Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

1-Propanol, 2,2-dimethyl-, tribromo derivative

Evaluation statement

30 June 2022

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AICIS evaluation statement

Subject of the evaluation

1-Propanol, 2,2-dimethyl-, tribromo derivative

Chemical in this evaluation

Name	CAS registry number
1-Propanol, 2,2-dimethyl-, tribromo derivative	36483-57-5

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

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

Based on international use data, the chemical is predominantly used as a reactive flame retardant in the manufacture of polymers and plastic products. The chemical also has use as an intermediate in the manufacture of chemicals.

Human health

Summary of health hazards

The critical health effects for risk characterisation include local effects (eye damage) and systemic long term effects (mutagenicity and carcinogenicity).

The chemical is a member of a small group of brominated substances called small brominated linear and branched alkyl alcohols (SBAA). Data on the structurally similar SBAA chemical, 2,2- bis(bromomethyl)propane-1,3-diol (BBMP; CAS No. 3296-90-0) are used to draw conclusions regarding the toxicity of chemical.

Based on the available data the chemical is expected to be bioavailable following exposure.

The chemical is considered to be genotoxic based on the weight of evidence from the available in vitro and in silico data, and the read across information on BBMP. The chemical was positive in in vitro assays with metabolic activation but negative in in vivo studies. However, given some limitations with these studies, it cannot be ruled out that the chemical has the potential to generate gene mutations in vivo. The analogue BBMP was positive in several in vitro and in vivo assays. In silico data indicate that the chemicals have the same potential genotoxic mode of action.

There are no carcinogenicity data on the chemical. BBMP is a multi-site carcinogen in 2 species with tumours of human relevance. The available data for BBMP suggest that the chemical can be expected to cause cancer following oral exposure. This is supported by in silico analysis.

Based on the available data, the chemical is not expected to cause developmental toxicity. The limited available data are inconclusive with respect to the effect of the chemical on fertility.

In an eye irritation study in rabbits, irreversible effects in the cornea were observed in one animal. Based on the available data, the chemical has low acute toxicity via the oral, dermal and inhalational routes and is not a skin irritant or skin sensitiser.

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 work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Some of these recommended classifications are based on read across principles (see **Supporting Information - Rationale**). If empirical data become available the chemical indicating that a lower (or higher) classification is appropriate, that data may be used to amend the default classification.

Health hazards	Hazard category	Hazard statement
Serious damage/eye irritation	Eye Dam. 1	H318: Causes serious eye damage.
Germ cell mutagenicity	Muta. 2	H341: Suspected of causing genetic defects
Carcinogenicity	Carc. 1B	H350: May cause cancer

Summary of health risk

Public

Based on the available use information, it is unlikely that the public will be exposed to the chemical. Although the public could come into contact with articles containing the chemical, as the chemical is a reactive flame retardant it will not be bioavailable. Therefore, 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 will vary depending on the method of application and work practices employed.

Given the critical systemic long term and local health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and ocular exposure 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 Evaluation Statement including recommended hazard classifications, 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 the chemical include, but are not limited to:

- using closed systems or isolating operations
- 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 the chemical.

Measures required to eliminate or manage risk arising from storing, handling, and using this hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health.

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

The conclusions of this evaluation are based on the information described in this statement.

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.

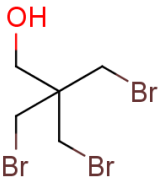
Supporting information

Rationale

There are limited experimental toxicological data available for the chemical. Given the close structural and physicochemical similarities to 2,2-bis(bromomethyl)propane-1,3-diol (BBMP; CAS No. 3296-90-0), the chemical is expected to have similar systemic toxicological effects. The chemical differs only by the replacement of one OH group with a Br group. This makes the chemical more polarised and more reactive compared to BBMP. For both chemicals nucleophilic substitution of the Br can take place and radical activation is possible. For both substances, the aliphatic halogen is a structural alert both for carcinogenicity and mutagenicity. The chemicals belong to the same Quantitative Structure Activity Relationship (QSAR) based clusters for genotoxicity and carcinogenicity (ECHA 2020; Wedebye et al. 2016).

