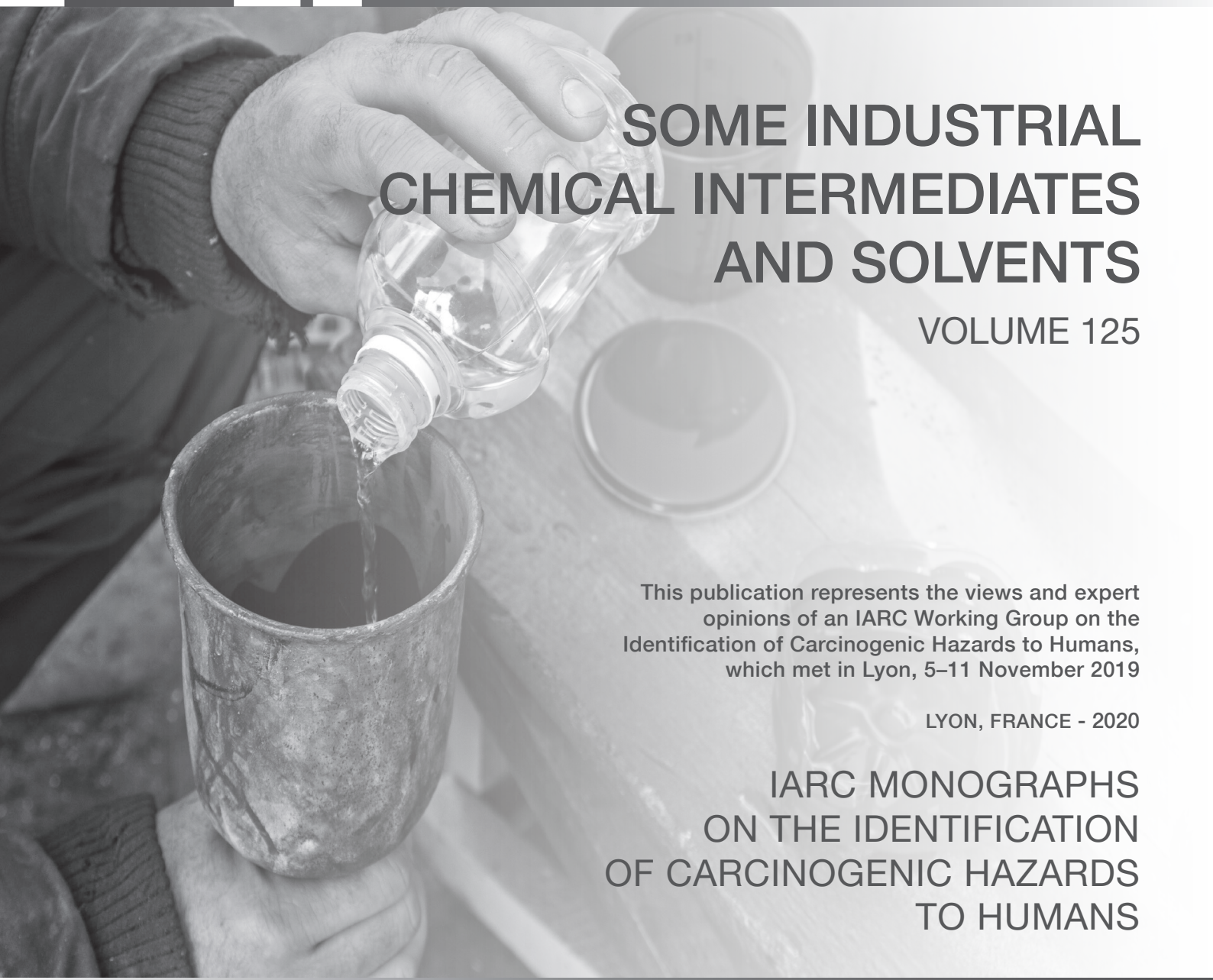
IARC MONOGRAPHS



SOME INDUSTRIAL CHEMICAL INTERMEDIATES AND SOLVENTS

VOLUME 125

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1-BROMO-3-CHLOROPROPANE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 109-70-6

Chem. Abstr. Serv. name: 1-bromo-3-chloropropane

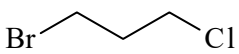
Preferred IUPAC name: 1-bromo-3-chloropropane

Synonyms: 1-chloro-3-bromopropane; 3-bromopropyl chloride; 3-chloropropyl bromide; bromochloropropane; bromochloropropane-1,3; trimethylene bromochloride; trimethylene chlorobromide; ω-chlorobromopropane.

1.1.2 Structural and molecular formulae, and relative molecular mass

Molecular formula: C_3H_6BrCl

Relative molecular mass: 157.44



1.1.3 Chemical and physical properties of the pure substance

Description: colourless liquid (NCBI, 2014)

Density (at 20 °C): 1.60 g/cm^3 (Lide, 1996)

Solubility: poorly soluble in water (2240 mg/L at 25 °C) (NCBI, 2014); soluble in oxygenated and chlorinated solvents (Ashford, 1994)

Vapour pressure: 0.85 kPa at 25 °C (ILO, 2017)

Vapour density: 5.4 (air = 1) (ILO, 2017)

Stability and reactivity: 1-bromo-3-chloropropane is flammable and considered moderately reactive to very reactive; it is also incompatible with strong oxidizing and reducing agents, and many amines, nitrides, azo/diazo compounds, alkali metals, and epoxides (NCBI, 2014)

*Octanol/water partition coefficient (*P*)*: log K_{ow} = 2.18 (ILO, 2017)

Melting point: –58.9 °C (NCBI, 2014)

Boiling point: 143.3 °C (ILO, 2017)

Flash point: 57 °C (ILO, 2017)

Henry's law constant: 2.5×10^{-4} atm m^3 mol^{-1} [25.3 Pa m^3 mol^{-1}] at 25 °C (NCBI, 2014)

Conversion factor: 1 ppm = 6.44 mg/m^3 at 25 °C and 101 kPa.

