National Institute for Public Health
and the Environment
*Ministry of Health, Welfare and Sport*

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RIVM letter report 2020-0144
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# Colophon



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# Synopsis

**An overview of the available data on the mutagenicity and carcinogenicity of 1-bromopropane**

RIVM has carried out a literature search for information on the potential mutagenic and carcinogenic properties of 1-bromopropane. This substance is used amongst others as a solvent for fats, waxes and resins.

The data found was summarised. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification.

The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

Keywords: 1-bromopropane, mutagenicity, carcinogenicity

# Publiekssamenvatting

## 1-Broompropaan: een overzicht van de beschikbare informatie over mogelijke kankerverwekkende en mutagene eigenschappen

De stof 1-broompropaan wordt onder andere gebruikt als oplosmiddel voor vetten, waxen en harsen. Het RIVM heeft in de wetenschappelijke literatuur onderzocht wat er bekend is over twee mogelijke schadelijke eigenschappen van deze stof. De vraag is of 1-broompropaan kankerverwekkend is en erfelijke veranderingen kan veroorzaken door schade aan het DNA (mutageen).

De gevonden informatie is samengevat. De Gezondheidsraad gebruikt de samenvattingen om de mutagene en kankerverwekkende eigenschappen te beoordelen. De Gezondheidsraad gebruikt de samenvattingen ook voor een advies voor de classificatie van de stof dat op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) wordt opgesteld.

De genoemde beoordeling wordt uitgevoerd door de Subcommissie Classificatie van carcinogene stoffen. Deze subcommissie valt onder de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen (GBBS) van de Gezondheidsraad. De GBBS richt zich op gezondheidsrisico's door blootstelling aan chemische stoffen op de werkplek.

Kernwoorden: 1-broompropaan, mutageniteit, carcinogeniteit

# Contents

# Summary

RIVM has carried out a literature search for information on the potential mutagenic and carcinogenic properties of 1-bromopropane. This substance is used amongst others as a solvent for fats, waxes and resins.

Available data on *in vitro* mutagenicity testing of 1-bromopropane included bacterial mutagenicity tests with Salmonella typhimurium strains TA97, TA98, TA100, TA1535, TA1537, TA1538 and Escherichia coli strain WP2 uvrA and a mouse lymphoma assay. The *in vivo* mutagenicity of 1-bromopropane was studied in a transgenic rodent mutation assay and two rodent dominant lethal assays. 1-Bromopropane was further tested in multiple *in vivo* micronucleus tests. Human data included assessment of DNA-damage using the comet assay in leukocytes of occupationally exposed subjects and in *ex vivo* treated human whole blood. Additionally, an *in vivo* rat study and an *in vitro* study focusing on DNA- and GSH-adduct formation upon 1-bromopropane exposure was included as well.
No data on the carcinogenicity of 1-bromopropane in humans were found and no oral or dermal animal carcinogenicity studies were available. 1-Bromopropane was investigated in an inhalation carcinogenicity study in rats and mice.
Most studies were considered of sufficient quality.

The data found was summarised. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification.

The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

# 1 Introduction

The aim of current research is to identify and summarize the available data from studies with laboratory models, test animals and humans on the substance 1-bromopropane. The focus of current literature review will be on the mutagenic and carcinogenic properties of this substance. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification. The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

Current RIVM-report does not include an assessment of the reported mutagenic and carcinogenic properties of 1-bromopropane, nor does it provide a recommendation for classification of the substance based on the CLP-criteria (1).

The literature search strategy which forms the basis of current literature overview is presented in chapter 2. In chapter 3 the substance identity of 1-bromopropane is provided. Chapter 4 presents information on international classifications of 1-bromopropane. Available information on monitoring (i.e. environmental and biological exposure monitoring) and manufacture and use is presented in chapters 5 and 6, respectively. A summary of the (toxico)kinetics of 1-bromopropane is described in chapter 7. Chapter 8 describes an overview of the data on mutagenicity. Finally, the data on carcinogenicity are presented in chapter 9.

# 2 Literature search strategy

A literature search for publications on genotoxicity and carcinogenicity of 1-bromopropane has been performed using various databases up to September 2020. Additionally, publications on (toxico)kinetics and monitoring were searched for as well. Below the literature search strategy is presented.

## 2.1 Embase

Table 1 presents the search terms and the results for the database Embase.

*Table 1. Search strategy and result for Embase.*

| Query | Search terms | Number of records |
|---|---|---|
| #1 | '1 bromopropane'/exp OR '1-bromopropane' OR '106-94-5':rn | 200 |
| #2 | 'toxicity'/mj OR 'genotoxicity'/exp OR 'genotoxicity assay'/exp OR 'mutagenicity'/exp OR 'mutagen testing'/exp | 88,789 |
| #3 | 'carcinogenicity'/exp OR 'carcinogen testing'/exp OR 'carcinogenesis'/exp | 265,219 |
| #4 | toxic*:ti,ab OR carcinogen*:ti,ab OR mutagen*:ti,ab OR 'mutat*':ti,ab OR genotox*:ti,ab OR epigen*:ti,ab OR 'genetic*':ti,ab OR 'micronucl*':ti,ab OR 'transgen*':ti,ab | 3,005,753 |
| #5 | #2 OR #3 OR #4 | 3,150,124 |
| #6 | #1 AND #5 | 87 |
| #7 | 'toxicokinetics'/exp OR toxicokinetic*:ti,ab | 13,377 |
| #8 | 'bioaccessibility' OR 'bioelut*':ti,ab | 2,329 |
| #9 | ((environment* OR human OR biologic*) NEAR/3 'exposure monitor*'):ti,ab | 74 |
| #10 | #1 AND (#7 OR #8 OR #9) | 5 |
| #11 | 'xenobiotic metabolism'/exp OR 'metal metabolism'/mj OR 'metabolism'/mj | 205,225 |
| #12 | 'metabolism':ti OR 'adme':ti,ab OR 'absorption distribution metabolism excretion':ti,ab | 227,093 |
| #13 | #11 OR #12 | 405,458 |
| #14 | #1 AND #13 | 14 |
| #15 | #6 OR #10 OR #14 | 96 |

## 2.2 PubMed

Table 2 presents the search terms and the results for the database Pubmed:

*Table 2. Search strategy and result for Pubmed.*

| Query | Search terms | Number of records |
|---|---|---|
| #1 | Search "1-bromopropane" [Supplementary Concept] OR 1-bromopropane[tw] | 157 |
| #2 | Search "Toxicity Tests"[Mesh] OR "Toxicology"[Mesh:NoExp] OR "Toxicogenetics"[Mesh] | 136,522 |
| #3 | Search "Carcinogenesis"[Mesh] OR "Mutagenesis"[Mesh] | 324,637 |
| #4 | Search toxic*[tw] OR carcinogen[tw] OR mutagen*[tw] OR mutat*[tw] OR genotox*[tw] OR epigen*[tw] OR genetic*[tw] OR micronucle*[tw] OR transgen*[tw] | 4,856,793 |
| #5 | Search (#2 OR #3 OR #4) | 4,931,223 |
| #6 | Search (#1 AND #5) | 100 |
| #7 | Search ("Toxicokinetics"[Mesh] OR "Toxicological Phenomena"[Mesh] OR toxicokinetic*[tw] OR bioaccessib*[tw] OR bioelut*[tw]) | 445,223 |
| #8 | Search (exposure monitor*[tw] AND (environment*[tw] OR human[tw] OR biologic*[tw])) | 459 |
| #9 | Search ("Metabolism"[Majr:NoExp] OR metabolism[ti] OR adme[tw] OR absorption distribution metabolism excretion[tw]) | 210,125 |
| #10 | Search #1 AND (#7 OR #8 OR #9) | 37 |
| #11 | Search #6 OR #10 | 112 |

## 2.3 Scopus

A search was performed in Scopus using the following search terms.

( ( ( CASREGNUMBER ( 106-94-5 ) ) OR ( TITLE-ABS-KEY ( 1-bromopropane ) ) ) AND ( TITLE-ABS-KEY ( toxic* OR carcinogen* OR mutagen* OR mutat* OR genotox* OR epigen* OR genetic* OR micronucle* OR transgen* ) ) ) OR ( ( ( CASREGNUMBER ( 106-94-5 ) ) OR ( TITLE-ABS-KEY ( 1-bromopropane ) ) ) AND ( TITLE-ABS-KEY ( toxicokinetic* OR bioaccessib* OR bioelut* OR ( ( environment* OR human OR biologic* ) W/3 exposure-monitor* ) ) OR TITLE-ABS-KEY ( adme OR absorption-distribution-metabolism-excretion ) OR TITLE ( metabolism ) ) )

This resulted in 114 records.

## 2.4 Toxcenter

Table 3 presents the search terms and the results for the database Toxcenter.

*Table 3. Search strategy and result for Toxcenter.*

| Query | Search terms | Number of records |
|---|---|---|
| #1 (L1) | SEA 106-94-5 | 2,261 |
| #2 (L2) | SEA TOXIC? OR CARCINOGEN? OR MUTAGEN? OR MUTAT? OR GENOTOX? OR EPIGEN? OR GENETIC? OR MICRONUCLE? OR TRANSGEN? | 5,338,682 |
| #3 (L3) | SEA L1 AND L2 | 631 |
| #4 (L4) | SEA L3/HUM,ANI | 57 |
| #5 (L5) | SEA L3 NOT L4 | 574 |
| #6 (L6) | SEA L5 AND 1-BROMOPROPANE/TI | 204 |
| #7 (L7) | SEA BIOACCESSIB? OR BIOELUT? OR (ENVIRONMENT? OR HUMAN OR BIOLOGIC?)(3W)EXPOSURE MONITOR? | 5,242 |
| #8 (L8) | SEA ADME OR ABSORPTION DISTRIBUTION METABOLISM EXCRETION OR METABOLISM/TI | 136,881 |
| #9 (L9) | SEA L1 AND (L7 OR L8) | 26 |
| #10 (L10) | SEA L9 NOT (L4 OR L6) | 21 |
| #11 (L11) | SEA L6 OR L10 | 225 |

Records of searches #4 and #11 were evaluated and manually selected. This resulted, in addition to Embase, Pubmed and Scopus, in 40 records.

## 2.5 ECHA database

The REACH registration dossier of 1-bromopropane (publicly available on ECHA website) was consulted[1].

## 2.6 Secondary sources

Secondary sources were consulted. These included e.g. IARC, SCOEL, WHO, IPCS, ATSDR, DFG; primarily consulted via echemportal[2]. Also RIVM-reports and evaluations and the RIVM-website 'Risico's van stoffen'[3] were consulted as well.

## 2.7 Overall evaluation of results literature search

The obtained records were evaluated, duplicates were removed, and records were included if considered relevant based on title and abstract. Additionally, publications cited in the selected publications, but not selected during the primary search, were reviewed if considered appropriate.
With respect to human health endpoints evaluated in current report (i.e. mutagenicity and carcinogenicity), this resulted in >20 studies for the endpoint mutagenicity and two studies for carcinogenicity.

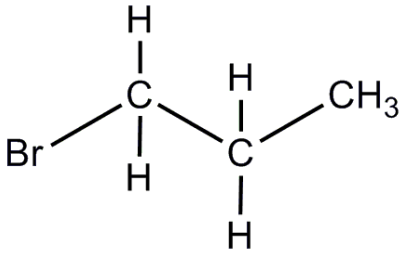
[1] https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/15004
[2] https://www.echemportal.org
[3] https://rvs.rivm.nl

# 3 Substance identification

## 3.1 Name and other identifiers of the substance

The identity of 1-bromopropane is presented in Table 4 below.

*Table 4. Substance identity and information related to molecular and structural formula of 1-bromopropane.*

| | |
|---|---|
| Name(s) in the IUPAC nomenclature or other international chemical name(s) | 1-bromopropane |
| Other names (usual name, trade name, abbreviation) | 1-propyl bromide; n-propyl bromide; propane, 1-bromo; propyl bromide; BP; nPB |
| ISO common name (if available and appropriate) | N/A |
| EC/EINECS number (if available and appropriate) | 203-445-0 |
| EC name (if available and appropriate) | 1-bromopropane |
| CAS number | 106-94-5 |
| Other identity code (if available) | TX4110000 [RTECS] |
| Molecular formula | $C_3H_7Br$ |
| Structural formula |  |
| SMILES notation (if available) | CCCBr |
| Molecular weight or molecular weight range | 122.99 |
| Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate) | N/A |
| Description of the manufacturing process and identity of the source (for UVBC substances only) | N/A |
| Degree of purity (%) (if relevant for the entry in Annex VI) | N/A |

N/A: Not applicable

## 3.2 Physico-chemical properties

The physico-chemical properties of 1-bromopropane are presented in Table 5 below.

*Table 5. Summary of physico-chemical properties.*

| Properties | Value | Reference | Comment |
|---|---|---|---|
| State of the substance at normal temperature and pressure | Liquid | (2) | |
| Melting/freezing point | -110°C (at 101.3 Pa) | (2) | |
| Boiling point | 71°C (at 101.3 kPa) | (2) | |
| Relative density | 1.35 (at 20°C) | (2) | |
| Vapour pressure | 14.7 kPa (at 20°C) | (2) | |
| Surface tension | - | | |
| Water solubility | 2450 mg/L (at 20°C) | (2) | |
| Partition coefficient n-octanol/water | 2.1 | (2) | |
| Flash point | 69°C (at 101.3 kPa) | (2) | |
| Flammability | Highly flammable | (2) | |
| Explosive properties | Non-explosive | (2) | |
| Self-ignition temperature | 490°C (at 101.3 kPa) | (2) | |
| Oxidising properties | - | | |
| Granulometry | - | | |
| Stability in organic solvents and identity of relevant degradation products | - | | |
| Dissociation constant (pKa) | - | | |
| Viscosity | 0.52 mPa · s (at 20 °C) | (2) | dynamic |

# 4 International classifications

## 4.1 European Commission

1-Bromopropane has currently a harmonized classification with entry number 602-019-00-5 in Annex VI of the CLP-Regulation (EC) 1272/2008 (1) as:

- Flam. Liq. 2 (H225: Highly flammable liquid and vapour)
- Skin Irrit. 2 (H315: Causes skin irritation)
- Eye Irrit. 2 (H319: Causes serious eye irritation)
- STOT SE 3 (H335: May cause respiratory irritation)
- STOT SE 3 (H336: May cause drowsiness or dizziness)
- Repr. 1B (H360FD: May damage fertility. May damage the unborn child)
- STOT RE 2* (H373**: May cause damage to organs through prolonged or repeated exposure)

## 4.2 The Health Council

1-Bromopropane has not previously been evaluated by the Health Council of the Netherlands.

## 4.3 IARC

IARC has evaluated 1-bromopropane in 2018 (3). IARC considered that there is inadequate evidence in humans for the carcinogenicity of 1-bromopropane, and that there is sufficient evidence in experimental animals for the carcinogenicity of 1-bromopropane. Overall, IARC concluded in 2018 that 1-bromopropane is possibly carcinogenic to humans (Group 2B).

## 4.4 Other countries

1-Bromopropane has the following classification in Japan[4]:

- Flam. Liq. 2 (H225: Highly flammable liquid and vapour)
- Acute Tox. 4 (H332: Harmful if inhaled)
- Eye Irrit. 2 (H319: Causes serious eye irritation)
- Repr. 1B (H360: May damage fertility or the unborn child)
- STOT SE 3 (H335: May cause respiratory irritation)
- STOT SE 3 (H336: May cause drowsiness or dizziness)
- Carc. 2 (H351: Suspected of causing cancer)
- STOT RE 1 (H372: Cause damage to organs through prolonged or repeated exposure (central nervous system))
- STOT RE 2 (H373: May cause damage to organs (liver, lung))
- Aquatic Acute 3 (H402: Harmful to aquatic life)
- Aquatic Chronic 3 (H412: Harmful to aquatic life with long lasting effects)

In Germany, 1-bromopropane is not included in the list of additional CMR substances in the context of worker protection[5].

