Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

1-Bromo-3-chloropropane and 1,3-dibromopropane

Evaluation statement

22 December 2022

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

1-Bromo-3-chloropropane and 1,3-dibromopropane

Chemicals in this evaluation

Name	CAS registry number
Propane, 1,3-dibromo-	109-64-8
Propane, 1-bromo-3-chloro-	109-70-6

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals in Australia. These chemicals have been assessed as a group as they are structurally similar and have similar use patterns and are expected to have similar toxicity.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

Based on international use information, these chemicals are mainly used as intermediates in the manufacture of other chemicals. Although one of the chemicals, 1-bromo-3-chloropropane has reported domestic use in dishwashing and laundry products, based on available information this is not expected to be widespread.

Human health

Summary of health hazards

Critical health effects for risk characterisation include repeat dose toxicity and carcinogenicity.

Based on the limited information available, these 2 chemicals are rapidly absorbed following inhalation, ingestion, or dermal contact. Urine and bile are the main routes of excretion.

Within 24 hours of oral administration of 1,3-dibromo[^{14}C]propane to rats, approximately 38% of the radioactivity was recovered in the urine and one-third of the ^{14}C dose was excreted in the bile, and less than 1% was detected in the faeces. Mercapturic acids were the major metabolites in urine. A large portion of the remaining dose was further metabolised by oxidative pathways to debrominated metabolites, which enter the tricarboxylic acid cycle and are converted to CO_2, indicating that oxidation is the main route of detoxication.

These chemicals have moderate acute oral toxicity and low acute dermal toxicity. The chemical, 1,3-dibromopropane was found to be slightly irritating to skin, non-irritating to eyes and non-sensitising to skin.

Limited information is available on the repeat dose toxicity of the chemicals. Based on the weight of evidence, the chemicals are expected to cause serious systemic health effects following repeated exposure. Similar to other halogenated alkanes, the liver and testes appear to be the target organs. Repeated (28 day) oral exposure to these chemicals resulted in significant liver toxicity (hypertrophy of the centrilobular hepatocytes and decreased vacuolation in the perilobular hepatocytes) in rats. Effects were observed at doses ≤100 mg/kg bw/day. Repeated (28 day) oral exposure to 1-bromo-3-chloropropane adversely affected the male reproductive system with signs of seminiferous tubular atrophy, and at higher doses (500 mg/kg bw/day) cell debris in the lumen of epididymis ducts and decrease in sperm observed in rats. Toxic effects were also seen in the brain (vacuolar degeneration in the thalamus and hypothalamus) and the spleen (increased hemosiderosis). Effects in the respiratory system were also observed after inhalation exposure to 1-bromo-3-chloropropane. The lowest observed effect level was 50 ppm/6h/day (0.322 mg/L/6h/day)

The generally positive results in bacterial and mammalian systems in vitro indicate potential genotoxicity. However in vivo results are generally negative and overall, there is not sufficient evidence to support hazard classification.

In the presence of metabolic activation, they were mutagenic in *Salmonella typhimurium* TA1535 and TA100 (strains that are indicators of base-substitution mutations), but not in *S. typhimurium* TA98, TA1537, and TA1538 (indicators of frameshift mutation). In the absence of metabolic activation, results in tests for reverse mutation in *S. typhimurium* strains TA1535, TA100, TA98, andTA1537 were negative. Inconsistent results were reported with *Escherichia coli* WP2 *uvrA*. These chemicals increased the frequency of chromosomal aberrations in cultured Chinese hamster lung cells. The chemical, 1-bromo-3-chloropropane increased the frequency of mutations in mouse heterozygousL5178 *Tk*+/– lymphoma cell assay but only in the presence of metabolic activation with rat S9 liver homogenate.

No increase in the frequency of *gpt* mutations was observed in the liver, bone marrow, glandular stomach, or testes of male *gpt* delta mice exposed to 1-bromo-3-chloropropane. The chemical did not increase the frequency of micronucleated peripheral blood reticulocytes in male ICR mice. However, chronic exposure to 1-bromo-3-chloropropane by inhalation at 45 mg/m^3, increased the frequency of chromosomal aberrations in the bone marrow of rats; however, there were limited study details available.

