

# Risks to human and animal health from the presence of bromide in food and feed

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**Abstract**

The European Commission mandated EFSA to assess the toxicity of bromide, the existing maximum residue levels (MRLs), and possible transfer from feed into food of animal origin. The critical effects of bromide in experimental animals are on the thyroid and central nervous system. Changes in thyroid hormone homeostasis could result in neurodevelopmental toxicity, among other adverse effects. Changes in thyroid hormone concentrations and neurophysiological parameters have also been observed in experimental human studies, but the evidence was limited. Dose–response modelling of decreased blood thyroxine concentrations in rats resulted in a reference point of 40 mg/kg body weight (bw) per day. The Scientific Committee established a tolerable daily intake (TDI) of 0.4 mg/kg bw per day and an acute reference dose (ARfD) of 0.4 mg/kg bw per day to protect against adverse neurodevelopmental effects. The TDI value is supported by the results of experimental human studies with a NOAEL of 4 mg/kg bw per day and 10-fold interindividual variability. The TDI and ARfD are considered as conservative with 90% certainty. Insufficient evidence related to the toxicological effects of bromide was available for animals, with the exception of dogs. Therefore, the reference point of 40 mg/kg bw per day was extrapolated to maximum safe concentrations of bromide in complete feed for other animal species. Bromide can transfer from feed to food of animal origin, but, from the limited data, it was not possible to quantify the transfer rate. Monitoring data exceeded the current MRLs for some food commodities, generally with a low frequency. A conservative safety screening of the MRLs indicated that the TDI and ARfD are exceeded for some EU diets. Dietary exposure assessment for animals was not feasible due to insufficient data. The Scientific Committee recommends data be generated to allow robust dietary exposure assessments in the future, and data that support the risk assessment.

**KEYWORDS**

animal health, bromide, feed, health-based guidance value, human health, mode of action, MRL

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## SUMMARY

The European Commission mandated EFSA to assess the toxicity of bromide for humans and animals, to derive toxicological reference values, to assess the existing maximum residue levels (MRLs) and the possible carry over from feed into food of animal origin.

Both food-producing and non-food-producing animals were within the scope of the mandate. Algae and seaweeds were the primary feed materials of interest for exposure assessment relevant to animal health. Bromine-containing compounds, where bromine is covalently bound and/or possess toxicological properties that are not attributable to the bromide ion (e.g. methyl bromide, brominated flame retardants, brominated vegetable oils) were not relevant to the hazard assessment.

Bromine is naturally occurring and widely distributed in the environment as bromide. Bromide can be present in food and feed as a result of natural occurrence, environmental contamination from anthropogenic activity, use of certain bio-cidal products and use in veterinary medicinal products in food-producing animals. When measuring bromide in food and feed, it is not possible to determine the contributions from these different sources.

Most modern studies use chromatographic methods that are coupled to mass spectrometry for determination of bromide. These methods measure total elemental bromine and are more suitable than traditional methods using gravimetric analysis, titration with silver nitrate, or photometry, which are not generally sufficiently specific or sensitive for the determination of bromide in food and feed. When combined with a chromatographic separation, mass spectrometric methods can distinguish between bromide and compounds that contain bromine.

Bromide concentrations in seawater are generally in the range of 65 mg/L to well over 80 mg/L. Concentrations of bromide in fresh water are lower and typically range from trace amounts to about 0.5 mg/L and up to around 1 mg/L in desalinated waters.

The bromide ion is stable and water-soluble. It can therefore be assumed to migrate from food when it is cooked in water, assuming that the concentration in the food is greater than in the water that is used for cooking. If water is lost from food as it is cooked or processed, then it can be assumed that bromide will be lost with that water, but if fats or oils are lost during cooking or processing, then the bromide may remain in the food and hence the concentration could increase.

In humans, bromide bioavailability from the gastrointestinal tract is almost complete ( $96 \pm 6\%$ ), similar to rodents but unlike dogs and horses (up to 46% and 38%, respectively). Bromide is primarily eliminated through the kidneys with an elimination half-life of  $285 \pm 34$  h in humans.

There is evidence that bromide can transfer from feed to food of animal origin but from the limited data, it is not possible to quantify the transfer rate. Uncertainty remains over the impact of feeding macroalgae to ruminants on levels of bromide in milk or meat, and whether any increase is due to direct transfer or bromide from the feed or conversion of bromoform to bromide.

Bromide has low acute toxicity in experimental animals. In repeat dose studies, mainly in rats, bromide has shown evidence of effects on the central nervous system (CNS), kidneys, thyroid and other endocrine organs, and on bodyweight gain. The effects occurring at the lowest doses are on thyroid hormone homeostasis and the CNS. Effects on the thyroid and nervous system in dams were also reported in reproductive and developmental studies in rats. Reported neurotoxicity was generally related to clinical signs, such as abnormal gait, at doses in excess of 100 mg Br<sup>-</sup>/kg bw per day. In one rat study, impaired performance in detailed functional observations was reported at doses of 184 mg Br<sup>-</sup>/kg bw per day, but not at 82 mg Br<sup>-</sup>/kg bw per day, with no associated histopathological findings. Based on the absence of any indication for genotoxicity, the negative result of a carcinogenicity study with design limitations and the mode of action (MOA) for thyroid effects, bromide is not expected to be carcinogenic to humans.

Effects on the thyroid include changes in serum thyroid hormone concentrations, particularly decreased serum total thyroxine (tT4), and triiodothyronine (tT3), and increased thyroid stimulating hormone (TSH), as well as increases in absolute/relative thyroid weights with morphological and histological changes. There is evidence that iodine deficiency decreases the iodine/bromide ratio in the thyroid and may increase the effects of bromide. The reported effects on the thyroid are supported by *in vitro* evidence of an MOA involving bromide competition of sodium/iodide symporter (NIS)-mediated iodide uptake in the thyroid. Based on the adverse outcome pathway, it is possible that changes in thyroid hormones may result in neurodevelopmental toxicity, depending on the timing, duration and effect size of thyroid hormone change.

In human studies, neurophysiological changes captured in electroencephalogram (EEG), including decrease in  $\delta 1$ - and  $\delta 2$ -activities, increased  $\beta$ -activities and mean frequency (mobility parameter) and visual evoked responses, have been observed in groups of women of childbearing age given capsules with 9 mg Br<sup>-</sup>/kg bw daily for 12 weeks. Statistically significant increases in serum-free T4 (fT4), tT4 and tT3 were observed at the end compared to concentrations at the start of a study in females receiving bromide capsules at 9 mg/kg bw per day, but all concentrations remained within normal limits. However, an increase in TSH, but no change in tT4 was reported in a follow-up study. The NOAEL from these studies was 4 mg/kg bw per day. The Scientific Committee noted that there was no explanation for the increase in mean tT4 concentration in one of these studies, but that the increase in mean TSH concentration is indicative of effects on the hypothalamic–pituitary–thyroid axis. The evidence obtained from studies in humans was not considered sufficient as a basis for establishing a health-based guidance value (HBGV).

Altered thyroid hormone (tT4) concentrations in rats were considered to be an early critical effect of bromide. Benchmark dose (BMD) modelling was performed on the data for decreased blood tT4 concentrations in studies conducted in rats in order to provide a potential reference point, with a benchmark response (BMR) of 20%. From the results of the modelling, a reference point of 40 mg/kg bw per day was identified for establishing a human HBGV. Based on the weight of evidence

and applicable uncertainties, the Scientific Committee established a tolerable daily intake (TDI) of 0.4 mg/kg bw per day. An uncertainty factor of 100 was applied, including interspecies toxicokinetic differences (4), interindividual variability (10) and uncertainty in the database as described in the uncertainty analysis (2.5). Based on the assumption of similar sensitivity between rats and humans for the endpoint selected, an interspecies uncertainty factor for toxicodynamic differences was not required. This TDI is supported by the NOEL of 4 mg Br<sup>-</sup>/kg bw per day from two studies in humans including a default uncertainty factor of 10 for interindividual variability. Considering the critical role that modest and transient perturbations of the thyroid hormones play in neurodevelopment during critical developmental windows, an acute reference dose (ARfD) equal to the TDI was established. Individuals who are iodine deficient may not be adequately protected by the TDI and ARfD. The impact of iodine deficiency is out of the scope of this assessment and warrants attention of public health authorities.

No sufficient relevant evidence related to the toxicological effects of bromide was available that was generated directly in specific species of food-producing and non-food-producing animals, with the exception of dogs. Effects reported in several species following bromide intake were limited to overt toxicity, whereas data on thyroid effects were available only for dogs. Therefore, the Scientific Committee adopted an extrapolation approach developed by the EFSA FEEDAP Panel to estimate maximum safe concentrations in complete feed (with 88% dry matter) for food-producing and non-food-producing species based on the reference point used to establish the TDI. For dogs, a maximum safe concentration of bromide of 103 mg/kg complete feed was established based on data in dogs. For cats, no maximum safe concentration in feed for bromide could be established due to the idiosyncratic response to bromide in this species.

A total of 46,965 bromide analytical results in matrices of foods intended for human consumption, i.e. raw agricultural commodities and processed food items collected in 29 European countries between 2013 and 2022 fulfilled the quality criteria applied and were considered in the assessment. The highest mean bromide concentrations were measured in the FoodEx2 food category 'Coffee, cocoa, tea and infusions', and in particular in dry forms of 'flowers used for herbal infusions' (i.e. herbal infusions from flowers) and 'herbal infusion materials from leaves and herbs'. Only a limited number of analytical data on bromide were available for feed ( $n=57$ ).

As requested in the terms of reference, the occurrence levels of bromide obtained from monitoring data were compared to the current MRLs of bromide in foods. The MRLs were exceeded for a few raw agricultural commodities, however, for the majority of them the exceedances were at low frequencies (< 10% of samples). The MRLs were exceeded with higher frequency in Brazil nuts (38% of samples), and in the food commodities of animal origin (up to 100% of samples of pig meat).

An exposure assessment for consumers was not requested in the terms of reference. A conservative screening of the MRLs was conducted for a hypothetical scenario in which bromide is present in foods at the concentrations of the MRLs and assuming that all such foods are consumed daily over the whole lifetime. This approach is defined as a high-level screening method and cannot be considered as a standard dietary exposure assessment. The chronic and acute outcomes of this scenario were compared to the TDI and ARfD, respectively. In the chronic calculation, the TDI was exceeded in 29 out of the 36 diets assessed by the model, with the highest exceedance calculated for Dutch toddlers, up to 528% of the TDI. Of the 29 diets, 17 covered adults or the general population. In the acute calculation, only the adult population is considered as relevant because the ARfD is set to protect during the pregnancy, the ARfD was exceeded for 54 raw commodities and for 31 processed commodities, with the highest exceedance calculated for boiled beetroots (486% of the ARfD). An additional screening was performed in which the MRL values were replaced with available monitoring data (considering upper bound and lower bound estimations) and the outcomes were compared to the TDI and ARfD. In the chronic calculations, the TDI was exceeded in one (lower bound) or two (upper bound) of the 36 diets assessed, with the highest exceedances, up to 127% of the TDI (lower bound) and up to 188% of the TDI (upper bound). In the acute calculations, according to the lower bound scenario, the ARfD was exceeded for two raw and two processed commodities (up to 151% for unprocessed chards) while in the upper bound scenario, the ARfD was exceeded for four raw and three processed commodities (up to 203% for watermelons). Data gaps were identified for drinking water and foods such as fish, other seafood, seaweed and algae, which are expected to be among the major contributors to dietary bromide intake in humans and/or animals, considering the presence of bromide in seawater.

Dietary exposure assessment and risk characterisation for food-producing and non-food-producing animals were not feasible due to lack of sufficient concentration data in feed materials and water for drinking.

The uncertainties associated with all areas of the assessment were identified. Based on expert judgement and a semi-formal Expert Knowledge Elicitation, the Scientific Committee concluded with 90% certainty that the TDI and ARfD are conservative. The Scientific Committee could not conclude on uncertainties in the risk to human health because an exposure assessment was not included in this opinion. The Scientific Committee could not characterise the uncertainty in the risk to animal health due to limitations in the toxicity data and the lack of data for exposure assessment.

The Scientific Committee recommends that, for better characterisation of the hazard of bromide, key additional studies be performed with relevant thyroid endpoints, according to agreed quality standards, including an in vivo developmental neurotoxicity study, and observational and/or experimental human studies. The Scientific Committee also recommends that further research be encouraged to better understand the MOA of bromide and identify other possible adverse outcomes. The Scientific Committee recommends that, for a complete risk assessment of bromide, dietary exposure assessments for humans and animals be performed. For this purpose, it is recommended that occurrence data for food and feed materials be generated and submitted by data providers, using more sensitive analytical methods. In particular, occurrence data are needed for fish and seafood; infant formulae and drinking water; algae and other aquatic animals and their products used as feed materials. Lastly, the Scientific Committee recommends that data related to transfer of bromide from feed to food of animal origin be generated.



## 1 | INTRODUCTION

### 1.1 | Background and terms of reference as provided by the requestor

#### 1.1.1 | Background

##### Bromide ion from the use of methyl bromide in plant protection products

Methyl bromide, formerly used as a post-harvest fumigant, has not been approved since 2008 in the EU. The maximum residue levels (MRLs) are set for bromide ion which is the main metabolite of methyl bromide.