1.1.4 Technical grade and impurities

The technical product typically consists of 95% primary and 5% secondary bromochloropropanes (Gerhartz, 1985).

1.2 Production and uses

1.2.1 Production process

1-Bromo-3-chloropropane is almost always produced by the free-radical addition of anhydrous hydrogen bromide to allyl chloride (Gerhartz, 1985).

1.2.2 Production volume

1-Bromo-3-chloropropane is identified as a High Production Volume chemical by the Organisation for Economic Co-operation and Development (OECD) (OECD, 2011). Currently, the majority of registered production plants are located in Asia, but production also occurs in Europe and in the USA (Chem Sources, 2019). In the European Union, the current total manufactured and/or imported volume is between 1 and 10 tonnes per year (ECHA, 2019). Data on recent aggregated production volumes in the USA were withheld to protect company proprietary data (US EPA, 2016). In 1978, production in the USA was reported as "probably greater than" 2.27×10^6 g [2.27 tonnes] per annum (NCBI, 2014).

1.2.3 Uses

1-Bromo-3-chloropropane is mainly used as an intermediate in the manufacture of pharmaceuticals, such as antianxiety agents, antidepressants and antipsychotics, antimigraine, local anaesthetics, and antihypertensives (Ashford, 1994; Raman et al., 2017). It is also used in the production of antibacterial, antiviral and antimalarial drugs, and β2-adrenoreceptor agonists (medications to treat bronchial asthma and chronic obstructive pulmonary disease), and in the production of quinazoline derivatives that are used as drugs against cancer, inflammation, and obesity and diabetes (Krishnegowda et al., 2002; Zhang et al., 2016). Apart from pharmaceuticals, 1-bromo-3-chloropropane is also used as an intermediate in the manufacture of pesticides and other chemicals (Gerhartz, 1985; NCBI, 2014).

1.3 Methods of measurement and analysis

1.3.1 Detection and quantification

Kuznetsova & Nogina (1994) describes an analytical method for the detection of 1-bromo-3-chloropropane in air. The sample was prepared by creation of a steam and gas mixture of 1-bromo-3-chloropropane and nitrogen and then absorption of 1-bromo-3-chloropropane using carbochrome C. Final separation was carried out by gas chromatography and a detection limit was reported at 0.01 mg/m^3 (sampling volume up to 5 L). [The Working Group noted that no other information on the method, such as the detection method, could be traced.]

No methods for detection in environmental samples (e.g. water and soil) were identified. One method for the determination and quantification of 1-bromo-3-chloropropane as an impurity in pharmaceuticals could be traced in the literature (Raman et al., 2017). In this study, 1-bromo-3-chloropropane was separated using gas chromatography (stationary phase: bonded and cross-linked polyethylene glycol) and mass spectrometry. The absolute detection limit was reported as 5 ppm (Raman et al., 2017).

1.3.2 Biomarkers of exposure

No data on biomarkers of exposure were available to the Working Group.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

1-Bromo-3-chloropropane is not known to occur naturally in the environment. The production and use of 1-bromo-3-chloropropane in the manufacture of pharmaceuticals and in organic syntheses may result in its release to the environment through various waste streams (NCBI, 2014).

(a) Air

If released to the atmosphere, 1-bromo-3-chloropropane will mainly exist in the vapour phase in the ambient atmosphere (NCBI, 2014). Vapour-phase 1-bromo-3-chloropropane is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of about 18 days (NCBI, 2014). In 1983, 1-bromo-3-chloropropane was detected in air at "source dominated" areas with a median value of 13 ng/m^3, but not in air at rural/remote or suburban/urban areas in the USA (Brodzinsky & Singh, 1983). In 1979, 1-bromo-3-chloropropane was qualitatively identified in air samples collected from a geographical area associated with the bromine industry in Arkansas, USA (DeCarlo, 1979). Pellizzari et al. (1978) reported that 1-bromo-3-chloropropane was detected in air near two production facilities in Alaska, USA. [The Working Group noted that no more recent data on environmental occurrence in air were available.]

(b) Water

If released to water, 1-bromo-3-chloropropane is not expected to adsorb to sediment or particulate matter based on its soil adsorption coefficient (K_{oc}) value (NCBI, 2014). This compound is expected to volatilize from water surfaces given its estimated Henry's law constant. Estimated volatilization half-lives for a model river and model lake are 8 hours and 6 days, respectively (NCBI, 2014). Bioconcentration in aquatic organisms are expected to be low based on an estimated bioconcentration factor value of 27 (NCBI, 2014).

(c) Soil

If released to soil, an estimated K_{oc} value of 63 suggests that 1-bromo-3-chloropropane will have high mobility (NCBI, 2014). Volatilization from dry soil surfaces is expected to be greater than from moist soil surfaces on the basis of physico-chemical properties (NCBI, 2014). 1-Bromo-3-chloropropane, inoculated with effluent from a biological waste treatment plant, reached 3% of the theoretical biochemical oxygen demand in 5 days, suggesting that biological degradation is slow (NCBI, 2014).

