSS) Dashboard. Washington (DC), USA: United States Environmental Protection Agency. Available from: http://actor.epa.gov/dashboard2/, accessed April 2016.

EPA (2015b). Toxicity Forecaster (ToxCast) Data. Washington (DC), USA: United States Environmental Protection Agency. Available from: http://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data, accessed 15 December 2015.

EPA (2015c). The ToxCast analysis pipeline: an R package for processing and modeling chemical screening data, version 1.0. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/chemical-research/toxcast-data-analysis-pipeline.

Frasch HF Dotson GS, Barbero AM et al. (2011b). In vitro dermal absorption of 1-bromopropane. *Dermatitis*, 22(5):286.

Frasch HF, Dotson GS, Barbero AM (2011a). In vitro human epidermal penetration of 1-bromopropane. *J Toxicol Environ Health A*, 74(19):1249–60. doi:10.1080/15287394.2011.595666 PMID:21830855

Garner CE, Sloan C, Sumner SC, Burgess J, Davis J, Etheridge A et al. (2007). CYP2E1-catalyzed oxidation contributes to the sperm toxicity of 1-bromopropane in mice. *Biol Reprod*, 76(3):496–505. doi:10.1095/biolreprod.106.055004 PMID:17093198

Garner CE, Sumner SC, Davis JG, Burgess JP, Yueh Y, Demeter J et al. (2006). Metabolism and disposition of 1-bromopropane in rats and mice following inhalation or intravenous administration. *Toxicol Appl Pharmacol*, 215(1):23–36. doi:10.1016/j.taap.2006.01.010 PMID:16513153

Garner CE, Yu X (2014). Species and sex-dependent toxicokinetics of 1-bromopropane: the role of hepatic cytochrome P450 oxidation and glutathione (GSH). *Xenobiotica*, 44(7):644–56. doi:10.3109/00498254.2013.879624 PMID:24438363

GESTIS (2015). 1-Bromopropane. GESTIS International Limit Values. Available from: http://limitvalue.ifa.dguv.de/.

Grenby TH, Young L (1959). The isolation of n-propyl-mercapturic acid from the urine of animals dosed with 1-bromopropane. Proceedings of the Biochemical Society.

Grenby TH, Young L (1960). Biochemical studies on toxic agents. 12. The biosynthesis of *n*-propylmercapturic acid from *n*-propyl halides. *Biochem J*, 75(1):28–33. doi:10.1042/bj0750028 PMID:13829194

Guo Y, Yuan H, Jiang L, Yang J, Zeng T, Xie K et al. (2015). Involvement of decreased neuroglobin protein level in cognitive dysfunction induced by 1-bromopropane in rats. *Brain Res*, 1600:1–16. doi:10.1016/j.brainres.2014.12.046 PMID:25557405

Han EH, Hwang YP, Lee KJ, Jeong TC, Jeong HG (2008). 1-Bromopropane induces macrophage activation via extracellular signal-regulated kinase 1/2 MAPK and NF-κB pathways. *Cancer Lett*, 262(1):28–36. doi:10.1016/j.canlet.2007.11.024 PMID:18164123

Han EH, Yang JH, Kim HK, Choi JH, Khanal T, Do MT et al. (2012). 1-Bromopropane up-regulates cyclooxygenase-2 expression via NF-κB and C/EBP activation in murine macrophages. *Food Chem Toxicol*, 50(5):1616–22. doi:10.1016/j.fct.2012.02.006 PMID:22353212

Hanley KW, Petersen M, Curwin BD, Sanderson WT (2006). Urinary bromide and breathing zone concentrations of 1-bromopropane from workers exposed to flexible foam spray adhesives. *Ann Occup Hyg*, 50(6):599–607. doi:10.1093/annhyg/mel020 PMID:16698849

Hanley KW, Petersen MR, Cheever KL, Luo L (2009). N-acetyl-S-(n-propyl)-l-cysteine in urine from workers exposed to 1-bromopropane in foam cushion spray adhesives. *Ann Occup Hyg*, 53(7):759–69. doi:10.1093/annhyg/mep051 PMID:19706636

Hanley KW, Petersen MR, Cheever KL, Luo L (2010). Bromide and N-acetyl-S-(n-propyl)-L-cysteine in urine from workers exposed to 1-bromopropane solvents from vapor degreasing or adhesive manufacturing. *Int Arch Occup Environ Health*, 83(5):571–84. doi:10.1007/s00420-010-0524-4 PMID:20229238