The chemicals were considered carcinogenic based on positive results seen in rats and mice in repeat dose studies with of 1-bromo-3-chloropropane. Statistically significant increases in incidences of hepatocellular carcinomas and adenomas, and bronchioloalveolar adenomas and carcinomas were observed.

In rats, there were also increased incidences of adenomas and adenocarcinoma in the large intestine, and trichoepitheliomas in the skin in males; hemangiosarcoma in the liver and mononuclear cell leukaemia in spleen in females.

In mice, there were also increased incidences of squamous cell papillomas of the forestomach, Harderian gland adenomas, and adenosquamous carcinoma and squamous cell carcinoma of lung.

The carcinogenicity is assigned to the C-Br bond and therefore, is considered applicable to 1,3-dibromopropane. No information was available on reproductive and developmental toxicity. Based on effects in the testes observed in repeated dose toxicity studies, similar effects on reproduction observed with other haloalkanes cannot be ruled out.

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as follows. This does not consider classification of physical and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity – inhalation	Acute Tox. 3	H331: Toxic if inhaled
Specific target organ toxicity (repeated exposure)	STOT Rep Exp. 2	H373: May cause damage to organs through prolonged or repeated exposure
Carcinogenicity	Carc 1B	H350: May cause cancer

Summary of health risk

Public

Australian use data are not available for the chemicals. International data suggests 1-bromo-chloropropane is used in dishwashing and laundry products. Concentration of the chemical in these products is not known. Due to the reactivity of C-Br bond, it is possible that the chemical is in reacted form in such formulations.1-bromo-chloropropane can cause cancer in experimental animals following repeated long-term exposure. Long-term exposure to the chemical caused adverse effects on the liver, lung, and testes. The public may be exposed to the chemical when using dishwasher and laundry products. However, exposure to the chemical during these uses is expected to be for very short periods. Overall, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure may vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local effects and systemic health effects following acute and repeated exposure, the chemicals could pose a risk to workers. Control measures to minimise dermal and inhalation effects are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management

frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *section 100* of the *Industrial Chemicals Act 2019* apply.

Supporting information

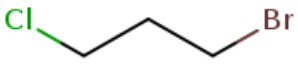
Grouping rationale

The 2 chemicals in this group are structurally similar, only differing in the halide group substituted on third carbon atom of the propane moiety. The critical reactions for these chemicals are likely to be nucleophilic substitution reactions involving the bromine atom, so they act as alkylating agents. These chemicals are expected to have similar toxicokinetics and toxicity.

Chemical identity

Chemical name	Propane, 1,3-dibromo-
CAS No.	109-64-8
Synonyms	1,3-dibromopropane propane, 1,3-dibromide
Structural formula	
Molecular formula	C3H6Br2
Molecular weight (g/mol)	202
SMILES	BrCCCBr

Chemical name	Propane, 1-bromo-3-chloro-
CAS No.	109-70-6
Synonyms	1,3-chlorobromopropane 3-bromopropyl chloride 1-bromo-3-chloropropane-

Structural formula	
Molecular formula	C3H6BrCl
Molecular weight (g/mol)	157.4
SMILES	ClCCCBr

Relevant physical and chemical properties

Chemical	Propane, 1-bromo-3-chloro-	Propane, 1,3-dibromo-
Physical form	Liquid	Liquid
Boiling point	143 °C at 101.8 kPa	167 °C at 101.8 kPa
Vapour pressure	9.1 mmHg at 25 °C	1.36 mmHg at 25 °C
Water solubility	2.2 mg/mL at 25°C	1.7 mg/mL at 25 °C
log K_{ow}	2.18	2.37

Introduction and use

Australia

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

International

The following international uses have been identified through the:

- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers
- Galleria Chemica (Chemwatch)
- Substances in preparations in Nordic countries (SPIN) database
- US Chemical Data Reporting under the Toxic Substances Control Act 2012/2016

- International Agency for Research on Cancer (IARC) monograph.

The chemicals have industrial use as an intermediate in the manufacture of other chemicals.

The chemical, 1-bromo-3-chloropropane, has reported use in dishwashing and laundry products. This source reported the use as commercial rather than consumer use (US EPA CDR 2016). No other evidence of use in dishwashing or laundry products was identified.