1.4.2 Occupational and general population exposure

Potential occupational exposure may occur through inhalation and dermal contact at workplaces where 1-bromo-3-chloropropane is produced or used. Since 1-bromo-3-chloropropane is used only as a chemical intermediate in the production of pharmaceuticals and pesticides, exposure of the general population is likely to be limited (NCBI, 2014); however, 1-bromo-3-chloropropane may occur as an impurity in drug substances (Raman et al., 2017).

1.5 Regulations and guidelines

No regulations or guidelines for this agent were available to the Working Group.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

Inhalation

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female Crj:BDF1 [B6D2F$_1$/Crlj] mice (age, 6 weeks) were treated by whole-body inhalation with 1-bromo-3-chloropropane (0, 25, 100, and 400 ppm v/v in clean air) (purity, > 99.8%) for 6 hours per day, 5 days per week, for 2 years (JBRC, 2005a, c). Survival rates were unaffected in all male and female groups exposed to 1-bromo-3-chloropropane, compared with controls. Survival to the end of 2 years for the groups at 0, 25, 100, and 400 ppm was 38/50, 33/50, 37/50, and 36/50 in males, and 30/50, 24/49, 32/50, and 33/50 in females, respectively. At cessation of treatment, body weights were significantly decreased in groups of males at 100 ppm (–10%) and 400 ppm (–15%) and in females at 400 ppm (–11%), relative to their respective control groups. All mice (except for one female at 25 ppm) underwent complete necropsy and full histopathological examination.

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase in the incidence of bronchioloalveolar adenoma ($P < 0.01$, Peto trend test), of bronchioloalveolar carcinoma ($P < 0.05$, Peto trend test), and of bronchioloalveolar adenoma or carcinoma (combined) ($P < 0.01$, Peto trend test) in male mice. The incidence of bronchioloalveolar adenoma, of bronchioloalveolar carcinoma, and of bronchioloalveolar adenoma or carcinoma (combined) was significantly increased in male mice at 25, 100, and 400 ppm ($P < 0.01$, Fisher exact test).

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of squamous cell papilloma of the forestomach in male mice. The incidence of forestomach squamous cell papilloma was significantly increased in male mice exposed at 400 ppm ($P < 0.05$, Fisher exact test).

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of hepatocellular adenoma in male mice. The incidence of hepatocellular adenoma was significantly increased in male mice at 400 ppm ($P < 0.01$, Fisher exact test). Inhalation of 1-bromo-3-chloropropane did not cause any significant change in the incidence of hepatocellular carcinoma or hepatoblastoma.

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of adenoma of the Harderian gland in male mice. The incidence of Harderian gland adenoma was significantly increased in male mice at 400 ppm ($P < 0.05$, Fisher exact test).

Exposure to 1-bromo-3-chloropropane by inhalation caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of bronchioloalveolar adenoma and of bronchioloalveolar adenoma or carcinoma (combined) in female mice. The incidence of bronchioloalveolar adenoma, of bronchioloalveolar carcinoma, and of bronchioloalveolar adenoma or carcinoma (combined) was significantly increased in female mice at 25, 100, and 400 ppm ($P < 0.01$, Fisher exact test). Inhalation of 1-bromo-3-chloropropane did not cause a statistically significant dose-related trend (Peto test or Cochran–Armitage test) in the incidence of bronchioloalveolar carcinoma in female mice.

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of squamous cell papilloma of the forestomach in female mice. The incidence of forestomach squamous