[4] https://www.nite.go.jp/chem/english/ghs/15-mhlw-0022e.html
[5] https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-905.pdf?__blob=publicationFile

In the state of California, 1-bromopropane is considered to cause cancer, adverse effects on fertility (male, female) and developmental toxicity[6].

1-Bromopropane has the following classification in Australia[7]:

- Flam. Liq. 2 (H225: Highly flammable liquid and vapour)
- Skin Irrit. 2 (H315: Causes skin irritation)
- Eye Irrit. 2A (H319: Causes serious eye irritation)
- STOT SE 3 (H335: May cause respiratory irritation)
- STOT SE 3 (H336: May cause drowsiness or dizziness)
- Carc. 2 (H351: Suspected of causing cancer)
- Repr. 1B (H360: May damage fertility or the unborn child)
- STOT RE 2 (H373: May cause damage to organs through prolonged or repeated exposure)

The substance 1-bromopropane is included in the Report on Carcinogens (14th edition) as 'reasonably anticipated to be human carcinogen'[8].

[6] https://oehha.ca.gov/media/downloads/proposition-65//p65list091319.pdf
[7] http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=3660
[8] https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html#toc1

# 5 Monitoring

## 5.1 Environmental exposure monitoring

Table 6 present analytical methods for determination of 1-bromopropane in air.

*Table 6. Methods for measurement of 1-bromopropane in air (taken from IARC 2018; (3)).*

| Sample method | Sample preparation | Assay method | Limit of detection | Reference |
|---|---|---|---|---|
| NIOSH 1025 | Active collection on activated charcoal; flow rate, 0.01–0.2 L/min (12 L); $CS_2$ desorption | GC/FID | 1 µg | NIOSH, 2003 (4) |
| OSHA 1017 | Active collection on activated charcoal; flow rate, 0.05 L/min (12 L); $CS_2$/DMF, 99:1 (v/v) desorption | GC/ECD | 5.9 µg/$m^3$ | OSHA, 2014 (5) |
| OSHA PV2061 | Active collection on activated charcoal; flow rate, 0.1 L/min (12 L); $CS_2$/DMF, 99:1 (v/v) desorption | GC/FID | 37 µg/$m^3$ | OSHA, 1999 (6) |
| IRSST 333-1 | Active collection on activated charcoal; flow rate, 0.2 L/min (5 L); desorption NR | GC/FID | 54 µg | IRSST, 2015 (7) |
| N/A | Diffusive sampler; carbon cloth KF-1500; $CS_2$ desorption | GC | 0.1 ppm | Kawai et al., 2001 (8) |
| N/A | Diffusive sampler; $CS_2$ desorption | GC/EID | 0.13 ppm | Ichichara et al., 2004 (9) |

$CS_2$, carbon disulfide; DMF, N,N-dimethylformamide; ECD, electron capture detection; EID, electron ionization detector; FID, flame ionization detector; GC, gas chromatography; N/A, not applicable

## 5.2 Biological exposure monitoring

Biological monitoring of exposure to 1-bromopropane includes analysis of 1-bromopropane and biomarkers of exposure including 1-bromopropane in urine, bromide ion in urine, and 1-bromopropane metabolites: N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys) and S-propylcysteine adducts on globin in urine. Table 7 presents an overview of available methods.

*Table 7. Methods for measurement of 1-bromopropane or biomarkers of exposure to 1-bromopropane in urine (taken from IARC 2018; (3)).*

| Sample method | Sample preparation | Assay method | Limit of detection | Reference |
|---|---|---|---|---|
| *1-bromopropane in urine* | | | | |
| N/A | Headspace collection; 5 mL urine into 20 mL vial; heated at 60 °C for 60 min | GC | 2 µg/L | Kawai et al., 2001 (8) |
| N/A | Headspace collection; 5 mL urine into 20 mL vial; Tenax GC trap | GC | 0.5 ng/L | Ichichara et al., 2004 (9) |
| *Bromide ion in urine* | | | | |
| N/A | 48 h urine void collection, interval composite specimens; nitric acid rinsed bottles; stored below −60 °C | ICP/MS | 100 µg/L | Hanley et al., 2010 (10), Hanley et al., 2006 (11); based on previous method of Allain et al., 1990 (12) |
| *AcPrCys in urine* | | | | |
| N/A | Solid phase extraction (C18) column; methanol/water (40:60) wash; acetone elution | LC/ESI-MS | 0.01 µg/L | Hanley et al., 2009 (13); Cheever et al., 2009 (14) |
| N/A | 1 mL urine in 1 mL ammonium formate buffer; pH adjusted to 2.4–2.6 with formic acid | LC/MS-MS | 2 µg/L | Eckert & Göen (2014) (15) |
| N/A | Urine dissolved in NaOH; mixed in ethanol; acidified to pH 3 with $H_3PO_4$; ethyl acetate extraction; column chromatography with 2% methanol in ethyl acetate | LC/MS-MS | NR | Valentine et al., 2007 (16) |
| *GSPrCys adducts* | | | | |
| N/A | Urine dissolved in NaOH; stirred with 1-bromopropane in ethanol; pH adjusted to 3 with HCl; washed with ice water and ethanol | LC/MS-MS | 2.5 pmol | Valentine et al., 2007 (16) |

AcPrCys, N-acetyl-S-(n-propyl)-L-cysteine; ESI, electrospray ionization; GC, gas chromatography; GSPrCys, globin-S-propylcysteine; HCl, hydrochloric acid; $H_3PO_4$, phosphoric acid; ICP/MS, inductively coupled plasma/mass spectrometry; LC, liquid chromatography; LC/MS-MS, liquid chromatography-tandem mass spectrometry; MS, mass spectrometry; NaOH, sodium hydroxide; NR, not reported; N/A, not applicable

# 6 Manufacture and uses

1-Bromopropane is produced by treating n-propanol with bromide in the presence of sulfuric acid; once the propanol is unstable, hydrobromic acid is added and n-propyl bromide is flashed from the hot mixture. The resultant product is condensed, neutralized and fractionated. The procedure can be modified by using bromine (gas) together with a reducing agent such as sulphur, sulphur dioxide, phosphorus, or sodium borohydride (3).

1-Bromopropane is a solvent for fats, waxes and resins and is primarily used as a chemical intermediate in the production of pesticides, quaternary ammonium compounds, flavours and fragrances, and pharmaceuticals in closed processes (3).

In the mid-to-late 1990s, 1-bromopropane was introduced as a non-toxic, fast-drying solvent that does not leave surface residue for cleaning metals, plastics, and optical, electrical and electronic components. It was marketed as a substitute solvent for ozone-depleting and other solvents such as trichloroethylene, tetrachloroethylene (perchloroethylene) and methylene chloride. 1-Bromopropane is used for vapour degreasing and immersion cleaning, liquid and spray adhesive applications, fabric dry cleaning, and aerosol spray products (3).

# 7 (Toxico)kinetics

## 7.1 Human data

As summarized by IARC (2018) and NTP (2011, 2013) (3, 17, 18), human data on kinetics of 1-bromopropane are available. These are presented below.

Absorption of 1-bromopropane has been demonstrated for the dermal and inhalation routes. Quantitative information on the extent of absorption of 1-bromopropane in humans is not available. In an *in vitro* study addressing the absorption characteristics of 1-bromopropane, heat-separated human epidermal membranes (collected from Caucasian female donors undergoing elective surgical procedures) were subjected to different exposure scenarios using neat 1-bromopropane or a saturated aqueous solution. 1-Bromopropane was found to be readily absorbed, although the absorption potential depended upon the type and duration of exposure. Further, losses due to evaporation were approximately two orders of magnitude greater than dermal absorption (19).

Data on the distribution of 1-bromopropane in humans were not found.

Information on excretion of 1-bromopropane in humans was available. Studies of exposed workers have reported the presence of non-metabolized 1-bromopropane in the urine. A significant correlation between the levels of 1-bromopropane in the urine and the levels of exposure to 1-bromopropane in the air was observed (8, 9). Bromide ion was also excreted in urine. In another study, workers exposed to 1-bromopropane at two facilities using 1-bromopropane adhesives showed a significant association of 48-hour urinary bromide ion concentration with 1-bromopropane exposure measured in the breathing zone (11).

Also metabolites of 1-bromopropane have been detected in the urine of occupationally exposed humans. The major metabolite is *N*-acetyl-*S*-propylcysteine which was detected in the urine of occupationally exposed workers and the concentration of which increases with increasing ambient exposure levels (10, 13, 16, 20).

## 7.2 Animal data

Studies in rats and mice have demonstrated that 1-bromopropane is well absorbed after inhalation (21, 22), oral exposure (23) or intraperitoneal administration (24).
The metabolism of 1-bromopropane has been investigated in several studies in experimental animals (21, 24-26). In contrast to humans, the urinary excretion of non-metabolized 1-bromopropane does not appear to have been reported in rodents. Earlier studies showed that conjugation of 1-bromopropane with GSH is the predominant metabolic pathway (27, 28). However, most of the 1-bromopropane metabolites that have been identified are formed from glutathione (GSH) conjugation as well as oxidation reactions.
Below, individual studies are presented.

In a rat inhalation study, male Wistar rats were via whole body inhalation exposed to 1-bromopropane vapour at concentrations of either 700 ppm (corresponding to 3,521 mg/m$^3$) (for 6 hours per day for 1 day or 4 or 12 weeks) or 1,500 ppm (corresponding to 7,545 mg/m$^3$) (for 6 hours per day on 5 days per week for 3 or 4 weeks). Blood concentration of 1-bromopropane was found to decrease rapidly and linearly in a time-dependent manner and was -upon 3 week exposure to 1500 ppm- below the detection limit 0.7 hours after the end of the exposure. On the other hand, bromide ion persisted longer in the blood and urine; the biological half-life of bromide ion was 4.7 to 15.0 days in blood and 5.0 to 7.5 days in urine (22).

In a study performed by Garner et al. (2006), the disposition and metabolism of 1-bromopropane was examined in male F344 rats and B6C3F1 mice upon inhalation exposure (target concentration: 800 ppm, corresponding to 4,024 mg/m$^3$) and intravenous administration (target dose levels: 5, 20, or 100 mg/kg bw) of radiolabelled ([1,2,3-$^{13}$C] and [$^{14}$C]) 1-bromopropane (21). By 4 hours following intravenous administration, the radioactivity recovered totalled 83–103%. Rats and mice exhaled a majority of the administered [$^{14}$C]-1-bromopropane dose as either volatile organic compounds (rats, 25% to 71%; mice, 39% to 48%) or carbon dioxide (rats, 10% to 30%; mice, 19% to 26%). The radioactivity was also excreted in urine (rats, 13% to 19%; mice, 14% to 23%) and feces (rats, < 2 %; mice, 3% to 4%) or retained in tissues and carcass (rats, ≤ 6%; mice, < 4%). A dose-dependency in distribution was noted, especially for rats. For rats, but not mice, the percentage of the dose exhaled as VOC increased between the mid and high dose groups; while the percentage of the dose exhaled as $^{14}CO_2$ or excreted in the urine decreased. In rats, the molar ratio of exhaled $^{14}CO_2$ to total released bromide, which decreased as dose increased, demonstrated that the proportion of 1-bromopropane metabolized via oxidation relative to other bromide releasing pathways was dose-dependent. In mice, metabolism and disposition were relatively insensitive to dose.
*N*-acetyl-*S*-propyl-cysteine, *N*-acetyl-*S*-(2-hydroxypropyl)cysteine, *N*-acetyl-3-(propylsulfinyl)alanine, 1-bromo-2-hydroxypropane-*O*-glucuronide, *N*-acetyl-*S*-(2-oxopropyl)cysteine, and *N*-acetyl-3-[(2-oxopropyl)sulfinyl]alanine were identified as the urinary metabolites characterized in rats and mice following both inhalation exposure and intravenous administration. Pretreatment of rats with 1-aminobenzotriazole (ABT; a chemical inhibitor of cytochrome P450) changed the proportion of radioactivity appearing in urine, VOC and $CO_2$, indicating that reduction in P450 content had a significant impact on 1-bromopropane metabolism. However, pretreatment with D,L-buthionine (S,R)-sulfoxime (BSO; a chemical inhibitor of glutathione) did not significantly affect 1-bromopropane disposition. Following ABT pretreatment, rat urinary metabolites were reduced in number from 10 to 1, *N*-acetyl-*S*-propylcysteine, which accounted for >90% of the total urinary radioactivity in ABT pretreated rats.

After intraperitoneal administration of a single dose of 200 mg/kg bw of [$^{14}$C]1-bromopropane (vehicle: arachis oil) in male Sprague-Dawley rats, 60% was exhaled unchanged within 4 hours, and only trace amounts were detected in the exhaled air after that time point. Exhaled

carbon dioxide accounted for only 1.4% of the total dose and approximately 25% of the administered dose was excreted in urine after 100 hours. However, when excretion is adjusted to the effective metabolized dose, approximately 45% was found to be excreted in the urine after 100 hours (24). In this study groups of rats were also treated orally with 1-bromopropane (200 mg/kg bw/day for 5 consecutive days). Urine was collected and pooled, and further analysed for metabolites. Examination of the urine for cysteine conjugates confirmed the presence of three mercapturic acids, *i.e. N*-acetyl-*S*-propylcysteine, *N*-acetyl-*S*-propylcysteine-*S*-oxide and *N*-acetyl-*S*-(2-hydroxypropyl)cysteine. In addition, two other conjugates were isolated and identified as *N*-acetyl-*S*-(3-hydroxypropyl)cysteine and *N*-acetyl-*S*-(2-carboxyethyl)cysteine (24).

In Sprague-Dawley rats exposed via inhalation to 1-bromopropane in concentrations up to 1,800 ppm (6 h/day, 5 days/week, for 8 weeks), Kim *et al.* (1999) showed that 1-bromopropane primarily induced CYP2E1 as the major form of CYP and that glutathione *S*-transferase (GST) enzymes played important roles in the metabolism (29).

The contribution of cytochrome P450 (CYP) 2E1 to the metabolism of 1-bromopropane was further assessed by Garner et al. (2007) in a study in which CYP2e1-/- (knockout) and wildtype mice were exposed to radiolabelled 1-bromopropane (800 ppm, corresponding to 4,024 mg/m$^3$) by whole body inhalation for 6 hours. Compared with the wildtype mice, the elimination half-life was much longer in the knockout mice (3.2 versus 1.3 hours), the ratio of GSH conjugation to 2-hydroxylation increased fivefold and the urinary concentration of *N*-acetyl-*S*-(2-hydroxypropyl)cysteine was reduced by approximately 50% (25).

In order to examine species- and sex-dependent differences in metabolism, Garner and Yu (2014) performed another study (26). Male and female F344 rats were exposed intravenously (5 and 20 mg/kg bw) and male and female F344 rats and B6C3F1 mice were exposed via inhalation exposure in a closed gas uptake system (starting concentrations: 70, 240, 800 and 2,700 ppm for 6 hour, corresponding to 352, 1,207, 4,024, 13,582 mg/m$^3$). Plasma bromide concentrations were determined to estimate total metabolized dose. Upon intravenous treatment, the microsomal rate of *p*-nitrophenol hydroxylation, a marker for CYP2E1 activity, was determined. In addition, rats were also pretreated with 1-aminobenzothriazole and D,L-buthionine (S,R)-sulfoximine (chemical inhibitors of cytochrome P450 and glutathione (GSH), respectively), prior to exposure to 1-bromopropane at 800 ppm (4,024 mg/m$^3$) within inhalation chambers.
Systemic clearance of 1-bromopropane in rat was rapid and decreased with increasing dose upon intravenous treatment. Activity of *p*-nitrophenol hydroxylase (as marker for CYP2E1 activity) in liver microsomes was increased approximately 1.5 fold by 24h following intravenous treatment.
Upon increase of inhalation chamber concentration of 1-bromopropane, the terminal elimination rates decreased. The percentage of 1-bromopropane metabolized decreased with increasing inhalation exposure. Half-life of 1-bromopropane in rats following inhibition of P450

(9.6 h) or depletion of GSH (4.1 h) increased relative to controls (2.0 h) upon exposure of 800 ppm 1-bromopropane, suggesting that both CYP450 and GSH are critical to the toxicokinetics of inhaled 1-bromopropane in rat. Further, inhalation exposure to 1-bromopropane resulted in 80% reduced rat liver GSH levels, regardless of the exposure level.
The results of this study suggest that in rat, the clearance of 1-bromopropane is saturable and that elimination is not only highly dependent on cytochrome P450 but also on GSH-dependent metabolism (26).