Hopkins AL, Groom CR, Alex A (2004). Ligand efficiency: a useful metric for lead selection. *Drug Discov Today*, 9(10):430–1. doi:10.1016/S1359-6446(04)03069-7 PMID:15109945

HSDB (2016). Hazardous Substances Data Bank. A Toxnet database. Bethesda (MD), USA: United States National Library of Medicine. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Huang Z, Ichihara S, Oikawa S, Chang J, Zhang L, Hu S et al. (2015). Hippocampal phosphoproteomics of F344 rats exposed to 1-bromopropane. *Toxicol Appl Pharmacol*, 282(2):151–60. doi:10.1016/j.taap.2014.10.016 PMID:25448045

Huang Z, Ichihara S, Oikawa S, Chang J, Zhang L, Subramanian K et al. (2012). Proteomic identification of carbonylated proteins in F344 rat hippocampus after 1-bromopropane exposure. *Toxicol Appl Pharmacol*, 263(1):44–52. doi:10.1016/j.taap.2012.05.021 PMID:22683646

Huang Z, Ichihara S, Oikawa S, Chang J, Zhang L, Takahashi M et al. (2011). Proteomic analysis of hippocampal proteins of F344 rats exposed to 1-bromopropane. *Toxicol Appl Pharmacol*, 257(1):93–101. doi:10.1016/j.taap.2011.08.023 PMID:21925529

IARC (1994). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 60:1–560. Available from: http://monographs.iarc.fr/ENG/Monographs/vol60/index.php. PMID:7869568

IARC (2000). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 77:1–529. Available from: http://monographs.iarc.fr/ENG/Monographs/vol77/index.php. PMID:11236796

IARC (2014). Table 1. Key characteristics of carcinogens. In: Instructions for authors. Lyon, France: International Agency for Research on Cancer. Available from: http://monographs.iarc.fr/ENG/Preamble/previous/Instructions_to_Authors_S4.pdf, accessed 28 January 2016.

IARC (2018). Supplementary material. IARC Monographs Volume 115. Available from: http://monographs.iarc.fr/ENG/Monographs/vol115/index.php.

IARC (2017). Some organophosphate insecticides and herbicides. *IARC Monogr Eval Carcinog Risks Hum*, 112:1–452. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

Ichihara G (2005). Neuro-reproductive toxicities of 1-bromopropane and 2-bromopropane. *Int Arch Occup Environ Health*, 78(2):79–96. doi:10.1007/s00420-004-0547-9 PMID:15812677

Ichihara G, Kitoh J, Yu X, Asaeda N, Iwai H, Kumazawa T et al. (2000b). 1-Bromopropane, an alternative to ozone layer depleting solvents, is dose-dependently neurotoxic to rats in long-term inhalation exposure. *Toxicol Sci*, 55(1):116–23. doi:10.1093/toxsci/55.1.116 PMID:10788566

Ichihara G, Li W, Ding X, Peng S, Yu X, Shibata E et al. (2004a). A survey on exposure level, health status, and biomarkers in workers exposed to 1-bromopropane. *Am J Ind Med*, 45(1):63–75. doi:10.1002/ajim.10320 PMID:14691970

Ichihara G, Li W, Shibata E, Ding X, Wang H, Li J et al. (2006). Exposure to 1-bromopropane adversely affects vibration sense and nerve conduction velocity of lower limbs and central nervous system in workers. *Clin Toxicol*, 44(5):668.

Ichihara G, Li W, Shibata E, Ding X, Wang H, Liang Y et al. (2004b). Neurologic abnormalities in workers of a 1-bromopropane factory. *Environ Health Perspect*, 112(13):1319–25. doi:10.1289/ehp.6995 PMID:15345346

Ichihara G, Miller J, Ziolkowska A, Itohara S, Takeuchi Y (2002). Neurological disorders in three workers exposed to 1-bromopropane. *J Occup Health*, 44(1):1–7. doi:10.1539/joh.44.1

Ichihara G, Yu X, Kitoh J, Asaeda N, Kumazawa T, Iwai H et al. (2000a). Reproductive toxicity of 1-bromopropane, a newly introduced alternative to ozone layer depleting solvents, in male rats. *Toxicol Sci*, 54(2):416–23. doi:10.1093/toxsci/54.2.416 PMID:10774824

ILO (2004). 1-Bromopropane ICSC: 1332. International Chemical Safety Cards (ICSC) database. Geneva, Switzerland: International Labour Organization. Available from: http://www.ilo.org/dyn/icsc/showcard.display?p_lang=en&p_card_id=1332&p_version=1, accessed 27 January 2016.