Table 3.1 Studies of carcinogenicity with 1-bromo-3-chloropropane in mice and rats treated by inhalation (whole-body exposure)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, Crj:BDF1 (M) Age, 6 wk 104 wk JBRC (2005a, c)	Purity, > 99.8% 0, 25, 100, 400 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 33, 37, 36	*Lung* Bronchioloalveolar adenoma 5/50, 21/50**, 20/50**, 26/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	Principal strengths: well-conducted GLP study; males and females used; study covered most of lifespan; multiple-dose study Other comments: no significant effect of treatment on survival
		Bronchioloalveolar carcinoma 3/50, 29/50**, 26/50**, 26/50**	Positive trend: $P < 0.05$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	
		Bronchioloalveolar adenoma or carcinoma (combined) 8/50, 35/50**, 35/50**, 39/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	
		Adenosquamous carcinoma 0/50, 0/50, 0/50, 1/50	NS	
		Squamous cell carcinoma 0/50, 0/50, 1/50, 0/50	NS	
		Bronchioloalveolar adenoma, bronchioloalveolar carcinoma, adenosquamous carcinoma, or squamous cell carcinoma (combined) 8/50, 35/50**, 35/50**, 39/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	
		Forestomach: squamous cell papilloma 1/50, 1/50, 2/50, 8/50*	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); * $P < 0.05$ (Fisher exact test)	
		Liver Hepatocellular adenoma 4/50, 10/50, 8/50, 14/50**	Positive trend: $P < 0.01$ (Peto test) and $P < 0.05$ (Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, Crj:BDF1 (M) Age, 6 wk 104 wk JBRC (2005a, c) (cont.)		Hepatocellular carcinoma 3/50, 5/50, 3/50, 3/50	NS	
		Hepatoblastoma 0/50, 0/50, 1/50, 1/50	NS	
		Harderian gland: adenoma 4/50, 4/50, 4/50, 13/50*	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); * $P < 0.05$ (Fisher exact test)	
Mouse, Crj:BDF1 (F) Age, 6 wk 104 wk JBRC (2005a, c)	Purity, > 99.8% 0, 25, 100, 400 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 30, 24, 32, 33	*Lung* Bronchioloalveolar adenoma 2/50, 19/49**, 25/50**, 30/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	Principal strengths: well-conducted GLP study; males and females used; study covered most of lifespan; multiple-dose study Other comments: no significant effect of treatment on survival
		Bronchioloalveolar carcinoma 2/50, 12/49**, 20/50**, 13/50**	** $P < 0.01$ (Fisher exact test)	
		Bronchioloalveolar adenoma or carcinoma (combined) 4/50, 23/49**, 33/50**, 38/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	
		Forestomach Squamous cell papilloma 0/50, 0/49, 1/50, 8/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ by Fisher exact test	
		Squamous cell carcinoma 0/50, 1/49, 0/50, 1/50	NS	
		Harderian gland: adenoma 3/50, 0/49, 2/50, 14/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/DuCrj (M) Age, 6 wk 104 wk JBRC (2005b, d)	Purity, > 99.8% 0, 25, 100, 400 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 40, 35, 38, 30	*Liver* Hepatocellular adenoma 1/50, 1/50, 2/50, 10/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	Principal strengths: well-conducted GLP study; males and females used; study covered most of lifespan; multiple-dose study Other comments: no significant effect of treatment on survival; historical control incidence of skin trichoepithelioma: 14/1747 (with a maximum of 4% in any single control group); historical control incidence of large intestine adenoma and adenocarcinoma: 0/1749; historical control incidence of bronchioloalveolar adenoma: 62/1749 (average, 3.5%; range, 0–10%)
		Hepatocellular carcinoma 0/50, 0/50, 1/50, 6/50*	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); * $P < 0.05$ (Fisher exact test)	
		Hepatocellular adenoma or carcinoma (combined) 1/50, 1/50, 3/50, 15/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	
		Haemangiosarcoma 1/50, 0/50, 0/50, 2/50	NS	
		Lung Bronchioloalveolar adenoma 2/50, 1/50, 1/50, 7/50	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test)	
		Bronchioloalveolar carcinoma 0/50, 2/50, 0/50, 0/50	NS	
		Large intestine Adenoma 0/50, 0/50, 0/50, 3/50	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test)	
		Adenocarcinoma 0/50, 0/50, 0/50, 1/50	NS	
		Skin: trichoepithelioma 0/50, 1/50, 0/50, 3/50	Positive trend: $P < 0.05$ (Peto test and Cochran–Armitage test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/DuCrj (F) Age, 6 wk 104 wk JBRC (2005b, d)	Purity, > 99.8% 0, 25, 100, 400 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 45, 39, 26	*Liver* Hepatocellular adenoma 1/50, 0/50, 2/50, 32/50** Hepatocellular carcinoma 0/50, 0/50, 0/50, 38/50** Hepatocellular adenoma or carcinoma (combined) 1/50, 0/50, 2/50, 43/50** Haemangioma 0/50, 0/50, 0/50, 1/50 Haemangiosarcoma 0/50, 0/50, 0/50, 6/50* Haemangioma or haemangiosarcoma (combined) 0/50, 0/50, 0/50, 7/50* *Spleen*: mononuclear cell leukaemia 5/50, 3/50, 5/50, 13/50* *Lung*: bronchioloalveolar adenoma 1/50, 0/50, 1/50, 5/50	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test) Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test) Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test) NS Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); * $P < 0.05$ (Fisher exact test) Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); * $P < 0.01$ (Fisher exact test) Positive trend: $P < 0.01$ by Peto test and Cochran–Armitage test; * $P < 0.05$ by Fisher exact test Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test)	Principal strengths: well-conducted GLP study; males and females used; study covered most of lifespan; multiple-dose study Other comments: no significant effect of treatment on survival; historical control incidence of skin trichoepithelioma: 3/1597 from 32 studies at laboratory (with a maximum of 2% in any single control group); historical control incidence of large intestine adenoma: 0/1597 from 32 studies at laboratory; historical control incidence of bronchioloalveolar adenoma: 30/1597 (average, 1.9%; range, 0–10%)

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/DuCrj (F) Age, 6 wk 104 wk JBRC (2005b, d) (cont.)		*Skin*: trichoepithelioma 0/50, 0/50, 1/50, 2/50 *Large intestine*: adenoma 0/50, 0/50, 0/50, 2/50	NS NS	

F, female; GLP, good laboratory practice; M, male; NS, not significant; ppm, parts per million; wk, week.

cell papilloma was significantly increased in female mice exposed at 400 ppm ($P < 0.01$, Fisher exact test). Inhalation of 1-bromo-3-chloropropane did not cause any significant change in the incidence of squamous cell carcinoma of the forestomach.

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of Harderian gland adenoma in female mice. The incidence of Harderian gland adenoma was significantly increased in female mice at 400 ppm ($P < 0.01$, Fisher exact test).