In 1988, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) reconfirmed the Acceptable Daily Intake (ADI) of 1.0 mg/kg bw for inorganic bromide, which was initially evaluated in 1966.

In 2013, EFSA provided a reasoned opinion on the review of the existing MRLs for methyl bromide in compliance with Article 12(1) of Regulation (EC) No 396/2005. The review also considered bromide ion as the main metabolite and assessed the Codex maximum limits (CXL) set for bromide ion.

EFSA concluded that the default MRL of 0.01 mg/kg for methyl bromide, as defined by Regulation (EC) No 396/2005 - and compliant with the Codex guideline levels for methyl bromide - provides a satisfactory level of protection for the European consumers, but that it was not demonstrated that the default MRL can be achieved in routine enforcement. For bromide ion, specific CXLs were available, but data were insufficient to determine whether the CXLs were derived from the pesticide use of methyl bromide or whether they were based on the natural occurrence of bromide ion.

EFSA considered that the ADI of 1.0 mg/kg bw established by JMPR for bromide ion, the main metabolite of methyl bromide, was not sufficiently supported by data and that the necessity of an acute reference dose (ARfD) for bromide ion should be re-assessed. Acute exposure calculations were not carried out because an ARfD was not available for this compound. As the toxicological reference values derived by JMPR and considered in this calculation (of the ADI) were not fully supported by EFSA, the risk assessment for bromide ion was subject to a high level of uncertainty.

In 2021, in the Standing Committee on the Food Chain and Animal Health, section Phytopharmaceuticals – Pesticides Residues, Member States requested to revise the MRLs for substances which occur naturally but for which Annex IV of Regulation (EC) No 395/2005 inclusion is not recommended. Bromide ion was selected as a first priority.

##### Bromide from biocidal uses

In 2019, the European Chemicals Agency (ECHA) opinion on the application for approval of the active substance 2,2-dibromo-2-cyanoacetamide (DBNPA) concluded that DBNPA is considered to have endocrine-disrupting properties with respect to humans as it meets the criteria set out in section A of Regulation (EU) No 2017/2100. The conclusion was based on the observed adverse effects in the thyroid gland in the studies on rats and dogs combined with data obtained from a literature search conducted on bromide effects on the thyroid. Bromide may substitute iodide in the sodium/iodide symporter of the thyroid, thus creating a relative iodide insufficiency for further synthesis of thyroid hormones. This shows a link between the observed adverse effects in the thyroid and endocrine activity, which is relevant for humans and non-target species.

##### Bromide ion in feed

During the discussions at the Standing Committee on the Food Chain and Animal Health, section Animal Nutrition on the update of the Feed Catalogue, concern was raised for animal and public health as regards the presence of bromide ion in feed, and in particular in algae and seaweed and derived products, and the possible carry over into food of animal origin. A discussion on possible regulatory measures on the presence of bromide ion in feed in the frame of Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in feed may be needed depending on the outcome of this assessment.

#### 1.1.2 | Terms of reference

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide an opinion which should address the following points:

- to assess the general toxicity of bromide ion for humans and animals based on the available data, including scientific literature, data previously evaluated by JMPR (if accessible), and any further information/data that is accessible to EFSA (e.g. data used by ECHA to conclude that 2,2-dibromo-2-cyanoacetamide [DBNPA] has endocrine-disrupting properties with respect to humans and non-target organisms pursuant to the criteria set out in Regulation (EU) No 2017/2100);
- to derive toxicological reference values for human and animal dietary risk assessment of bromide ion (if possible);
- to compare the existing MRLs for bromide ion with the available monitoring data from 2012 to 2021 and screen the safety of those MRLs (provided toxicological reference values can be derived);

- to assess the risks for animal health and transfer from feed to food of animal origin related to the presence of bromide ion in feed, in particular in algae and seaweed and derived products.

## 1.2 | Interpretation of the terms of reference

The focus of the assessment is bromide ion<sup>1</sup> in food and feed. Bromide-producing sources, such as bromine, are relevant if they contribute to levels of bromide in food and feed. Toxicological effects of bromine-containing compounds that are not attributable to bromide (e.g. methyl bromide, brominated flame retardants, brominated vegetable oils) are not relevant to the hazard assessment of the bromide ion. Bromate is relevant to the mandate only under conditions of bromide oxidation that result in bromate in animals and humans. The hazard characterisation of bromide is based on the weight of evidence from the scientific literature taking into account existing reviews by authoritative bodies. The aim is to establish a human health-based guidance value (HBGV) of relevance to chronic exposure and, if needed, acute exposure.

The levels of bromide obtained from monitoring data will be compared to the current MRLs of bromide in foods. If monitoring data are not available for all food products for which MRLs exist, appropriate data from the literature will be used. A preliminary exposure assessment will be based on the MRLs and compared to the HBGV(s). Exposure to bromide from drinking water will also be considered. A human dietary exposure assessment will not be conducted in the current assessment but may be recommended as a follow-up activity if the preliminary assessment indicates a safety concern.

Both food-producing and non-food-producing animals<sup>2</sup> are within the scope of the mandate. Algae and seaweeds are the primary sources of interest for bromide in feed. Animal dietary exposure assessment will be based on available occurrence data. Exposure to bromide from veterinary or medical products is out of scope for both animals and humans.

## 1.3 | Supporting information

### 1.3.1 | Physicochemical properties

Bromide, CAS number 24959-67-9, is an inorganic anion, Br<sup>-</sup>, with an average relative molecular mass of 79.904 g/mol. Naturally occurring bromine consists of 50.57% <sup>79</sup>Br and 49.43% <sup>81</sup>Br. It is the third in size halogen of the periodic table, between chloride and iodine (F < Cl < Br < I).

Bromide commonly exists as salts with sodium, potassium and other cations, which are usually very soluble in water. It also forms the strong acid, hydrobromic acid (HBr) and the weaker hypobromous (HOBr), bromous (HBrO<sub>2</sub>) and bromic (HBrO<sub>3</sub>) oxyacids. Basic solutions of OBr<sup>-</sup> are stable at 0°C but rapidly disproportionate to Br<sup>-</sup> and BrO<sup>3-</sup> at temperatures of about 50°C and above (Cotton & Wilkinson, 1962; WHO, 2009).

### 1.3.2 | Historical and current uses

Bromide has been used in compounds for medical applications and as part of active substances in biocidal products (e.g. disinfectants) or pesticides (fumigants). The use of methyl bromide was authorised in the European Union until 2008 as a fumigant with fungicide, herbicide, insecticide, nematocidal and rodenticide properties, either as a soil fumigant or as post-harvest treatment. The MOA of methyl bromide is based on methylation of protein S-H groups resulting in non-specific enzyme inhibition, rather than on bromide-mediated activity. Since 2008, methyl bromide has not been authorised within the EU<sup>3</sup> and there are no import tolerances currently established at EU level related to uses in third countries (EFSA, 2013a). As an ozone-depleting agent, its use has been phased out worldwide, and in 2021, all the MRLs for bromide established by the Codex Alimentarius Commission were revoked (CCPR, 2021).

In medical applications, bromide has been used in the treatment of seizures including epilepsy in humans and in animals since the 1850s (Baird-Heinz et al., 2012). In humans, use is reported mostly historically; it was widely used and was available over-the-counter through the early 20th century (Baird-Heinz et al., 2012). The efficacy of bromide alone has been questioned and it has been replaced by more efficacious treatments, but it continued to be used in children to treat severe epilepsy until more recently (Friedlander, 2000; Korinthenberg et al., 2007; Nabatame et al., 2010). Two products containing potassium bromide are still listed by EMA for human use,<sup>4</sup> one of which has been discontinued and the other (850 mg/tablet), marketed in Germany, is intended for use in children at dose levels between 40 and 70 mg/kg bw per day. Bromide is not currently listed as an authorised medicine for human use by the US FDA.

<sup>1</sup>The term 'bromide' refers to 'bromide ion' throughout the opinion, including instances where the term 'inorganic bromide' was used in the source cited.

<sup>2</sup>Animals belonging to species normally nourished, bred or kept, but not consumed by humans, except horses (Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 25.4.2008, p. 1. <https://eur-lex.europa.eu/eli/reg/2008/429/oj>.

<sup>3</sup>OJ L 258, 26.9.2008, p. 68. <https://eur-lex.europa.eu/Legal-content/EN/TXT/PDF/?uri=OJ:L:2008:258:FULL>.

<sup>4</sup><https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database>.



In veterinary medicine, bromide has been evaluated through the mutual recognition procedure (MRP) or decentralised procedure (DP) for medicines in Europe and is currently authorised by national authorities<sup>5</sup> (EMA, 1997, 1999) for use in the form of sodium or potassium bromide (tablets or capsules of 325 or 600 mg/tablet),<sup>6</sup> in food-producing (cattle) and in non-food-producing animals. Potassium bromide is prescribed mostly in dogs for the control of seizures associated with idiopathic epilepsy, a common neurologic disorder in dogs (Baird-Heinz et al., 2012), at dose levels ranging between 25 and 68 mg/kg bw per day as bromide, with an expected serum bromide concentration of 800–2000 µg/mL. It has been typically administered in conjunction with phenobarbital, although it is also used alone more recently (Baird-Heinz et al., 2012; Dewey et al., 2009; Platt & Cherubini, 2010; Trepanier, 1995).

In biocides applications, bromide compounds include inorganic salts (e.g. ammonium bromide, sodium bromide) or compounds that release bromide after application (e.g. 2,2-dibromo-2-cyanoacetamide (DBNPA) and 2-bromo-2-(bromomethyl) pentanedinitrile (DBDCB)). Some biocidal products generate bromide by reaction between two reagents (e.g. from sodium bromide and sodium hypochlorite). Among the potential bromide releasers, only DBNPA is used in biocidal products for food and feed area disinfection.

Commercially, bromide is produced from its soluble salts found in seawater, salt lakes, inland seas and brine wells. It is extracted using evaporation ponds, mostly in the United States and Israel. The mass of bromine in the oceans is about three hundred times lower than that of chloride.<sup>7</sup>

Other uses of bromide include laboratory reagents; special soaps; spectroscopy; infrared transmission; production of photography-grade silver bromide; lithography; petroleum industry fluids; pharmaceutical intermediate, in the manufacture of fibres and stabilisation of nylon.<sup>8</sup>

### 1.3.3 | Environmental levels

Bromine is widely distributed in the environment as bromide (JMPR, 1984). Bromide is commonly found alongside sodium chloride but in smaller quantities, because of their similar physical and chemical properties. Bromide concentrations in seawater are generally in the range of 65 mg/L to well over 80 mg/L whereas chloride is present at concentrations of around 18,980 mg/L (normal sea water chloride concentration), but in some places, it can be higher e.g. the Arabian Gulf where the concentration of chloride is over 23,000 mg/L (Al-Mutaz, 2000; WHO, 2009). Concentrations of bromide in fresh water are lower and typically range from trace amounts to about 0.5 mg/L. In desalinated waters, concentrations of bromide may be up to around 1 mg/L.

Flury and Papritz (Flury & Papritz, 1993) stated that bromide does not adsorb to negatively charged soil minerals which means that it moves approximately as fast as water in soil and is ideal to use as a tracer. This review collated concentrations of bromide in various rock types and water environments including rainwater. It stated that data on bromide in soils are scarce, but bromine content varies considerably ranging from as small as 0.3 up to 852 mg/kg. Larger concentrations are found in soil close to the sea and seaborne aerosols are the main natural source of bromide in terrestrial ecosystems. Those authors stated that, at that time, the three major anthropogenic releases of bromide into the environment were from mining, from emissions of 1,2-dibromoethane (a scavenger in leaded fuel), and from the use of fertilisers and pesticides in agriculture (Flury & Papritz, 1993).

Bromide levels in rainwater are variable, possibly due to factors including pollution (JMPR, 1984; Lundström & Olin, 1986; VanBriesen, 2014). In freshwater, bromide levels range from a few tens to a few hundred µg/L (Neal et al., 2007; WHO, 2009).

Natural bromide levels are enhanced by industrial pollution and by the use of agricultural chemicals. One of the largest uses of bromine in the past was in the manufacture of ethylene dibromide, the bulk of which was utilised as a scavenger of lead from petrol. Another large historical agricultural source of bromide in soil derived from the use of methyl bromide as a soil fumigant. This was applied to soil under protection (in glasshouses) or in the open for control of nematodes and other pests, weeds and microorganisms.

### 1.3.4 | Methods of analysis

Traditionally, bromides may be determined either gravimetrically (by weight analysis) or by titration with silver nitrate. In the presence of chloride and iodide, a potentiometric method may be used (as with chlorine) (Getzendaner, 1975). In the absence of iodide, bromide may be oxidised to bromine, which is then determined in the distillate. These methods, however, are not sufficiently specific or sensitive for the determination of bromide in food, and methods using modern chromatographic methods with mass spectrometry or other instrumental methods are more generally used nowadays. Inductively coupled plasma-mass spectrometric (ICP-MS) methods convert all entities containing bromine (organic

<sup>5</sup>MRI Index maintained by the Heads of EU medicines agency: <https://mri.cts-mrp.eu/portal/home>.