Recently, a cross-fostering study was conducted in rats to examine the disposition of bromine ion in the brain of female Wistar rats and their offspring (30). Rats were exposed to 700 ppm (corresponding to 3,521 $mg/m^3$) 1-bromopropane 6 hours/day during GD1–20. Also non-pregnant female rats were exposed similarly. After birth, cross-fostering was performed between exposed dams and non-exposed dams. The pups were subdivided into the following four groups: exposure group (1-bromopropane exposed pups were raised by their birth mother exposed to 1-bromopropane), postnatal exposure group (control pups were raised by 1-bromopropane exposed mother), gestation exposure group (1-bromopropane exposed pups were raised by control mother), and control group (control pups were raised by control mother). Bromine ion concentrations in the brain were measured temporally.
On GD20, bromine concentrations were significantly higher (approximately 47%) in the brain of exposed virgin rats than in the brain of exposed pregnant rats. On GD20, brains from fetuses had significantly higher bromine concentrations (approximately 68%) than brains from their 1-bromopropane exposed dams. Analyses of the brains from pups from the different exposure groups showed that uptake of bromine via the milk during the postnatal period was higher than through the placenta during gestation (30).

# 8 Germ cell mutagenicity

An overview of the available data on germ cell mutagenicity of 1-bromopropane can be found in tables 8-11.

*Table 8. Summary table of in vitro mutagenicity tests with 1-bromopropane*

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| *Micro-organisms* | | | | | |
| NTP, 2011 (17) | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: number of histidine-independent (revertant) colonies<br><br>Statistical analysis: not used | *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 | 0, 33, 100, 333, 1,000, 3,333, 10,000 µg 1-bromopropane/plate;<br>Purity: 99%;<br>20 min incubation;<br>+/-S9[a,b];<br><br>Positive controls:<br>-S9: sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-o-phenylenediamine (TA98).<br>+S9: 2-aminoanthracene (all strains) | No increase in histidine-independent (revertant) colonies for TA97 (+/-S9), TA98 (+/-S9), TA100 (+/-S9), TA1535 (+/-S9)<br><br>The high concentration was limited by toxicity in some trials and by the limit concentration of 10,000 µg/plate in those trials where only slight toxicity was observed. | Non-GLP; non-guideline; appropriate results were obtained with negative (solvent) and positive controls |
| | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: number of histidine-independent (revertant) colonies<br><br>Statistical analysis: not used | *Salmonella typhimurium* strains TA98 and TA100 | 0, 500, 1,000, 1,500, 2,500, 3,500, 5,000, 7,500 (+S9), 10,000 (+S9) µg 1-bromopropane/plate;<br>Purity: 99%;<br>20 min incubation;<br>+/-S9[a];<br><br>Positive controls:<br>-S9: sodium azide (TA100) and 4-nitro-o- | No increase in histidine-independent (revertant) colonies for TA98 (+/-S9) and TA100 (+/-S9)<br><br>The high concentration was limited by toxicity in some trials and by the limit concentration of 10,000 µg/plate in those trials where only slight toxicity was observed. | Non-GLP; non-guideline; appropriate results were obtained with negative (solvent) and positive controls<br><br>Performed simultaneously with *Escherichia coli* mutagenicity test of NTP (see below) |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | | | phenylenediamine (TA98).<br>+S9: 2-aminoanthracene (all strains) | | |
| | *Escherichia coli* mutagenicity test<br><br>Effect parameter: number of histidine-independent (revertant) colonies<br><br>Statistical analysis: not used | *Escherichia coli* strain WP2 *uvrA*/pKM101 | 0, 500 (-S9), 1,500 (-S9), 2,500, 3,500, 5,000, 7,500 (+S9), 10,000 (+S9) µg 1-bromopropane/plate;<br>Purity: 99%;<br>20 min incubation;<br>+/-S9[a];<br><br>Positive controls:<br>-S9: methyl methanesulfonate<br>+S9: 2-aminoanthracene | No increase in histidine-independent (revertant) colonies (+/-S9)<br><br>The high concentration was limited by toxicity in some trials and by the limit concentration of 10,000 µg/plate in those trials where only slight toxicity was observed. | Non-GLP; non-guideline; appropriate results were obtained with negative (solvent) and positive controls |
| Barber et al., 1981 (31) | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: number of histidine-independent (revertant) colonies<br><br>Statistical analysis: not used | *Salmonella typhimurium* strains TA98, TA100, TA1535 | 0, 1.1, 2.3, 4.9, 9.0, 20.3 µmol/plate 1-bromopropane;<br>Purity 99.85%;<br>Closed system incubation (designed for highly volatile substances), 48h;<br>+/-S9[a]<br><br>Positive controls:<br>-S9: methyl-*N*-nitro-*N*'-nitrosoguianidine (TA100, TA1535), ICR-191 (TA98)<br>+S9: 2-aminoanthracene | Increased histidine-independent (revertant) colonies) for TA100:<br>-S9: 85 (control), 153, 174, -, 527, 1616<br>+S9: 96 (control), 127, 102, 236, 486, 1556<br><br>Increased histidine-independent (revertant) colonies) for TA1535:<br>-S9: 20 (control), 22, 30, 63, 364, 1768 | Non-GLP; non-guideline; appropriate results were obtained with negative (solvent) and positive controls |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | | | | +S9: 19 (control), 23, 31, 104, -, 1584<br><br>No increase in histidine-independent (revertant) colonies for TA98 (+/-S9) | |
| Anonymous, 1994 (32) | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: number of histidine-independent (revertant) colonies<br><br>Statistical analysis: not used | *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 | 0, 100, 500, 1,000, 5,000 and 10,000 µg 1-bromopropane/plate;<br>Purity: ≥99%;<br>48 hours incubation;<br>+/-S9[a];<br><br>Positive controls: yes, but not specified which substance Negative control: 1% DMSO | No increase in histidine-independent (revertant) colonies (+/-S9) (however, results not presented quantitatively)<br><br>Cytotoxicity seen at 5000 µg/plate (+S9) and 10000 µg/plate (+/-S9) | Data derived from REACH registration dossier. Original study report not available.<br><br>Stated to be according to OECD TG 471; GLP. However, limitations noted: selection of strains not fully in line with TG as no E.coli WP2 or S. typhimurium TA102 strain was included. Moreover, very limited description of outcome of the study. |
| Anonymous, 2009a (33) | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: no information<br><br>Statistical analysis: no information | *Salmonella typhimurium* strain TA97, TA98, TA100, and TA1535 | Concentration levels: no information<br>Purity: no information<br>Incubation period: no information<br>+/-S9[c];<br><br>Positive controls: no information | No effects observed (+/-S9) (however, results not presented quantitatively)<br><br>No cytotoxicity | Data derived from REACH registration dossier. Original study report not available.<br><br>Stated to be according to OECD TG 471; GLP. However, limitations noted: selection of strains not fully in line with TG as no E.coli |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | | | Negative control: no information | | WP2 or S. typhimurium TA102 strain was included. Not clear whether applied concentration levels were high enough. Moreover, very limited description of design and outcome of the study. Due to the limitations of the available summary, the quality of the study and the described results cannot be evaluated. |
| Anonymous, 1994b (34) | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: no information<br><br>Statistical analysis: no information | *Salmonella typhimurium* strain TA 98, TA 100, TA 1535 and TA 1537 | Concentration levels: no information<br>Purity: no information<br>Incubation period: no information<br>+/-S9[c];<br><br>Positive controls: no information<br>Negative control: no information | No effects observed (+/-S9)<br>(however, results not presented quantitatively)<br><br>No cytotoxicity | Data derived from REACH registration dossier. Original study report not available.<br><br>Stated to be according to OECD TG 471; GLP. However, limitations noted: selection of strains not fully in line with TG as no E.coli WP2 or S. typhimurium TA102 strain was included. Not clear whether applied concentration levels were high enough.<br>Moreover, very limited description of design and outcome of the study. Due to the limitations of the available summary, the |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | | | | | quality of the study and the described results cannot be evaluated. |
| Anonymous, 1991 (35) | *Salmonella typhimurium* mutagenicity test<br><br>Effect parameter: number of histidine-independent (revertant) colonies<br><br>Statistical analysis: not used for detection of level of mutagenicity | *Salmonella typhimurium* strain TA 98, TA 100, TA 1535, TA 1537 and TA 1538 | 50, 250, 1250, 2500 and 5000 µg/plate 1-bromopropane;<br>Purity: not specified;<br>Incubation period: not specified;<br>+/-S9[d];<br><br>Positive controls: yes, but not specified which substance<br>Negative control: DMSO (% not specified) | No effects (+/-S9) (however, results not presented quantitatively)<br><br>No cytotoxicity | Data derived from REACH registration dossier. Original study report not available.<br><br>Stated to be according to OECD TG 471; GLP. However, limitations noted: selection of strains not fully in line with TG as no E.coli WP2 or S. typhimurium TA102 strain was included. Moreover, very limited description of design and outcome of the study. Due to the limitations of the available summary, the quality of the study and the described results cannot be evaluated. |
| Anonymous, 1998 (36) | *Salmonella typhimurium* and *Escherichia coli* mutagenicity test<br><br>Effect parameter: number of histidine-independent | *Salmonella typhimurium* strain TA 98, TA 100, TA 1535 and TA 1537<br><br>*Escherichia coli* strain WP2 *uvrA* | Concentration-range finder: 0, 10, 100, 500, 1000 and 5000 µg/plate 1-bromopropane<br>Main test: 0, 313, 625, 1250, 2500 and 5000 µg/plate 1-bromopropane<br>Purity: no information | No effects (+/-S9) in both *Salmonella typhimurium* and *Escherichia coli* (however, results not presented quantitatively) | Data derived from REACH registration dossier. Original study report not available.<br><br>Stated to be equivalent to OECD TG 471 (according to Japan: guidelines for screening mutagenicity |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | (revertant) colonies<br><br>Statistical analysis: not used | | Incubation period: no information;<br>+/-S9[d]<br><br>Positive controls: 2-aminoanthracene, 9-aminoacridine and 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (not specified for the different strains)<br>Negative control: yes, but not specified | Cytotoxicity not determined | testing of chemicals); GLP-status not specified.<br>Very limited description of design and outcome of the study. Due to the limitations of the available summary, the quality of the study and the described results cannot be evaluated. |
| Anonymous, 1997 (37) | Four *in vitro* genetic toxicity assays performed on 1-bromopropane. No information about the type of the tests are available. | No information | Concentration levels: no information<br>Purity no information<br>Incubation period: no information<br>Not specified whether tested +/-S9;<br><br>Positive controls: no information<br>Negative control: no information | The registration dossier states: "Negative results were seen for all concentrations in Tests 2, 3 and 4. A positive result was seen at 500 ppm in Test 1, indicating cytotoxicity at or above this dosage level." | Data derived from REACH registration dossier. Original study report not available.<br><br>Guideline or GLP-status: not specified<br><br>Very limited description of design and outcome of the study. The quality of the study and the described results cannot be evaluated |
| *Mammalian cells* | | | | | |
| Anonymous, 1996 (38) | *In Vitro* Mammalian Cell Gene Mutation Test using the Thymidine Kinase | mouse lymphoma L5178Y cells | 1-bromopropane<br><br>-S9<br>First experiment: 0, 125, 250, 500, 1000 and 1500 µg/mL | -S9:<br>increase in mutant frequency, increase in the number of small colonies at dose levels | Data derived from REACH registration dossier. Original study report not available. Details on study design and outcome well described, though noticing that data |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | Gene (mouse lymphoma assay)<br><br>Effect parameter: mutant frequency | | Second experiment: 0, 250, 500, 1000, 1250 and 1500 µg/mL<br><br>+S9[a]<br>First experiment: 0, 125, 250, 500, 1000, 1500 and 2000 µg/mL<br>Second experiment: 0, 500, 1000, 1500, 2000 and 2500 µg/mL<br><br>Purity: 99.3%<br><br>Positive controls:<br>-S9: methylmethanesulfonate<br>+S9: cyclophosphamide<br><br>Negative control: DMSO (% not specified) | between 1000 and 1500 µg/mL.<br><br>$RCE_0$:<br>1500 µg/mL: 21%/33% ($1^{st}$/$2^{nd}$ experiment)<br>1250 µg/mL: 46% ($2^{nd}$ experiment)<br><1250 µg/mL: no significant differences between treated and control<br><br>Number of viable cells 2 day posttreatment (cloning efficiency): similar as control<br><br>+S9:<br>no increase in the mutant frequency in the first experiment. A significant increase in the mutant frequency together with an increase in the number of small colonies at 1500 and 2000 µg/mL in the second experiment. | on mutant frequency not presented quantitatively.<br><br>OECD TG 476 (1997); GLP |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | | | | $RCE_0$:<br>First experiment: 59% at 2000 µg/mL, no marked differences with control at lower concentrations<br>Second experiment: all cells dead at 2500 µg/mL (3h post-treatment); 9% at 2000 µg/mL; 36% at 1500 µg/mL;<br><1500 µg/ml no significant differences between treated and control<br><br>Number of viable cells 2 day posttreatment (cloning efficiency): similar as control | |

[a] metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat liver
[b] metabolic activation enzymes and cofactors from Aroclor 1254-induced male Syrian hamster liver
[c] metabolic activation: source not specified
[d] metabolic activation: S9 mix derived from rats liver