Inhalation of 1-bromo-3-chloropropane resulted in increased incidence and/or severity of non-neoplastic lesions in the nasal cavity in mice (respiratory metaplasia, atrophy, and eosinophilic change of the olfactory epithelium, and glandular respiratory metaplasia at 400 ppm in males and females, and exudate at 400 ppm in females only). Exposure to 1-bromo-3-chloropropane resulted in an increase in the incidence of non-neoplastic lesions of the nasopharynx (eosinophilic change at 400 ppm in males and at 100 and 400 ppm in females; exudate at 400 ppm in females). 1-Bromo-3-chloropropane resulted in increased incidence of non-neoplastic lesion of the lung (bronchioloalveolar hyperplasia at 25, 100, and 400 ppm in males and females). Exposure to 1-bromo-3-chloropropane resulted in an increase in the incidence of non-neoplastic lesions of the forestomach (squamous cell hyperplasia at 400 ppm in males and at 100 and 400 ppm in females). [The Working Group noted that this GLP study used males and females, and multiple doses.]

3.2 Rat

Inhalation

In a study that complied with GLP, groups of 50 male and 50 female F344/DuCrj rats (age, 6 weeks) were treated by whole-body inhalation with 1-bromo-3-chloropropane (0, 25, 100, and 400 ppm, v/v in clean air) (purity, > 99.8%) for 6 hours per day, 5 days per week, for 2 years (JBRC, 2005b, d). Survival rates appeared to be significantly reduced in groups of males and females at 400 ppm. Survival up to 2 years for the groups at 0, 25, 100, and 400 ppm was 40/50, 35/50, 38/50, and 30/50 in males, and 38/50, 45/50, 39/50, and 26/50 in females, respectively. At cessation of treatment, body weights were significantly decreased, relative to their respective control groups, in males (–25%) and in females (–20%) in the groups at 400 ppm. All rats underwent complete necropsy and full histopathological examination.

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of hepatocellular adenoma, of hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined) in male rats. The incidence of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) was significantly increased in male rats at 400 ppm ($P < 0.01$, Fisher exact test). The incidence of hepatocellular carcinoma was significantly increased in male rats at 400 ppm ($P < 0.05$, Fisher exact test).

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of bronchioloalveolar adenoma in male rats. The incidence of bronchioloalveolar adenoma was not significantly increased in any group of exposed male rats by pairwise comparison. Inhalation of 1-bromo-3-chloropropane did not cause any dose-related change in the incidence of bronchioloalveolar carcinoma in male rats. The incidence of bronchioloalveolar carcinoma was not significantly increased in any group of exposed male rats by pairwise comparison.

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of adenoma of the large intestine in male rats.

The incidence of adenoma was not significantly increased in any group of exposed male rats (controls, 0/50; 25 ppm, 0/50; 100 ppm, 0/50; and 400 ppm, 3/50) by pairwise comparison. The incidence of adenocarcinoma of the large intestine was not significantly increased in any group of exposed male rats (controls, 0/50; 25 ppm, 0/50; 100 ppm, at 0/50; and 400 ppm, 1/50). [The incidence of adenoma and of adenocarcinoma of the large intestine in the group at 400 ppm exceeded the incidence (0/1749 and 0/1749, respectively) observed in the historical control group of male F344/DuCrj rats from 35 studies conducted in this laboratory.]

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.05$, Peto trend test) in the incidence of trichoepithelioma of the skin in male rats. The incidence of trichoepithelioma of the skin was not significantly increased in male rats exposed at 25, 100, and 400 ppm (controls, 0/50; 25 ppm, 1/50; 100 ppm, 0/50; and 400 ppm, 3/50). [The incidence of trichoepithelioma in the group at 400 ppm exceeded the upper bound of the range observed in the historical control group of male F344/DuCrj rats from 35 studies conducted in this laboratory (incidence, 14/1747; with a maximum of 4% in any single control group).]

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of hepatocellular adenoma, of hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined) in female rats. The incidence of hepatocellular adenoma, of hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined) was significantly increased in female rats at 400 ppm ($P < 0.01$, Fisher exact test). Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of haemangiosarcoma of the liver in female rats. The incidence of liver haemangiosarcoma was significantly increased in female rats at 400 ppm ($P < 0.05$, Fisher exact test).

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of mononuclear cell leukaemia of the spleen in female rats. The incidence of mononuclear cell leukaemia of the spleen was significantly increased in female rats at 400 ppm ($P < 0.05$, Fisher exact test).

Inhalation of 1-bromo-3-chloropropane caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of bronchioloalveolar adenoma in female rats. The incidence of bronchioloalveolar adenoma was not significantly increased in any group of exposed female rats by pairwise comparison.

The incidence of trichoepithelioma of the skin was not significantly increased in any group of exposed female rats (controls, 0/50; 25 ppm, 0/50; 100 ppm, 1/50; and 400 ppm, 2/50). [The incidence of trichoepithelioma in the group at 400 ppm exceeded the upper bound of the range observed in the historical control group of female F344/DuCrj rats from 32 studies conducted in this laboratory (incidence, 3/1597; with a maximum of 2% in any single control group).]

Inhalation of 1-bromo-3-chloropropane did not cause any dose-related change in the incidence of adenoma of the large intestine in female rats. The incidence of adenoma of the large intestine was not significantly increased in any group of exposed female rats (controls, 0/50; 25 ppm, 0/50; 100 ppm, 0/50; and 400 ppm, 2/50). [The incidence of adenoma in the group at 400 ppm exceeded the incidence (0/1597) observed in the historical control group of female F344/DuCrj rats from 32 studies conducted in this laboratory.]