<sup>6</sup>Veterinary products of KBr listed in MRI: Libromide 325 mg tablets; Vetbromide 600 mg tablets.

<sup>7</sup>Bromine: Powering Science and Technologies (BSEF) available online at: <https://www.bsef.com/>.

<sup>8</sup>National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 253877, Potassium Bromide. <https://pubchem.ncbi.nlm.nih.gov/compound/Potassium-Bromide>.

compounds, bromide, etc.) into elemental constituents, i.e. bromine, and so will measure total elemental bromine that is present in the sample.

Getzendaner reviewed methods available at that time for the measurement of total bromine in foods (Getzendaner, 1975). Organic bromine, focussing at that time on fumigants such as methyl bromide, ethylene dibromide and 1,2-dibromo-3-chloropropane, was first converted to the inorganic form prior to measurement as combined total bromide. Measurement at that time was usually by titration or photometry, but it was noted that X-ray fluorescence and neutron activation analysis were becoming widely used.

There is a European standard for the determination of bromide residues, which specifies a gas chromatography (GC) method for the determination of total bromide (including some organic bromine present) as inorganic bromide in non-fatty foods.<sup>9</sup> The method is applicable to beets, carrots, chicory, endives, cereal grains, lettuce, potatoes, spinach, strawberries and tomato. The method involves taking an aqueous ethanolic extract of the test sample and evaporating it to dryness before ashing in the presence of sodium hydroxide. The ash is solubilised with sulfuric acid before treating with ethylene oxide in di-isopropyl ether. Inorganic bromide is converted to 2-bromoethanol, which is analysed by gas chromatography with electron capture detection.

Instrumental neutron activation analysis (INAA) was used to measure 17 trace metals and elements including bromine in cockles (*Anadara Granosa* L.) (Ibrahim, 1994).

The phenol red spectrophotometric method has also been used for the screening of bromide in a variety of vegetables and fungi (Baso-Cejas et al., 2007).

An ion chromatography with conductivity detection (IC-CD) method was developed for the simultaneous analysis of bromide, fluoride, chloride, nitrite, nitrate, phosphate and sulfate in edible seaweeds (Gómez-Ordóñez et al., 2010).

Methods including a digestion step by microwave-induced combustion before measurement with inductively coupled plasma-mass spectrometry (ICP-MS) have been used for the determination of total elemental bromine, chlorine and iodine in soya bean and soya products (Barbosa et al., 2013); the determination of total elemental bromine and iodine in shrimp and its parts (Hartwig et al., 2014); and the bromine and iodine content of milk whey proteins (da Silva et al., 2016). For total elemental bromine, the limit of quantification obtained by ICP-MS was seven times lower in comparison with ion chromatography determination (da Silva et al., 2016). Microwave energy was also used to assist the solubilisation of edible seaweed samples by tetramethylammonium hydroxide followed by ICP-MS for the analysis of total elemental iodine and bromine (Romarís-Hortas et al., 2009). A similar approach was used for a variety of plant-based foods (Nguyen & Ludwig, 2014).

While the ICP-MS methods measure total elemental bromine, the inclusion of capillary electrophoresis in the inductively coupled plasma-mass spectrometric method (CE-ICP-MS) allows for iodine and bromine speciation and was applied to the analysis of tomato leaves, salt and seaweed (Chen et al., 2007). This method can also distinguish between bromide and different organic and inorganic compounds containing bromine. A GC method with electron capture detection (ECD) has been used for measuring total bromine in agricultural products. An inductively coupled plasma optical emission spectrometry (ICP-OES) and ICP-MS were used to measure total elemental bromine in wheat and pea seedlings in a study on biogeochemical cycles (Shtangeeva et al., 2015).

'Eco-friendly' alternatives have been developed more recently. A 'green' analytical method developed for the determination of halogens and sulfur in pet food used microwave-induced combustion with ion chromatography and conductivity or mass spectrometric detection (IC-CD and IC-MS) (de Mello et al., 2020). A vortex-assisted matrix solid-phase dispersion was used as an eco-friendly alternative for the determination of halogens in edible seaweed (de Melo Malinowski et al., 2022).

In summary, most modern studies use chromatographic methods that are coupled to mass spectrometry for detection, and these methods measure total elemental bromine and are more suitable than traditional methods using gravimetric analysis, titration with silver nitrate, or photometry, which are not generally sufficiently specific or sensitive for the determination of bromide in food and feed. When combined with a chromatographic separation, mass spectrometric methods can distinguish between bromide and compounds that contain bromine.

### 1.3.5 | Previous assessments

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has evaluated bromide in the context of its evaluation of methyl bromide. In JMPR (1965) concluded that it was probable that most if not all of the residue persisting in foodstuffs fumigated with methyl bromide would be in the form of the bromide ion, but since nothing was known about the chronic oral toxicity of methyl bromide, no acceptable daily intake (ADI) could be assigned to methyl bromide as a residue. In 1966, JMPR confirmed that no ADI could be established for methyl bromide and concluded that the safety of food products treated with methyl bromide could be assessed on the basis of their bromide content because by far the major part, if not all, of the residue which persists in foodstuffs fumigated with methyl bromide in accordance with ordinary commercial practice is in the form of bromide (JMPR, 1967). JMPR subsequently established an ADI for bromide of 0–1.0 mg/kg bw (JMPR, 1967) based on the minimum pharmacologically effective dose in humans of 900 mg KBr, equivalent to 600 mg Br<sup>-</sup> or 10 mg/kg bw per day in a 60-kg adult. Although not clearly stated in the JMPR monograph, the Scientific Committee assumed that an uncertainty factor of 10 was applied to allow for intra-individual variation.

<sup>9</sup>European Standard method EN 13191–1:2000 titled 'Non-fatty food - Determination of bromide residues - Part 1; available at <https://standards.iteh.ai/catalog/standards/sist/a1a71146-6473-4ed3-ba22-38380c133bed/sist-en-13191-1-2001>.

JMPR subsequently evaluated bromide, in the light of newer studies in experimental animals and human volunteers (JMPR, 1988). It was noted that, at high doses, bromide resulted in effects on the nervous system, but the main effects were on endocrine organs, particularly the thyroid, adrenal glands and testes. The effect on the thyroid was attributed to interaction with iodide uptake and was considered to be the most sensitive effect in animal experiments. A NOAEL of 12 mg Br<sup>-</sup>/kg bw per day was identified based on effects of NaBr on the thyroid in rats. JMPR also reported a number of human volunteer studies, including a series of studies in females receiving doses of NaBr equal to 0, 4 and 9 mg Br<sup>-</sup>/kg bw per day, showing marginal effects on neurophysiological data (EEG and visual evoked response) at the highest dose, but no effects on thyroid hormones (Sangster et al., 1982, 1983, 1986). JMPR considered the neurophysiological changes to be within normal limits and concluded that the NOAEL in human volunteer studies was 9 mg Br<sup>-</sup>/kg bw per day. Taking into account the NOAELs from both the rat and human studies, the JMPR confirmed the previously established ADI for bromide of 0–1.0 mg/kg bw.

EMA noted the JMPR conclusions but concluded that more recent human volunteer studies indicated a NOAEL of 4 mg Br<sup>-</sup>/kg bw per day, and therefore set an ADI of 0.4 mg/kg bw, applying a safety (uncertainty) factor of 10 (EMA, 1997). EMA did not provide references in its summary report but noted that the NOAEL was based on studies in which changes in electroencephalograph (EEG) measurements were the most sensitive indicator of bromide toxicity.

The WHO has published an evaluation of the toxicity of bromide in the context of developing guidelines for drinking water quality (WHO, 2009). This drew on the data published by JMPR, but also noted the evaluation by EMA (1997) and adopted the EMA ADI of 0.4 mg/kg bw, i.e. 24 mg/person for a 60-kg person. Assuming a relative source contribution of 50% of the ADI from drinking water, the WHO concluded that the drinking water value for a 60-kg adult consuming 2 L water per day would be up to 6 mg/L. For a 10-kg child consuming 1 L water per day, the value would be up to 2 mg/L.

In 2013, EFSA published a reasoned opinion on the review of the existing MRLs for methyl bromide (EFSA, 2013a). These MRLs are established for bromide, the main metabolite of methyl bromide in food and feed. The 2013 EFSA opinion noted that the toxicological profile of bromide had been evaluated by JMPR but considered that the ADI of 1.0 mg/kg bw for bromide was not sufficiently supported by the data and that an ARfD for bromide should be reassessed.

The Biocidal Products Committee (BPC) of the European Chemicals Agency (ECHA) has published opinions on 1,2-dibromo-2,4-dicyanobutane (DBDCB) (ECHA BCP, 2015) and on 2,2-dibromo-2-cyanoacetamide (DBNPA) (ECHA BPC, 2021), both of which release bromide. The BPC noted that the only systemic effect of DBDCB was enlargement of the thyroid gland, observed in dogs, which was attributed to the release of bromide. Similarly, the BPC concluded that DBNPA has adverse effects on the thyroid gland in studies on rats and dogs and that these effects were attributable to bromide.

The Risk Assessment Committee (RAC) of ECHA has assessed ammonium bromide in the context of harmonised classification and labelling at the EU level, taking into account unpublished reports submitted by sponsors, studies published in the scientific literature and read-across from other bromide salts (ECHA RAC, 2020). The evaluation considered whether ammonium bromide met the ECHA criteria for specific target organ toxicity (STOT), i.e. that effects are observed at doses ≤ 100 mg/kg bw per day. The RAC considered a proposal that the thyroid should be classified as a target organ and noted the conflicting results of a number of studies with respect to doses at which thyroid effects occurred. The RAC concluded that the reported effects on thyroid in rats, and the related MOA can be relevant for humans, but that the severity of effects on the thyroid were not sufficient to fulfil the criteria for classification. For neurotoxicity, the RAC concluded that the human case reports of poisoning, supported by the evidence from animal studies, warranted a classification of 'causes damage to the nervous system through prolonged or repeated exposure'. The RAC further concluded that classification for effects on sexual function and fertility, on development and effects on or via lactation was justified. More recently, the RAC has evaluated sodium, potassium and calcium bromide (ECHA RAC, 2024), based on the same data set as for ammonium bromide (primarily on ammonium bromide and sodium bromide). The RAC concluded that bromide salts meet the criteria for classification with respect to effects on the nervous system, thyroid and reproduction and development.

### 1.3.6 | Legislation

Active substances are approved for use as plant protection products under Regulation (EC) No 1107/2009<sup>10</sup> and included in Annex to Regulation (EU) 540/2011.<sup>11</sup> The fumigant methyl bromide was not approved by Commission Decision 2008/753/EC<sup>12</sup> and remained not approved by Commission Decision 2011/120/EU<sup>13</sup> based on the EFSA assessment<sup>14</sup> of a new application.

<sup>10</sup>Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

<sup>11</sup>Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

<sup>12</sup>Commission Decision of 18 September 2008 concerning the non-inclusion of methyl bromide in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance. OJ L 258, 26.9.2008, p. 68–69.

<sup>13</sup>Commission Decision of 21 February 2011 concerning the non-inclusion of methyl bromide in Annex I to Council Directive 91/414/EEC. OJ L 47, 22.2.2011, p. 19–20.

<sup>14</sup>Conclusion on the peer review of the pesticide risk assessment of the active substance methyl bromide. EFSA Journal 2011;9(1):1893.

Regulation (EC) No 396/2005<sup>15</sup> establishes the rules on maximum residue levels in food and feed of plant or animal origin at European level. As methyl bromide as such is highly volatile and therefore cannot be quantified in food and feed, the MRLs are set for bromide in Regulation (EC) No 396/2005 to ensure that compliance with MRLs can be monitored and enforcement action can be taken by Member States. Non-approved substances in the EU might still be authorised in third countries, however for bromide no import tolerances for methyl bromide were notified in the framework of the MRL review (EFSA, 2013a), nor have any new import tolerances been requested by an applicant since then.

In addition, use of methyl bromide as a fumigant has been phased out globally according to the Montreal Protocol on Substances that Deplete the Ozone Layer.<sup>16</sup>

## 1.4 | Consultation

In line with its policy on openness and transparency, EFSA consulted EU Member States and interested parties through an online public consultation held between 5 July and 6 September 2024. The comments received were considered by the working group and incorporated into the current Opinion, where appropriate, before adoption of the opinion by the EFSA Scientific Committee. The technical report of the outcome of the public consultation (EFSA-Q-2022-00329) is published separately as Annex A.

## 2 | DATA AND METHODOLOGIES

### 2.1 | Problem formulation

#### 2.1.1 | Overall aim of the assessment

The objective is to screen the safety for human health of the current bromide MRLs in relation to the presence of bromide in foods, and to assess the risk of adverse effects in food-producing and non-food-producing animals associated with the dietary exposure to bromide from animal feed.

#### 2.1.2 | Target populations

The target population of the current human health assessment is the European population, including specific sensitive subgroups in terms of bromide hazard (e.g. pregnant women, infants, children, individuals with iodine deficiency).

The target population for the exposure assessment is the European population including various age groups (e.g. infants, children, adults).

In the context of animal health, the targets for the assessment are food-producing animals, non-food producing animals (including fur animals and pet animals), as defined in Regulation (EC) No 767/2009, hereafter referred collectively as 'food producing and non-food producing animals'.

