TOXICITY ASSESSMENT OF BROMINATED HALOACETIC ACIDS

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A toxicological evaluation was undertaken to identify the most sensitive point of departure (PoD) for each brominated haloacetic acid, which was then used to determine a health-based guidance value (HBGV), from which a drinking water guideline value (GV) was derived.

Literature Search

Toxicological data were collated from several sources. Publicly available data from the following international and national bodies were collated, using multiple chemical identifiers, including CAS and EC numbers, to ensure a comprehensive search:

- European Chemicals Agency (ECHA)
- Committee on Toxicity (COT)
- European Food Safety Authority (EFSA)
- Organisation for Economic Co-operation and Development (OECD)
- Joint Expert Committee on Food Additives (JECFA)
- World Health Organisation (WHO), including the International Programme on Chemical Safety (IPCS) and Environmental Health Criteria (EHC) Monographs
- Agency for Toxic Substances and Disease Registry (ATSDR)
- US Environmental Protection Agency (US EPA)
- National Toxicology Program (NTP)
- Health Canada
- Australian Industrial Chemicals Introduction Scheme (AICIS)

A standard assessment template was populated for each chemical.

Where available, authoritative reviews and HBGVs derived b authoritative bodies were used to ensure that reliable, peer reviewed data have been used. In the absence of HBGVs derived by authoritative bodies, data presented in authoritative reviews were used and preliminary HBGVs were derived.

Hazard Data

Data on the most sensitive hazards associated with each brominated haloacetic acid following oral exposure were collected. The critical studies and endpoints were collated from each authoritative body, as well as published HBGVs (tolerable/acceptable daily intakes (TDI/ADI), reference doses (RfD) or derived no effect levels (DNEL)) from authoritative reviews where available. If no HBGVs were available, a provisional PoD[1] (No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL) or Benchmark Dose (BMD[2])) and HBGV was determined based on toxicity data cited in the authoritative body reports.

The HBGVs were derived based on the most sensitive POD and using uncertainty factors (UFs) to account for interspecies differences, intraspecies variabilities, differences in study quality and duration and severity of endpoint.

[1] The NOAEL is the highest tested dose at which no adverse effects were observed in a toxicity study. If a NOAEL cannot be determined due to observed effects at the lowest dose tested, the LOAEL (the lowest dose at which adverse effects are identified) may be determined.

[2] The BMD is the tested dose that causes a predetermined change in response for an adverse effect. This change is response is known as the benchmark response (BMR) and is usually a 5% or 10% change in response rate when compared to a control group.

In cases where insufficient toxicological data were available to derive a HBGV, a read across approach was used, which used data from surrogate chemicals to predict the toxicity of the target chemical.

For each brominated haloacetic acid, the HBGV was based on the most sensitive human health endpoint. For chemicals known to have a carcinogenic potential, the risk assessment considered both a cancer- and non-cancer endpoint.

Dibromoacetic acid (DBAA)

The WHO IPCS derived a TDI of 20 µg/kg bw/day based on reproductive toxicity in male rats (IPCS, 2000). However, other authoritative bodies disregarded this TDI as only male reproductive endpoints were measured in the study.

In the initial statement of reasons, the California Office of Environmental Health Hazard Assessment (OEHHA) derived a no significant risk level (NRSL)[3] of 2.8 µg/day {OEHHA, 2008 #12}, based on the NTP carcinogenicity study in rodents entitled 'Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)' (NTP, 2007; OEHHA, 2020).

The chronic toxicity/carcinogenicity study was carried out in male and female mice (n=50/sex/dose) administered doses of 0, 50, 500 or 1000 mg/L DBAA (equivalent to 0, 4, 45 or 87 mg/kg bw/day in males and 0, 2, 35 or 65 mg/kg bw/day in females) in drinking water for 2 years. There was a statistically significant increase in the incidence of hepatocellular adenomas, hepatocellular carcinomas and hepatoblastomas in male mice in all dose groups (NTP, 2007; OEHHA, 2020).

A human cancer slope factor (CSF) of 0.25 mg/kg bw/day was calculated for a 70 kg adult using a linear multi-stage model and used as the basis to derive the NSRL of 2.8 µg/day for 1 excess cancer in 100,000 people (OEHHA, 2020). Comments from the public consultation and the final statement of reasons for this derivation have still to be published.

OEHHA also derived health-protective concentrations for cancer and non-cancer effects i.e. the concentration that protects against carcinogenic and non-carcinogenic effects of a chemical in tap water (OEHHA, 2022).