IRSST (2015). 1-Bromopropane and solvent substitution. Montreal, Canada: Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail. Available from: http://www.irsst.qc.ca/en/laboratories/references-tools/workplace-air-contaminant/substance/i/52.

Ishidao T, Kunugita N, Fueta Y, Arashidani K, Hori H (2002). Effects of inhaled 1-bromopropane vapor on rat metabolism. *Toxicol Lett*, 134(1-3):237–43. doi:10.1016/S0378-4274(02)00171-6 PMID:12191883

Jones AR, Walsh DA (1979). The oxidative metabolism of 1-bromopropane in the rat. *Xenobiotica*, 9(12):763–72. doi:10.3109/00498257909042344 PMID:532220

JSOH (2015). Japan Society for Occupational Health, Recommendation of occupational exposure limits (2015-2016) *J Occup Health*, 57:344–417. PMID:26522617

Judson RS, Magpantay FM, Chickarmane V, Haskell C, Tania N, Taylor J et al. (2015). Integrated model of chemical perturbations of a biological pathway using 18 in vitro high-throughput screening assays for the estrogen receptor. *Toxicol Sci*, 148(1):137–54. doi:10.1093/toxsci/kfv168 PMID:26272952

Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N et al. (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*, 25(7):1287–302. doi:10.1021/tx3000939 PMID:22519603

Kawai T, Takeuchi A, Miyama Y, Sakamto K, Zhang ZW, Higashikawa K et al. (2001). Biological monitoring of occupational exposure to 1-bromopropane by means of urinalysis for 1-bromopropane and bromide ion. *Biomarkers*, 6(5):303–12. doi:10.1080/13547500110034817 PMID:23889306

Kim H, Chung Y-H, Jeong J-H, Lee Y-M, Sur G-S, Kang J-K (1999b). Acute and repeated inhalation toxicity of 1-bromopropane in SD rats. *J Occup Health*, 41(2):121–8. doi:10.1539/joh.41.121

Kim KW, Kim HY, Park SS, Jeong HS, Park SH, Lee JY et al. (1999a). Gender differences in activity and induction of hepatic microsomal cytochrome P-450 by 1-bromopropane in Sprague-Dawley rats. *J Biochem Mol Biol*, 32:232–8.

Kirk-Othmer (1978). Encyclopedia of Chemical Technology, 3rd ed., Vol. 1–26. New York (NY), USA: John Wiley & Sons. V4, p 257.

Lee SK, Jeon TW, Kim YB, Lee ES, Jeong HG, Jeong TC (2007). Role of glutathione conjugation in the hepatotoxicity and immunotoxicity induced by 1-bromopropane in female BALB/c mice. *J Appl Toxicol*, 27(4):358–67. doi:10.1002/jat.1214 PMID:17265426

Lee SK, Jo SW, Jeon TW, Jun IH, Jin CH, Kim GH et al. (2005). Hepatotoxic effect of 1-bromopropane and its conjugation with glutathione in male ICR mice. *Arch Pharm Res*, 28(10):1177–82. doi:10.1007/BF02972983 PMID:16276976

Lee SK, Kang MJ, Jeon TW, Ha HW, Yoo JW, Ko GS et al. (2010). Role of metabolism in 1-bromopropane-induced hepatotoxicity in mice. *J Toxicol Environ Health A*, 73(21-22):1431–40. doi:10.1080/15287394.2010.511546 PMID:20954070

Li W, Shibata E, Zhou Z, Ichihara S, Wang H, Wang Q et al. (2010). Dose-dependent neurologic abnormalities in workers exposed to 1-bromopropane. *J Occup Environ Med*, 52(8):769–77. doi:10.1097/JOM.0b013e3181eaded7 PMID:20657306

Liu F, Ichihara S, Mohideen SS, Sai U, Kitoh J, Ichihara G (2009). Comparative study on susceptibility to 1-bromopropane in three mice strains. *Toxicol Sci*, 112(1):100–10. doi:10.1093/toxsci/kfp173 PMID:19638432