The chemicals have non-industrial use in the manufacture of pharmaceutical products and pesticides

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

Workers

The chemicals in this group are not listed on the HCIS and no specific exposure standards are available (SWA).

International regulatory status

Exposure standards

The following exposure standards were identified for the chemicals (Chemwatch):

1-bromo-3-chloropropane

Maximum Permissible Concentration (MPC) of hazardous substances in the air of the working area = 3 mg/m^3 (Russia and Belarus).

1,3-dibromopropane

The following Protective Action Criteria (PAC) (formerly known as Temporary Emergency Exposure Limits (TEELs)) are available for the chemical (Chemwatch; US DOE 2018):

- PAC-1 = 3.1 mg/m^3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, these effects are not disabling, are transient and reversible upon cessation of exposure.'
- PAC-2 = 34 mg/m^3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one

hour, could experience irreversible or other serious, long lasting, adverse health effects or an impaired ability to escape.'
- PAC-3 = 100 mg/m^3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience life-threatening adverse health effects or death.'

As stated by the US Department of Energy (DOE), these values are intended for use until Acute Exposure Guideline Levels (AEGLs), or Emergency Response Planning Guidelines (ERPGs) are adopted for chemicals.

Other

The International Agency for Cancer Research (IARC) concluded that 1-bromo-3-chloropropane is possibly carcinogenic to humans (Group 2B).

Health hazard information

Toxicology information for 1,3-dibromoropane and 1-bromo-3-chloropropane is limited. The 2 chemicals differ only by the substitution of bromine atom by a chlorine atom on position 3 of the propane moiety. The 2 would be expected to behave very similarly and are expected to have similar toxicity. Where information on a toxicity end point of one of the 2 chemicals was not available, information obtained for the other chemical, or from a structurally similar chemical was used as surrogate data.

Toxicokinetics

Information on the oral, dermal or inhalation absorption of 1,3-dibromoropane or 1-bromo-3-chloropropane is not available. The chemicals are expected to be bioavailable following oral, dermal and inhalation exposure based on their molecular weight, log Kow values and vapour pressures. The oral and inhalation bioavailability is supported by observation of effects following acute and chronic exposures.

Metabolism of 1,3-dibromopropane has been studied in rats. Following oral administration of the chemical in rats, 2 conjugated metabolites, S-(3-hydroxypropyl)cysteine and N-acetyl-S-(3-hydroxypropyl)cysteine were isolated from the urine (Jones and Wells 1981). An oxidation product, identified as beta-bromolactic acid, was also isolated as a urinary metabolite. Within 6 hours after administration, 3.5% of the dose was exhaled as CO_2 at a rate indicating that complete oxidation was occurring at a steady rate (Jones and Wells 1981). It was proposed that conjugation of 1,3-dibromopropane, or its metabolite, 3-bromopropanol, with glutathione (GSH) leads to the cysteine conjugate of S-(3- hydroxypropyl)cysteine and its mercapturic acid. Several other breakdown pathways for 1,3-dibromopropane have been suggested by the authors, including metabolism via beta-bromolactate and ultimately to CO_2 and oxalate. The many combinations of these possible biotransformations allow for the formation of more than 30 metabolites from 1,3-dibromopropane.

In another metabolism study (James et al. 1981), following oral administration of 1,3-dibromo[^{14}C]propane to rats (2 mmol/kg), peak levels of radioactivity were rapidly attained in the blood and were maintained for several hours. Within 24 hours approximately 38% of the radioactivity was recovered in the urine and less than 1% was detected in the faeces and one-third of the ^{14}C dose was excreted in the bile. Paper chromatography of urine from treated rats showed eight ^{14}C-metabolites. Six of these were present in amounts not exceeding 4% of the dose. The major extracted metabolite was identified as N-acetyl-S-[1-bromo-3-propyl)cysteine, presumably formed from 1-bromo-3-

propyl-S-glutathione arising from 1,3-dibromopropane binding to GSH. Consistent with this observation, it was also noted that administration of 1,3-dibromopropane to the rat resulted in a decline in the GSH content of the liver. Biliary excretion of sulfur-containing metabolites ensued, and enterohepatic cycling occurred since little radioactivity was detected in faeces. The maintained blood levels of radioactivity observed was consistent with the existence of this process.