Therefore, read across information from BBMP, along with the in silico data were used to determine the genotoxic and carcinogenic endpoints of the chemical. The IMAP assessments of BBMP (NICNAS 2018) should be read in conjunction with this evaluation.

Chemical identity

Chemical name	1-Propanol, 2,2-dimethyl-, tribromo derivative
CAS No.	36483-57-5
Synonyms	tribromoneopentyl alcohol (TBNPA) 2,2-dimethylpropan-1-ol, tribromo derivative 3,3,3-tribromo-2,2-dimethyl-propan-1-ol pentaerythritol tribromide
Structural formula	
Molecular formula	C5H9Br3O
Molecular weight (g/mol)	324.84
SMILES	OCC(CBr)(CBr)CBr

Relevant physical and chemical properties

Measured physical and chemical property data for the chemical were retrieved from the registration dossier for the chemical submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (EU), the ECHA CLH opinion (ECHA 2020) and the EPI Suite experimental database (Danish QSAR; REACH).

Physical form	Solid, white to off-white flakes
Melting point	68.96 °C at 101 kPa
Boiling point	299.7 °C
Vapour pressure	0 ± 0.21 kPa at 25°C
Water solubility	1.93 g/L at 20 °C
Henry's law constant	1.28E-8 atm-m^3/mol at 25 °C
pKa	14.2 ± 0.5 at 25°C
log K_{ow}	2.6

Introduction and use

Australia

No information is available on the use of tribromoneopentyl alcohol (TBNPA) in Australia.

International

The following international uses have been identified through the:

- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossier
- Galleria Chemica (Chemwatch)
- Substances in Preparations in Nordic Countries (SPIN) database
- European Chemicals Agency (ECHA) publications (ECHA 2019; ECHA 2021).

The chemical has reported use as a reactive flame retardant in the manufacture of plastic products including polyurethanes and polyester resins. It is not thought to be used in flexible polyurethane foam (US EPA 2015).

The chemical has reported site limited uses as an intermediate in chemical synthesis.

The chemical has the following reported uses in the Substances and Preparations in Nordic countries (SPIN) database:

- manufacture of rubber and plastic products
- specialised construction activities
- adhesives and sealants.

Consumer preparations were identified. However, it should be noted that the information in the SPIN database does not distinguish between direct use of the chemical and use of the materials that are produced from chemical reactions involving the chemical.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (Safe Work Australia).

International regulatory status

Exposure standards

No specific exposure standards were identified.

European Union

The chemical is included in the *Candidate List for substances of very high concern (SVHC) for eventual inclusion in Annex XIV* (ECHA 2021). This is due to concerns relating to carcinogenicity. In the European Union (EU), inclusion in the Candidate List brings immediate obligations for suppliers of the substance, such as:

- supplying a safety data sheet
- communicating on safe use
- responding to consumer requests within 45 days
- notifying ECHA if the article they produce contains an SVHC in quantities above one tonne per producer/importer per year and if the substance is present in those articles above a concentration of 0.1% (w/w).

Health hazard information

Toxicokinetics

No information is available on the absorption, distribution, metabolism and excretion of TBNPA. The chemical has a moderate molecular weight (324.8 g/mol) and a log K_{ow} value of 2.6. It is expected to be bioavailable following exposure.

Based on the structural similarity to BBMP, the chemical is expected to be rapidly absorbed following oral exposure and metabolised in the liver to a glucuronide conjugate. The rate of glucuronidation may be species specific with rate of glucuronidation in rodent cells shown to be significantly higher than in human hepatocytes (NICNAS 2018). The chemical is considerably less soluble compared to BBMP and this may reduce its bioavailability.

Acute toxicity

Based on the available data, the chemical has low acute toxicity following oral, dermal and inhalation exposure.

Oral

In an acute oral toxicity study conducted in accordance with Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 423, female Wistar rats (n=3) were treated with a single oral dose of the chemical. The reported median lethal dose (LD50) was >2000 mg/kg bw. Reported sub-lethal signs of toxicity included lethargy, restless behaviour, hunched posture, ventro-lateral recumbency, uncoordinated movements, laboured respiration, piloerection, salivation, ptosis and hypothermia (REACH).