Liu F, Ichihara S, Valentine WM, Itoh K, Yamamoto M, Sheik Mohideen S et al. (2010). Increased susceptibility of Nrf2-null mice to 1-bromopropane-induced hepatotoxicity. *Toxicol Sci*, 115(2):596–606. doi:10.1093/toxsci/kfq075 PMID:20211940

Majersik JJ, Caravati EM, Steffens JD (2007). Severe neurotoxicity associated with exposure to the solvent 1-bromopropane (n-propyl bromide). *Clin Toxicol (Phila)*, 45(3):270–6. doi:10.1080/15563650701226218 PMID:17453879

Mathias PI, Cheever KL, Hanley KW, Marlow KL, Johnson BC, B'hymer C (2012). Comparison and evaluation of urinary biomarkers for occupational exposure to spray adhesives containing 1-bromopropane. *Toxicol Mech Methods*, 22(7):526–32. doi:10.3109/15376516.2012.686536 PMID:22519856

Mirza T, Gérin M, Bégin D, Drolet D (2000). A study on the substitution of trichloroethylene as a spot remover in the textile industry. *AIHAJ*, 61(3):431–8. doi:10.1080/15298660008984555 PMID:10885896

Mohideen SS, Ichihara G, Ichihara S, Nakamura S (2011). Exposure to 1-bromopropane causes degeneration of noradrenergic axons in the rat brain. *Toxicology*, 285(1-2):67–71. doi:10.1016/j.tox.2011.04.005 PMID:21527306

Mohideen SS, Ichihara S, Subramanian K, Huang Z, Naito H, Kitoh J et al. (2013). Effects of exposure to 1-bromopropane on astrocytes and oligodendrocytes in rat brain. *J Occup Health*, 55(1):29–38. doi:10.1539/joh.12-0118-OA PMID:23183024

Morgan DL, Nyska A, Harbo SJ, Grumbein SL, Dill JA, Roycroft JH et al. (2011). Multisite carcinogenicity and respiratory toxicity of inhaled 1-bromopropane in rats and mice. *Toxicol Pathol*, 39(6):938–48. doi:10.1177/0192623311416374 PMID:21859883

NIOSH (2002a). NIOSH health hazard evaluation report. Custom Products, Inc.; Mooresville, NC. Reh CM, Mortimer VD, Nemhauser JB, Trout D (authors). HETA No. 98-0153-2883. Cincinnati (OH), USA: Hazard Evaluations and Technical Assistance Branch, United States Department of Health and Human Services, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: http://www.cdc.gov/niosh/hhe/reports/pdfs/1998-0153-2883.pdf.

NIOSH (2002b). NIOSH health hazard evaluation report. STN Cushion Company; Thomasville, NC. Harney JM, Hess J, Reh CM, Trout D (authors). HETA No. 2000-0410-2891. Cincinnati (OH), USA: Hazard Evaluations and Technical Assistance Branch, United States Department of Health and Human Services, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: http://www.cdc.gov/niosh/hhe/reports/pdfs/2000-0410-2891.pdf.

NIOSH (2003a). Method 1025: 1- and 2-Bromopropane. NIOSH manual of analytical methods. 4th Edition. DHHS (NIOSH) Publication No. 2003-152. Cincinnati (OH), USA: United States Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: http://www.cdc.gov/niosh/docs/2003-154/pdfs/1025.pdf.

NIOSH (2003b). NIOSH health hazard evaluation report. Marx Industries, Inc.; Sawmills, NC. Harney JM, Nemhauser JB, Reh CM, Trout D, Schrader S (authors). HETA Report No. 99-0260-2906. Cincinnati (OH), USA: Hazard Evaluations and Technical Assistance Branch, United States Department of Health and Human Services, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: http://www.cdc.gov/niosh/hhe/reports/pdfs/1999-0260-2906.pdf.

NIOSH (2008). Health hazard evaluation report: evaluation of 1-bromopropane use in four New Jersey commercial dry cleaning facilities. Eisenberg J, Ramsey R (authors). HETA No. 2008-0175-3111. Cincinnati (OH), USA: Hazard Evaluations and Technical Assistance Branch, United States Department of Health and Human Services, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: http://www.cdc.gov/niosh/hhe/reports/pdfs/2008-0175-3111.pdf.