Limited Information on toxicokinetics of 1-bromo,3-chloropropane is available. In a study in male MOL: Wist rats 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 (IARC 2020).

Acute toxicity

Oral

Based on available data, these chemicals have moderate acute oral toxicity, warranting hazard classification

In an acute oral toxicity study, conducted in accordance with Organisation for Economic Cooperation and Development (OECD) TG 401, the oral median lethal dose (LD_{50}) values in rats were between 1300 and 2000 mg/kg bw (males) and between 800 and 1300 mg/kg bw (females) for 1-bromo-3-chloropropane. Reported signs of toxicity include decrease in locomotor activity, a prone position and ataxic gait (NITE Chemical Management Team 2009).

A single dose oral toxicity study contained results for LD_{50}values of 734 mg/kg bw (males) and 671 mg/kg bw (females) for 1,3-dibromopropane. No study details were available. (NIHSa)

Dermal

Based on limited available data, these chemicals have low acute dermal toxicity.

An LD50 value in rats for 1,3-dibromopropane was reported as >2000 mg/kg bw. No study details were available (REACH).

In an acute dermal toxicity study (EEC 84/449/EEC B.3 (GLP) LD50 values of >2000 mg/kg bw in rats and 3000 mg/kg bw for rabbits were reported for 1-bromo-3-chloropropane. No study details were available ((NITE Chemical Management Team 2009).

Inhalation

Based on very limited data available these chemicals are reported to have high acute inhalation toxicity. Median lethal concentration (LC50) values of 7.27 mg/L and 6.5 mg/L were reported for 1-bromo-3-chloropropane for rats exposed to vapours for 4 hours. No study details were available (NITE Chemical Management Team 2009).

Corrosion/Irritation

Skin irritation

Based on the limited data available the chemicals are reported to be slightly irritating to skin.

In an irritation study in rabbits with 1,3-dibromopropane, erythema reversed in 5-6 days. No study details were available (REACH).

In a dermal irritation test (EEC 84/449/EEC B.3 (GLP)) 1-bromo-3-chloropropane was applied to the skin of rabbits for 4hrs. Oedema scores of 1 on days 3 and 4 and mean redness scores of 0.67 on day 3 and 1 on day 4 were reported. Oedema and erythema were not observed at other timepoints (unreported) (NITE Chemical Management Team 2009).

Eye irritation

Based on the limited data available the chemicals are slightly irritating to eyes.

in a rabbit eye irritation test (Directive 84/449/EEC B.5 (GLP)) with 1-bromo-3-chloropropane, temporary corneal opacity and transient iridial inflammation were observed but the effects were completely reversible at 7 days after treatment (NITE Chemical Management Team 2009).

No reliable data are available for 1,3-dibromopropane. It was reported to be non-irritating in a study (REACH), but no study details were available and only the iritis score (0) at 24 hrs was reported.

Sensitisation

Skin sensitisation

Based on the limited data available the chemicals are not considered to be skin sensitisers.

In a guinea pig maximisation test conducted according to OECD TG 406, 1,3-dibromopropane was found to be non-sensitising (REACH). No study details were available.

No information is available on the sensitisation effects of 1-bromo-3-chloropropane.

These chemicals did not have a structural alert for protein binding for sensitisation based on the mechanistic profiling functionality of the OECD QSAR Toolbox v4.2 (OECD 2022). These chemicals were predicted to be non-sensitising using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.28.1.6) and the expert rule-based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 6.0.1), (Lhasa Limited).

Repeat dose toxicity

Limited information is available on the repeat dose toxicity of 1,3-dibromopropane and 1-bromo-3-chloropropane. Based on the weight of evidence, these chemicals are expected

to cause serious systemic health effects following repeated exposure, warranting classification. Similar to other halogenated alkanes (Lag et al. 1991; NICNAS 2013a; NICNAS 2013b), the liver and testes appear to be the target organs. Effects in the respiratory tract were also observed after inhalation exposure.