Inhalation of 1-bromo-3-chloropropane resulted in increased incidence and/or severity of non-neoplastic lesions in the nasal cavity in male rats (inflammation of the respiratory epithelium at 25, 100, and 400 ppm; squamous metaplasia of the respiratory epithelium, respiratory

metaplasia of glands, atrophy, necrosis, and respiratory metaplasia of the olfactory epithelium at 400 ppm). Exposure to 1-bromo-3-chloropropane resulted in increased incidence and/or severity of non-neoplastic lesions in the nasal cavity in female rats (respiratory metaplasia of glands at 100 and 400 ppm; inflammation of the respiratory epithelium, squamous metaplasia of the respiratory epithelium, atrophy and necrosis of the olfactory epithelium at 400 ppm). Exposure to 1-bromo-3-chloropropane resulted in increased incidence and/or severity of non-neoplastic lesions in the liver in male rats (clear cell focus at 100 and 400 ppm; acidophilic and basophilic focus at 400 ppm). Exposure to 1-bromo-3-chloropropane resulted in an increase in the incidence and/or severity of non-neoplastic lesions in the liver in female rats (bile duct hyperplasia at 100 and 400 ppm; clear cell, acidophilic cell, and basophilic cell focus at 400 ppm). Exposure to 1-bromo-3-chloropropane resulted in an increase in the incidence of non-neoplastic lesions of the spleen (deposit of haemosiderin at 400 ppm in males). Exposure to 1-bromo-3-chloropropane resulted in an increase in the incidence of a non-neoplastic lesion of the bone marrow (increased haematopoiesis at 400 ppm in females). [The Working Group noted that this GLP study used males and females, and multiple doses.]

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

A single intraperitoneal injection of 1-bromo-3-chloropropane at a dose of 1300 µmol/kg body weight (bw) [205 mg/kg bw] resulted in concentrations of ~15 nmol/mL in plasma, ~100 nmol/g in kidney, and ~30 nmol/g in testis 1 hour after dosing in male MOL:WIST rats (Låg et al., 1991).

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether 1-bromo-3-chloropropane is genotoxic; or alters cell proliferation, cell death, or nutrient supply. Insufficient data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is genotoxic

Table 4.1, Table 4.2, and Table 4.3 summarize the studies evaluated that report genetic and related effects of 1-bromo-3-chloropropane.

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.1.

Several studies investigated the genotoxic effects of exposure to 1-bromo-3-chloropropane in experimental animals in vivo. No increase in the frequency of *gpt* mutations was observed in the liver, bone marrow, glandular stomach, or testis of male *gpt* delta mice exposed to 1-bromo-3-chloropropane at a dose of 30, 100, or 300 mg/kg bw per day by oral gavage for 28 days (JECDB, 2000a). Unlike the positive control (mitomycin C), 1-bromo-3-chloropropane did not increase the frequency of micronucleated

Table 4.1 Genetic and related effects of 1-bromo-3-chloropropane in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
DNA damage (alkaline elution)	Rat, MOL:WIST (M)	Kidney	–	3000 µmol/kg bw [472 mg/kg bw]	Intraperitoneal injection, 1×	Purity, NR	Låg et al. (1991)
Mutation in *gpt* delta (*gpt* and Spi-)	Mouse, C57BL/6 *gpt-delta* (M)	Liver, bone marrow, stomach, and testis	–	300 mg/kg bw	Oral, 1×/day, 7 days/week, 4 weeks		JECDB (2000a)
Chromosomal aberrations	Rat	Bone marrow	(+)	45 mg/m^3	Inhalation, chronic	Source and purity, NR Rat strain and sex, NR Duration and dosing regimen, NR	Eitingon (1971)
Micronucleus formation	Mouse, ICR (M)	Peripheral blood reticulocytes	–	645 mg/kg bw	Oral, 1×	Source and purity, NR	Kim & Ryu (2010)

bw, body weight; F, female; *gpt*, guanine phosphoribosyltransferase; HID, highest ineffective dose; LED, lowest effective dose (units as reported); M, male; NR, not reported; Spi, sensitive to prophage P2 interference.

[a] –, negative; (+), positive in a study that was poorly reported.

Table 4.2 Genetic and related effects of 1-bromo-3-chloropropane in non-human mammals in vitro

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
Gene mutation, *Tk* locus	L5178Y mouse, lymphoma cells	–	+	500 µg/mL (–S9); 200 µg/mL (+S9)	Seifried et al. (2006)
Chromosomal aberrations	Chinese hamster, lung cells	+	+	1600 µg/mL (–S9); 185 µg/mL (+S9)	Kim & Ryu (2006)
Chromosomal aberrations	Chinese hamster, lung cells	+	+	2000 µg/mL (–S9); 250 µg/mL (+S9)	JETOC (1997a)
Chromosomal aberrations	Chinese hamster, lung cells	±	+	1420 µg/mL (–S9); 250 µg/mL (+S9)	JECDB (2000b)

HIC, highest ineffective concentration; LEC, lowest effective concentration; S9, 9000 × *g* supernatant from rat liver; Tk, thymidine kinase.

[a] –, negative; +, positive; ±, equivocal.