#### 2.1.3 | Relevant compounds

Bromide salts and bromide-releasing sources (substances for which bromide is a major metabolite or breakdown product) are relevant to the toxicological assessment of bromide. Bromate is relevant only in the context of its formation as an oxidation product of bromine/bromide. Bromide concentrations in food and drinking water and in feed and water for drinking are relevant to the exposure assessments for humans and animals, respectively.

### 2.2 | Hazard identification and characterisation

#### *Human health*

Pertinent data relevant to the hazard identification and hazard characterisation from existing safety assessments were taken into consideration. Additional hazard information relevant to human health was identified through a comprehensive literature search in two bibliographic databases (PubMed and Web of Science) as described in the Protocol (Annex B). The general eligibility criteria are summarised in Table 1 of the protocol. Eligibility criteria for inclusion of studies relevant to hazard identification are presented in Tables 2–4 of the protocol. Citations of key full text articles were also screened

<sup>15</sup>Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

<sup>16</sup><https://ozone.unep.org/treaties/montreal-protocol/annex-e-group-i-methyl-bromide>.



for any additional potentially relevant studies. Toxicological studies with no published primary sources are cited either as the unpublished study reports which were obtained in full or as summaries of data reviewed and published by ECHA. Relevant epidemiological and toxicity studies, including all reported toxicological endpoints, adverse health effects and dose–response data were identified and summarised. Information on absorption, distribution, metabolism and elimination and available physiologically based kinetic models from human and experimental animal kinetic studies were collected. Identification of any adverse effect reported or cited in the literature was reviewed, with focus on health outcomes judged to be most relevant and most sensitive endpoints that may have an impact on the establishment of the HBGV(s). Evidence relevant to bromide MOA reported in the literature, as well as evidence related to species differences pertinent to the MOA and observed outcomes in different species were also reviewed.

The results of the study selection processes for human health are reported in the flowcharts in Annex C. The list of studies excluded after full-text screening is documented, along with the reasons for excluding them. The studies selected for inclusion in the assessment were further appraised according to general study quality considerations, such as sufficient details on the study design, methodology, performance and outcome of the study, as presented in Appendix A. Limitations in the body of evidence are documented in the uncertainty analysis (Section 3.5). Hazard information in humans and experimental animals was evaluated with a narrative literature review considering the weight of evidence across different lines of evidence, as described in the Protocol (Annex B). Dose–response relationships for endpoints were assessed and the most sensitive relevant endpoint(s) were used for the derivation of a reference point for establishment of HBGV(s) for humans.

### Animal health

A literature search for bromide toxicity, kinetics, exposure and transfer into animal tissues was performed by the FEEDCO unit for food-producing and non-food-producing animals in preparation for this mandate and details are available in the published external scientific report.<sup>17</sup> Eligibility criteria for inclusion of studies are presented in Tables 5 and 6 of the Protocol (Annex B). An additional targeted literature search was conducted in two bibliographic databases (PubMed and Web of Science) for reported evidence in association with the thyroid. Citations of key full-text articles were also screened for any additional potentially relevant studies. Evidence of bromide toxicity and health effects in food-producing and non-food-producing animals was obtained, including all reported toxicological endpoints, adverse health outcomes and dose–response data. Data relevant to the health of food-producing and non-food-producing animals also included data on bromide ADME properties, kinetics and available physiologically based kinetic models in relevant species. Interpretation of the compiled information on adverse effects and their dose–response relationships was based on the EFSA Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017). A weight of evidence approach was used to integrate evidence across different lines of evidence, as described in the protocol (Annex B). The results of the study selection processes for animal health are reported in the flowcharts in Annex C.

The studies selected for inclusion in the assessment were further appraised according to general study quality considerations, such as sufficient details on the study design, methodology, performance and outcome of the study, as presented in Appendices C. Limitations in the body of evidence are documented in the uncertainty analysis (Section 3.9).

In experimental studies, the doses provided as mg/kg feed (on an as is basis or as dry matter (DM) basis) were converted to mg/kg bw per day and vice versa. Data needed for this conversion, such as the body weight of the animals and the feed DM intake (DMI) are not always provided in the publications. If not provided, default values reported in the EFSA Guidance on the assessment of feed additives for the target species (EFSA FEEDAP Panel, 2017), and as provided in the EFSA scientific report on the animal dietary exposure (EFSA, Ardizzone, et al., 2019), were used. In studies with growing animals where data on body weight gain were not provided, the average body weight was calculated based on initial and final body weight, if provided.

## 2.3 | Occurrence data submitted to EFSA

### 2.3.1 | Data collection and validation

Following an European Commission mandate to EFSA, a call for annual collection of chemical contaminant occurrence data in food and feed, including bromine and bromide, was issued by the former EFSA Dietary and Chemical Monitoring Unit (now Integrated Data Unit) in December 2010 with a closing date defined for each year.<sup>18</sup> European national authorities, research institutions, academia, food business operators and other stakeholders are invited annually to submit analytical data on bromine and bromide in food and feed. In addition, the data collected through the official control activities on pesticide residues carried out in the EU Member States, including the results of the EU-coordinated control programme and the national control programmes, and submitted to EFSA were also considered. It is noted that the data on pesticide residues are collected for raw agricultural commodities (RACs), as defined in Annex I of Reg. EC 396/2005, whereas occurrence data on contaminants are collected based on food definition according to FoodEx2 food classification system (see Section 2.5.1).

<sup>17</sup><https://www.efsa.europa.eu/en/supporting/pub/en-7938>.

<sup>18</sup><https://www.efsa.europa.eu/en/call/call-continuous-collection-chemical-contaminants-occurrence-data-food-and-feed-2023>.



The data for the present assessment were provided by organisations from 25 EU countries, Norway, Switzerland, the United Kingdom (UK), Northern Ireland<sup>19</sup> and Bosnia-Herzegovina.

Analytical data were reported to EFSA as bromide, bromine, bromides and methyl bromide. Since all of these are monitored as bromide, they were all treated as bromide.

The data submission to EFSA followed the requirements of the EFSA Guidance on Standard Sample Description (SSD) for Food and Feed (EFSA, 2010b) and the EFSA Guidance on Standard Sample Description version 2.0 (EFSA, 2013b). Occurrence data were managed following the EFSA standard operational procedures (SOPs)<sup>20</sup> on 'Data collection and validation' and on 'Analysis of data from the S-DWH for the assessment of dietary exposure'.

By February 2024, a total of 57,497 analytical results on bromide in food and feed were available in the EFSA database. Data received after that date were not included for further evaluation in this opinion.

## 2.3.2 | Data analysis

Following EFSA's Technical report on handling of occurrence data for dietary exposure assessment (EFSA, 2021) to guarantee an appropriate quality of the data used in the exposure assessment, the initial data set was carefully evaluated by applying several data cleaning and validation steps. Special attention was paid to the identification of duplicates and to the accuracy of different parameters, such as 'Sampling strategy', 'Sampling year', 'Sampling country', 'Analytical methods', 'Reporting unit', 'Limit of detection/quantification', and the codification of analytical results under FoodEx classification (EFSA, 2011a, 2015). The outcome of the data analysis is presented in Section 3.2.1 and Annex D, Table D.1.

The left-censored data (LCD) (results below limit of detection (LOD) or below limit of quantification (LOQ)) were treated by the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO-IPCS, 2009). The same method is indicated in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010a) as an option in the treatment of left-censored data. The guidance suggests that the lower bound (LB) and upper bound (UB) approach should be used for chemicals likely to be present in the food, including contaminants. The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as lower than the LOD (< LOD) or the LOQ (< LOQ). The UB is obtained by assigning the numerical value of the LOD to values reported as < LOD and LOQ to values reported as < LOQ (maximum possible value), depending on whether LOD or LOQ is reported by the laboratory.

## 2.4 | Consumption data

### 2.4.1 | Food consumption data

Food consumption data included in EFSA Pesticide Residue Intake Model version 3.1 (PRIMo v.3.1) were used for the screening of bromide MRLs. This standard tool was developed by EFSA in 2007 and is used at EU level to perform the dietary risk assessment for pesticide residues in the framework of setting and reviewing of maximum residue levels for pesticides under Regulation (EC) No 396/2005 and in the peer review of pesticides under Regulation (EU) No 1107/2009. The model is built on dietary food consumption surveys including consumption data and unit weights provided by Member States. The latest version currently in force was released in 2018 and updated in 2019 (EFSA, 2018, 2019a). The model is based on 36 population groups from various European countries (e.g. French infants, Dutch toddlers) considered for chronic exposure estimates, and 39 European population groups (20 for children up to 14 years and 19 for adults) considered for acute exposure estimates (for more details, see Appendix G). The chronic exposure calculations in PRIMo 3.1 are performed by summing up the exposure to residues expected in unprocessed RACs and in processed products derived from RACs. In contrast, the acute exposure calculations are performed individually for the RACs and the processed products. It is noted that PRIMo 3.1 does not include consumption data for algae, drinking water, infant formulae, fish and seafood (only limited consumption data are available for fish, fish products and other marine and freshwater food products).

### 2.4.2 | Feed consumption data

No estimates of feed consumption by food-producing and non-food-producing animals were used because the lack of data on the occurrence of bromide in feed materials prevented exposure assessment.

<sup>19</sup>In accordance with the Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, and in particular Article 5(4) of the Windsor Framework in conjunction with Annex 2 to that Framework, for the purposes of this scientific opinion references to Member States include the United Kingdom in respect of Northern Ireland.

<sup>20</sup><https://www.efsa.europa.eu/en/corporate/pub/sops>.

## 2.5 | Food and feed classification

### 2.5.1 | Food

Occurrence data were codified according to the FoodEx2 classification system. FoodEx was developed by EFSA in 2009 with the objective of simplifying the linkage between occurrence data and food consumption data (EFSA, 2011a). Following its first publication, a testing phase was carried out in order to highlight strengths and weaknesses and to identify possible issues and needs for refinement. Based on the outcome of the testing phase, EFSA published in 2015 the FoodEx2 revision 2 (EFSA, 2015).

The FoodEx2 catalogue hosts several hierarchies used for different data collections, e.g. 'Reporting hierarchy' for the collection of occurrence data and 'Exposure hierarchy' for the collection of food consumption data. It consists of a large number of individual food items aggregated into food groups and broader food categories in a hierarchical parent-child relationship. It contains 21 main food categories at the first level of the 'Exposure hierarchy', which are further divided into subcategories, resulting in seven levels with more than 4000 items in total.

#### 2.5.1.1 | Classification according to MRLs

Regulation (EC) No. 396/2005 applies to food and feed of plant and animal origin in or on which pesticide residues may be present. Annex I to that Regulation lays down the list of food and feed products for which the maximum residue levels of pesticides (MRLs) set by Regulation (EC) No 396/2005 apply.

### 2.5.2 | Feed

Regarding the feed, FoodEx2 has 14 main feed categories integrated with broader feed commodities at lower levels defined according to the Catalogue of feed materials as described in Commission Regulation (EU) No 68/2013,<sup>21</sup> as amended.

## 2.6 | Comparison of the occurrence data to the current MRLs in EU

In the current assessment, the maximum occurrence levels collected within the occurrence data collection for each food product as defined in Annex I of Regulation (EC) No 396/2005 are compared to the relevant existing MRL established in Regulation (EC) No 839/2008.<sup>22</sup> No modifications were made since then for the MRLs for bromide. Nomenclature from the FoodEx2 classification system has been linked to the food categorisation system as defined in Annex I of Regulation (EC) No 396/2005. In practice, the FoodEx2 food codes were matched to the most appropriate food groups up to level 2, 3 or 4 as appropriate.

The comparison was performed for foods for which both occurrence data and MRLs are available. For commodities (food products) with existing MRLs but for which insufficient occurrence data are available to conclude, appropriate data were sought in the literature. The proportion of samples exceeding the MRLs and the range of exceedance are reported per food commodity.

## 2.7 | Screening of existing MRLs

As specified in the terms of reference, the Scientific Committee performed the screening of existing MRLs for bromide. For this purpose, the Pesticide Residue Intake Model (PRIMo) version 3.1<sup>23</sup> was used (EFSA, 2018, 2019a). This approach is defined as a high-level screening method and cannot be considered as a standard dietary exposure assessment.

PRIMo is a tool specifically developed to carry out risk assessment of pesticide residues in feed and foods included in Annex I of Regulation (EU) 396/2005. The tool is typically used to assess chronic and acute dietary consumer exposure using the median or highest pesticide residue levels expected for each food commodity, respectively. These levels are derived from supervised field trials conducted during pesticide pre-authorisation assessments or MRL reviews. For chronic exposure, it is assumed that all food commodities (e.g. fruits, vegetables, cereals, meat, etc.) for which the pesticide is/will be authorised contains the median residue concentrations and is based on mean food consumption over the whole lifetime. For the acute exposure, it is assumed that a consumer is eating, within a short period of time (one day or meal), a large portion of the food commodity containing the highest pesticide residue level measured in the supervised residue trials. In its typical use, PRIMo incorporates the assessments of proposed MRLs and existing MRLs based on authorised uses for pesticides against the chronic (ADI) or acute toxicological reference dose (ARfD), respectively, such that the final output of

<sup>21</sup>Commission Regulation (EU) No 68/2013 of 16 January 2013 on the Catalogue of feed materials. OJ L 29, 30.1.2013, p. 1–64.