For non-cancer effects, an acceptable daily dose (ADD) of 0.003 mg/kg bw/day was determined from a LOAEL of 1 mg/kg bw/day, based on testicular lesions and decreased incidence of morphologically normal sperm in male rabbits. The LOAEL was divided by an UF of 3000 to give the ADD of 0.003 mg/kg bw/day (Veeramachaneni et al. (2007) cited in OEHHA (2022)). The resulting health-protective concentration was 5 µg/L, calculated using an 80% allocation of the ADD to drinking water and daily intake of the chemical from tap water of 0.053 L/kg-day.

For cancer effects, the human CSF of 0.25 mg/kg bw/day was converted to a health-protective concentration of 0.03 µg/L, using a total lifetime exposure of 0.129 L/kg-day. This health-protective concentration was selected as the Public Health Goal (PHG)[4]. It was noted by OEHHA that the cancer PHG would also protect against non-cancer effects (OEHHA, 2022).

[3] The NSRL is defined by OEHHA as part of the Proposition 65 regulation is one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}. The NSRL for a carcinogen is calculated by estimating the human cancer potency of the chemical and taking into account differences in body size between humans and animals.

[4] A PHG is the level of a chemical contaminant in drinking water that does not pose a significant risk to health. PHGs are not regulatory standards. For carcinogens, the PHGs are set at a level where the cancer risk is one per one million persons exposed over a 70-year lifetime.

The NTP (2007) study is selected as the critical study for the derivation of a drinking water GV for use in the UK. The most sensitive effect was an increase in the incidence of multiple hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) in male mice in all dose groups. NTP do not determine a point of departure but considered the data to show clear evidence of carcinogenicity.

A LOAEL of 4 mg/kg bw/day could be determined based on hepatocellular adenoma, carcinoma and/or hepatoblastoma and alveolar/ bronchiolar adenoma. OEHHA derived a lower confidence limit of the BMD (BMDL05) of 1.25 mg/kg bw/day based on hepatocellular adenoma, carcinoma and/or hepatoblastoma data.

To derive a provisional TDI, an UF of 3000 (recommended by EFSA for a genotoxic carcinogen when using a BMDL05 (EFSA, Date unknown)) could be applied to the BMDL05 of 1.25 mg/kg bw/day to give a provisional TDI of 0.4 µg/kg bw/day.

Based on a 60 kg adult drinking 2 L of water per day, and using a 20 % allocation of the TDI to drinking water, the **drinking water GV would be 3 µg/L**. This GV based on carcinogenic effects would also be protective for non-carcinogenic effects.

Bromochloroacetic acid (BCAA)

In their initial statement of reasons, the OEHHA derived a NRSL of 0.74 µg/day (OEHHA, 2010), based on the NTP carcinogenicity study in rodents entitled 'Toxicology and Carcinogenesis Studies of Bromochloroacetic Acid (CAS No. 5589-96-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)' (NTP, 2009; OEHHA, 2019a).

The chronic toxicity/carcinogenicity study was carried out in male and female mice (n=50/sex/dose) administered doses of 0, 250, 500 or 1000 mg/L BCAA (equivalent to 0, 25, 50 or 90 mg/kg bw/day in males and 0, 15, 30 or 60 mg/kg bw/day in females) in drinking water for 2 years. There was a statistically significant increase in the incidence of combined hepatocellular adenomas, carcinomas and hepatoblastomas in male mice in all dose groups, and a statistically significant increase in combined hepatocellular adenomas and carcinomas in female mice in all dose groups (NTP, 2009; OEHHA, 2019a).

A human CSF of 1 mg/kg bw/day was calculated for a 70 kg adult using a multistage polynomial model for cancer and used as the basis of the NSRL for 1 excess cancer in 100,000 people (OEHHA, 2019a). It is noted that in order to achieve sufficient goodness of fit in modelling of female mouse liver tumour data, the top two dose groups were removed from the analysis by OEHAA.

In the public consultation of final statement of reasons, comments were made regarding the use of an excess lifetime cancer risk of 1 in 100,000; the uncertainty in estimating a CSF based on liver tumour data when all dose groups had a tumour response of 90-100 % and lack of dose response information, leading to considerable uncertainty of the BMDL05; the use of a BMDL05 rather than BMDL10 in the NSRL derivation; the deviation from traditional methods of expressing tumour data i.e. comparing animals with tumours against those with live animals at the time of the occurrence of the first tumour rather than the total number of animals in the group, which was deemed concerning; the human relevance of the mouse tumours being debatable; and the allometric scaling factor used for mice being over conservative leading to an overestimation of the cancer risk of BCAA. OEHHA provided responses to all comments to justify their approach.