In an acute oral toxicity study in rats (species not specified), the reported LD50 was 1630 mg/kg bw. Reported sub-lethal signs of toxicity included changes in urine composition, haematuria, bladder inflammation, necrosis and scarring (CCOHS 2019). No further details are available.

Dermal

In an acute dermal toxicity study conducted in accordance with OECD TG 402, Wister rats (5/sex) were treated with a single dose of the chemical. The reported LD50 was >2000 mg/kg bw. Erythema, necrosis, scales, scars and/or scabs were reported in the treated skin area of the animals (REACH).

Inhalation

In an acute inhalation toxicity study in rats, the reported median lethal concentration (LC50) was >714 mg/m^3 for an exposure period of 7 hours. No details on sub-lethal effects were reported (CCOHS 2019). No further details are available.

Corrosion/Irritation

Skin irritation

Based on the available data, TBNPA is not considered to be a skin irritant.

In a skin irritation study conducted in accordance with OECD TG 404, male New Zealand White (NZW) rabbits (n=3) were treated with the pure chemical for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48, 72 hours after patch removal. No skin irritation reaction was observed in the study (mean primary dermal irritation index=0) (REACH).

Application of 500 mg of the chemical to the skin of rabbits resulted in slight irritation (CCOHS 2019). No further details are available.

Eye irritation

Based on the available data, the chemical is considered to cause eye irritation. Based on effects in the cornea that were not fully reversed during the observation period, classification is warranted.

In an eye irritation study conducted in accordance with OECD TG 405, the chemical (pure) was instilled into one eye each of 3 male NZW rabbits. Observations were recorded at 1, 24, 48, 72 hours, and 7, 14 and 21 days. Mean scores were reported over the entire observation period limiting comparison with classification criteria. Mean scores for animal 1 (1 hour–14 day) were: corneal opacity 1/4, iritis 1/2, conjunctival redness 2/3 and chemosis 3/4. Mean scores for animal 2 (1 hour–21 day) were: corneal opacity 1/4, iritis 1/2, conjunctival redness 2/3 and chemosis 4/4. Mean scores for animal 3 (1 hour–21 day) were: corneal opacity 1/4, iritis 1/2, conjunctival redness 2/3 and chemosis 4/4. The observed effects were reversible in 2/3 animals within 14 days. Some corneal opacity effects persisted in one animal within the observation period of 21 days (REACH).

Application of 100 mg of the chemical to the eye of rabbits resulted in slight irritation (CCOHS 2019). No further details are available.

Sensitisation

Skin sensitisation

Based on the available data, the chemical is not considered to be a skin sensitiser.

In a local lymph node assay (LLNA) conducted in accordance with OECD TG 429, female CBA mice (5/dose) received topical applications of the chemical at 1, 5 and 10% in acetone/olive oil (4:1 v/v). The reported mean stimulation indices (SI) were 1.1, 1.1 and 0.9 for the chemical at 1, 5 and 10%, respectively. No 3 fold increase in lymphocyte proliferation was reported in the study and; therefore, an EC3 value could not be determined (REACH).

Repeat dose toxicity

Oral

Based on the available data, TDPNA is not expected to cause severe adverse systemic effects following repeated oral exposure. The liver and kidney effects are not sufficiently severe as to warrant hazard classification.

In a sub-acute repeated dose study conducted in accordance with OECD TG 407, Sprague Dawley (SD) rats (low to mild doses, 5/sex/dose, control and high dose, 10/sex/dose) were administered the chemical (97% purity) by gavage at 30, 150 or 500 mg/kg bw/day for 28 days followed by 14 day recovery. No mortality or treatment related clinical signs of toxicity were reported. Slight increases in liver and kidney weights were reported in both sexes at ≥150 mg/kg bw/day. Minimal liver centrilobular hypertrophy and increased salt concentrations in blood were also reported. However, these findings were not statistically significant, and the effects were fully reversed at the end of the study. The no observed adverse effect level (NOAEL) was determined to be 500 mg/kg bw/day (ECHA 2019; REACH).