Unlike the vicinal dibromide, ethylene dibromide (NICNAS 2013a), these chemicals do not appear to be nephrotoxic. This may be explained by differences in the ability to cause DNA damage (Lag et al 1991). These chemicals did not cause DNA damage in the kidney following intraperitoneal injection (see genotoxicity section) and minimal to no necrosis in the kidney was observed in rats following a single intraperitoneal (i.p.) injection (Lag et al. 1991).

Oral

In a 28 day repeat dose toxicity study, conducted in accordance with OECD TG 407, Crj:CD(SD)IGS rats (6/sex/dose) were administered 1,3-dibromopropane (99.8%) by gavage at 10, 50 or 250 mg/kg bw/day. Increases in total protein and lipid, increased liver weight, hypertrophy of the centrilobular hepatocytes and decreased vacuolation in the perilobular hepatocytes were observed in females at 50 mg/kg bw/day, and in both sexes at 250 mg/kg bw/day. No treatment related changes were noted in the 10 mg/kg bw/day group. These changes mostly disappeared or were diminished after a 14-day recovery period. The no observed effect level (NOEL) for 1,3-dibromopropane was considered to be 10 mg/kg bw/day for both sexes, based on hypertrophy of hepatocytes (NIHSa). The full study is available in Japanese language.

In a 28 day repeat dose toxicity study, Crj:CD(SD)IGS rats (5/sex/dose) were administered 20 or 100 mg/kg bw/day 1-bromo-3-chloropropane, and ten rats per sex were administered 500 mg/kg bw/day of the chemical for 28 days by gavage. Nine of 10 males in the 500 mg/kg bw/day group died or were sacrificed because of a moribund condition. Absolute and relative liver and kidney weights were significantly increased in all rats given 100 mg/kg bw/day and above 1-bromo-3-chloropropane. Histopathological examination revealed centrilobular hypertrophy of the hepatocytes. Seminiferous tubular atrophy was apparent in males given 100 mg/kg bw/day and above. In the 500 mg/kg bw/day group, cell debris in the lumen of epididymis ducts and decrease in sperm were observed in some animals. Vacuolar degeneration in the thalamus and hypothalamus in the brain, and enhanced haemosiderosis in the spleen were also observed in this group. A NOEL of 20 mg/kg/day was established from this study based on hypertrophy of hepatocytes and atrophy of the seminiferous tubules (NIHSb). The full study is available in Japanese language.

Dermal

No data are available.

Inhalation

Limited data are available. In rat and mouse 13-week inhalation tests, 1-bromo-3-chloropropane is reported to cause morphological changes such as hyperplasia of respiratory epithelia and disarrangement of olfactory epithelia in the nasal cavity and nasopharynx, and hyperplasia and erosion of the forestomach. The lowest observed effect level was 50 ppm/6h/day (0.322 mg/L/6h/day) (NITE Chemical Management Team 2009). No other study details are available.

In a long-term inhalation study in rats with 1-bromo-3-chloropropane, liver changes including fatty degeneration and focal proliferation of the interstitial tissue cells and reduction in spermatozoa motility, degenerative changes in spermatogonia and spermatozoa were

reported after inhalation at 0.045 mg/L. The duration of the study and other study details were not available (NITE Chemical Management Team 2009).

In carcinogenicity studies (see **Carcinogenicity Section**), whole body exposure to 1-bromo-3-chloropropane vapours resulted in increased incidence and/or severity of non-neoplastic lesions in the nasal cavity in rats and mice (respiratory metaplasia, atrophy, and eosinophilic change of the olfactory epithelium), and glandular respiratory metaplasia at higher doses.

Increased incidence of non-neoplastic lesions in spleen (in males) and bone marrow (in females), and lesions in the liver (bile duct hyperplasia) was reported in rats. In mice, increased incidence of non-neoplastic lesions of the lung (bronchioloalveolar hyperplasia) and the forestomach (squamous cell hyperplasia) was noted (JBRC 2005a; JBRC 2005b; JBRC 2005c; JBRC 2005d).

Genotoxicity

The generally positive results in bacterial and mammalian systems in vitro indicate potential genotoxicity. However in vivo results are generally negative and overall there is not sufficient evidence to support hazard classification.