*Table 9. Summary table of in vivo animal mutagenicity tests with 1-bromopropane*

| Reference | Species | Experimental period and design | Concentration/Dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| Stelljes et al., 2019 (39); Anonymous, 2016 (40) | Mouse, B6C3F1, Big Blue® transgenic; female; 7 animals/ exposure group (chamber control and 1-bromopropane treated groups) | *In vivo* transgenic rodent mutation assay<br><br>4-week exposure period; sampling of lung, liver and colon three days after last exposure<br><br>Statistical analysis mutant frequency: ANOVA and Dunnett's test | 0, 62.8, 125, 258 ppm 1-bromopropane (analytical concentrations, corresponding to 0, 316, 629, 1298 mg/m$^3$)[a]; Purity: not specified<br><br>Inhalation, whole body; 6h/day, 5 days per week for 4 weeks<br><br>Positive control: N-Ethyl-N-nitrosourea (ENU), 40 mg/kg bw/d for 3 consecutive days, oral gavage | No increase in the mutant frequency of treated animals compared to the untreated controls.<br><br>No treatment-related clinical signs. | OECD TG 488; GLP; appropriate results were obtained with positive control<br><br>Anonymous (2016) only includes results for lung and liver.<br><br>Applied concentrations were probably not high enough, given that no general toxicity was noticed |
| Yu et al., 2008 (41) | Mouse, ICR, male; 20 males/ exposure group (negative control and 1-bromopropane | Rodent dominant lethal assay<br><br>Treatment with 1-bromopropane for 10 consecutive days; Mating during 6 weeks sequential mating periods of one week each to non-treated female mice (1:2) | 0, 300, 600 mg/kg bw/d 1-bromopropane, for 10 consecutive days<br>Purity: 99%<br>Oral, via gavage (vehicle: corn oil) | No effects on dominant lethality observed<br><br>No treatment-related clinical signs. | Non-GLP; non-guideline; appropriate results were obtained with positive control. |

| Reference | Species | Experimental period and design | Concentration/Dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| | treated groups; 15 males/group for positive control) | Males were sacrificed at the end of mating; pregnant females were sacrificed on days 15–17 of gestation.<br><br>Clinical signs, gross findings, mating index, gestation index, the numbers of corpora lutea, implantations, live fetuses, resorptions and dead fetuses, pre- and post-implantation losses, and dominant lethal mutation rate were examined.<br><br>Statistical analysis: Bartlett's test for variance homogeneity, followed by (in case of no deviations from variance homogeneity) ANOVA multiple comparison test and Dunnett's t-test; or followed by (in case of deviations from variance homogeneity) a non-parametric comparison test (Kruskal-Wallis (H) Test) and Dunn's Rank Sum test. Litter data such as numbers of the corpora lutea, resorptions and dead fetuses were statistically evaluated using the statistical unit as a litter. | Positive control: cyclophosphamide (i.p. 40 mg/kg bw/day for 5 days) | | Applied dose levels were probably not high enough, given that no general toxicity was noticed. |

| Reference | Species | Experimental period and design | Concentration/Dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| Saito-Suzuki et al., 1982 (42) | Rat, Sprague-Dawley, male; 15 males/ exposure group (negative and positive control and 1-bromopropane treated groups | Rodent dominant lethal assay.<br><br>Treatment with 1-bromopropane for 5 consecutive days;<br>Mating during 8 weeks sequential mating periods of one week each to non-treated female mice (1:1);<br>Pregnant females were killed 13 or 14 days after copulation.<br>Number of corpora lutea, implants, live embryos and early and late embryonic death was examined and dominant lethality rate was calculated.<br><br>Statistical analysis: Fisher's exact method and Mann-Whitney U test | 0, 400 mg/kg bw/day 1-bromopropane, for 5 consecutive days;<br>Purity>98%;<br>Oral, via gavage (vehicle: olive oil)<br><br>Positive control:<br>1,2-Dibromo-3-chloropropane (oral gavage, 50 mg/kg bw/d) | No effects on dominant lethality observed<br><br>The study authors did not report the presence or absence of clinical signs. | Non-GLP; non-guideline; appropriate results were obtained with positive control<br><br>Not clear whether applied dose levels were high enough, given that findings on general toxicity were not reported by study authors. |

[a] converted conform the CLP-Guidance (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf)

*Table 10. Summary table of in vivo animal cytogenetic tests with 1-bromopropane*

| Reference | Species | Experimental period and design | Concentration/dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| *Inhalation* | | | | | |
| NTP, 2011 (17) | Mouse, B6C3F1/N, male and female;<br>10/sex/ exposure concentration (chamber control or exposed) | *In vivo* mouse micronucleus test (peripheral blood); upon 3 month exposure;<br><br>Effect parameters: determination of frequency of micronuclei in 2,000[c] NCEs; additionally, determination of percentage of PCEs per 1,000 erythrocytes.<br><br>Statistical analysis using a one-tailed Cochran-Armitage trend test, followed by pairwise comparison between each exposed group and the chamber control group. | 0, 62.1, 124, 247, 497 ppm 1-bromopropane (analytical concentrations, corresponding to 0, 314, 629, 1,258, 2,515 mg/m$^3$)[a];<br>Purity: 99%<br>Inhalation, whole body; 6h plus t90[b] (10 min)/day, 5 days per week for 3 months<br><br>Positive control: not included | No increases in the frequencies of micronucleated NCEs in peripheral blood of male and female mice.<br><br>No effect on percentages of PCEs noticed in peripheral blood of male and female mice. | Non-GLP; non-guideline.<br><br>Applied concentration levels were probably not high enough, given the lack of treatment-related bone-marrow toxicity upon exposure to the selected concentrations of 1-bromopropane. |
| Anonymous, 1998 (43) | Rat, Sprague-Dawley, male and female;<br><br>10 animals/ sex/concentration | *In vivo* rat micronucleus test (bone marrow)<br><br>Effect parameter: determination of frequency of micronuclei in 1,000 PCEs.<br><br>Toxicity: not examined | 0, 50, 300 and 1800 ppm (nominal concentrations, corresponding to 0, 252, 1,509 and 9,054 mg/m$^3$)[a] 1-bromopropane;<br>Purity: no information<br><br>Inhalation, whole body; 6h/day, 5 days per week for 8 weeks | No increases in the frequencies of micronucleated PCEs | Data derived from REACH registration dossier. Original study report not available; however, details on study design and outcome well described. |

| Reference | Species | Experimental period and design | Concentration/dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| | | Statistical analysis: Kastenbaum et al. method | positive controls: not included | | Not clear whether applied concentration levels were high enough, given that (bone marrow) toxicity was not examined/reported by study authors<br><br>Non-GLP; non-guideline |
| *Intraperitoneal* | | | | | |
| Anonymous, 1995a (44) | Mouse, Swiss, male and female; 5-8 animals/sex/dose (experiment 3: males only) | *In vivo* mouse micronucleus test (bone marrow); upon 2 day exposure<br><br>Effect parameters: determination of frequency of micronuclei in 2,000 PCEs; additionally, determination of ratio of PCE and NCE by scoring of 1,000 erythrocytes.<br><br>Statistical analysis using Chi-square test (micronucleated PCE) and Student's t-test (PCE/NCE ratio). | Three experiments were subsequently performed.<br>Experiment 1: 0, 100, 400, 800 mg/kg bw/day<br>Experiment 2: 0, 800 mg/kg bw/day<br>Experiment 3: 0, 600 mg/kg bw/day<br>1-bromopropane for 2 consecutive days;<br>Purity: 99.3%;<br>Intraperitoneal (vehicle: corn oil)<br><br>Positive control: Cyclophosphamide (oral, 50 mg/kg bw/d) | Experiment 1: PCE/NCE ratio in vehicle controls lower than observed typically. Mortality 5/8 males at 800 mg/kg bw.<br><br>Experiment 2: Piloerection in all treated animals 2h after first treatment. Mortality 6/8 males 24h after first treatment.<br>No increase in frequencies of micronucleated PCE in females; no change in PCE/NCE ratio in females (males not considered). | Data derived from REACH registration dossier. Original study report not available; however, details on study design and outcome well described<br><br>OECD TG 474; GLP<br><br>Deviations TG: only a single dose was evaluated in the main test (experiments 2/3). |

| Reference | Species | Experimental period and design | Concentration/dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| | | | | Experiment 3: Piloerection in 5/8 males at 2h after the second treatment.<br>No increase in frequencies of micronucleated PCE.<br>No change in PCE/NCE ratio. | Appropriate results were obtained with positive control and negative (vehicle) control. |
| Anonymous, 1995b (45) | Mouse, Swiss, female;<br><br>Number of animals/dose: no information | *In vivo* mouse micronucleus test (bone marrow)<br><br>Effect parameter: no information<br><br>Toxicity: not examined<br><br>Statistical analysis: no information | dose levels: no information<br>purity: no information<br>vehicle: no information<br><br>intraperitoneal administration<br><br>positive controls: no information | No effects observed (however, results not presented quantitatively) | Data derived from REACH registration dossier. Original study report not available.<br><br>Stated to be according to OECD TG 474; GLP.<br>However, very limited description of design and outcome of the<br>Not clear whether the applied dose levels were appropriate.<br>Due to the limitations of the available summary, the quality of the study and the described results cannot be evaluated. |

| Reference | Species | Experimental period and design | Concentration/dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| Anonymous, 2009b (46) | Mouse, B6C3F1, male and female;<br><br>Number of animals/dose: no information | *In vivo* mouse micronucleus test (bone marrow)<br><br>Effect parameter: no information<br><br>Toxicity: not examined<br><br>Statistical analysis: no information | dose levels: no information<br>purity: no information<br>vehicle: no information<br><br>intraperitoneal administration<br><br>positive controls: no information | No effects<br>(however, results not presented quantitatively) | Data derived from REACH registration dossier. Original study report not available.<br>Stated to be according to OECD TG 474; GLP.<br>However, very limited description of design and outcome of the study. Not clear whether the applied dose levels were appropriate. Due to the limitations of the available summary, the quality of the study and the described results cannot be evaluated. |

[a] converted conform the CLP-Guidance (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf)
[b] t90 = the time to achieve 90% of the target concentration after the beginning of vapour generation
[c] a discrepancy is noted. The material and methods of NTP (2011) describes that the frequency of micronuclei is determined using 2,000c NCEs, whereas the results are presented as frequency of micronuclei per 1,000 NCEs.
NCE: normochromatic erythrocytes, PCE: polychromatic erythrocytes

*Table 11. Summary table of additional data on 1-bromopropane (A: in vitro, B: in vivo animal, C: in vivo human).*
*A: in vitro*

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| *Mammalian cells* | | | | | |
| Hasspieler et al., 2016 (47) | *DNA single strand breaks (hydroxylapatite DNA chromatography)*<br><br>Effect parameter: radioactivity (disintegrations/ min) in the DS fraction divided by the sum of the radioactivity in the SS and DS fractions<br><br>Statistical analysis: yes, but not specified | Human hepatoma cell line (HepG2) | 25 to 500 ppm 1-bromopropane; incubation at 37°C (incubation period not specified, 0-24h).<br>Purity: unknown<br>-S9<br><br>Positive control: 4-nitroquinoline *N*-oxide<br>Negative control: Solvent (not specified) | No effects observed on DNA strand breaks<br><br>(cytotoxicity at 500 ppm as measured with the neutral red uptake) | Non-GLP |
| | *DNA repair (UDS)*<br><br>Effect parameter: level of incorporation of [$^3$H]thymidine over background levels | Human hepatoma cell line (HepG2) | 25 to 500 ppm 1-bromopropane; incubation at 37°C (incubation period not specified, 0-24h).<br>Purity: unknown<br>-S9<br><br>Positive control: 4-nitroquinoline *N*-oxide | No effect observed on DNA repair<br><br>(cytotoxicity at 500 ppm as measured with the neutral red uptake) | Non-GLP |

| Reference | Method | Microorganism or cell type | Concentration range | Results | Remark |
|---|---|---|---|---|---|
| | Statistical analysis: yes, but not specified | | Negative control: Solvent (not specified) | | |
| Toraason et al., 2006 (48) | *In vitro* comet assay<br><br>Effect parameter: mean tail moment<br><br>Statistical analysis: ANOVA | Human leukocytes (derived from unexposed, non-smoking, adult male (n=1)) | Experiment 1: 0, 0.01, 0.1 or 1 mM 1-bromopropane; 8 h incubation at 37°C.<br>Experiment 2: 0, 1 mM 1-bromopropane; 1, 2, 4, and 8h incubation at 37°C.<br>Purity: unknown<br>-S9<br><br>Positive control: 0.5, 1, or 2Gy of X-rays at a dose rate of 1 Gy/min<br>Negative control: Solvent (1% DMSO) | Experiment 1: Significant increases in tail moment at 1 mM 1-bromopropane<br>Experiment 2: significant increases in tail moment upon 4h and 8h incubation with 1-bromopropane | Non-GLP; a single donor used. |
| *Other* | | | | | |
| Nepal et al., 2019 (49) | *In vitro* DNA-adduct ($N^7$-propyl guanine) formation; | Calf thymus DNA | 0, 0.5 or 1 mg/mL 1-bromopropane;<br>Purity: not specified<br>1, 2, 4, 6h incubation at 37°C<br>+/- liver homogenate | Formation of $N^7$-propyl guanine; independent of presence of liver homogenate | Non-GLP |
| | *In vitro* GSH-adduct (S-propyl GSH) formation; | Free GSH | 1 mg/mL 1-bromopropane;<br>Purity: not specified<br>2h at 37°C;<br>In presence of active or heat-denatured liver homogenate | GSH-depletion and formation of S-propyl GSH only in presence of active liver homogenate | |

SS: single strand, DS: double strand

*B: in vivo animal*

| Reference | Species | Experimental period and design | Dose and route | Observations and results | Remark |
|---|---|---|---|---|---|
| Nepal et al., 2019 (49) | Rat, Sprague-Dawley, male; 5/dose | *In vivo* DNA- and GSH-adduct formation; upon single or triple daily treatment;<br><br>Sacrifice 6h upon final treatment; liver, testes, kidney, spleen, lung and heart removed; DNA extracted from tissue; determination of S-propyl GSH and $N^7$-propyl guanine | 0, 200 or 1000 mg/kg bw once or daily for 3 consecutive days; Intraperitoneal (vehicle: corn oil) | $N^7$-propyl guanine formed in dose- and time-dependent manner in liver> spleen> testes> lung. No DNA-adduct formation in heart.<br><br>GSH-depletion: mainly in liver kidney and testes; S-propyl GSH formation: in liver> testes> spleen> kidney> lung> heart. | Non-GLP |

*C: In vivo human*

| Reference | participants | Experimental period and design | Data on exposure | Observations and results | Remark |
|---|---|---|---|---|---|
| Toraason et al., 2006 (48) | 64 workers (18 males, 46 females) from two facilities situated in US, sprayers and other workers; no control group;<br><br>NIOSH performed a Health Hazard Evaluation (HHE); a | DNA damage; DNA strand breaks (comet assay); venous blood, peripheral leukocytes.<br><br>1-Bromopropane exposure assessment: personal air monitoring breathing zone;<br><br>Biomarkers of exposure: Br in blood and urine<br><br>Effect parameter: mean tail moment of an individual sample and the | High exposure group (sprayers): up to 83±85 ppm (corresponding to 418±428 $mg/m^3$)[a] 1-bromopropane 8h TWA<br>Low exposure group (non-sprayers): up to 5±1 ppm (corresponding to 25±1 $mg/m^3$)[a] 1-bromopropane 8h TWA | No statistical significant differences in levels of DNA damage between the two exposure groups;<br><br>Higher tail moments (non-sprayers) and higher dispersion coefficients (sprayers) at the end-of-week in the same individuals as compared to start-of-week. | Non-GLP; non-guideline;<br>No matched control (non-exposed) population included; limited number of participants |

| Reference | participants | Experimental period and design | Data on exposure | Observations and results | Remark |
|---|---|---|---|---|---|
| | subpopulation of the HHE consented to participate in this study; data of this HHE can be found at CDC/NIOSH-website. | corresponding dispersion coefficient<br><br>Statistical analysis: Pearson correlation analysis and multiple linear regression analysis to determine relationship between 1-bromopropane exposure and DNA damage | | | |

[a] converted conform the CLP-Guidance (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf)

## 8.1 Summary of *in vitro* mutagenicity tests

Data on *in vitro* mutagenicity testing of 1-bromopropane are presented in Table 8 above.

1-Bromopropane was not mutagenic in either of two independent bacterial mutagenicity assays performed by NTP, each conducted with and without induced rat liver activation enzymes. Bacterial strains tested included Salmonella typhimurium strains TA97, TA98, TA100, and TA1535, and Escherichia coli strain WP2 uvrA/pKM101 (17).

1-Bromopropane did induce mutations in Salmonella typhimurium strains TA100 and TA1535 in both the presence and absence of metabolic activation in a study that was designed for testing highly volatile chemicals; a negative result was obtained for strain TA98 (31).

Additionally, the REACH registration dossier on 1-bromopropane presents five additional bacterial mutagenicity assays. 1-Bromopropane was not mutagenic in both the presence and absence of metabolic activation in these assays which included Salmonella typhimurium strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 and Escherichia coli strain WP2 uvrA (32-36). However, it is noted that for these studies, the original study report or publication was not available. Moreover, the summaries as presented in the REACH registration dossier of most of these studies included a very limited description of the design and/or outcome of the study. Due to these limitations, the quality of the study and/or the described results cannot be evaluated.