NIOSH (2009). Current Intelligence Bulletin 61: a strategy for the assignment of new NIOSH skin notations. Cincinnati (OH), USA: United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2009-147. Available from: http://www.cdc.gov/niosh/docs/2009-147/.

NIOSH (2013). OSHA/NIOSH Hazard Alert: 1-bromopropane. DHHS (NIOSH) Publication No. 2013-150. Cincinnati (OH), USA: United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: http://www.cdc.gov/niosh/docs/2013-150/pdfs/2013-150.pdf.

NTP (2011). Toxicology and carcinogenesis studies of 1-bromopropane (CAS No. 106–94–5) in F344/N rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser*, 564(564):1–190. PMID:21921963

NTP (2013). Report on carcinogens monograph on 1-bromopropane. *Rep Carcinog Monogr*, 13(13-5982):1–168. PMID:24810716

O'Neil MJ, editor (2013). The Merck index. An encyclopedia of chemicals, drugs, and biologicals. 15th ed. Whitehouse Station (NJ), USA: Merck and Co. Royal Society of Chemistry; ISBN: 978-1849736701.

Ohnishi A, Ishidao T, Kasai T, Arashidani K, Hori H (1999). [Neurotoxicity of 1-bromopropane in rats] *J UOEH*, 21(1):23–8. PMID:10202789

OSHA (1999). Sampling and analytical methods. Method PV2061: 1-bromopropane. Washington (DC), USA: United States Department of Labor, Occupational Safety and Health Administration. Available from: https://www.osha.gov/dts/sltc/methods/partial/pv2061/2061.html.

OSHA (2014). Chemical sampling information. Method 1017: 1-bromopropane. Washington (DC), USA: United States Department of Labor, Occupational Safety and Health Administration. Available from: https://www.osha.gov/dts/chemicalsampling/data/CH_222006.html.

Prasch AL, Teraoka H, Carney SA, Dong W, Hiraga T, Stegeman JJ et al. (2003). Aryl hydrocarbon receptor 2 mediates 2,3,7,8-tetrachlorodibenzo-p-dioxin developmental toxicity in zebrafish. *Toxicol Sci*, 76(1):138–50. doi:10.1093/toxsci/kfg202 PMID:12883077

Raymond LW, Ford MD (2007). Severe illness in furniture makers using a new glue: 1-bromopropane toxicity confounded by arsenic. *J Occup Environ Med*, 49(9):1009–19. doi:10.1097/JOM.0b013e318145b616 PMID:17848857

Saito-Suzuki R, Teramoto S, Shirasu Y (1982). Dominant lethal studies in rats with 1,2-dibromo-3-chloropropane and its structurally related compounds. *Mutat Res*, 101(4):321–7. doi:10.1016/0165-1218(82)90125-2 PMID:7110159

Samukawa M, Ichihara G, Oka N, Kusunoki S (2012). A case of severe neurotoxicity associated with exposure to 1-bromopropane, an alternative to ozone-depleting

or global-warming solvents. *Arch Intern Med*, 172(16):1257–60. doi:10.1001/archinternmed.2012.3987 PMID:22893012

Sclar G (1999). Encephalomyeloradiculoneuropathy following exposure to an industrial solvent. *Clin Neurol Neurosurg*, 101(3):199–202. doi:10.1016/S0303-8467(99)00034-7 PMID:10536908

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:26600562

Stolzenberg SJ, Hine CH (1979). Mutagenicity of halogenated and oxygenated three-carbon compounds. *J Toxicol Environ Health*, 5(6):1149–58. doi:10.1080/15287397909529820 PMID:393836

Stolzenberg SJ, Hine CH (1980). Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. *Environ Mutagen*, 2(1):59–66. doi:10.1002/em.2860020109 PMID:7035158

Subramanian K, Mohideen SS, Suzumura A, Asai N, Murakumo Y, Takahashi M et al. (2012). Exposure to 1-bromopropane induces microglial changes and oxidative stress in the rat cerebellum. *Toxicology*, 302(1):18–24. doi:10.1016/j.tox.2012.07.006 PMID:22824114

Tachizawa H, MacDonald TL, Neal RA (1982). Rat liver microsomal metabolism of propyl halides. *Mol Pharmacol*, 22(3):745–51. PMID:7155131

Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect*, 121(7):756–65. doi:10.1289/ehp.1205784 PMID:23603828

Toraason M, Lynch DW, DeBord DG, Singh N, Krieg E, Butler MA et al. (2006). DNA damage in leukocytes of workers occupationally exposed to 1-bromopropane. *Mutat Res*, 603(1):1–14. doi:10.1016/j.mrgentox.2005.08.015 PMID:16412685

UNEP (2001). 2001 Report of the Chemicals Technical Options Committee. Montreal protocol on substances that deplete the ozone layer. Available from: http://ozone.unep.org/en/treaties-and-decisions/montreal-protocol-substances-deplete-ozone-layer, accessed 15 November 2015.

UNEP (2010). Chemicals Technical Options Committee (CTOC). 2010 Assessment report. Montreal protocol on substances that deplete the ozone layer. Available from: https://acd-ext.gsfc.nasa.gov/Documents/O3_Assessments/Docs/WMO_2010/2010assessment/CTOC_2010_Assessment_Report.pdf, accessed 11 January 2018.

Valentine H, Amarnath K, Amarnath V, Li W, Ding X, Valentine WM et al. (2007). Globin S-propyl cysteine and urinary N-acetyl-S-propylcysteine as internal biomarkers of 1-bromopropane exposure. *Toxicol Sci*, 98(2):427–35. doi:10.1093/toxsci/kfm126 PMID:17517825

Wang H, Ichihara G, Ito H, Kato K, Kitoh J, Yamada T et al. (2002). Biochemical changes in the central nervous system of rats exposed to 1-bromopropane for seven days. *Toxicol Sci*, 67(1):114–20. doi:10.1093/toxsci/67.1.114 PMID:11961224

Wang H, Ichihara G, Ito H, Kato K, Kitoh J, Yamada T et al. (2003). Dose-dependent biochemical changes in rat central nervous system after 12-week exposure to 1-bromopropane. *Neurotoxicology*, 24(2):199–206. doi:10.1016/S0161-813X(02)00195-X PMID:12606292

Wang TH, Wu ML, Wu YH, Tsai WJ, Lin KP, Wang CL et al. (2015). Neurotoxicity associated with exposure to 1-bromopropane in golf-club cleansing workers. *Clin Toxicol (Phila)*, 53(8):823–6. doi:10.3109/15563650.2015.1064939 PMID:26161839

Yamada T, Ichihara G, Wang H, Yu X, Maeda K, Tsukamura H et al. (2003). Exposure to 1-bromopropane causes ovarian dysfunction in rats. *Toxicol Sci*, 71(1):96–103. doi:10.1093/toxsci/71.1.96 PMID:12520079

Yoshida Y, Liu JQ, Nakano Y, Ueno S, Ohmori S, Fueta Y et al. (2007). 1-BP inhibits NF-kappaB activity and Bcl-xL expression in astrocytes in vitro and reduces Bcl-xL expression in the brains of rats in vivo. *Neurotoxicology*, 28(2):381–6. doi:10.1016/j.neuro.2006.05.015 PMID:16815550

Yoshida Y, Nakano Y, Ueno S, Liu J, Fueta Y, Ishidao T et al. (2009). Effects of 1-bromopropane, a substitute for chlorofluorocarbons, on BDNF expression. *Int Immunopharmacol*, 9(4):433–8. doi:10.1016/j.intimp.2009.01.007 PMID:19189864

Yu WJ, Kim JC, Chung MK (2008). Lack of dominant lethality in mice following 1-bromopropane treatment. *Mutat Res*, 652(1):81–7. doi:10.1016/j.mrgentox.2008.01.001 PMID:18291709

Zhang L, Nagai T, Yamada K, Ibi D, Ichihara S, Subramanian K et al. (2013). Effects of sub-acute and sub-chronic inhalation of 1-bromopropane on neurogenesis in adult rats. *Toxicology*, 304:76–82. doi:10.1016/j.tox.2012.12.009 PMID:23266320

Zhong Z, Zeng T, Xie K, Zhang C, Chen J, Bi Y et al. (2013). Elevation of 4-hydroxynonenal and malondialdehyde modified protein levels in cerebral cortex with cognitive dysfunction in rats exposed to 1-bromopropane. *Toxicology*, 306:16–23. doi:10.1016/j.tox.2013.01.022 PMID:23395825