In vitro

1,3-dibromopropane

- In a bacterial reverse mutation test (OECD TG 471), 1,3-dibromopropane was tested on *S. typhimurium* TA100, TA1535, TA98, TA1537, *E. coli* WP2 uvrA at concentrations up to 1250 µg/plate. The chemical was reported to be mutagenic in *S. typhimurium* TA100 and TA1535 with metabolic activation (NIHSa).
- In a chromosomal aberration test (OECD TG473), 1,3-dibromopropane induced structural, but not numerical, chromosomal aberrations in Chinese hamster lung (CHL/IU) cells both with and without metabolic activation at concentrations up to 180 µg/mL (NIHSa).
- In an in vitro gene mutation study in mammalian cells, 1,3-dibromopropane was reported to not cause mutagenic changes to mouse bone marrow (REACH). No study details are available.

1-bromo-3-chloropropane

1-bromo-3-chloropropane was genotoxic in vitro in mammalian and non-mammalian systems (IARC 2020):

- At a concentration of 787 µg/mL, 1-bromo-3-chloropropane induced aberrant whole chromosome segregation in *Aspergillus nidulans*.
- Several results from reverse mutation assays in *S. typhimurium* TA1535, TA100, TA98, and TA1537 were available. The chemical was tested at concentrations up to 10,000 µg/plate. In the presence of metabolic activation, the chemical 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). Inconsistent results were reported in 2 tests in *E. coli* WP2 uvrA.
- Three in vitro mammalian chromosomal aberration tests, using cultured Chinese hamster lung cells (CHL/IU), were conducted to assess the potential of 1-bromo-3-

chloropropane to induce chromosomal aberrations. A dose dependent increase in chromosomal structural aberrations was observed after short term treatment, with or without metabolic activation. The lowest effective concentration of 1-bromo-3-chloropropane was consistent across these studies, and the effect was decreased in the presence of metabolic activation.
- In a gene mutation test, 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 at concentration up to 500 µg/mL.

In vivo

1,3-dibromopropane

- No increase in renal DNA damage in male MOL:WIST rats, as assessed by alkaline elution, 48 hours after a single i.p. injection of up to 606 mg/kg bw of 1-bromo-chloropropane (Lag et al. 1991).

1-bromo-3-chloropropane

Several studies investigated the genotoxic effects of exposure to 1-bromo-3-chloropropane in experimental animals in vivo (IARC 2020):

- No increase in the frequency of gpt gene mutations was observed in the liver, bone marrow, glandular stomach, or testes 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.
- No increase in the frequency of micronucleated peripheral blood reticulocytes was observed in male ICR mice given a single oral dose of up to 645 mg/kg bw.
- No increase in renal DNA damage in male MOL:Wist rats, as assessed by alkaline elution, 48 hours after a single intraperitoneal injection of up to 470 mg/kg bw of 1-bromo-chloropropane.
- In a study reported to be poorly documented, an increase in frequency of chromosomal aberrations was observed in the bone marrow of rats following chronic inhalation exposure to 1-bromo-3-chloropropane at 45 mg/m^3, but not at 5.4 mg/m^3.

In silico

The chemicals have alerts for chromosomal damage as alkylating agents (Lhasa limited; OECD 2022). The chemicals were predicted to be negative (in domain) in in vivo comet assay and in vivo micronucleus test using OASIS–TIMES (version 2.28.1.6), although metabolites were predicted to be positive in the in vivo comet assay.

Carcinogenicity

Available data indicates that chemicals in this group may be carcinogenic, warranting hazard classification.

There is sufficient evidence for carcinogenicity in experimental animals based on an increased incidence of malignant neoplasms in mice and rats exposed to 1-bromo-3-chloropropane. In male and female rats, significant dose related increases in incidence of tumours were seen in the liver and lung. In males, significant dose related increases in tumours were also seen in the large intestine and skin. In females, significant dose related increases in tumours were seen in the spleen. In male and female mice, significant dose related increases in incidence of tumours were seen in the lung, forestomach, and Harderian gland in the eye. In male mice, significant dose related increases in tumours were seen in the liver. No human data are available (IARC 2020).