An *in vitro* mouse lymphoma assay using the TK gene was presented (38). An increased mutant frequency was noted in cultured L5178Y mouse lymphoma cells upon 1-bromopropane treatment. However, the increase in mutant frequency was noted at cytotoxic concentrations.

## 8.2 Summary of *in vitro* cytogenetic tests

Data on *in vitro* cytogenetic testing of 1-bromopropane are not available.

## 8.3 Summary of human data on mutagenicity

Human data on mutagenicity of 1-bromopropane are not available.

## 8.4 Summary of *in vivo* animal mutagenicity tests

Data on *in vivo* animal mutagenicity testing of 1-bromopropane are presented in Table 9 above.

Stelljes et al. (2019)/Anonymous (2016) conducted an *in vivo* transgenic rodent mutation assay (39, 40). B6C3F1 Big Blue® transgenic mice were exposed via whole body inhalation to 0, 62.8, 125, 258 ppm 1-bromopropane (analytical concentrations, corresponding to 0, 316, 629, 1298 mg/m$^3$) 6h/day, 5 days per week for 4 weeks. All animals survived through the experimental period, and no gross abnormalities were noticed. There were no treatment-related clinical findings, and body weight, food consumption or organ weights were not affected by treatment. No elevation in mutant frequency of the *cII* transgene in lung, colon or liver was observed and no dose-response

relationship was evident upon exposure to 1-bromopropane (data not presented quantitatively by the study authors but only in a figure).

Yu et al. (2008) conducted a dominant lethal assay in male ICR mice administered 1-bromopropane (300 or 600 mg/kg bw/d for 10 consecutive days; oral via gavage) and mated once weekly for 6 weeks to untreated female mice (41). 1-Bromopropane did not induce dominant lethal mutations. No treatment related changes in clinical signs, gross findings, mating index, gestation index, number of corpora lutea and implantations, pre-implantation loss, live fetuses, resorptions, dead foetuses or post-implantation loss were observed. An increase in pre-implantation loss at the fifth week following treatment was noticed, though this was considered by the study authors to be due to low sperm quality (Tables 12, 13, 14).

Previously, Saito-Suzuki et al. (1982) conducted a dominant lethal assay in male Sprague-Dawley rats administered 1-bromopropane (using oral via gavage administration of 400 mg/kg bw/d for 5 consecutive days) and mated to untreated female rats once weekly for 8 successive weeks (42). The study authors did not report the presence or absence of clinical signs. 1-Bromopropane did not induce dominant lethal mutations. No significant treatment-related changes in most indicators of fertility or embryonic deaths compared with the vehicle controls were noticed. The one exception was a marginally elevated frequency of dead implants observed at mating week 8, in the absence of a significant dominant lethal mutation index (Table 15).

*Table 12. Mating and pregnancy status of mice in dominant lethal test with 1-bromopropane 300 or 600 mg/kg bw/d for 10 consecutive days; oral via gavage (Yu et al., 2008)*

| Group | Test week | No. of females paired | No. of females mated | No. of females pregnant | Mating index (%) | Gestation index (%) |
|---|---|---|---|---|---|---|
| Vehicle control | 1 | 40 | 38 | 36 | 95.0 | 94.7 |
| | 2 | 40 | 40 | 39 | 100 | 97.5 |
| | 3 | 40 | 39 | 39 | 97.5 | 100 |
| | 4 | 40 | 38 | 36 | 95.0 | 94.7 |
| | 5 | 40 | 40 | 36 | 100 | 90.0 |
| | 6 | 40 | 39 | 37 | 97.5 | 94.9 |
| | | | | | | |
| 1-BP - 300 mg/kg bw | 1 | 40 | 35 | 31 | 87.5 | 88.6 |
| | 2 | 40 | 37 | 37 | 92.5 | 100 |
| | 3 | 40 | 37 | 36 | 92.5 | 97.3 |
| | 4 | 40 | 37 | 36 | 92.5 | 97.3 |
| | 5 | 40 | 37 | 31 | 92.5 | 83.8 |
| | 6 | 40 | 38 | 37 | 95.0 | 97.4 |
| | | | | | | |
| 1-BP - 600 mg/kg bw | 1 | 40 | 39 | 37 | 97.5 | 94.9 |
| | 2 | 40 | 34 | 34 | 85.0 | 100 |
| | 3 | 40 | 38 | 38 | 95.0 | 100 |
| | 4 | 40 | 40 | 39 | 100 | 97.5 |
| | 5 | 40 | 37 | 37 | 92.5 | 100 |
| | 6 | 40 | 40 | 37 | 100 | 92.5 |
| | | | | | | |
| Positive controls | 1 | 30 | 25 | 23 | 83.3 | 92.0 |
| | 2 | 30 | 27 | 27 | 90.0 | 100 |
| | 3 | 30 | 25 | 24 | 83.3 | 96.0 |
| | 4 | 30 | 27 | 26 | 90.0 | 96.3 |
| | 5 | 30 | 26 | 24 | 86.7 | 92.3 |
| | 6 | 30 | 24 | 23 | 80.3 | 95.8 |

*Table 13. Corpora lutea, live and dead implants in mice following treatment with 1-bromopropane 300 or 600 mg/kg bw/d for 10 consecutive days; oral via gavage (Yu et al., 2008)*

| Group | Test week | No. of corpora lutea | No. of implantations | No. of live fetuses | No. of resorptions | No. of dead fetuses | Fetal death[a] |
|---|---|---|---|---|---|---|---|
| Vehicle control | 1 | 15.2±2.8 | 14.1±2.7 | 13.1±2.5 | 1.1±1.3 | 0.1±0.4 | 1.3±1.2 |
| | 2 | 15.2±2.2 | 14.3±2.0 | 13.5±2.1 | 0.5±0.9 | 0.2±0.4 | 0.7±1.0 |
| | 3 | 13.7±2.0 | 13.5±2.0 | 12.6±2.0 | 0.7±1.0 | 0.1±0.4 | 0.8±1.0 |
| | 4 | 15.6±1.9 | 15.1±2.1 | 14.3±2.2 | 0.6±0.8 | 0.2±0.5 | 0.8±0.9 |
| | 5 | 14.1±1.9 | 13.6±2.4 | 12.9±2.8 | 0.7±1.0 | 0.1±0.2 | 0.7±1.1 |
| | 6 | 15.9±2.4 | 14.8±2.4 | 14.2±2.6 | 0.7±2.2 | 0.1±0.3 | 0.8±2.1 |
| | | | | | | | |
| 1-BP - 300 mg/kg bw | 1 | 14.8±1.9 | 13.8±1.7 | 12.8±1.3 | 0.8±0.9 | 0.1±0.4 | 1.0±1.1 |
| | 2 | 15.2±2.0 | 14.4±2.2 | 13.3±2.5 | 0.8±1.2 | 0.3±0.6 | 1.1±1.1 |
| | 3 | 15.0±3.2 | 14.4±2.8 | 13.4±2.7 | 0.9±1.1 | 0.2±0.5 | 1.1±1.2 |
| | 4 | 15.6±2.2 | 14.5±1.9 | 13.3±2.2 | 1.0±1.5 | 0.3±0.5 | 1.3±1.6 |
| | 5 | 14.7±2.1 | 13.8±2.9 | 12.7±3.3 | 1.0±1.7 | 0.1±0.3 | 1.1±1.8 |
| | 6 | 15.6±2.4 | 14.5±2.8 | 13.4±3.1 | 0.8±1.0 | 0.1±0.2 | 0.8±1.0 |
| | | | | | | | |
| 1-BP - 600 mg/kg bw | 1 | 15.9±2.4 | 14.6±2.5 | 13.6±2.3 | 0.9±1.3 | 0.1±0.3 | 1.0±1.4 |
| | 2 | 14.8±1.8 | 14.0±1.7 | 13.1±1.6 | 0.6±0.9 | 0.3±0.7 | 0.9±1.2 |
| | 3 | 15.0±2.9 | 14.5±2.8 | 13.9±2.8 | 0.5±0.8 | 0.1±0.4 | 0.6±0.8 |
| | 4 | 15.3±2.1 | 14.8±2.5 | 14.3±2.6 | 0.4±0.7 | 0.2±0.4 | 0.5±0.9 |
| | 5 | 15.8±2.0 | 13.8±3.2 | 13.7±3.2 | 0.4±0.7 | 0.2±0.5 | 0.6±0.9 |
| | 6 | 15.1±2.1 | 13.9±2.4 | 13.3±2.7 | 0.5±0.7 | 0.2±0.4 | 0.7±0.7 |
| | | | | | | | |
| Positive controls | 1 | 14.0±2.4 | 11.8±2.5[b] | 6.0±2.6[b] | 5.5±2.3[b] | 0.1±0.3 | 5.6±2.3[b] |
| | 2 | 12.7±2.4[b] | 10.7±2.3[b] | 5.4±2.6[b] | 5.3±2.8[b] | 0.0±0.2 | 5.3±2.8[b] |
| | 3 | 14.0±2.3 | 13.1±2.3 | 10.3±2.7[b] | 2.8±1.6[b] | 0.0±0.2 | 2.8±1.6[b] |
| | 4 | 15.0±2.4 | 13.9±2.4 | 12.9±3.2 | 0.7±1.2 | 0.2±0.4 | 0.9±1.2 |
| | 5 | 14.8±2.6 | 13.8±3.3 | 13.1±3.2 | 0.6±0.9 | 0.2±0.5 | 0.8±1.0 |
| | 6 | 15.7±1.9 | 13.7±2.6 | 13.1±2.4 | 0.5±0.8 | 0.1±0.3 | 0.7±0.8 |

[a] Fetal deaths = no. of resorptions + no. of dead fetuses.
[b] Significant differences from control group ($p < 0.01$).

*Table 14. Pre- and post-implantation losses and dominant lethal mutation rate in mice following treatment with 1-bromopropane 300 or 600 mg/kg bw/d for 10 consecutive days; oral via gavage (Yu et al., 2008)*

| Group | Test week | Pre-implantation loss (%) | Post-implantation loss (%) | Dominant lethal mutation rate (%) |
|---|---|---|---|---|
| Vehicle control | 1 | 7.1±9.7 | 6.6±7.7 | |
| | 2 | 5.8±8.8 | 5.0±7.3 | |
| | 3 | 1.6±3.6 | 6.3±7.6 | |
| | 4 | 3.7±6.6 | 5.4±6.0 | |
| | 5 | 3.9±9.1 | 5.7±9.0 | |
| | 6 | 6.5±9.3 | 4.4±8.0 | |
| | | | | |
| 1-BP - 300 mg/kg bw | 1 | 6.3±8.5 | 6.6±7.1 | 0.17 |
| | 2 | 5.8±8.2 | 7.8±8.3 | 2.17 |
| | 3 | 3.2±6.7 | 7.1±8.0 | 0.3 |
| | 4 | 6.0±10.3 | 8.8±9.7 | 3.14 |
| | 5 | 6.7±15.3 | 7.7±13.7 | 2.98 |
| | 6 | 9.6±18.8 | 6.6±8.7 | 3.68 |
| | | | | |
| 1-BP - 600 mg/kg bw | 1 | 8.1±9.7 | 6.4±8.5 | -0.26 |
| | 2 | 5.1±6.7 | 6.0±7.6 | 0.88 |
| | 3 | 2.9±6.9 | 4.1±5.3 | -2.71 |
| | 4 | 3.4±8.0 | 3.6±5.7 | -2.03 |
| | 5 | 12.9±16.9[a] | 0.8±2.7[b] | -4.66 |
| | 6 | 7.4±12.5 | 5.3±7.2 | 0.27 |
| | | | | |
| Positive controls | 1 | 15.3±12.9[b] | 48.8±19.2[b] | 45.27 |
| | 2 | 14.9±13.4[b] | 49.1±19.9[b] | 46.54 |
| | 3 | 5.9±9.1 | 21.7±13.1[b] | 15.76 |
| | 4 | 7.6±15.1 | 6.9±9.8 | 2 |
| | 5 | 8.2±15.7 | 4.6±6.2 | 0.08 |
| | 6 | 12.1±13.8 | 3.9±4.7 | 0.34 |

[a] Significant differences from control group ($p < 0.05$).
[b] Significant differences from control group ($p < 0.01$).

*Table 15. Dominant lethal mutation test in SD rat with 400 mg/kg bw 1-bromopropane for 5 consecutive days via oral gavage (Saito-Suzuki et al. (1982)) (42)*

| Group | Time of mating after treatment (weeks) | Number of females with implants | Number of corpora lutea per female [a] | Number of implants per female [a] | Number of live embryos per female [a] | Mean dead implants [b] (%) | Dominant lethal mutation index [c] |
|---|---|---|---|---|---|---|---|
| Vehicle control | 1 | 14 | 17.4±3.4 | 15.1±2.1 | 13.9±2.7 | 7.7 | |
| | 2 | 13 | 18.5±3.9 | 16.5±1.1 | 15.6±1.3 | 5.2 | |
| | 3 | 15 | 17.7±2.8 | 16.4±1.6 | 15.3±1.9 | 6.7 | |
| | 4 | 12 | 17.3±2.1 | 16.9±1.8 | 15.7±1.7 | 7.1 | |
| | 5 | 15 | 17.4±1.8 | 15.9±2.9 | 15.1±2.7 | 4.8 | |
| | 6 | 14 | 16.3±1.6 | 15.9±1.5 | 15.2±1.6 | 4.1 | |
| | 7 | 15 | 16.4±2.0 | 15.6±1.5 | 15.0±1.5 | 3.8 | |
| | 8 | 14 | 16.5±1.1 | 15.9±1.0 | 15.3±2.3 | 4.4 | |
| | | | | | | | |
| 1-BP; 400 mg/kg bw/d | 1 | 14 | 16.0±1.6 | 14.9±2.0 | 14.2±2.1 | 4.2 | -2.1 |
| | 2 | 15 | 16.8±1.7 | 16.0±1.9 | 15.3±2.0 | 4.2 | 1.8 |
| | 3 | 15 | 17.5±2.2 | 16.2±2.4 | 15.2±3.0 | 6.8 | 0.4 |
| | 4 | 13 | 17.2±1.6 | 16.3±1.9 | 15.5±1.8 | 5.0 | 1.3 |
| | 5 | 14 | 16.8±1.6 | 15.8±2.2 | 14.6±2.0 | 7.5 | 3.3 |
| | 6 | 14 | 15.6±1.2 | 14.8±1.5 | 14.0±2.0 | 5.5 | 8.0 |
| | 7 | 15 | 16.1±1.3 | 15.5±1.5 | 14.9±2.1 | 4.5 | 0.9 |
| | 8 | 15 | 17.8±2.7 | 15.5±2.9 | 13.9±3.6 | 11.2** | 9.3 |
| | | | | | | | |
| Positive control[d] | 1 | 15 | 15.9±0.7 | 15.6±0.7 | 12.9±1.8 | 17.6** | 7.6 |
| | 2 | 15 | 16.6±1.3 | 15.9±1.1 | 13.8±2.4* | 13.1* | 11.6 |
| | 3 | 15 | 16.7±2.1 | 13.1±5.6 | 11.7±5.9 | 9.2 | 23.1 |
| | 4 | 11 | 17.3±2.6 | 15.0±3.3 | 7.8±5.0** | 50.8** | 50.1 |
| | 5 | 12 | 16.8±2.0 | 13.7±3.2* | 6.1±4.9** | 59.5** | 59.6 |
| | 6 | 12 | 16.9±1.6 | 16.1±1.2 | 14.9±1.8 | 7.3 | 2.0 |
| | 7 | 13 | 15.1±3.6 | 14.3±4.2 | 13.2±4.2 | 14.2 | 11.8 |
| | 8 | 12 | 16.7±2.2 | 15.7±2.5 | 14.2±2.5* | 9.2* | 7.3 |

[a] values represent the mean±SD
[b] values are given as mean per pregnancy
[c] (1-live embryo per test female/live embryo per control female) × 100
[d] 1,2-Dibromo-3-chloropropane (DBCP) via oral gavage at 50 mg/kg bw/d; in this study, multiple halogenated 3-carbon compounds were tested and a comparison was made with the structural similar compound and known mutagen DBCP
*, **, ***, significantly different from control at $p<0.05$, $p<0.01$ and $p<0.001$, respectively

## 8.5 Summary of *in vivo* animal cytogenetic tests

Data on *in vivo* animal cytogenetic testing of 1-bromopropane are presented in Table 10 above.