<sup>22</sup><http://data.europa.eu/eli/reg/2008/839/oj>.

<sup>23</sup>PRIMo description: <https://www.efsa.europa.eu/en/applications/pesticides/tools>.

the tool is given as % of ADI and % of ARfD (EFSA, 2018). In this opinion, comparison of the calculated 'intake of bromide' based on MRLs is compared to the TDI and ARfD established for bromide as a screening of MRL safety.

The theoretical maximum daily intake (TMDI) assessment of bromide is an atypical application of the PRIMo tool, in which the existing MRLs for bromide are used instead of the median and highest residue levels of field trial data. This implementation assumes the presence of bromide in the foods at levels equal to the MRLs and assesses consumer exposure and risk conservatively under conditions of maximum bromide residue levels. It is also an atypical application of the PRIMo tool for a non-pesticide exposure assessment since methyl bromide is no longer in use as plant protection product.

## 2.8 | Screening of monitoring data

Although not requested in the mandate, further screening was performed based on the monitoring data submitted to EFSA. For each raw agricultural commodity, a statistical analysis was performed to derive the input value to be considered in the calculations. The principles of deriving these input values are following the same principles as establishing MRLs on the basis of occurrence data. For commodities with number of observations (obs)  $\geq 59$ , the input values cover the 95th percentile (P95) at the upper confidence interval (CI95). For the commodities with  $< 59$  obs, but at least 29 obs, the 90th percentile was considered ( $29 \leq \text{obs} < 59$ , P90%), while for commodities with  $< 29$  obs but at least 5 obs, the 50th percentile (median) was considered ( $5 \leq \text{obs} < 29$ , P50%). The commodities that did not have data for at least five samples were not considered. The estimations were calculated for both LB and UB levels.

For the screening based on monitoring data, the Scientific Committee considered it appropriate to calculate two scenarios; the first scenario was based on a lifetime consumption and the second scenario was based on consumption over a short period of time (one day or meal).

### *Contribution of bromide from drinking water*

Currently, there are no legal requirements setting the maximum levels of bromide in drinking water intended for human consumption applicable at EU level. EFSA received only very limited occurrence data analysed in last 10 years with the LOQs ranging from to 0.5–10 mg/kg, which did not allow any robust estimation of the exposure to bromide from drinking water.

## 2.9 | Animal dietary exposure assessment

Data available in EFSA databases relevant to bromide occurrence in feed were not sufficient (see Section 3.2.2) for conducting a dietary exposure assessment for food-producing and non-food-producing animals. The peer-reviewed literature was searched for relevant data and for evidence on exposure of food-producing and non-food-producing animals to bromide. No sufficient data or other evidence was found.

A dietary exposure assessment of food-producing and non-food-producing animals to bromide was not feasible due to the lack of sufficient data.

## 3 | ASSESSMENT

### 3.1 | Hazard identification and characterisation

#### 3.1.1 | Toxicokinetics

##### *Evidence in humans*

After oral administration, bromide is rapidly absorbed and distributed throughout the extracellular water space. In a study designed to assess the kinetics of bromide, healthy adult volunteers were given a dose of 30 mg of sodium bromide solution/kg bw (23.3 mg Br<sup>-</sup>/kg bw) (Vaiseman et al., 1986). The bioavailability of bromide was found to be complete in the fasting state, with an oral bioavailability of  $96 \pm 6\%$ . The volume of distribution was  $0.408 \pm 0.017$  L/kg bw. Bromide is eliminated from the body primarily through the kidneys. The half-life of bromide after oral and intravenous administration was found to be  $285.6 \pm 33.6$  h and  $225.6 \pm 36$  h, respectively. The apparent clearance of bromide was  $26 \pm 1.7$  mL/day per kg bw (Vaiseman et al., 1986).

In another study, a single oral dose of sodium bromide (50 mg Br<sup>-</sup>/kg bw) was administered to healthy volunteers (Miller & Kornhauser, 1994). The volume of distribution was found to be  $0.274 \pm 0.030$  L/kg bw, which is slightly lower than the value reported by Vaiseman et al. (1986). The clearance values were also lower, at  $16.8 \pm 2.76$  mL/day per kg bw.

It is worth noting that a low salt diet may significantly prolong the half-life of bromide and potentially increase its toxicity (Vaiseman et al., 1986). Langley-Czerwinski (1958) demonstrated the competition between chloride and bromide for tubular reabsorption, leading to the conclusion that an elevated chloride load would enhance bromide clearance and result in a reduction of its half-life (Langley-Czerwinski, 1958).

## Evidence in experimental animals

### Rats

#### Absorption

In rats, both chloride and bromide are fully absorbed in the intestine (Pavelka, 2004).

#### Distribution

Bromides have physicochemical properties most similar to those of chloride and, to a lesser extent, to iodide, and their distribution and action are directly related to these other halides (Pavelka, 2004). The distribution of both chloride and bromide is mostly extracellular, except for erythrocytes and acinar cells of the gastric wall, which can contain both ions (Rauws, 1983). In the extracellular fluid, bromide ions replace an equivalent amount of chloride ions, so the molar sum of total halides remains constant at approximately 110 mmol/L. Bromide can penetrate the blood–brain barrier and undergoes enterohepatic circulation. The volume of distribution of bromide in rats is reported to be 3 L/kg bw (Rauws, 1983).

Chloride is transported more readily than bromide into the cerebrospinal fluid. Due to elimination by cerebrospinal fluid flow at the same rate for both ions, bromide never reaches the same cerebrospinal fluid/plasma ratio as chloride. As a result, plateau levels in the central nervous system are reached later than in plasma (Rauws, 1983). In a kinetic study with male Wistar rats ( $n=5$ , 10 weeks old), bromide concentration and half-life were determined for a list of organs and tissues (15 compartments including blood) in rats exposed for 17 days via drinking water containing 50 mg  $^{82}\text{Br}/\text{L}$  (Pavelka, Babický, Vobecký, Lener, & Svandová, 2000; Pavelka, Babický, Vobecký, & Lener, 2000). The half-life values ranged from 94 h in the thyroid gland to 235 h in the liver, and in most of the studied tissues, the values were shorter than the whole body elimination half-life of about 198 h (Pavelka, Babický, Vobecký, Lener, et al., 2000).

In lactating Wistar rats (8–10 weeks old, 5 per group) orally exposed to sodium bromide (drinking water, 1 or 5 g/L, equivalent to 220 mg  $\text{Br}^-$  per day), bromide was distributed into milk and was then transferred to their pups. This transfer occurred already 3 h after exposure to  $^{82}\text{Br}$  with 3% of the applied amount to the mother retrieved in the body of the young and gradually increasing during the next 22 h (up to 17%) (Vobecký et al., 2005). In another study using  $^{82}\text{Br}$  in feed, a shorter half-life of only 44 h was determined in lactating Wistar rats (10 weeks old,  $n=6$ ) compared to non-lactating rats (133 h, 10 weeks old,  $n=5$ ) and a longer half-life of 269 h in breast-fed pups (Pavelka et al., 2009).

The half-life of bromide in thyroids of female Wistar rats (10 weeks old,  $n=5$ ), exposed to  $^{82}\text{Br}$  via the diet, has been determined after a 16-day experimental period (Vobecký et al., 1997). The authors found a half-life value (110 h) very close to the measured value of the biological half-life of iodine and consistent with the iodine half-life (106 h) published earlier (Singh et al., 1994). The almost identical half-life values of bromine and iodine in the rat thyroid are considered as evidence that the biological behaviour of bromine within this tissue, unlike other organs, is more akin to that of iodine rather than that of chlorine (Vobecký et al., 1996). van Leeuwen & Sangster (1987) had concluded that there is a direct correlation between concentrations of bromide in mammalian thyroid and concentrations in blood.

#### Metabolism

There is no enzymatic metabolism involved in bromide clearance, indicating that bromide is not likely to induce drug metabolising enzymes.

#### Elimination

The kidneys are the primary route of excretion for both chloride and bromide. After glomerular filtration, most of both halogen ions are reabsorbed in renal tubules and, due to the similarity of their physicochemical properties, bromide and chloride compete for tubular reabsorption (Rauws, 1983). Thus, at a higher chloride exposure, bromide renal tubular reabsorption will decrease, causing a decrease in its half-life and an increase in its clearance, as observed in both humans (Vaiseman et al., 1986) and dogs (Fantinati et al., 2021; March et al., 2002; Trepanier & Babish, 1995b).

An inverse relationship between the half-life of bromide in Wistar rats (3 females and 2 males per group) and sodium intake regardless of the anion ( $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ,  $\text{ClO}_4^-$ , and  $\text{SCN}^-$ ) was reported (Pavelka et al., 2005). Observed half-lives of bromide ranged from  $104 \pm 23$  h to  $325 \pm 18$  h with sodium intake of  $142.3 \pm 11.7$  mg/day and  $37.8 \pm 4.2$  mg/day, respectively. Bromide clearance was 60 mL/day per kg bw in rats maintained on typical diets and decreased to 7.2 mL/day per kg bw with a salt-free diet (Rauws, 1983).

Distribution and elimination processes of bromide are both linear until very high doses (19.2 g/kg bw) (Rauws, 1983). Thus, it is feasible to predict bromide plasma levels at steady state based on single or multi-compartment models (Rauws, 1975).

### Cats

The pharmacokinetics of bromide were studied in seven healthy male neutered cats (Boothe et al., 2002). Potassium bromide (in gelatine capsules) was orally administered at a dose of 20 mg  $\text{Br}^-/\text{kg}$  bw per day until steady-state serum bromide



concentrations were reached. The serum bromide maximum concentration measured at 8 weeks was  $1.1 \pm 0.2$  mg/mL (steady state was reached at  $5.3 \pm 1.1$  weeks), and the mean elimination half-life was  $270 \pm 34$  h. Following oral exposure, the volume of distribution at steady state ( $V_{dss}/F^{24}$ ) of bromide in cats was  $0.44 \pm 0.09$  L/kg bw and the clearance (CL/F) was  $30 \pm 4.3$  mL/day per kg bw. The authors noted that while the volume of distribution of bromide in cats and dogs is similar, the clearance of bromide might be greater in cats compared to dogs, as indicated by the apparent differences in half-life between cats and dogs (Table 1) (Boothe et al., 2002).

## Dogs

The pharmacokinetics of bromide in beagle female dogs were studied after a single oral ( $n=4$ ) and intravenous ( $n=4$ ) administration of 20 mg  $Br^-$ /kg bw, given as a 4% solution of NaBr (diet restricted in chloride, 0.4% dry matter). These authors found that the oral bioavailability of bromide was 46% (half of the bioavailability of bromide in humans), and the volume of distribution was  $0.45 \pm 0.07$  L/kg bw. The total body clearance was  $9.0 \pm 3.9$  mL/day per kg bw, and the half-life was  $1100 \pm 215$  h.

The effect of dietary chloride on bromide kinetics observed in humans (Langley-Czerwinski, 1958) was also shown in dogs. Female beagle dogs (4 per group) were fed for 8 weeks with rations containing different chloride levels corresponding to 32, 64 and 193 mg  $Cl^-$ /kg bw per day (0.2, 0.4 and 1.3% of the diet, sodium content of 0.1, 0.25 and 0.7%, respectively). After 2 weeks of treatment, all dogs received a single oral dose of 14 mg  $Br^-$ /kg bw as an aqueous solution. The mean half-life decreased from 1656 h to 576 h and the AUC (serum bromide) decreased from 1948 to 309 mg day/L as NaCl in the diet increased. However, it had no impact on bromide  $C_{max}$  and  $T_{max}$  (Trepanier & Babish, 1995a). A case of bromism was reported in a 3-year-old Tibetan Mastiff (55 kg, neutered), who was successfully treated for idiopathic epilepsy since the age of 1-year-old (Fantinati et al., 2021). The dog owner changed the diet, to one with a 53% lower chloride content compared to the former diet. Neurological examination revealed an abnormal gait, with severe symmetric four-limb ataxia and frequent falls. Consequently, potassium bromide dosage was then lowered by 15%. Neurologic signs progressively improved, as serum bromide levels decreased back to the levels as before the change in diet (from 2800 mg/L to 1500 mg/L).

In a steady-state pharmacokinetic study of bromide in six beagle dogs (three males and three females), serum, urine and cerebrospinal fluid bromide concentrations were measured after administering 20 mg  $Br^-$ /kg bw (as KBr) every 12 h in feed over 115 days (March et al., 2002). The half-life was 365 h (293–487), and the serum steady-state concentration was 2450 (1780–2690) mg/L. The clearance was 16.4 mL/day per kg bw (range: 14.9–22.5) while the renal clearance was 8.2 mL/day per kg bw (range: 6.0–12.6) and the volume of distribution was 0.4 L/kg bw (range: 0.32–0.46). The CSF:serum bromide ratio was 0.77 at steady state; the authors suggested that the shorter half-life observed compared to Trepanier and Babish (1995a, 1995b) was related to the higher dietary chloride content as dietary chloride intake has a direct impact on bromide kinetics (March et al., 2002). The authors considered these dietary Cl levels as low to medium concentrations compared with other commercial diets.