Table 4.3 Genetic and related effects of 1-bromo-3-chloropropane in non-mammalian systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Aspergillus nidulans	Whole chromosome segregation	+	NA	5 mM [787 µg/mL]		Crebelli et al. (1995)
Salmonella typhimurium TA1535	Reverse mutation	–	+	2000 µg/plate (+/–S9 from rat liver)	Purity, NR Cytotoxicity, NR	JETOC (1997b)
Salmonella typhimurium TA1535	Reverse mutation	–	+	1250 µg/plate (–S9 from rat liver); 156 µg/plate (+S9 from rat liver)		JECDB (2000c)
Salmonella typhimurium TA100	Reverse mutation	–	– (+S9 from rat liver) + (+S9 from hamster liver)	10 000 µg/plate (–S9 from rat or hamster liver, or +S9 from rat liver); 1000 µg/plate (+S9 from hamster liver)		Seifried et al. (2006)
Salmonella typhimurium TA100	Reverse mutation	–	–	1.0 µmol/plate (157.4 µg/plate) (rat liver microsomes +/– NADPH co-factors)	Low concentration tested	Låg et al. (1994)
Salmonella typhimurium TA100	Reverse mutation	–	–	2000 µg/plate (+/–S9 from rat liver)	Purity, NR Cytotoxicity, NR	JETOC (1997b)
Salmonella typhimurium TA100	Reverse mutation	–	+	1250 µg/plate (–S9 from rat liver); 625 µg/plate (+S9 from rat liver)		JECDB (2000c)
Salmonella typhimurium TA98	Reverse mutation	–	–	10 000 µg/plate (+/–S9 from rat or hamster liver)		Seifried et al. (2006)
Salmonella typhimurium TA98	Reverse mutation	–	–	2000 µg/plate (+/–S9 from rat liver)	Purity, NR Cytotoxicity, NR	JETOC (1997b)
Salmonella typhimurium TA98	Reverse mutation	–	–	5000 µg/plate (+/–S9 from rat liver)		JECDB (2000c)
Salmonella typhimurium TA1537 and TA1538	Reverse mutation	–	–	2000 µg/plate (+/–S9 from rat liver)	Purity, NR Cytotoxicity, NR	JETOC (1997b)
Salmonella typhimurium TA1537	Reverse mutation	–	–	1250 µg/plate (+/–S9 from rat liver)		JECDB (2000c)
Escherichia coli WP2 *uvrA*	Reverse mutation	–	–	2000 µg/plate (+/–S9 from rat liver)	Purity, NR Cytotoxicity, NR	JETOC (1997b)
Escherichia coli WP2 *uvrA*	Reverse mutation	+	+	588/412 µg/plate (1st/2nd replicate; –S9 from rat liver); 1201/1715 µg/plate (1st/2nd replicate; +S9 from rat liver)		JECDB (2000c)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NADPH, nicotinamide adenine dinucleotide phosphate reduced form; NR, not reported; S9, 9000 × *g* supernatant

[a] –, negative; +, positive

peripheral blood reticulocytes in male ICR mice given a single oral dose of up to 645 mg/kg bw (Kim & Ryu, 2010). In addition, in contrast to other members of the halogenated propane family, 1-bromo-3-chloropropane did not increase renal DNA damage in male MOL:WIST rats, as assessed by alkaline elution, 48 hours after a single intraperitoneal injection of up to 3000 µmol/kg bw [470 mg/kg bw] (Låg et al., 1991). A chronic exposure to 1-bromo-3-chloropropane by inhalation at 45 mg/m^3, but not at 5.4 mg/m^3, increased the frequency of chromosomal aberrations in the bone marrow of rats (Eitingon, 1971) [the Working Group noted that the experimental details were poorly documented].

(ii) Non-human mammalian cells in vitro

See Table 4.2.

1-Bromo-3-chloropropane increased the frequency of mutations in the mouse heterozygous L5178 *Tk*$^{+/-}$ lymphoma cell assay in the presence, but not in the absence, of metabolic activation by a rat S9 liver homogenate (Seifried et al., 2006). Several studies reported that exposure of Chinese hamster lung cells to 1-bromo-3-chloropropane increased the frequency of chromosomal aberrations (JETOC, 1997a; JECDB, 2000b; Kim & Ryu, 2006). The lowest effective concentration of 1-bromo-3-chloropropane was consistent across these studies, and was decreased in the presence of metabolic activation (JETOC, 1997a; JECDB, 2000b; Kim & Ryu, 2006).

(iii) Non-mammalian experimental systems

See Table 4.3.

1-Bromo-3-chloropropane induced aberrant whole chromosome segregation in *Aspergillus nidulans* (Crebelli et al., 1995).

In the absence of metabolic activation, 1-bromo-3-chloropropane gave negative results in tests for reverse mutation in *Salmonella typhimurium* strains TA1535, TA100, TA98, and TA1537 (JETOC, 1997b; JECDB, 2000c; Seifried et al., 2006). In the presence of metabolic activation, 1-bromo-3-chloropropane was generally mutagenic in *S. typhimurium* strains that are indicators of base-substitution mutations (TA1535 and TA100), but not in *S. typhimurium* strains that are indicators of frameshift mutations (TA98, TA1537, and TA1538) (JETOC, 1997b; JECDB, 2000c; Seifried et al., 2006). Inconsistent results were reported in two tests in *Escherichia coli* WP2 *uvrA* (JETOC, 1997b; JECDB, 2000c).