An *in vivo* mouse micronucleus test (peripheral blood) was performed by NTP upon inhalation exposure. Male or female B6C3F1/N mice (10/sex/concentration) were exposed 6h plus t90 (i.e., 10 min; the time to achieve 90% of the target concentration after the beginning of vapour generation)/day, 5 days per week for 3 months to 0, 62.1, 124, 247, 497 ppm (analytical concentrations; corresponding to 0, 314, 629, 1,258, 2,515 mg/$m^3$, as converted conform the CLP-guidance) 1-bromopropane via inhalation. No increases in the frequencies of micronucleated normochromatic erythrocytes were seen. The percentage of PCEs in the peripheral blood of male and female mice was unaltered by 1-bromopropane exposure, suggesting a lack of chemical-associated bone-marrow toxicity (17).

The REACH-registration dossier presents additionally four *in vivo* micronucleus tests (bone marrow), three in mouse with intraperitoneal exposure and one in rat with inhalation exposure.
No increases in the frequencies of micronucleated polychromatic erythrocytes were seen in male and female Sprague-Dawley rats (10/sex/concentration) exposed via whole body inhalation to 0, 50, 300 and 1,800 ppm (nominal concentrations, corresponding to 0, 252, 1,509 and 9,054 mg/$m^3$, as converted conform the CLP-guidance) 1-bromopropane for 6h/day, 5 days per week for 8 weeks (43).
No increase in frequencies of micronucleated polychromatic erythrocytes were seen in male Swiss mice upon treatment with 600 mg/kg bw 1-bromopropane intraperitoneally (44). Preceding experiments within this study using dose levels (intraperitoneal) up to 800 mg/kg bw revealed a too low PCE/NCE ratio in vehicle control animals (i.e. lower than typically observed) and/or mortality in the high dose. Therefore a third experiment was carried out using males animals only and a single dose level of 600 mg/kg bw showing negative results with respect to micronuclei formation. An increase in PCE/NCE ratio was however not noticed.
Finally, 1-bromopropane was also found to be negative in micronucleus studies (very limited details provided) in female Swiss mice and male and female B6C3F1/N mice using intraperitoneal exposure (45, 46).
However, it is noted that for the additional studies derived from the REACH registration dossier, the original study report or publication was not available. Though details on study design and outcome were well described for some of these studies, the summaries as presented in the REACH registration dossier of some of these studies included a very limited description of the design and/or outcome of the study. Due to these limitations, the quality of the study and/or the described results cannot be evaluated. Moreover, lack of clarity regarding a proper dose or concentration selection was noted for some of the studies.

## 8.6 Summary of additional data

Additional data for 1-bromopropane are presented in Table 11 above.

Hasspieler et al. (2016) employed a battery of human cell bioassays using the human hepatoma cell-line, HepG2, to assess the cytotoxic and genotoxic potential of 1-bromopropane and other environmental pollutants (47). 1-Bromopropane did not induce DNA single-strand breaks or DNA repair in human hepatoma cell-line HepG2 at concentrations between 25 and 500 ppm. However, cytotoxicity was evident at 500 ppm as measured with the neutral red uptake assay.

Nepal et al. (2019) measured DNA- and glutathione-adducts in 1-bromopropane exposed rats (49). Male Sprague-Dawley rats were i.p. treated with 0, 200 or 1000 mg/kg bw 1-bromopropane once or daily for 3 consecutive days. $N^7$-propyl guanine DNA adducts were noticed in a dose- and time-dependent manner, mainly in liver followed by spleen, testes and lung. Similarly, glutathione depletion and S-propyl GSH adducts were noticed upon 1-bromopropane treatment.
In an *in vitro* experiment, Nepal et al. (2019) incubated calf thymus DNA for up to 6 h with 1-bromopropane (0, 0.5 and 1 mg/ml) showing $N^7$-guanine DNA adduct formation, being unaffected by addition of liver homogenates (49). Incubation of free GSH with 1-bromopropane for 2 hours resulted in GSH depletion and S-propyl GSH adduct only in the presence of active liver homogenates.

NIOSH did an assessment of DNA damage induced by 1-bromopropane in ex vivo treated human whole blood (48). Treated whole blood cultures from one single (n=1) unexposed, non-smoking, male individual were incubated with 1-bromopropane either at a concentration of 0, 0.01, 0.1 or 1 mM for 8h at 37°C or at a concentration of 0 and 1 mM for 1, 2, 4 and 8h at 37°C. DMSO was used as vehicle with a maximum final concentration of 1%. Metabolic activation was not included. DNA damage was assessed using the comet assay. Apoptosis was assessed using the DNA diffusion assay.
1-Bromopropane induced statistical significant increases in DNA damage at the highest concentration tested (1 mM) as indicated by increased comet tail moment. Statistically significant increases were evident after 4 and 8h of exposure to 1 mM 1-bromopropane. In addition, 1-bromopropane increased the number of apoptotic cells (cells with diffuse DNA) starting at 0.1 mM.

In addition to an assessment of DNA damage in *ex vivo* incubated human whole blood, NIOSH assessed DNA damage in peripheral leukocytes of workers occupationally exposed to 1-bromopropane (48). A total of 64 workers (18 males and 46 females; see table 16 for details) from two facilities where 1-bromopropane was used as a solvent for spray adhesives in foam cushion fabrication were included in this study. A subgroup of workers defined as "sprayers" operated spray guns and applied adhesives dissolved in 1-bromopropane. All other participants defined as "non-sprayers" worked elsewhere in the facilities and were considered to be at lower risk of exposure to 1-bromopropane. Exposure to 1-bromopropane was assessed from personal-breathing zone samples collected for 1–3 days up to 8 h per day for calculation of 8 h time weighted average (TWA) 1-bromopropane concentrations (measurements done with 50 participants). Start-of- and end-of-work week blood and urine samples were collected and bromide (Br) was measured as a biomarker of exposure.

DNA damage was assessed using the alkaline single cell gel electrophoresis (comet) assay. Additionally, genotyping of glutathione S-transferase M1 and T1 (GSTM1 and GSTT1) was performed.

*Table 16. Workers demographics (48).*

| | **Facility A** | | **Facility B** | |
|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** |
| *N* | 18 | 24 | 3 | 19 |
| Age | 20±10 | 31±12 | 25±5 | 36±5 |
| Smokers | 5 | 7 | 2 | 9 |
| Sprayers | 3 | 10 | 0 | 6 |
| GSTM1 null | 12 | 13 | 2 | 7 |
| GSTT1 null | 5 | 3 | 1 | 4 |

Values are numbers of workers except for age, which is the mean±SD of the participants age in decades.

Table 17 presents a summary of indices of 1-bromopropane exposure. Overall, TWA exposures to 1-bromopropane of non-sprayers at both facilities were considerably lower than exposures experienced by sprayers. 1-Bromopropane TWA concentrations ranged from 0.2 to 271 parts per million (ppm) at facility A, and from 4 to 27 ppm at facility B. 1-Bromopropane TWA concentrations were highest for sprayers at facility A and were, on average, four-fold higher than sprayers at facility B. Also, urine and serum Br concentrations from all workers at facility A were an order of magnitude greater than correspondingly classified workers at facility B.
1-Bromopropane TWA concentrations were statistically significantly correlated with blood and urine Br concentrations (table 3 in NIOSH report).

*Table 17. Environmental and internal 1-bromopropane exposure indices (48)*

| | **Facility A** | | **Facility B** | |
|---|---|---|---|---|
| | **Non-sprayer** | **Sprayer** | **Non-sprayer** | **Sprayer** |
| *N* | 29 | 13 | 16 | 6 |
| 1-bromopropane TWA (ppm) | 2±2 | 83±85 | 5±1 | 21±5 |
| Start-of week urine Br (mg/dl) | 26±14 | 122±96 | 2±1 | 6±5 |
| End-of week urine Br (mg/dl) | 28±9 | 238±179 | 2±2 | 10±14 |
| Start-of week serum Br (mg/dl) | 2.3±0.8 | 14.9±8.8 | 0.3±0.1 | 0.8±0.3 |
| End-of week serum Br (mg/dl) | 2.6±0.7 | 19.5±11.4 | 0.3±0.1 | 0.9±0.3 |

Values are mean±S.D.

DNA damage in leukocytes was assessed by examining the mean tail moment of an individual sample and the corresponding dispersion

coefficient (Table 18). Overall, though the high exposure group (sprayers) showed significantly increased levels of urine and serum bromide compared with the low exposure group (non-sprayers), no statistical significant differences were seen in the levels of DNA damage between the two exposure groups. Comparison of tail moments from peripheral leukocytes demonstrated that at both facilities sprayers had greater, but not statistically significantly greater, comet tail moments than non-sprayers. When comparing start-of-week and end-of-week results, comet tail moments at facility A increased during the week, while at facility B, comet tail moments decreased. The only statistically significant effect was noticed with non-sprayers at facility A where end-of-week tail moments were significantly greater than start-of-week tail moments. Also, tail moment dispersion coefficients increased significantly during the course of the week in sprayers at facility A (i.e. the subgroup of workers having the highest 1-bromopropane exposure).

*Table 18. Summary of comet analysis for 1-bromopropane exposed sprayers and non-sprayers (48).*

| | **Facility A** | | **Facility B** | |
|---|---|---|---|---|
| | **Non-sprayer** | **Sprayer** | **Non-sprayer** | **Sprayer** |
| *N* | 29 | 13 | 16 | 6 |
| Start-of-week tail moment | 2517±641 | 2867±895 | 2856±359 | 3430±984 |
| End-of-week tail moment | 3080±697[a] | 3178±762 | 2770±504 | 2974±280 |
| Start-of-week tail moment dispersion coefficient[b] | 562±354 | 496±259 | 580±243 | 596±234 |
| End-of week tail moment dispersion coefficient | 678±422 | 752±349[a] | 653±210 | 616±165 |
| GSTM1 null | 603±355 | 669±300 | 633±214 | 522±98 |
| GSTM1 positive | 787±504 | 886±413 | 668±220 | 709±179 |

Values are mean±S.D. GST1 rows are for end-of-week tail moment dispersion coefficients.
[a] end-of-week values are significantly greater than corresponding start-of-week values for same individuals (paired *t*-test, $p<0.05$).
[b] dispersion coefficient is defined as the variance divided by the mean

Application of linear regression models that included adjustments for gender, age, smoking status, facility, and GSTM1 and GSTT1 polymorphism, revealed a statistically significant association between start-of week tail moment and serum Br exposure quartiles (table 5 of NIOSH report). End-of-week values for tail moment were significantly and positively associated 1-bromopropane TWA quartiles and serum Br quartiles.

# 9 Carcinogenicity

## 9.1 Observations in humans

Data on the carcinogenicity of 1-bromopropane in humans were not found.

## 9.2 Animal experiments

The carcinogenicity studies of 1-bromopropane in experimental animals are summarized in Table 19. In these studies, animals were exposed to the substance via inhalation. No oral or dermal carcinogenicity studies were available.

*Table 19. Summary of animal carcinogenicity studies on 1-bromopropane exposure.*
*(Effect described in this table concern statistically significant effects unless otherwise specified)*

| Reference | Species | Experimental period and design | Concentration and route | Observations and results | Remarks |
|---|---|---|---|---|---|
| NTP, 2011 (17); Morgan et al, 2011 (50) | Rat, F344/N, male and female<br><br>50/sex/ exposure concentration (chamber control or exposed) | Carcinogenicity study<br><br>Statistical analysis tumour incidences: the Poly-κ test (with κ =3) was used to assess neoplasm and nonneoplastic lesion prevalence | 0, 125, 250, 500 ppm[a] 1-bromopropane (corresponding to 0, 629, 1,258, 2,515 mg/m$^3$)[b]; Purity≥99.9%;<br><br>Inhalation, whole body; 6h plus t90[c] (10 min)/day, 5 days per week for 105 weeks | <u>Observations</u><br>Twice daily observation;<br>body weights were measured initially and weekly for the first 13 weeks and then every 4 weeks through week 93, every 2 weeks thereafter;<br>Clinical observations were recorded approximately every 4 weeks through week 93, every 2 weeks thereafter, and at the end of the study;<br><br>Complete necropsies and histopathologic examinations were performed on all animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were processed and stained with H&E for microscopic examination.<br><br><u>Results</u><br>Survival: reduced survival in males (500 ppm)<br><br>Clinical findings: head mass and torso/ventral ulcer/abscess in males<br><br>Nonneoplastic lesions:<br>*Systemic*: chronic suppurative inflammation with Splendore-Hoeppli material (multiple tissues);<br>*Nose*: chronic suppurative inflammation (500 ppm males and females); chronic active inflammation (125, 250 and 500 ppm females); hyperplasia of the glands (125, 250 and 500 ppm males and females); respiratory epithelial hyperplasia (125 ppm and 500 ppm females); respiratory | GLP; non-guideline. |

| Reference | Species | Experimental period and design | Concentration and route | Observations and results | Remarks |
|---|---|---|---|---|---|
| | | | | metaplasia of the olfactory epithelium (500 ppm females);<br>*Larynx*: chronic active inflammation (250 ppm males and females, 500 ppm females); squamous metaplasia (500 ppm females);<br>*Trachea*: chronic active inflammation and epithelial hyperplasia (500 ppm females);<br>*Lung*: chronic suppurative inflammation (500 ppm females);<br><br>Neoplastic lesions:<br>*Intestine:* adenoma of the large intestine - colon or rectum (500 ppm females, stat. sign.; 125 and 250 ppm females and 250 and 500 ppm males, not stat. sign., though outside historical controls);<br>*Skin:* keratoacanthoma (250 and 500 ppm males); combined incidences of keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (125, 250 and 500 ppm males; and exposure-related trend); combined incidences of squamous cell papilloma, keratoacanthoma, basal cell adenoma, or basal cell carcinoma (exposure related trend in females; 500 ppm females, not stat. sign., though outside historical controls);<br>*Multiple tissues:* mesothelioma (500 ppm males);<br>*Pancreas:* pancreatic islet adenoma (125, 250 and 500 ppm males); pancreatic islet carcinoma (125 ppm and 250 ppm: not stat. sign., but at our exceeding upper range of historical control); combined pancreatic islet adenoma/carcinoma (125 and 250 ppm males); | |

| Reference | Species | Experimental period and design | Concentration and route | Observations and results | Remarks |
|---|---|---|---|---|---|
| NTP, 2011 (17); Morgan et al, 2011 (50) | Mouse, B6C3F1/N, male and female<br><br>50/sex/ exposure concentration (chamber control or exposed) | Carcinogenicity study<br><br>Statistical analysis tumour incidences: the Poly-κ test (with κ =3) was used to assess neoplasm and nonneoplastic lesion prevalence | 0, 62.5, 125, 250 ppm[a] 1-bromopropane (corresponding to 0, 314, 629, 1,258 mg/m$^3$)[b]; Purity≥99.9%;<br><br>Inhalation, whole body; 6h plus t90[c] (10 min)/day, 5 days per week for 105 weeks | <u>Observations</u><br>Twice daily observation;<br>body weights were measured initially and weekly for the first 13 weeks and then every 4 weeks through week 93, every 2 weeks thereafter;<br>Clinical observations were recorded approximately every 4 weeks through week 93, every 2 weeks thereafter, and at the end of the study;<br><br>Complete necropsies and histopathologic examinations were performed on all animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were processed and stained with H&E for microscopic examination.<br><br><u>Results</u><br>Survival: no treatment-related findings<br><br>Clinical findings: no treatment-related findings<br><br>Nonneoplastic lesions:<br>*Lung*: Cytoplasmic vacuolization of bronchiolar epithelium (62.5, 125 ppm and 250 ppm males); bronchiolar regeneration (62.5, 125 ppm and 250 ppm males and females)<br>*Nose*: cytoplasmic vacuolization of respiratory epithelium (62.5, 125 and 250 ppm males; 125 and 250 ppm females); respiratory epithelial hyperplasia (125 and 250 ppm males; 62.5, 125 and 250 ppm females); respiratory metaplasia of olfactory epithelium (62.5 and 125 ppm | GLP; non-guideline. |

| Reference | Species | Experimental period and design | Concentration and route | Observations and results | Remarks |
|---|---|---|---|---|---|
| | | | | males; 125 and 250 ppm females); olfactory epithelial atrophy (250 ppm females)<br>*Larynx*: cytoplasmic vacuolization of respiratory epithelium (62.5, 125 ppm and 250 ppm males)<br>*Trachea*: cytoplasmic vacuolization of respiratory epithelium (62.5, 125 ppm and 250 ppm males; 62.5 and 125 ppm females); respiratory epithelial hyperplasia (62.5 and 250 ppm males; 62.5, 125 and 250 ppm females); respiratory metaplasia of olfactory epithelium (62.5 and 125 ppm males; 125 and 250 ppm females); olfactory epithelial atrophy (250 ppm females)<br><br>Neoplastic lesions:<br>*Lung*: alveolar/bronchiolar adenoma (250 ppm females); alveolar/bronchiolar carcinoma (62.5 and 125 ppm females); combined alveolar/bronchiolar adenoma or carcinoma (62.5, 125 and 250 ppm females; concentration-related trend) | |