## Sheep

A study in sheep (6-year-old merino ewes) aimed to determine the kinetic parameters of bromide in order to aid in designing and optimising therapeutic regimens for the treatment of epilepsy (Quast et al., 2015). In this study, 120 mg  $Br^-$ /kg bw was administered either via intravenous injection (as NaBr,  $n=8$ ) or oral ingestion through an orogastric tube (as KBr,  $n=8$ ). The bioavailability of bromide after oral ingestion was found to be 92%, indicating efficient absorption with a  $T_{max}$  of  $108 \pm 125$  h and a  $C_{max}$  of  $453.86 \pm 43.37$  mg/L. After intravenous injection, the  $C_{max}$  was found to be  $822.11 \pm 93.61$  mg/L. The volume of distribution was found to be  $0.286 \pm 0.031$  L/kg bw and the clearance was  $0.836 \pm 0.255$  mL/h per kg bw. The half-life of bromide after oral and intravenous administration was  $347 \text{ h} \pm 94 \text{ h}$  and  $388 \text{ h} \pm 115 \text{ h}$ , respectively. The mean residence time was  $414 \pm 150$  h after oral administration. Additionally, the study observed numerous peaks in the oral concentration–time curve approaching the  $C_{max}$  value, which suggests ongoing rumen and omasum redistribution. This phenomenon is likely due to bidirectional bromide flux through chloride channels.

## Horses

After a single oral dose of 120 mg/kg bw potassium bromide (80 mg  $Br^-$ /kg bw), the  $C_{max}$  was  $284 \pm 15$  mg/L,  $T_{max}$  was  $5.3 \pm 1.0$  h, AUC was  $31,889 \pm 7358$  mg.h/L and the half-life was  $75 \pm 14$  h. The clearance was  $65 \pm 15$  mL/day per kg bw and the volume of distribution was  $0.285 \pm 0.048$  L/kg bw (Raidal & Edwards, 2008). The observed half-life and the volume of distribution are in the same range as reported by Fielding et al. (2003) of 125 h and  $0.255 \pm 0.015$  L/kg bw, respectively, after intravenous injection of 30 mg/kg bw sodium bromide (23 mg  $Br^-$ /kg bw). The apparent clearance was  $33.6 \pm 2.16$  mL/day per kg bw. Using the latter clearance value by Fielding et al. (2003), Raidal and Edwards (2008) derived an oral bioavailability of 32%–38% of bromide in horses which is half of that reported in humans but similar to dogs (Raidal & Edwards, 2008).

Reported kinetic parameters for the different species are summarised in Table 1.

<sup>24</sup>Volume of distribution at steady-state after oral exposure; F: bioavailable dose after oral exposure.



**TABLE 1** Summary of reported serum half-lives, clearance and volume of distribution after oral exposure of bromide; mean (SD or range).

Species	Half-life, hours	Apparent clearance, mL/day per kg bw	Volume of distribution, L/kg bw	Bioavailability, %	Dose, mg Br <sup>-</sup> /kg bw
Human	285 (34)	16.8–26	0.27–0.41	96 (6)	18 <sup>a</sup> –50 <sup>b</sup>
Rat	198 (22)	60	3	100	50 mg Br <sup>-</sup> /L for 17 days <sup>c</sup>
Cat	270 (34)	30 (4.3)	0.44 (0.09)	NR	20 (steady-state) <sup>d</sup>
Dog	365 (293–487)	16.4 (14.9–22.5)	0.45 (0.07)	46	20 single dose <sup>e</sup> or repeated <sup>f</sup> (115 days)
Sheep	347 (94)	20 (6.1)*	0.29 (0.03)	92	120
Horse	75 (14)	65 (15)	0.29 (0.05)	32–38	80

\*Clearance after i.v. injection; NR: not reported.

<sup>a</sup>Half-life, clearance, volume of distribution, bioavailability.

<sup>b</sup>Clearance, bioavailability.

<sup>c</sup>Half-life.

<sup>d</sup>Half-life, clearance, volume of distribution.

<sup>e</sup>Bioavailability.

<sup>f</sup>Half-life, clearance, volume of distribution.

### 3.1.2 | Transfer to food of animal origin

Rauws (1975) discussed compartmental kinetic models for deriving the internal dose of bromide from single and repeated exposure (e.g. steady-state plasma concentration). Based on this model and the kinetic information for different species and the steady-state tissue/plasma ratio for these species, it would have been possible to extrapolate the concentration in different tissues from an oral exposure. However, the only tissue/plasma ratio reported comes from a rat study and after 17 days of exposure, which is not sufficient to reach steady state (Pavelka et al., 2002). Since the half-life of bromide in rats is estimated at around 8 days, the duration of the study would need to be at least five half-lives, i.e. 40 days of exposure. Given these data gaps, it is not possible to estimate the amount of bromide in food of animal origin from the exposure to the animal.

However, a few studies in the literature provide evidence for transfer of bromide to tissues that are relevant as human food. Bromide excretion in the milk of lactating dairy cows was observed when it is present in their diet (Lynn et al., 1963). Based on a review of total bromide in milk from various locations in the United States where methyl bromide was not used, Lynn et al. (1963) concluded that the naturally occurring bromide in feed corresponds to milk concentrations of 1–5 mg Br/kg. In a pilot experiment, the impact of sodium bromide supplementation on milk production in lactating cows was investigated. One lactating cow was administered daily doses of 12.5 g of NaBr for 5 consecutive days. Blood and milk samples were collected and subsequently analysed for total bromide content. Milk bromide was correlated with increasing blood levels and varied from 10 to 60 mg Br<sup>-</sup>/kg milk.

In a more comprehensive follow-up study reported in the same publication, sodium bromide was incorporated into concentrate feed at concentrations of 50, 100 and 200 mg Br<sup>-</sup>/kg DM and administered consecutively (from low to high) to four cows for 22, 18 and 28 days corresponding to intakes of 175, 350 and 700 mg Br<sup>-</sup>/day, respectively (based on a mean feed intake of 3.5 kg concentrate per day and cow). At the end of the respective feeding periods, the mean concentration of bromide in milk was 2, 4 and 12 mg Br<sup>-</sup>/kg milk after feeding with 50, 100 and 200 mg Br<sup>-</sup>/kg feed concentrate DM, respectively. Concentrate feed was given to the cows at the rate of 1 kg concentrate feed per 4 kg of milk produced. The authors concluded that milk bromide apparently reached a steady state after 20–30 days. They also noted that a total diet containing 43 mg Br<sup>-</sup>/kg DM resulted in 10–20 mg Br<sup>-</sup>/kg milk (Lynn et al., 1963). Despite several limitations in this study (including lack of information regarding feed intake, relatively low milk production, small number of cows involved ( $n=4$ ) and absence of statistical analysis), the study provides evidence for transfer of dietary bromide to milk.

Bromide transfer to milk and deposition in tissues were reported in nine dairy cows at early lactation (3 cows/treatment, group penned) fed on a total mixed ration supplemented with NaBr at 0, 46.5 and 93.1 mg Br<sup>-</sup>/kg diet DM for 35 days (Vreman et al., 1985). The basal bromide content in the feed was 14.9 mg Br<sup>-</sup>/kg diet DM with an additional bromide intake through drinking water of 2.7 mg/L. The corresponding total bromide in feed was 14.9 (control), 61.4 and 108.0 mg Br<sup>-</sup>/kg diet DM and total bromide intake (from feed and water) was estimated to be 0.43 (control), 1.78 and 3.12 mg Br<sup>-</sup>/kg bw per day. At the start of the study, the milk bromide concentration was 2.8 mg/kg. At the end of the dosing period, the milk bromide concentration was 6.1, 17.4 and 30.5 mg/kg, respectively. Bromide was also measured in blood (21, 58 and 95 mg/kg fresh weight (fw), respectively), muscles (3.0, 9.4 and 20.8 mg/kg fw, respectively), liver (3.8, 11.5 and 27.1 mg/kg fw, respectively) and kidney (14.2, 31.4 and 87.5 mg/kg fw, respectively).

Transfer of dietary bromide to eggs was reported in 60 Hisex White cross laying hens (365 days of age, bw 1.4 kg; 15 hens/treatment, group penned) fed diets supplemented with NaBr at 0 (control), 10, 50 and 250 mg Br<sup>-</sup>/kg diet, corresponding to 0, 0.6, 3.0 and 15.0 mg Br<sup>-</sup>/kg bw per day for 28 days followed by 14-day recovery period (Kutsan et al., 2020). The background bromide content of the compound feed was 2.0 mg/kg. Bromide content was determined separately in egg white, yolk and shell. Bromide increased in egg white with increasing dietary bromide (10.4, 23.0, 65.4 and 243.5 mg Br<sup>-</sup>/kg, respectively). Bromide content in egg white from the three supplemented groups exceeded the control value even 14 days after the end of the supplementation period.

### 3.1.2.1 | Transfer of bromide from algae to milk and meat

Algae, and particularly macroalgae (seaweeds), have been used as feed for livestock for many years, but recently there has been increasing interest in their use as a ruminant feed due to the presence of bromophenols and their potential to reduce rumen methanogenesis. While several studies have demonstrated the effectiveness of macroalgae in reducing enteric methane emissions by ruminants, only two studies have been identified which have examined the effect on feeding marine algae on levels of bromide in milk of dairy cows. Stefenoni et al. (2021) reported a large (8-fold) increase in bromide concentration in the milk of cows supplemented with dietary *Asparagopsis taxiformis* (control = 5.1 mg/kg, treatment = 40.4 mg/kg) (Stefenoni et al., 2021). Although data for bromide concentration in milk are scarce, the authors concluded that the elevated bromide content was likely to be the result of *A. taxiformis* supplementation. Krizsan et al. (2023) also reported an eightfold increase (from 5.1 to 43.2 mg/L) in the bromide content of milk from cows fed a diet supplemented with *A. taxiformis* for 21 days (Krizsan et al., 2023).

Reductions in enteric methane observed when macroalgae are included in ruminant diets have been attributed to the bromoform and di-bromochloromethane content of the seaweeds and not the bromide (Machado et al., 2016). It is not clear whether bromide in milk and meat originates from direct transfer of bromide present in the feed or from the metabolic conversion of bromoform present in the feed to bromide.

Dietary supplementation with the seaweed *Ulva lactuca* (UL) at 150 g UL/kg diet to broiler chickens for 14 days ( $n=60$ , 22-day-old male Ross 308 broilers; initial bw 758 g; 10 replicate pens per treatment, 3 chickens per pen) resulted in increased bromine content in the meat (Costa et al., 2022). The bromine content of UL was 694 mg/kg, resulting in an intake of 0.4, and 18.3 mg Br<sup>-</sup>/kg bw per day, for control and UL diets, respectively. Bromine content in meat increased from 0.12 to 0.30 mg/100 g fresh weight (fw) (Costa et al., 2022).

### 3.1.3 | Toxicity in experimental animals

Experimental animal studies relevant to the assessment are described in Tables 2, 3. Where exposure to the animals was reported in units of drinking water concentration (mg/L), the equivalent doses were calculated using EFSA default conversion factors (EFSA Scientific Committee, 2012). The studies reporting on effects of bromide on the thyroid (Table 3) were appraised for risk of bias (RoB) and the outcome is summarised in Appendix A.

The Scientific Committee took note of summaries of study reports available on ECHA's website<sup>25</sup> relating to data submitted by industry in the context of classification and labelling of ammonium bromide and obtained the unpublished reports of the key studies. Several of these reports are unpublished studies on ammonium bromide or sodium bromide conducted according to OECD testing guidelines for toxicity testing.

#### 3.1.3.1 | Acute and repeat dose studies

Studies reported in the JMPR monograph indicate that bromide has a very low acute oral toxicity, with reported LD50 values greater than 3000 mg/kg bw in rats and mice (JMPR, 1988).

The results of subacute and subchronic studies in rats are summarised in Tables 2, 3. These studies have shown that bromide can cause effects on the CNS, kidneys, thyroid and other endocrine organs, and on bodyweight gain. Reports of neurotoxicity were generally related to clinical signs reported during routine observations, such as abnormal gait, at doses in excess of 100 mg Br<sup>-</sup>/kg bw per day. A 90-day dietary study with ammonium bromide, conducted in accordance with OECD TG 408, reported clinical signs of neurotoxicity and impaired performance in detailed neurotoxicity screening at doses of 184 mg Br<sup>-</sup>/kg bw per day, but not at 82 mg Br<sup>-</sup>/kg bw per day, with no associated histopathological findings (Study Report, 2000a). Similarly, a 90-day gavage study, conducted in accordance with OECD TG 408, reported changes in activity in a functional observational battery at 136 and 388 mg Br<sup>-</sup>/kg bw per day, but not at 47 mg Br<sup>-</sup>/kg bw per day (Study Report, 2016b). One study reported findings indicative of impaired spatial working memory in rats dosed by gavage for 28 days with 33 mg Br<sup>-</sup>/kg bw per day (only dose tested) (Safdari et al., 2017). In the absence of information related to the general toxicity of the rats, this study is not considered to be a robust basis for hazard assessment.

The effects seen at the lowest doses were changes in thyroid hormones levels in serum (see Section 3.1.3.5 and Table 3).