4.2.2 Alters cell proliferation, cell death, and nutrient supply

In male and female Crj:BDF1 mice treated for 2 years by inhalation (JBRC, 2005a, c; see Section 3.1), an increase in the incidence and/or severity of the following non-neoplastic lesions was reported: respiratory metaplasia, atrophy, and eosinophilic change of the olfactory epithelium, and glandular respiratory metaplasia; nasopharyngeal eosinophilic change; bronchioloalveolar hyperplasia; and squamous cell hyperplasia in the forestomach.

In F344/DuCrj rats treated for 2 years by inhalation (JBRC, 2005b, d; see Section 3.2) an increase in the incidence and/or severity of the following non-neoplastic lesions was reported: respiratory epithelium squamous metaplasia, metaplasia of glands, atrophy and necrosis of the olfactory epithelium (in males and females). In the liver, foci (clear cell, acidophilic and basophilic types) were observed in males and females; while bile duct hyperplasia was observed in females. In bone marrow, increased haematopoiesis was observed in female rats.

4.2.3 Other data relevant to key characteristics

1-Bromo-3-chloropropane failed to activate both human and mouse constitutive androstane receptor (CAR) in a dual-luciferase reporter

assay using HepG2 human liver cells exposed at 1, 3, 10, and 30 μM (Imai et al., 2013).

In F344/DuCrj rats treated with 1-bromo-3-chloropropane by inhalation for 2 years (see Section 3.2), an increase in the incidence and/or severity of inflammation of the respiratory epithelium was detected in males and females (JBRC, 2005b, d).

1-Bromo-3-chloropropane was not tested in high-throughput screening assays of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the Government of the USA (Thomas et al., 2018).

5. Summary of Data Reported

5.1 Exposure characterization

1-Bromo-3-chloropropane is a High Production Volume chemical that is used as an intermediate in the manufacture of a wide range of pharmaceuticals. Minor uses include the manufacture of pesticides and other chemicals. Potential occupational exposure may occur at workplaces where 1-bromo-3-chloropropane is produced or used, whereas exposure of the general population is likely to be limited; however, actual exposure levels have not been reported in humans.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

In one well-conducted study that complied with good laboratory practice (GLP) in male and female mice treated by whole-body inhalation, 1-bromo-3-chloropropane caused a significant increase, with a significant positive trend, in the incidence of bronchioloalveolar adenoma, of bronchioloalveolar carcinoma, and of bronchioloalveolar adenoma or carcinoma (combined) in males; and a significant increase in the incidence of bronchioloalveolar adenoma (with a significant positive trend), of bronchioloalveolar adenoma or carcinoma (combined) (with a significant positive trend), and of bronchioloalveolar carcinoma in females. In male mice, there were also significant increases in the incidence, with a significant positive trend, of squamous cell papilloma of the forestomach, hepatocellular adenoma, and Harderian gland adenoma. In female mice, there were also significant increases in the incidence, with a significant positive trend, of squamous cell papilloma of the forestomach and of Harderian gland adenoma.

In one well-conducted GLP study in male and female rats treated by whole-body inhalation, 1-bromo-3-chloropropane caused a significant increase, with a significant positive trend, in the incidence of hepatocellular adenoma, of hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined) in males and females, and in the incidence of haemangiosarcoma of the liver in females. There was a significant increase, with a significant positive trend, in the incidence of mononuclear cell leukaemia of the spleen in females. There was a significant positive trend in the incidence of bronchioloalveolar adenoma in males and females, and of skin trichoepithelioma and of adenoma of the large intestine in males.

5.4 Mechanistic evidence

No informative data were available on the absorption, distribution, metabolism, or excretion of 1-bromo-3-chloropropane.

There is consistent and coherent evidence in experimental systems that 1-bromo-3-chloropropane exhibits key characteristics of carcinogens (alters cells proliferation, cell death, or nutrient supply). In male and female rats and mice, there were dose-related increases in incidence and/or

severity of various proliferative non-neoplastic lesions, including both hyperplasia and metaplasia, in point-of-contact and distal tissues after chronic exposure by inhalation. A minority of the Working Group considered this evidence suggestive, as the findings were observed in 2-year studies of carcinogenicity, by which time the induction of benign and malignant tumours had already occurred. There is suggestive evidence that 1-bromo-3-chloropropane induces chronic inflammation, on the basis of findings in male and female rats exposed chronically by inhalation of increased incidence and/or severity of inflammation of the respiratory epithelium. There is suggestive evidence that 1-bromo-3-chloropropane is genotoxic, with incoherent findings across different experimental systems (general lack of genotoxic effects in experimental models in vivo, but generally positive results in mammalian and bacterial models in vitro).

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of 1-bromo-3-chloropropane.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-bromo-3-chloropropane.

6.3 Mechanistic evidence

There is *strong evidence* in experimental systems that 1-bromo-3-chloropropane exhibits key characteristics of carcinogens.

6.4 Overall evaluation

1-Bromo-3-chloropropane is *possibly carcinogenic to humans (Group 2B).*

6.5 Rationale

The evaluation of 1-bromo-3-chloropropane as Group 2B is based on *sufficient evidence* of cancer in experimental animals, and on *strong* mechanistic evidence. The evidence regarding cancer in humans is *inadequate*, as no data were available. The *sufficient evidence* for carcinogenicity in experimental animals is based on an increased incidence of malignant neoplasms in two species. A small minority view considered that the mechanistic evidence is *limited*. Overall, there is *strong evidence* in experimental systems that 1-bromo-3-chloropropane exhibits key characteristics of carcinogens; 1-bromo-3-chloropropane alters cell proliferation, cell death, or nutrient supply.

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