In a repeated dose study conducted in accordance with OECD TG 408, SD rats (10/sex/dose) were administered the chemical (97% purity) by gavage at 50, 150 or 450 mg/kg bw/day for 90 days followed by 28 day recovery. No mortality and gross pathological changes were observed. A minimal increase in blood urea nitrogen and creatinine was correlated with morphological changes in the kidneys and the urinary bladder. Hyperplasia of the transitional epithelium of the bladder was only observed at doses ≥150 in males and 450 mg/kg bw/day in females. In kidneys, increased eosinophilic droplets were noted in the tubular epithelium in the cortex of 6 males treated at 150 mg/kg bw/d and all males treated at

450 mg/kg bw/d but not in females. A singe incidence of papillary necrosis was also observed in males at 450 mg/kg bw/day. Clinical signs of perineum wet with urine were observed in both sexes. All the effects were fully reversed at the end of the recovery period. NOAEL values of 50 and 150 mg/kg bw/day were reported for males and females, respectively (ECHA 2019; REACH).

In a non-guideline repeated dose toxicity study, SD rats (5/sex/dose) were administered the chemical (98.4% purity) by gavage once daily at 100, 300 or 1000 mg/kg bw/day for 14 days. Body weight loss and severe clinical signs were reported in males at 1000 mg/kg bw/day before their termination on day 4. Urine staining was reported in both sexes at the highest dose. Pathological findings included abnormal contents and pale jejunum in males and enlarged liver with dark spots in one female at 1000 mg/kg bw/day (ECHA 2019; REACH).

In a non-guideline repeated dose toxicity study, SD rats (5/sex/dose) were administered the chemical (98% purity) in feed at 10, 30, 100 or 300 mg/kg bw/day for 30 days. No mortality was reported. Renal tubular damage and transitional cell hyperplasia were reported in males at ≥100 mg/kg bw/day. An increase in serum urea nitrogen content was observed in males at 300 mg/kg bw/day. No effects were reported in females at any dose. NOAEL values of 30 and 300 mg/kg bw/day were reported for males and females, respectively (ECHA 2019; REACH).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

Overall, based on the weight of evidence, classification is warranted. Based on in silico data the chemicals have the same potential genotoxic mode of action. The chemical was reported to be positive in in vitro assays with metabolic activation but negative in in vivo studies. Although the negative results in in vivo micronucleus test may indicate that the chemical does not induce clastogenic effects there are limitations in this study. In addition, the fact that liver has not been proven to be a target organ, limits the use of the results from the other in vivo study. Hence, it cannot be ruled out that the chemical has the potential to generate gene mutations in vivo. The analogue BBMP was reported to be positive in several in vitro and in vivo assays.

In vitro

Mixed results were reported in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation (S9) at concentrations up to 1500 µg/plate. The chemical was reported to be negative in all strains in the absence of S9 mix. Positive results were reported only in strains TA 100 and TA 1535 with metabolic activation at 15–500 µg/plate (ECHA 2019; REACH).

Positive results were reported in a mammalian chromosome aberration assay (OECD TG 473) in human lymphocytes with activation and without metabolic activation at a concentration of 1000 µg/mL (ECHA 2019; REACH).

A mammalian gene mutation assay (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma cells L5178Y mouse lymphoma cells was conducted. In 2 experiments the chemical (97% purity) was reported to be negative without metabolic activation but was positive with metabolic activation at concentrations up to 500 µg/plate (ECHA 2019; REACH).

In vivo

In a GLP compliant unscheduled DNA synthesis (UDS) test conducted in accordance with OECD TG 486, the chemical was administered as a single dose by gavage to SD rats (4/sex/dose) at 670 and 2000 mg/kg bw. There were no significant signs of DNA damage in liver cells at any of the doses tested (ECHA 2019; REACH).

In a GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, NMRI mice (5/sex/dose) were administered TBNPA in feed at single doses of 75, 150 or 300 mg/kg bw. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity. However, it is unclear whether there was systemic exposure including in the bone marrow. The exposure in this study was much lower compared to doses tested for the analogue chemical BBMP (ECHA 2019; REACH). In 2 OECD TG 474 mouse peripheral blood micronucleus tests with BBMP, positive results were reported at 400 mg/kg bw/d and 1300 mg/kg bw/d for males and at 600 mg/kg bw/d for females. A positive in vivo comet assay in urinary bladder at of 600 mg/kg bw/d was also identified (NICNAS 2018, ECHA 2019).