BCAA was not included in the latest publication of PHGs from OEHHA and therefore no health-protective concentrations have been determined for BCAA (OEHHA, 2022).

The NTP (2009) study is selected as the critical study for the derivation of a drinking water GV for use in the UK. The most sensitive effect was an increase in the incidence of hepatocellular adenoma and carcinoma in male and females in all dose groups, and hepatoblastoma in males

in all dose groups. NTP do not determine a PoD but considered the data to show sufficient evidence of carcinogenicity.

A LOAEL of 15 mg/kg bw/day could be determined based on hepatocellular adenoma and carcinomas in female mice.

To derive a provisional TDI, an UF of 1000 (10 for inter- and intra-species differences and 10 for use of a LOAEL and the cancer endpoint) could be applied to the LOAEL of 15 mg/kg bw/day to give a provisional TDI of 15 µg/kg bw/day.

Based on a 60 kg adult drinking 2 L of water per day, and using a 20 % allocation of the TDI to drinking water, the **drinking water GV would be 100 µg/L**. This GV based on carcinogenic effects would also be protective for non-carcinogenic effects.

Bromodichloroacetic acid (BDCAA)

In their initial statement of reasons, the OEHHA derived a NRSL of 0.95 µg/day {OEHHA, 2016 #13}, based on the NTP carcinogenicity study in rodents entitled 'Toxicology Studies of Bromodichloroacetic Acid (CAS No. 71133-14-7) in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F1/N Mice (Drinking Water Studies)' (NTP, 2015; OEHHA, 2019b).

The chronic toxicity/carcinogenicity study was carried out in male and female mice (n=66/sex/dose) administered doses of 0, 250, 500 or 1000 mg/L BDCAA (equivalent to 0, 11, 21 or 43 mg/kg bw/day in males and 0, 13, 28 or 57 mg/kg bw/day in females) in drinking water for 2 years. There was a statistically significant increase in the incidence of malignant mesothelioma in male rats in all dose groups and a significant increase in mammary gland fibroadenoma and carcinoma was seen in female rats in all dose groups (NTP, 2015; OEHHA, 2019b).

A human CSF of 0.74 mg/kg bw/day was calculated for a 70 kg adult using a multisite carcinogenicity model and used as the basis of the NSRL for 1 excess cancer in 100,000 people (OEHHA, 2019b). It is noted that in order to achieve sufficient goodness of fit in modelling of male rat liver tumour data and female rat mammary gland tumour data, the top dose group was removed from the analysis by OEHHA. Comments from the public consultation and the final statement of reasons have still to be published.

The NTP (2015) study is selected as the critical study for the derivation of a drinking water GV for use in the UK. The most sensitive effect was an increased incidence of hepatocellular carcinoma and hepatoblastoma in male rats in all dose groups. NTP do not determine a point of departure but considered the data to show sufficient evidence of carcinogenicity.

A LOAEL of 11 mg/kg bw/day could be determined based on hepatocellular carcinomas in male rats.

To derive a provisional TDI, an UF of 1000 (10 for inter- and intra-species differences and 10 for a cancer endpoint) could be applied to the LOAEL of 11 mg/kg bw/day to give a provisional TDI of 11 µg/kg bw/day.

Based on a 60 kg adult drinking 2 L of water per day, and using a 20 % allocation of the TDI to drinking water, the **drinking water GV would be 73 µg/L (rounded to 70 µg/L)**. This GV based on carcinogenic effects would also be protective for non-carcinogenic effects.

Monobromoacetic acid (MBAA)

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registrants derived a DNEL of 50 µg/kg bw/day based on reproductive toxicity in female rats. The prenatal developmental toxicity study (OECD 416) was carried out in female Wistar rats (n=24/dose) administered doses of 0, 4.7, 11.6 and 21.9 mg/kg bw/day via drinking water from GD6-15. The

most sensitive effect was maternal toxicity (a decrease in body weight change) seen in the mid dose group.

A NOAEL of 4.7 mg/kg bw/day was derived based on maternal toxicity. To derive a DNEL, an UF of 100 (4 for interspecies differences (allometric scaling), 2.5 for other interspecies differences, 10 for intraspecies differences) was applied to the NOAEL to give a DNEL of 50 µg/kg bw/day.