Rat study

In a well conducted study that complied with good laboratory practice (GLP), male and female F344/DuCrj rats (age, 6 weeks) (n=50/sex/dose) were treated by whole body inhalation to 1-bromo-3-chloropropane (at a target concentration of 0, 25, 100 or 400 ppm (v/v in clean air),) for 6 hours/day, 5 days/week for 2 years (104 weeks) (JBRC 2005d; IARC 2020). Incidences of neoplastic lesions were statistically analysed by Fisher's exact test. A positive trend of the dose-response relationship for the neoplastic incidence was analysed by Peto's test. The following observations were made at the end of the 2 year treatment period:

- Survival rates were significantly reduced in both males and females at 400 ppm.
- In the liver there were significant dose-related increases in the incidence of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma and carcinoma (combined) in male and female rats. In the lung, there were significant dose related increases in the incidence of bronchioloalveolar adenoma in male and female rats.
- In males, there were significant dose related increases in incidences of adenoma of the large intestine and skin trichoepithelioma.
- In females there were significant increases in incidences of haemangiosarcoma of the liver and mononuclear cell leukaemia of the spleen.
- In the nasal cavity there were increased incidences and/or severity of non-neoplastic lesions in both males and females. Inflammation of the respiratory epithelium at 25, 100, and 400 ppm; and squamous metaplasia of the respiratory epithelium, respiratory metaplasia of glands, atrophy, necrosis, and respiratory metaplasia of the olfactory epithelium at 400 ppm were observed.
- In the liver, foci (clear cell, acidophilic and basophilic types) were observed in both sexes from 100 ppm; while bile duct hyperplasia was observed only in females.
- In the spleen, haemosiderin deposits were noted in males at 400 ppm.
- In the bone marrow, increased haematopoiesis was observed in female rats at 400 ppm.

Mouse study

In a well conducted study that complied with good laboratory practice (GLP), male and female Crj:BDF1 [B6D2F1/Crlj] mice (age, 6 weeks) (n=50/sex/dose) were treated by whole body inhalation to 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. Incidences of neoplastic lesions were statistically analysed by Fisher's exact test. A positive trend of the dose response relationship for the neoplastic incidence was analysed by Peto's test.

The following observations were made at the end of the 2 year treatment period:

- Survival rates were unaffected in all male and female groups exposed to 1-bromo-3-chloropropane, compared with controls. In male and female mice, incidences of

bronchioloalveolar adenoma, bronchioloalveolar carcinoma, and bronchioloalveolar adenoma or carcinoma (combined) were significantly increased at all doses.
- In male and female mice there was a significant dose related increase in incidences of squamous cell papilloma of the forestomach and adenoma of the Harderian gland.
- In male mice there was a significant dose related increase in the incidence of hepatocellular adenoma.
- In the nasal cavity there were increased incidences 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 non-neoplastic lesions of the nasopharynx at 100 ppm (females) and 400 ppm (both sexes).
- Increased incidences of non-neoplastic lesion of the lung (bronchioloalveolar hyperplasia) were noted at all doses and in the forestomach (squamous cell hyperplasia) at 100 ppm (females) and 400 ppm (both sexes).

No information is available on the carcinogenicity of 1,3-dibromopropane. The chemical has the same alerts for carcinogenicity as chloropropane (alkylating agent; aliphatic halogen) as 1-bromo-3-chloropropane (alkylating agent; aliphatic halogen) (Lhasa Ltd; OECD 2022).

The carcinogenicity of 1-bromo-3-chloropropane is attributed to the reactivity of C-Br bond, which is also present in 1,3-dibromopropane.

Conclusion

There was clear evidence of carcinogenicity with tumours formed at multiple sites, in 2 species and in both sexes and following oral and inhalation exposure. Although a mode of action has not been established, the chemical caused non-neoplastic lesions at sites where tumours were observed. A genotoxic mode of action cannot be discounted.

IARC (IARC 2020) reviewed the carcinogenicity studies and concluded that there is sufficient evidence in experimental animals for the carcinogenicity of 1-bromo-3-chloropropane, and strong evidence in experimental systems that 1-bromo-3-chloropropane exhibits key characteristics of carcinogens (alters cells proliferation, cell death, or nutrient supply).

Reproductive and development toxicity

No information is available. Effects on reproduction (effects in testes and sperm) were observed with other haloalkanes (NICNAS 2013a; NICNAS 2013b). As the chemical caused effects in the testes in repeated dose toxicity studies similar effects on reproduction cannot be ruled out.

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