#### 3.1.3.2 | Developmental and reproductive toxicity studies

##### Reproductive studies

One three-generation reproductive study in rats has been conducted with sodium bromide. Reduced fertility and numbers of live pups were reported at a dietary concentration equivalent to about 340 mg Br<sup>-</sup>/kg bw per day. At lower doses (equivalent to 5–84 mg Br<sup>-</sup>/kg bw per day), the only effect reported was a dose related decrease in serum tT4 concentration (van Leeuwen et al., 1983). Significantly dose dependent decreased tT4 concentrations in the serum in both groups of the

<sup>25</sup>ECHA Information on biocidal active chemical substances: <https://echa.europa.eu/information-on-chemicals/biocidal-active-substances>.

F0 parent animals were reported after 6 weeks, with males being more sensitive. Total T4 concentration in serum was significantly decreased as soon as 3 days of treatment and it remained constant during an experimental period of 12 weeks.

In an unpublished report (Study report 2001, summary in (ECHA RAC, 2020)), a dose-range finding study for reproductive toxicity was conducted on ammonium bromide in rats at dietary concentrations equivalent to 0, 104, 198 and 410 mg Br<sup>-</sup>/kg bw per day for males and 0, 186, 370, 631 mg Br<sup>-</sup>/kg bw per day for females, dosing from 2 weeks prior to mating through to PND77. Clinical signs of neurotoxicity (e.g. hunched posture, decreased motor activity, ataxia), and decreased fertility and pup viability were observed with a NOEL of 104 mg Br<sup>-</sup>/kg bw per day. In another unpublished report (Study Report, 2016a), a two-generation study conducted in rats with gavage administration of sodium bromide equal to 0, 39, 136 and 272 (M)/388 (F) mg Br<sup>-</sup>/kg bw per day showed reduced fertility and effects on reproductive organs, with a NOEL of 39 mg Br<sup>-</sup>/kg bw per day.

#### *Developmental studies.*

A developmental study was conducted in pregnant rats given a single concentration of sodium bromide in drinking water, equivalent to about 175 mg Br<sup>-</sup>/kg bw per day from GD5 to 15, with observations focussed on the brain. Decrements in pup weight, effects on the brain and increased size of the olfactory glomeruli indicated delays in postnatal development (Disse et al., 1996). Unpublished developmental studies in rats dosed with ammonium bromide during GD6-19 reported skeletal anomalies in fetuses, in the absence of maternal toxicity, with a lowest LOAEL of 82 mg Br<sup>-</sup>/kg bw per day (Study Report, 1995, 2000b, 2007). No fetal anomalies were seen in two developmental studies in rabbits with sodium bromide at doses up to the maternally toxic dose of 310 mg Br<sup>-</sup>/kg bw per day (Study report, 2008 a summary in ECHA RAC (2020), Study report (2008).

Administration of bromide in drinking water at concentrations equivalent to doses of 90 and 450 mg Br/kg bw per day during lactation, or during both gestation and lactation, resulted in a significant trend for a decrease in the body weight of pups. An increase of thyroid weight relative to body weight was also observed in pups in both groups. However, this was likely due to the decreased body weights since the absolute thyroid weight was not increased. Furthermore, a decrease of milk production in the dams was demonstrated at the higher dose (Pavelka, 2002, 2009). The amount of bromide received daily by the pups, relative to body weight, was estimated to be three times lower than that received by the dams (Vobecký et al., 2005). According to Pavelka (Pavelka, 2009), the effects on pup weight in this study commenced on PND4; only about one-half of the young of top dose group survived and their general condition was very poor.

#### 3.1.3.3 | *Genotoxicity studies*

According to a personal communication cited by JMPR, sodium and ammonium bromide did not exert mutagenicity in *Salmonella* Typhimurium strains TA98 and TA100 with or without metabolic activation (JMPR, 1988). One recent study has reported on chromosomal aberrations, but with insufficient detail to assess the data (Almaaty et al., 2022).

Some additional information of relevance to bromide can be obtained from studies on biocidal products that release bromide published by the BPC. DBDCB is totally debrominated prior to systemic distribution, releasing two bromide ions from one molecule of DBDCB, together with 2-methyleneglutaronitrile (2-MGN). This reaction also occurs in blood in vitro, and the Scientific Committee considered it likely that it also occurs in cultured cells in vitro. The BPC concluded that DBDCB did not induce mutations in a bacterial Ames test or a mammalian cell gene mutation test (in hamster lung cells) with and without metabolic activation. An in vitro chromosomal aberration assay (in CHO cells) showed an increased frequency of aberrant metaphases, with and without activation, at concentrations exerting marked cytotoxicity. An in vitro UDS assay in cultured human fibroblasts produced negative results, with and without activation. Negative results were obtained in two in vivo assays in mice: a bone marrow micronucleus test at doses sufficient to exert systemic toxicity, and a dominant-lethal assay (ECHA, 2015).

Similarly, the BPC evaluated DBNPA, which is readily debrominated. According to the BPC, no indication for mutagenic potential was found in vitro or in vivo for DBNPA (ECHA, 2019).

The ECHA Risk Assessment Committee (RAC) received reports of a bacterial reverse mutation test, a mammalian cell mutation test and a mouse in vivo micronucleus test performed with ammonium bromide, and of a bacterial reverse mutation test, a mammalian chromosomal aberration test, and an in vitro unscheduled DNA synthesis test performed with sodium bromide. All these studies were conducted in compliance with the OECD guidelines in force at the time. The Scientific Committee noted that the positive effects were not observed in vitro, that the in vivo micronucleus test was conducted at ammonium bromide doses up to 1600 mg/kg bw per day, at which systemic toxicity is observed, and that bromide is fully absorbed, and it is expected to be distributed in all tissues.

Overall, the Scientific Committee concluded that the available data do not provide indications that bromide has mutagenic potential.

#### 3.1.3.4 | *Carcinogenicity*

One carcinogenicity study was identified, with potassium bromide administered to groups of male and female Fischer (F344) rats in the diet at 0 and 500 mg/kg for 2 years (Mitsumori et al., 1990). This dietary concentration of potassium bromide was equal to dose levels of 16.5 and 20.0 mg Br<sup>-</sup>/kg bw per day in males and females respectively. The authors

concluded that there were no treatment-related changes. The Scientific Committee noted that this study was conducted at a single dose level, which was low in comparison to the doses mostly used in studies of other effects and therefore inadequate to draw conclusions on carcinogenicity.

### 3.1.3.5 | *Effects on the thyroid and thyroid hormone system*

#### 3.1.3.5.1 | *Organ weight, histopathology, and morphological changes*

##### *Thyroid weight*

Effects on the thyroid in bromide-exposed rats are characterised by a dose-dependent increase in relative weight of the organ with morphological changes in both sexes. In a 90-day study, a statistically significant increase of thyroid weight relative to body weight was observed at the highest dose (388 mg Br<sup>-</sup>/kg bw per day) only in female rats (Study Report, 2016b). However, there was no effect on absolute thyroid weight. An increase in thyroid weight relative to body weight was also reported with a statistically significant increase at the highest dose (1797 mg Br<sup>-</sup>/kg bw per day) after 4 weeks and at 1348 mg Br<sup>-</sup>/kg bw per day after 12 weeks by Loeber et al. (1983).

Thyroid weight relative to body weight were also significantly increased in rat pups exposed to bromide via lactation (Pavelka et al., 2002). A dose-related increase in thyroid weight relative to body weight after 13 weeks of exposure to bromide was demonstrated in female rats starting from 84 mg Br<sup>-</sup>/kg bw per day. In male rats, relative thyroid weight was only increased at the highest dose (1348 mg Br<sup>-</sup>/kg bw per day), with decreased bw gain during the entire study (van Logten et al., 1974). This sex difference in rats was not observed under conditions of a low iodine diet after 4 weeks of treatment (Buchberger et al., 1990). In this study, an increase of the absolute thyroid weight in both sexes was reported in bromide treated groups in one study. Absolute thyroid weight was not reported in other studies.

##### *Histopathology – Morphological changes*

Histopathological changes in the rat thyroid were reported after a 4–13-week bromide administration at doses  $\geq$  337 mg Br<sup>-</sup>/kg bw per day (van Leeuwen et al., 1976; Loeber et al., 1983; van Logten et al., 1974). An increase in the number of follicles and a decrease in their size were also reported by Loeber et al. (Loeber et al., 1983). The height of follicular epithelium was increased, while the colloid was decreased in amount and was more granular in appearance, after a longer exposure time (12 weeks) at the highest dose only. There was no evidence of pathological continuum in the thyroid (no differences in the subjective severity score between 4 and 12-week time points and no signs of progression through thyroid follicular cell hyperplasia at any time point). Overall, the observed pattern of hormonal and histological changes is evidence of activation of the hypothalamus-pituitary-thyroid (HPT) axis, and this is further supported by the time-related increased number of TSH producing cells in the pituitary gland at 4- and 12-week sampling points (conducted only for animals belonging to the top dose).

van Leeuwen et al. (1976) also demonstrated thyroid effects in male and female rats, at 10-fold lower doses (35–140 mg Br<sup>-</sup>/kg bw per day) under low chloride intake. Histological and ultrastructural changes in thyroid of bromide exposed male rats, was also observed at lower doses (0.9–36 mg/kg bw per day) and at several times of exposure (16, 66 and 133 days) (Velický et al., 1998; Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997).

Velický et al. reported morphological changes in the thyroid, characterised by increased number of microfollicles, increased mitotic activity with statistically significant higher numbers of proliferating cell nuclear antigen (PCNA) positive nuclei (Velický et al., 1998; Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997). However, the level of positive PCNA thyroid follicular cells decreased with the time of exposure, indicating that there was no progression despite continued exposure. Ultrastructural analysis (Velický et al., 2004) performed on the follicular cells showed an enlargement of tubular structures (endoplasmic reticulum), an increased number of subapical granules with elongation of the microvilli facing the lumen of the follicles and increased surface pits. The overall pattern of morphological changes described by the study's authors is suggestive of thyroid follicular cell hypertrophy. The extent of morphological changes appeared to increase with the dose of bromide but after 16- and 66-day treatment they did not differ conspicuously at any given dose. Indeed, the most obvious histological features were seen at 6 and 12 mg Br<sup>-</sup>/kg bw per day, but at the highest dose of 36 mg Br<sup>-</sup>/kg bw per day, there was no corresponding increase in the severity of the lesion.

Overall, *in vivo* experimental studies conducted in rats indicate that exposure to bromide induces thyroid follicular activation which is expected to be associated with increased production of thyroglobulin. However, several limitations were recorded for the Velický et al. studies questioning the consistency of the perturbation of the HPT axis at lower doses (see Appendix A). This is also substantiated by lack of changes in TSH, lack of a clear dose response, low magnitude of the effect, if any, and by the variability of some parameters (e.g. tT4 levels). The risk of bias and the inconsistencies identified in these studies do not allow firm conclusions to be drawn on the dose–response relationship of bromide effects on the HPT axis. Although these results do not contradict the conclusions by Loeber et al. (1983), on bromide induced thyroid follicular cell activation, they are not considered as sufficient evidence of an adverse perturbation of the HPT axis.

The OECD TG 408 90-day study indicates decreased tT3 and tT4 and increased TSH at 136 mg Br<sup>-</sup>/kg bw per day as compared to concurrent controls, suggesting a bromide effect on the HPT axis (Study Report, 2016b). Consistently, at this dose, the reduced colloid at histopathological examination likely reflects a condition of follicular cell activation consequent to



sustained TSH stimulation. No effects were seen at 47 mg Br<sup>-</sup>/kg bw per day. These results are in line with the pattern of changes observed in Loeber et al. (1983).

Additional supportive morphological evidence:

- Cozzolino et al. (2005) observed flattening of the walls of vessels in the peripheral capillary networks in female rat thyroid after oral exposure to 0.9–8 mg Br<sup>-</sup>/kg bw per day for 16 and 66 days; an increase in number and density of meshes in the capillary network of the follicle was noted with increasing bromide and longer treatment period (Cozzolino et al., 2005).
- Depletion of colloid (mild–moderate) was observed in two male and two female rats at 136–388 mg Br<sup>-</sup>/kg bw day after 13 weeks in an OECD guideline study (Study Report, 2016b).
- Evidence available in other experimental vertebrate models corroborate the effect of bromide on the thyroid, such as a significant decrease of intrafollicular T4 content in Zebrafish *Eleuthero* embryos exposed to NaBr for 48 h (Thienpont et al., 2011). Bromide-induced hyperplasia was also observed in thyroid gland of exposed guppies (Canton et al., 1983).

### 3.1.3.5.2 | Hypothyroxinaemia and hormone levels

There was a statistically significant decrease of male rat serum tT4 after both 4- and 12-week treatment at 1348 mg Br<sup>-</sup>/kg bw per day via the diet. Also, at 112 mg Br<sup>-</sup>/kg bw per day, the tT4 level was significantly reduced after the 4-week exposure period. TSH levels were also significantly increased in the highest dose group (Loeber et al., 1983). The decrease in the tT4 level occurred concomitantly with other hormone changes; an increase in the insulin level after 4 and 12 weeks and a decrease in GH after 12 weeks. Follicle stimulating hormone (FSH) increased at the highest exposure starting at 4 weeks; the FSH level increase was dose-dependent after 12 weeks, luteinising hormone (LH) decreased after 4 weeks and testosterone decreased at high dose after 4 and 12 weeks. Body weight was decreased at the highest dose after 12 weeks. In another study, a dose-dependent decrease in serum tT4 was also observed in all bromide-exposed F0 male rats after 6 weeks (5–1348 mg Br<sup>-</sup>/kg bw per day, in the diet) and at the two highest levels in females (337 and 1348 mg Br<sup>-</sup>/kg bw per day) (van Leeuwen et al., 1983).