In silico (QSAR)

The chemical presents alerts for mutagenicity based on the molecular structure as profiled by the OECD QSAR Toolbox v4.2 (OECD 2018). As an aliphatic halogen, the chemical has potential to interact with DNA, causing toxic and mutagenic effects. Short chain polyhalogenated alkanes can cause genotoxic effects through alkylation or as cross-linking agents (either directly or after metabolic transformation, e.g. glutathione (GSH) conjugation via GSH transferases). The process of reductive dehalogenation to yield haloalkenes produces reactive radical species, which can cause oxidative damage to DNA.

Carcinogenicity

No data are available for the chemical. BBMP is classified as hazardous (Category 1B; H350 – May cause cancer) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). Based on the weight of evidence from the genotoxicity and in silico data for the chemical and the read across information from BBMP (NICNAS 2018), the chemical is expected to cause cancer following oral exposure, and warrants hazard classification.

There are several alerts for mutagenicity and carcinogenicity for SBAAs in the QSAR models applied (Wedebye et al. 2016). The chemical has a structural alert as aliphatic halogen for in vitro mutagenicity (Ames test), in vivo mutagenicity (micronucleus, in rats and mice) and carcinogenicity (genotoxic and non-genotoxic) as profiled by the OECD QSAR Toolbox v4.2 (OECD 2018), which suggests carcinogenic potential through mutagenic or genotoxic mode of action.

Based on the similar structural, physicochemical and genotoxic mode of action, TBNPA is expected to have carcinogenic profiles similar to BBMP. BBMP caused tumours at multiple

sites in rats and mice (NICNAS 2018) and the International Agency for Research on Cancer (IARC) has classified BBMP as 'possibly carcinogenic to humans (Group 2B)' (IARC 2000).

Reproductive and development toxicity

Based on the data available, the chemical is not expected to cause developmental toxicity. There are limited data available regarding effects on fertility although observations in repeated dose studies do not raise a concern. Due to differences in QSAR based clustering for the chemical and BBMP (Wedebye et al. 2016), read across is not considered appropriate for this endpoint.

In a GLP compliant 28-day repeated dose study conducted in accordance with OECD (TG 407) (see **Repeated dose toxicity** section), SD rats (5/sex/dose) were administered the chemical (97% purity) by gavage at 30, 150 and 500 mg/kg bw/day for 28 days followed by 14 day recovery. No adverse effects on the reproductive organs were observed. No treatment related changes in the oestrus cycle, sperm count and motility, or organ weights (ovaries, seminal vesicles, testis, ureter, uterus and vagina) were reported. (ECHA 2019; REACH).

In the oral 90-day repeated dose study conducted in accordance with OECD TG 408 (see **Repeated dose toxicity** section), SD rats (10/sex/dose) were administered the chemical (97% purity) by gavage at 50, 150 or 450 mg/kg bw/day for 90 days followed by 28 day recovery. Very few fertility parameters were evaluated in this study. No test item related changes in the ovary and uterus weights were reported. In the males, no significant intergroup differences in sperm motility, sperm morphology and sperm counts were observed.

In a GLP compliant prenatal developmental toxicity study conducted in accordance with OECD TG 414, pregnant SD rats (20/dose) were administered the chemical by gavage once daily at 100, 300 and 500 (reduced from 1000 after day 3 of treatment) mg/kg bw/day on gestational days (GD) 6–18. Dams were sacrificed on GD 20 and, developmental and reproductive toxicity parameters were assessed. Mortality was reported (2 dams) on GD 7 or 8 at 1000 mg/kg bw/day and the dose level was subsequently reduced to 500 mg/kg bw/day. No significant toxicologically relevant effects on reproductive, gestational or developmental parameters were observed. Minor effects on ossification reported at 300 and 500 mg/kg bw/day were within historical control values. Based on these observations, a NOAEL of 500 mg/kg bw/day was established for maternal and developmental toxicity (ECHA 2019; REACH).

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