[a] analytical concentrations (as determined by GC) are in line with the target concentrations
[b] converted conform the CLP-Guidance (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf)
[c] t90 = the time to achieve 90% of the target concentration after the beginning of vapour generation

***2-year rat carcinogenicity study (NTP, 2011)***

A 2-year rat carcinogenicity study was performed by NTP (17, 50). In this 2-year GLP study, male and female F344/N rats (50/sex/exposure concentration) were exposed to 1-bromopropane (purity≥99.9%) vapour via whole body inhalation at concentrations of 0, 125, 250, or 500 ppm (corresponding to 0, 629, 1,258, 2,515 mg/m$^3$, as converted conform the CLP-guidance), 6h plus $t_{90}$ (i.e., 10 min; the time to achieve 90% of the target concentration after the beginning of vapour generation) per day, 5 days per week for up to 105 weeks (17, 50). The exposure concentrations were selected based on results of previous 14- and 90-day inhalation studies.

Survival of male rats exposed to 500 ppm 1-bromopropane was significantly less than that of the chamber controls (Table 20). Survival of exposed female rats decreased with increasing 1-bromopropane exposure concentration, but survival in each exposed group was not significantly different from that of controls.

*Table 20. Survival of F344/N rats in the 2-year inhalation study of 1-bromopropane (17, 50).*

| | **Exposure concentration** | | | |
|---|---|---|---|---|
| **ppm:** | **0** | **125** | **250** | **500** |
| **mg/m$^3$:** | **0** | **629** | **1,258** | **2,515** |
| *Male* | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 24 | 20 | 28 | 35 |
| Natural deaths | 3 | 4 | 4 | 2 |
| Animals surviving to study termination | 23 | 26 | 18 | 13 |
| Percentage probability of survival at end of study[a] | 46 | 52 | 36 | 26 |
| Mean survival (days)[b] | 679 | 671 | 654 | 639 |
| Survival analysis[c] | p=0.009 | p=0.844N | p=0.262 | p=0.033 |
| | | | | |
| *Female* | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Accidental deaths[d] | 0 | 0 | 0 | 2 |
| Moribund | 13 | 17 | 17 | 23 |
| Natural deaths | 3 | 0 | 3 | 1 |
| Animals surviving to study termination | 34 | 33 | 30 | 24 |
| Percentage probability of survival at end of study[a] | 68 | 66 | 60 | 50 |
| Mean survival (days)[b] | 702 | 692 | 683 | 637 |
| Survival analysis[c] | p=0.028 | p=0.858 | p=0.419 | p=0.054 |

[a] Kaplan-Meier determinations.
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test is in the chamber control column, and the results of pairwise comparisons with the controls are in the exposed group columns. A lower mortality in an exposed group is indicated by N.
[d] censored for survival analyses.

Mean body weights of exposed male and female rats were more or less similar to those of the chamber controls throughout the study.

In males, clinical findings that appeared to be related to 1-bromopropane exposure included head mass (0 ppm, 1/50; 125 ppm, 2/50; 250 ppm, 5/50; 500 ppm, 9/50) and torso/ventral ulcer/abscess (2/50, 7/50, 6/50, 20/50). No clinical findings related to exposure to 1-bromopropane were observed in females.

Macroscopically, in male and female rats exposed to 1-bromopropane, there was an exposure-related increased incidence of soft, pale-yellow to green, variably sized nodules. These lesions were predominantly located in the nose and/or skin, but other sites included bone, ear, Harderian gland, larynx, lung, muscle, peritoneum, preputial gland, and prostate gland. The incidences of these lesions were greater in males (2, 3, 6, 15 for the control, low, mid and high concentration groups, respectively) than in females (1, 2, 0, 7 for the control, low, mid and high concentration groups, respectively). In addition, the number of animals with multiple masses was increased in the 500 ppm groups. In most cases, these lesions were microscopically shown to be suppurative inflammation, many with Splendore-Hoeppli (S-H) material.

Nonneoplastic lesions included chronic suppurative inflammation noticed in multiple tissues and lesions of the respiratory system. Table 21 presents organ distribution and incidence of suppurative inflammation with S-H material. Table 22 presents an overview of nonneoplastic lesions of the respiratory system.
*Systemic chronic suppurative inflammation with S-H material:*
The number of animals with multiple masses was increased in the 500 ppm groups (males and females). These lesions were located predominantly in the nose and/or skin but also in the bone, ear, Harderian gland, larynx, lung, muscle, peritoneum, preputial gland, and prostate. In most cases, these lesions were microscopically shown to be suppurative inflammation, many with S-H material.
Both male and female rats had concentration-related increases in the incidences of chronic suppurative inflammation that contained S-H material. These lesions were not seen in controls.
*Nose:* Statistically significantly increased incidences of chronic suppurative inflammation were noticed in female and male rats of the 500 ppm group.
Chronic active inflammation was present in many animals of both sexes, including the chamber controls, but in females, the incidences in all exposed groups were significantly increased compared with that in the chamber controls.
The incidences of respiratory epithelial hyperplasia were statistically significantly increased in 125 ppm and 500 ppm females, and the incidence of respiratory metaplasia of the olfactory epithelium was significantly increased in 500 ppm females.
The incidences of glandular hyperplasia were statistically significantly increased in all exposed male and female groups.
*Larynx:* The incidences of chronic active inflammation in 250 ppm males and females and 500 ppm females were statistically significantly increased.
In females, the incidence of squamous metaplasia was statistically significantly greater in the 500 ppm group than that in the chamber controls.

*Trachea:* In the 500 ppm females, the incidences of chronic active inflammation and epithelial hyperplasia were statistically significantly increased. Both lesions also occurred in males, but the incidences were not statistically significantly increased.
*Lung:* The incidence of suppurative inflammatory lesions with S-H material was statistically significantly increased in the 500 ppm females compared with chamber controls. This lesion was also noticed in males (250 and 500 ppm), though this increase did not reach statistical significance.

*Table 21. Organ distribution and incidence of suppurative inflammation with Splendore-Hoeppli material in F344/N rats exposed to via inhalation 1-bromopropane for 2 years (17, 50).*

| | **Exposure concentration** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **ppm:** | **0** | | **125** | | **250** | | **500** | |
| **mg/m³:** | **0** | | **406** | | **1,622** | | **6,488** | |
| **organ** | **males** | **females** | **males** | **females** | **males** | **females** | **males** | **females** |
| Peritoneum | 0[a] | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Preputial gland | 0 | - | 1 | - | 0 | - | 1 | - |
| Prostate | 0 | - | 0 | - | 0 | - | 1 | - |
| Skin | 0 | 0 | 1 | 1 | 2 | 0 | 10 | 1 |
| Bone | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 |
| Skeletal muscle | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Larynx | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| Lung | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 4 |
| Nose | 0 | 0 | 1 | 1 | 2 | 3 | 7 | 7 |
| Trachea | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| Ear | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Harderian gland | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 |
| Kidney, pelvis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Grand total[b] | 0 | 0 | 3 | 2 | 5 | 7 | 29 | 18 |
| No. of animals with at least one lesion | 0 | 0 | 3 | 2 | 4 | 4 | 17 | 14 |

[a] number of animals with a lesion
[b] total number of lesions for all animals in the treatment group

*Table 22. Incidences of selected nonneoplastic lesions of the respiratory system in (A) male and (B) female F344/N rats exposed to 1-bromopropane via inhalation for 2 years (17, 50).*
*A: Males*

| | **Exposure concentration** | | | |
|---|---|---|---|---|
| **ppm:** | **0** | **125** | **250** | **500** |
| **mg/m³:** | **0** | **406** | **1,622** | **6,488** |
| *Nose:* | | | | |
| Inflammation, Suppurative, Chronic | 0/50 | 1/48 (4.0)[a] | 2/48 (4.0) | 7/50** (4.0) |
| Inflammation, Chronic Active | 29/50 (1.6) | 33/48 (1.4) | 34/48 (1.5) | 35/50 (1.5) |
| Epithelium, Accumulation, Hyaline Droplet | 44/50 (1.0) | 39/48 (1.5) | 36/48 (1.3) | 44/50 (1.3) |
| Glands, Hyperplasia | 5/50 (2.0) | 14/48* (2.0) | 14/48** (2.0) | 15/50** (2.0) |
| *Larynx:* | | | | |
| Inflammation, Suppurative, Chronic | 0/50 | 0/50 | 0/50 | 1/50 (4.0) |
| Inflammation, Chronic Active | 21/50 (1.4) | 28/50 (1.3) | 31/50* (1.4) | 26/50 (1.3) |
| Metaplasia, Squamous | 4/50 (1.0) | 6/50 (1.0) | 8/50 (1.1) | 5/50 (1.2) |
| *Trachea:* | | | | |
| Inflammation, Chronic Active | 1/50 (2.0) | 1/50 (1.0) | 1/50 (1.0) | 4/50 (1.5) |
| Epithelium, Hyperplasia | 1/50 (2.0) | 0/50 | 0/50 | 1/50 (2.0) |
| *Lung:* | | | | |
| Inflammation, Suppurative, Chronic | 0/50 | 0/50 | 1/50 (4.0) | 3/50 (4.0) |

*B: Females*

| | **Exposure concentration** | | | |
|---|---|---|---|---|
| **ppm:** | **0** | **125** | **250** | **500** |
| **mg/m³:** | **0** | **406** | **1,622** | **6,488** |
| *Nose:* | | | | |
| Inflammation, Suppurative, Chronic | 0/50 | 1/50 (4.0) | 3/49 (4.0) | 7/50** (4.0) |
| Inflammation, Chronic Active | 24/50 (1.3) | 37/50** (1.5) | 37/49** (1.5) | 36/50** (1.3) |
| Epithelium, Accumulation, Hyaline Droplet | 48/50 (1.1) | 48/50 (1.8) | 48/49 (1.7) | 47/50 (1.9) |
| Glands, Hyperplasia | 6/50 (2.0) | 23/50** (2.0) | 28/49** (2.0) | 30/50** (2.0) |
| Respiratory Epithelium, Hyperplasia | 5/50 (1.2) | 13/50* (1.3) | 9/49 (1.7) | 18/50** (1.5) |
| Olfactory Epithelium, Metaplasia, Respiratory | 3/50 (1.7) | 4/50 (1.8) | 6/49 (1.8) | 9/50* (2.2) |

| | Exposure concentration | | | |
|---|---|---|---|---|
| **ppm:** | **0** | **125** | **250** | **500** |
| **mg/m³:** | **0** | **406** | **1,622** | **6,488** |
| *Larynx:* | | | | |
| Inflammation, Suppurative, Chronic | 0/50 | 0/50 | 0/50 | 3/50 (4.0) |
| Inflammation, Chronic Active | 18/50 (1.1) | 25/50 (1.5) | 30/50** (1.4) | 32/50** (1.5) |
| Metaplasia, Squamous | 3/50 (1.3) | 2/50 (1.5) | 6/50 (1.3) | 21/50** (1.7) |
| *Trachea:* | | | | |
| Inflammation, Chronic Active | 0/50 | 4/50 (1.0) | 1/50 (1.0) | 6/50**# (1.7) |
| Epithelium, Hyperplasia | 0/50 | 0/50 | 0/50 | 4/50* (1.8) |
| *Lung:* | | | | |
| Inflammation, Suppurative, Chronic | 0/50 | 0/50 | 0/50 | 4/50* (4.0) |

[a] in parentheses: average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
[#] a small discrepancy is noted related to the presentation of the statistical results of the rat carcinogenicity study by NTP (2011) and by Morgan et al. (2011). In this report the results as presented and evaluated by NTP (2011) have been primarily used.

Table 23 presents a summary of the neoplastic lesions.
*Large intestine:* The incidence of adenoma of the large intestine (colon or rectum) in 500 ppm females was statistically significantly increased when compared to chamber controls (p≤0.05) and a positive concentration-related trend was noticed. Incidences of adenoma of the large intestine in 125 ppm and 250 ppm females and in 250 ppm and 500 ppm males were slightly increased (not statistically significant) compared with that of the chamber controls and exceeded historical control rates.
Large intestine adenomas were found to be polypoid masses that protruded into the intestinal lumen. The epithelium lining the glands had fewer goblet cells than the epithelium from normal glands and was occasionally thickened by multiple layers of slightly enlarged neoplastic epithelial cells with basophilic cytoplasm and enlarged nuclei. There were variable numbers of mixed inflammatory cells in the stroma around the glands and in the stalk. No invasion of the submucosa of the large intestine was observed.
*Skin:* The incidences of keratoacanthoma in 250 ppm and 500 ppm males were significantly increased (p≤0.05 and p≤0.01, respectively) when compared to chamber controls. The incidences of combined keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma were significantly increased in all exposed groups of males with an exposure-related trend (p=0.003). In female rats, there was a significant exposure-related trend (p=0.05) in the combined incidences of squamous cell papilloma, keratoacanthoma, basal cell adenoma, or basal cell carcinoma. The incidence in the 500 ppm group was not statistically significantly increased, though exceeded the historical control range.