OEHHA derived a health-protective concentration for non-cancer effects. They did not identify carcinogenicity studies for MBAA.

For non-cancer effects, an ADD of 0.017 mg/kg bw/day was determined. A NOAEL of 5 mg/kg bw/day was derived based on muscular degeneration and pulmonary oedema in pigs, which was divided by an UF of 3000 to give the ADD of 0.017 mg/kg bw/day (Dalgaard (Dalgaard-Mikkelsen et al. (1955) cited in OEHHA (2022)). The resulting PHG was 25 µg/L.

The prenatal developmental toxicity study (unnamed study, 1993) is selected as the critical study for the derivation of a drinking water GV for use in the UK

Based on a 60 kg adult drinking 2 L of water per day, and using a 20 % allocation of the TDI to drinking water, the **drinking water GV would be 333 µg/L (rounded to 330 µg/L)**.

Tribromoacetic acid (TBAA)

No toxicity data were identified for TBAA. As TBAA is primarily metabolised to DBAA (NTP, 2021) (by reductive dehalogenation), toxicity data for DBAA can be used as a surrogate for TBAA in a read-across approach

To derive a provisional TDI, an UF of 6000 (3000 recommended by EFSA for a genotoxic carcinogen when using a BMDL05 and 2 for use of read-across) could be applied to the BMDL05 of 1.25 mg/kg bw/day to give a provisional TDI of 0.2 µg/kg bw/day.

Based on a 60 kg adult drinking 2 L of water per day, and using a 20 % allocation of the TDI to drinking water, the **drinking water GV would be 1 µg/L**. This GV based on carcinogenic effects would also be protective for non-carcinogenic effects.

Chlorodibromoacetic acid (CDBAA)

No toxicity data were identified for CDBAA. As CDBAA is metabolised to BCAA (NTP, 2021) (by reductive dehalogenation), toxicity data for BCAA can be used as a surrogate for CDBAA in a read-across approach.

To derive a provisional TDI, an UF of 1000 (10 for inter- and intra-species differences,10 for use of a LOAEL and the cancer endpoint and 2 for using read-across) could be applied to the LOAEL of 15 mg/kg bw/day to give a provisional TDI of 15 µg/kg bw/day.

Based on a 60 kg adult drinking 2 L of water per day, and using a 20 % allocation of the TDI to drinking water, the **drinking water GV would be 50 µg/L**. This GV based on carcinogenic effects would also be protective for non-carcinogenic effects.

Summary

A summary of all GV and data are provided in the summary table below.

Summary table

Chemical	**POD**	**Effect**	**POD value (mg/kg bw/day)**	**UF**	**Provisional TDI (µg/kg bw/day)**	**GV (µg/L)**
DBAA	BMDL05	Liver carc	1.25	3000	0.4	3
BCAA	LOAEL	Liver carc	15	1000	15	100
BDCAA	LOAEL	Liver carc	23	1000	23	73
MBAA	NOAEL	Maternal tox	4.7	100	50	333
TBAA read-across from DBAA	BMDL05	Liver carc	1.25	6000	0.2	1
CDBAA read-across from BCAA	LOAEL	Liver carc	15	2000	7.5	50

Abbreviations

ADD	Acceptable daily dose
ADI	Acceptable daily intake
AICIS	Australian Industrial Chemicals Introduction Scheme
ATSDR	Agency for Toxic Substances and Disease Registry
BCAA	Bromochloroacetic acid
BDCAA	Bromodichloroacetic acid
BMD	Benchmark Dose
BMR	Benchmark response
CDBAA	Chlorodibromoacetic acid
COT	Committee on Toxicity
CSF	Cancer slope factor
DBAA	Dibromoacetic acid
DNEL	Derived no effect level
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
GV	Guideline value
HBGV	Health-based guidance value
IPCS	International Programme on Chemical Safety
JECFA	Joint Expert Committee on Food Additives
LOAEL	Lowest Observed Adverse Effect Level
MBAA	Monobromoacetic acid
NOAEL	No Observed Adverse Effect Level
NSRL	No significant risk level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEHHA	California Office of Environmental Health Hazard Assessment
PHG	Public Health Goal
POD	Point of departure
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference doses
TBAA	Tribromoacetic acid
TDI	Tolerable daily intake
UF	Uncertainty factors

US EPA	US Environmental Protection Agency
WHO	World Health Organisation

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