Keratoacanthomas were well-demarcated, variably sized, crateriform masses in the dermis composed of squamous epithelium that formed thick folds. The centre of the mass was filled with abundant keratin. Squamous cell carcinomas were characterized as masses composed of cords of pleomorphic squamous cells infiltrating the dermis and/or subcutis. There were varying amounts of keratin and fibrous connective tissue, which separated the cords of squamous cells within the neoplasms. Basal cell adenomas were well-demarcated masses composed of cords and lobules of basal cells with areas of sebaceous or squamous differentiation. Basal cell carcinomas had a similar appearance, but the cells in the carcinomas were more pleomorphic. The carcinomas were locally invasive and often contained areas of necrosis.
*Malignant mesothelioma:* The incidence of malignant mesothelioma in 500 ppm male rats was statistically significantly ($p \leq 0.05$) increased compared to chamber controls.
This neoplasm was found in the epididymis in all affected animals with other tissues variably affected, particularly the testis, which was affected in all but one animal. These mesotheliomas were characterized by numerous, complex, papillary structures composed of pedunculated, fibrovascular stalks covered by one to several layers of cuboidal to flattened mesothelial cells. The stroma was prominent and often contained clusters of pleomorphic mesothelial cells that sometimes formed disorganized tubular structures. There was often extensive invasion of skeletal muscle and adipose tissue but minimal invasion of underlying tissues at other sites.
*Pancreatic islets:* In male rats, the incidences of pancreatic islet adenoma were significantly increased ($p \leq 0.05$) in all exposed groups compared with the chamber controls, but were within the range of historical control data.
The incidences of pancreatic islet carcinoma were increased (though not statistically significantly) in the 125 ppm and 250 ppm males and met or exceeded the upper range of the historical controls.
The combined incidences of pancreatic islet adenoma or carcinoma were significantly increased ($p \leq 0.05$) in the 125 ppm and 250 ppm males when compared to chamber controls (and met or exceeded the upper range of the historical controls). No statistical significant increase was noticed in the 500 ppm males.
Adenomas were usually discrete, well-circumscribed masses of islet cells that were 1 mm in diameter or larger and compressed the surrounding acinar tissue. Occasionally, adenomas were encapsulated by a thin band of fibrous connective tissue. In some adenomas, groups of exocrine pancreatic acini were present within the adenomas at their periphery. Carcinomas, which tended to be larger than adenomas, were characterized by varying degrees of atypia and pleomorphism of the neoplastic cells, and they typically invaded the surrounding fibrous capsule or pancreatic tissue.

*Table 23. Incidences of neoplastic lesions in (A) male and (B) female F344/N rats exposed to 1-bromopropane via inhalation for 2 years (17, 50).*
*A: Males*

| | **Exposure concentration** | | | | **Historical control data[a]** |
|---|---|---|---|---|---|
| **ppm:** | **0** | **125** | **250** | **500** | |
| **mg/m³:** | **0** | **629** | **1,258** | **2,515** | |
| *Intestines:* | | | | | |
| adenoma of colon | 0/50 | 0/50 | 0/50 | 1/50 | |
| adenoma of rectum | 0/50 | 0/50 | 2/50 | 0/50 | |
| combined incidence adenoma colon/rectum | 0/50 | 0/50 | 2/50 | 1/50 | 0/349 |
| *Skin:* | | | | | |
| basal cell adenoma | 0/50 | 1/50 | 2/50 | 1/50 | 4/349 (1.2% ± 1.1%; range 0%-2%) |
| basal cell carcinoma | 0/50 | 2/50 | 1/50 | 2/50 | 4/349 (1.1% ± 2.3%; range 0%-6%) |
| keratoacanthoma | 0/50[b] | 3/50 | 6/50* | 6/50** | 10/349 (2.9% ± 3.7%; range 0%-8%) |
| squamous cell carcinoma | 1/50 | 1/50 | 0/50 | 2/50 | 1/349 (0.3% ± 0.8%; range 0%-2%) |
| combined incidence keratoacanthoma and squamous cell carcinoma | 1/50[c] | 4/50 | 6/50* | 8/50** | 11/349 (3.2% ± 3.5%; range 0%-8%) |
| combined incidence keratoacanthoma, squamous cell carcinoma, basal cell adenoma or basal cell carcinoma | 1/50[d] | 7/50* | 9/50** | 10/50** | 19/349 (5.5% ± 4.5%; range 0%-10%) |
| *Multiple tissues:* | | | | | |
| malignant mesothelioma | 0/50[e] | 2/50 | 2/50 | 4/50* | 5/349 (1.4% ± 2.2%) |
| *Pancreas:* | | | | | |
| adenoma | 0/50[f] | 5/50* | 4/50* | 5/50* | 20/349 (5.7% ± 3.9%; range 0%-12%) |
| carcinoma | 3/50 | 7/50 | 5/50 | 3/50 | 17/349 (4.9% ± 3.3%; range 2%-10%) |
| combined incidence adenoma/carcinoma | 3/50 | 10/50* | 9/50* | 8/50 | 37/349 (10.6% ± 4.8%; range 6%-18%) |

*B: Females*

| | Exposure concentration | | | | Historical control data[a] |
|---|---|---|---|---|---|
| **ppm:** | **0** | **125** | **250** | **500** | |
| **mg/m³:** | **0** | **629** | **1,258** | **2,515** | |
| *Intestines:* | | | | | |
| adenoma of colon | 0/50 | 1/50 | 1/50 | 1/50 | |
| adenoma of rectum | 0/50 | 0/50 | 1/50 | 4/50 | |
| combined incidence adenoma colon/rectum | 0/50[g] | 1/50 | 2/50 | 5/50* | 0/350 |
| *Skin:* | | | | | |
| keratoacanthoma | 1/50 | 0/50 | 1/50 | 1/50 | |
| squamous cell papilloma | 0/50 | 0/50 | 0/50 | 1/50 | |
| basal cell adenoma | 0/50 | 1/50 | 0/50 | 1/50 | |
| basal cell carcinoma | 0/50 | 0/50 | 0/50 | 1/50 | |
| combined incidence keratoacanthoma, squamous cell papilloma, basal cell adenoma or basal cell carcinoma | 1/50[h] | 1/50 | 1/50 | 4/50 | 2/350 (0.6% ± 1.0%; range 0%-2%) |

[a] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet in F344/N rats (7 studies in total; 2001-2003)
[b] overall exposure-related trend (P=0.008) by the Poly-3 test
[c] overall exposure-related trend (P=0.006) by the Poly-3 test
[d] overall exposure-related trend (P=0.003) by the Poly-3 test
[e] overall exposure-related trend (P=0.031) by the Poly-3 test
[f] overall exposure-related trend (P=0.043) by the Poly-3 test
[g] overall exposure-related trend (P=0.004) by the Poly-3 test
[h] overall exposure-related trend (P=0.050) by the Poly-3 test
* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test

***2-year mouse carcinogenicity study (NTP, 2011)***

A 2-year mouse carcinogenicity study was performed by NTP (17, 50). In a 2-year GLP study, male and female B6C3F1/N mice (50/sex/exposure concentration) were exposed to 1-bromopropane (purity≥99.9%) vapour via whole body inhalation at concentrations of 0, 62.5, 125 or 250 ppm (corresponding to 0, 314, 629, 1258 mg/m$^3$, as converted conform the CLP-guidance), 6h plus $t_{90}$ (i.e., 10 min; the time to achieve 90% of the target concentration after the beginning of vapour generation) per day, 5 days per week for up to 105 weeks (17, 50). The exposure concentrations were selected based on results of previous 14- and 90-day inhalation studies.

Survival was not affected upon 1-bromopropane exposure. Mean body weights of exposed male and female mice were more or less similar to those of the chamber controls throughout the study. No clinical findings related to exposure to 1-bromopropane were observed in mice.

Treatment-related neoplasms and nonneoplastic lesions were mainly found in the respiratory tract of mice. Treatment-related neoplasms were only found in female mice and not in male mice. Tables 24 and 25 present an overview of these non-neoplastic lesions and neoplasms, respectively.

*Lung:* Cytoplasmic vacuolization of bronchiolar epithelium showed a statistically significantly increased incidence (p≤0.01) in male mice. This lesion did not occur in chamber control mice.
Cytoplasmic vacuolization of bronchiolar epithelium often accompanied bronchiolar regeneration. Bronchiolar regeneration occurred in most exposed male and female mice (statistically significant increase in all exposed groups (p≤0.01)) but not in chamber controls (except for a single control male with minimal regeneration). The incidences were similar among exposed groups, although slight exposure concentration–related increases in severities were noted.
Statistically significant or biologically relevant changes were observed in the incidences of neoplasms of the lungs of female mice exposed to 1-bromopropane. In female mice, there were treatment-related increased incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and combined alveolar/bronchiolar adenoma or carcinoma. The incidence of alveolar/bronchiolar adenoma in 250 ppm females were significantly increased (p≤0.01). The incidences of alveolar/bronchiolar carcinoma in 62.5 ppm and 125 ppm females were significantly increased (p≤0.01 and p≤0.05, respectively). The incidences of combined alveolar/bronchiolar adenoma or carcinoma were statistically significantly increased in all exposed groups (62.5 ppm: p≤0.01, 125 ppm: p≤0.05, 250 ppm: p≤0.01) and showing a concentration-related trend. Histologically, alveolar/bronchiolar carcinomas varied from moderately differentiated, circumscribed lesions to anaplastic, poorly circumscribed, infiltrative lesions. They were variable in size and shape, and their growth patterns were papillary or solid with regions of squamous metaplasia, spindle cell differentiation, and necrosis. Alveolar/bronchiolar adenomas were usually smaller, well-differentiated, circumscribed lesions that often compressed the adjacent parenchyma, and most were papillary.
*Nose:* There were exposure concentration–related increased incidences of cytoplasmic vacuolization of respiratory epithelium in male and female mice; the incidences were significantly increased in all exposed groups of males (p≤0.01) and in 125 ppm and 250 ppm females (p≤0.05 and p≤0.01, respectively). This lesion did not occur in chamber control mice.
There were exposure-related increased incidences of respiratory epithelial hyperplasia in the dorsal meatus(es) in Level I in mice of both sexes; the incidences in all exposed female groups (p≤0.01) and in 62.5 ppm (p≤0.01) and 250 ppm (p≤0.05) males were significantly increased. Although present in controls, the incidence and severity of respiratory epithelial hyperplasia increased with increasing exposure concentration, and lesions in male mice were more severe than those in females.
There were exposure-related increased incidences of respiratory metaplasia of olfactory epithelium in male mice and exposure concentration-related increases in female mice; incidences of this lesion were significantly increased in 62.5 ppm and 125 ppm males (p≤0.01 and p≤0.05, respectively) and 125 ppm and 250 ppm females (p≤0.05 and p≤0.01, respectively). This lesion was not observed in chamber control mice.
Olfactory epithelial atrophy was increasingly observed in 250 ppm females (p≤0.05). In males, the incidences of this lesion were slightly

increased in all exposed groups, but these increases lacked statistical significance.
*Larynx and trachea:* There were increased incidences of cytoplasmic vacuolization of respiratory epithelium in the larynx and the trachea of exposed males and in the trachea of females. The incidences were significantly increased in both tissues in all exposed groups of males ($p \leq 0.01$; except 62.5 ppm $p \leq 0.05$) and in the trachea of 62.5 ppm and 125 ppm females ($p \leq 0.01$). This lesion did not occur in chamber control mice.
*Other findings:* Hepatocellular carcinomas were not observed in 250 ppm females (data not shown); the incidence was significantly less than in the concurrent chamber controls and lower than the historical control range for inhalation studies (39/350 (11% ± 5%; range 6%-20%)). The incidences of combined hepatocellular adenomas or carcinomas in 62.5 and 250 ppm females were significantly less than that in the chamber controls. The incidence of skin sarcoma in 250 ppm females was also significantly less than that in the chamber controls.

*Table 24. Incidences of nonneoplastic lesions in (A) male and (B) female B6C3F1/N mice exposed to 1-bromopropane via inhalation for 2 years (17, 50).*
*A: Males*

| | **Exposure concentration** | | | |
|---|---|---|---|---|
| **ppm:** | **0** | **62.5** | **125** | **250** |
| **mg/m³:** | **0** | **314** | **629** | **1,258** |
| *Lung:* | | | | |
| Bronchiole, vacuolization cytoplasmic | 0/50 | 18/50** (1.7)[a] | 19/49** (1.7) | 17/49** (1.8) |
| Bronchiole, regeneration | 1/50 (1.0) | 44/50** (1.0) | 38/49** (1.3) | 47/49** (1.6) |
| Bronchiole, necrosis | 0/50 | 0/50 | 0/49 | 1/49 (3.0) |
| *Nose:* | | | | |
| Respiratory epithelium, vacuolization cytoplasmic | 0/50 | 12/50** (1.8) | 19/50** (1.9) | 20/50** (2.2) |
| Respiratory epithelium, hyperplasia | 16/50 (1.3) | 29/50** (2.0) | 23/50 (2.0) | 26/50* (2.7) |
| Olfactory epithelium, metaplasia, respiratory | 0/50 | 7/50** (1.6) | 6/50* (1.3) | 3/50 (1.3) |
| Olfactory epithelium, atrophy | 2/50 (2.0) | 4/50 (2.3) | 7/50 (2.3) | 4/50 (1.8) |
| *Larynx:* | | | | |
| Vacuolization cytoplasmic | 0/48 | 5/50* (1.4) | 10/48** (1.1) | 11/50** (1.6) |
| *Trachea:* | | | | |
| Vacuolization cytoplasmic | 0/49 | 15/50** (1.5) | 24/47** (1.8) | 24/50** (2.3) |

*B: Females*

| | **Exposure concentration** | | | |
|---|---|---|---|---|
| **ppm:** | **0** | **62.5** | **125** | **250** |
| **mg/m³:** | **0** | **314** | **629** | **1,258** |
| *Lung:* | | | | |
| Bronchiole, vacuolization cytoplasmic | 0/50 | 3/50 (1.7) | 4/50 (1.5) | 3/50 (1.3) |
| Bronchiole, regeneration | 0/50 | 45/50** (1.2) | 43/50** (1.3) | 49/50** (1.6) |
| Bronchiole, necrosis | 0/50 | 0/50 | 1/50 (3.0) | 0/50 |
| *Nose:* | | | | |
| Respiratory epithelium, vacuolization cytoplasmic | 0/50 | 3/50 (1.3) | 5/50* (1.6) | 8/50** (1.6) |
| Respiratory epithelium, hyperplasia | 11/50 (1.1) | 25/50** (1.4) | 28/50** (1.5) | 27/50** (1.7) |
| Olfactory epithelium, metaplasia, respiratory | 0/50 | 4/50 (1.0) | 5/50* (1.0) | 14/50** (1.1) |
| Olfactory epithelium, atrophy | 0/50 | 0/50 | 0/50 | 6/50* (1.3) |
| *Larynx:* | | | | |
| Vacuolization cytoplasmic | 0/50 | 3/50 (1.3) | 2/50 (2.0) | 2/50 (2.5) |
| *Trachea:* | | | | |
| Vacuolization cytoplasmic | 0/50 | 8/49** (1.5) | 7/50** (1.9) | 4/50 (2.0) |

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
[a] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

*Table 25. Incidences of neoplasms in female B6C3F1/N mice exposed to 1-bromopropane via inhalation for 2 years (17, 50).*

| | **Exposure concentration** | | | | **Historical control data neoplasms[a]** |
|---|---|---|---|---|---|
| **ppm:** | **0** | **62.5** | **125** | **250** | |
| **mg/m³:** | **0** | **314** | **629** | **1,258** | |
| *Lung:* | | | | | |
| Alveolar/bronchiolar adenoma, multiple | 0/50 | 0/50 | 0/50 | 2/50 | |
| Alveolar/bronchiolar adenoma (includes multiple) | 1/50[b] | 6/50 | 4/50 | 10/50** | 18/350 (5.1% ± 3.8%; range 2%-12%) |
| Alveolar/bronchiolar carcinoma, multiple | 0/50 | 2/50 | 1/50 | 1/50 | |
| Alveolar/bronchiolar carcinoma (includes multiple) | 0/50 | 7/50** | 5/50* | 4/50 | 9/350 (2.6% ± 2.8%; range 0%-6%) |
| Alveolar/bronchiolar adenoma or carcinoma combined | 1/50[c] | 9/50** | 8/50* | 14/50** | 27/350 (7.7% ± 3.6%; range 2%-12%) |

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
[a] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet in B6C3F1/N mice (7 studies in total; 2001-2003)
[b] overall exposure-related trend (P=0.007) by the Poly-3 test
[c] overall exposure-related trend (P<0.001) by the Poly-3 test

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