In two studies performed with rats exposed to lower bromide doses (0.9–36 mg Br<sup>-</sup>/kg bw per day, by drinking water exposure to 10–400 mg/L), fluctuation in tT4 and tT3 over time were observed, but without a clear pattern of consistency in terms of temporality and the effect size was very limited (Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997). For both tT4 and tT3, values were decreased by 25% and 20%, respectively, compared to the control group. This was corroborated by a lack of change in TSH (see Table 3 for details). According to the authors, the decrease in plasma tT4 was correlated with persisting morphological changes in the thyroid tissues (Velický et al., 1998; Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997). However, due to the poor description in the methodology, along with variability, small sample size and failure to replicate reductions in tT4 at the dose group common across both studies, the changes in hormone levels, if any, were considered questionable and not biologically relevant. This was supported by the assessment of the histopathological data as reported in Section 3.1.3.5.1, indicating that at the doses reported by Velický et al. (Velický et al., 1998; Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997), there is no sufficient evidence of an adverse perturbation of the HPT axis.

In another study from a different laboratory, exposure of female rats to bromide (90–450 mg Br<sup>-</sup>/kg bw per day) for 14 days before mating, through gestation until delivery and during lactation caused marked hypothyroxinaemia in the dams (tT4) and their pups, with the effect being more pronounced in pups (marked decrease of tT4 and tT3) (Pavelka et al., 2002). The decrease in thyroid hormones at high doses was confirmed in a later study designed to test the time dependency of bromide effect on the thyroid (Pavelka, 2012a, 2012b).

Thyroid hormone levels were measured in the week 4 of an OECD-compliant 90-day study where rats were dosed with sodium bromide by oral gavage at doses of 47–388 mg Br<sup>-</sup>/kg bw per day (Study Report, 2016b). There was a statistically significant decrease ( $p \leq 0.01$ ) of tT3 (males only) and of tT4 (males and females) at 388 mg Br<sup>-</sup>/kg bw per day. At 136 mg Br<sup>-</sup>/kg bw per day, differences from control in tT3 ( $p \leq 0.05$ , males) and tT4 ( $p \leq 0.01$ , males and females) were less marked, and values were comparable to the historical control values. Although not statistically significant (probably due to wide variation in individual results) mean TSH levels were 36% and 74% higher than controls in the two highest doses in male groups, respectively. There was no significant effect on TSH in females.

In contrast to the above studies, a significant increase of tT4 levels in serum of male rats was reported in another study after 28 days at the highest dose level tested (186 mg Br<sup>-</sup>/kg bw per day) (Newsome et al., 1978). The authors suggested that the reason these results were not consistent with those of other studies could be attributed to alteration of thyroid hormone turnover, i.e. a reduced peripheral tT4 metabolism.

### 3.1.3.5.3 | Iodine deficiency in bromide toxicity

Bromide toxicity depends upon the state of iodine supply in the animal. The effects of oral administration of large bromide doses (372–1490 mg Br<sup>-</sup>/kg bw per day) for 4 weeks on the biosynthesis of thyroid hormones were studied in iodine-deficient rats (Buchberger et al., 1990). Specifically, HPT disruption under conditions of low iodine intake was significantly enhanced by bromide intake (Buchberger et al., 1990). The decrease of tT3, rT3 and tT4 in the thyroid tissue and the decrease of tT4 and fT4 levels and increase of TSH in serum due to iodine deficiency were enhanced by bromide intake for 28 days (Buchberger et al., 1990).



Other studies (Pavelka, 2004; Vobecký et al., 1997) also demonstrated that signs of hypothyroidism (serum thyroid hormone levels) are enhanced under simultaneous low iodine intake. The thyroid I/Br molar concentration ratio decreased with increasing bromide intake (0.93–9.31 mg Br/kg bw per day) and/or duration. A decrease of the I/Br concentration ratio in rat thyroid (from approximately 40 to 6) was also reported after 16 and 66 days at doses of approximately 0.4–4 mg Br<sup>-</sup>/kg bw per day (Velický, Titlbach, Dusková, et al., 1997). The magnitude of the decrease in the I/Br ratio depended on the level of iodine supply to the animal. A fivefold lower I/Br ratio was observed in thyroid of rats with marginal iodine deficiency compared to animals with sufficient or higher iodine intake (Pavelka, 2004). In a 56-day experiment, the effect of bromide on relative thyroid weight in adult male rats exposed to sodium bromide via drinking water (450 mg Br<sup>-</sup>/kg bw per day) was more pronounced with a diet of very low iodine content compared to a standard diet, and increased with time of exposure (Pavelka, 2004, 2012a; Velický, Titlbach, Dusková, et al., 1997). It has been demonstrated that up to 40% of the iodine in the thyroid may be replaced by bromine with increasing bromide intake in rats (exposed via drinking water) (Vobecký et al., 2000).

In summary, bromide has a very low acute oral toxicity in rodents. Available studies did not provide indications that bromide is genotoxic or carcinogenic. Bromide is neurotoxic at dose in excess of 100 mg Br<sup>-</sup>/kg bw per day. In a three-generation study in rats, reduced fertility and a lower number of live pups were reported at a dietary concentration equivalent to 340 mg Br<sup>-</sup>/kg bw per day. Bromide effects on the thyroid were reported in several studies including an OECD TG 408 90-day study in rats. The effects reported included increase of the absolute/relative thyroid weight, histopathological and morphological changes, with statistically significant and dose-dependent decreases in serum thyroid hormones, mainly tT4. The observed pattern of hormone and histological changes is evidence of activation of the HPT axis, supported by a time-related increase in the number of TSH producing cells. I/Br ratio was also modified in the thyroid of rats exposed to bromide. One study provided evidence that HPT disruption depends on the state of iodine supply in the animals. Effects on the thyroid were also seen in dams and pups following exposure to bromide, including marked hypothyroxinaemia in the dams and a more pronounced decrease of tT4 and tT3 in the pups.

**TABLE 2** Summary of toxicity studies in experimental animals excluding studies on thyroid.<sup>26</sup>

Compound Purity	Species Number of animals Sex and Age	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
<b>Mouse – Adult</b>					
NaBr Altromin GmbH, Lippe 99.5%	NMRI mouse 20/group M Age/weight not specified	Diet 0, 400, 1200, 3600, 10,800 mg/kg NaBr Equivalent to 0, 62, 186, 559, 1676 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> (Br <sup>-</sup> in basal diet not measured) 36 days	Body weight, evasion time, spontaneous treadmill performance and nocturnal motility were recorded for a total of 128 days from 42 days before the start of administration of the test diets. Body weight was decreased at all doses in a dose-dependent manner. Behavioural changes were observed at all except the lowest dose.	LOAEL: 62 mg Br <sup>-</sup> /kg bw per day Based on body weight	Hansen and Hübner (1983)
<b>Rat – Adult</b>					
NaBr JT Baker Chemicals 99.5%	Wistar rat 8/group F 110–130 g	Diet 0, 300, 1200, 4800, 19,200 mg/kg NaBr Equivalent to 0, 28, 112, 447, 1788 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> (Br <sup>-</sup> in basal diet not measured) 4 weeks	Decreased BW gain in week 3. Clinical signs of CNS effects increased relative kidney weight at the top dose. No effects on terminal BW, feed consumption, brain or liver weight and no histopathological changes. At the top dose, around 50% of chloride was replaced by bromide in plasma, brain, kidneys and liver	NOAEL: 447 mg Br <sup>-</sup> /kg bw per day LOAEL: 1788 mg Br <sup>-</sup> /kg bw per day	van Logten et al. (1973)
KBr No info on sources or purity	F344 rat 60 M + 60 F 4 weeks old	Diet 0, 500 mg/kg KBr Equal to 0 and 16.5 (M) or 20.0 (F) mg Br <sup>-</sup> /kg bw per day (Br <sup>-</sup> in basal diet not measured) 104 weeks	Survival to 104 weeks was 42%, 43% and 40% for control, and treated M and F rats, respectively. Minor changes in clinical chemistry and urinalysis were considered incidental and not treatment related. Incidence of mononuclear cell leukaemia in F was significantly higher than controls (11/60 vs. 4/60), but not statistically significant compared to historical controls.	NOAEL: 16.5 mg Br <sup>-</sup> /kg bw per day	Mitsumori et al. (1990)
KBr Wako Chemical Co (Osaka, Japan) No info on purity	F344 rat 3/group M 5 weeks old	Drinking water 0, 1750 mg/L for up to 8 weeks Equivalent to 106 mg Br <sup>-</sup> /kg bw per day <sup>c</sup> (Br <sup>-</sup> in basal diet not reported)	No effects on hyaline droplet formation or cell proliferation kidney	NOAEL: 106 mg Br <sup>-</sup> /kg bw per day (the only dose tested)	Umemura et al. (1993)

(Continues)

<sup>26</sup>In chronological order within each section of the table.

TABLE 2 (Continued)

Compound Purity	Species Number of animals Sex and Age	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
NH <sub>4</sub> Br Purity: 99.94% No info on source	SD rat 5/sex/group Age/weight not specified	Diet 0, 100, 500, 1000 mg/kg bw per day NH <sub>4</sub> Br (nominal) Equal to 0, 82, 408, 816 mg Br <sup>-</sup> /kg bw per day 4 weeks	Clinical signs of neurotoxicity at 500 (M) and 1000 (M + F) mg/kg bw per day Decreased bw gain and feed consumption at top dose. Decreased absolute but not relative testes weight at all doses, with uncertain toxicological significance. Decreased absolute kidney weights (M) and absolute epididymis weights (M + F) at 500 and 1000 mg/kg bw per day. Changes in absolute heart liver and lung weights at 1000 mg/kg bw per day.	NOAEL = 82 mg Br <sup>-</sup> /kg bw per day LOAEL = 408 mg Br <sup>-</sup> /kg bw per day	Study report, 1999 in (ECHA RAC, 2020)
NH <sub>4</sub> Br Purity: 99.94% No info on source	SD rat 15/sex/groups (all dose groups) 25/sex/groups (control and high dose groups) OECD TG 408	Diet 0, 100, 225, 500, 750 mg/kg bw per day NH <sub>4</sub> Br (nominal) Equal to 0, 82, 184, 408, 612 mg Br <sup>-</sup> /kg bw per day 13 weeks + 4 weeks on untreated diet for 10 animals from control and high dose groups	Clinical signs of neurotoxicity at all except the lowest dose, commencing from approximately 8 weeks of treatment. Neurotoxicological findings included increased limpness, decreased alertness, increases in landing foot splay, and decreases in fore and hind limb grip strength at the mid and high dose. One low dose male showed slight limpness. No treatment-related histopathological changes in the nervous system Reduced bw gain in M ≥ 225 mg/kg bw per day and in F at 750 mg/kg bw per day. Decreased feed consumption in M ≥ 500 mg/kg bw per day. Decreased epididymis weight at the top dose, not related to lower bw No histopathological changes reported.	NOAEL = 82 mg Br <sup>-</sup> /kg bw per day LOAEL = 184 mg Br <sup>-</sup> /kg bw per day	Study Report (2000a)
KBr No info on purity	Wistar rat 7/group M 200 g	Gavage 50, 100, 150 mg KBr/kg bw Equal to 0, 33, 67, 100 mg Br <sup>-</sup> /kg bw in acute study 50mg KBr/kg bw per day 0, 33 mg Br <sup>-</sup> /kg bw per day in 28-day study	Tested in object recognition task, which indicates spatial working memory. Decreased recognition index at top doses and decreased discrimination index only at top dose following single administration. Reduction in frequency of exploration, and decreased discrimination and recognition index following 28-day administration. No information on general health of the animals	NOAEL = 67 mg Br <sup>-</sup> /kg bw per day in acute study LOAEL = 100 mg Br <sup>-</sup> /kg bw per day in acute study LOAEL = 33 mg Br <sup>-</sup> /kg bw per day in 28-day study (only dose tested)	Safdari et al. (2017)

TABLE 2 (Continued)

Compound Purity	Species Number of animals Sex and Age	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
KBr ≥99% purity	Albino rat 5/group M 110–130 g	Gavage 100 mg Br <sup>-</sup> /kg bw per day 30 days	Decreased serum total antioxidant capacity, catalase and GST. Dilation of the sinusoids and vacuolar degeneration in the liver. Chromosomal aberrations in bone marrow were assessed but with insufficient information to interpret. Significant upregulation (mRNA) of TGF-β1, VEGF, and COX-2 relative gene expression in liver tissue.	LOAEL = 100 mg Br <sup>-</sup> /kg bw per day (the only dose tested)	Almaaty et al. (2022)
<b>Rat – Reproductive and developmental studies</b>					
NaBr Purity 99.84% No info on source	CrI: CD BR VAF/Plus rat 25/group F OECD TG 414	Gavage 0, 100, 300, 1000 mg/kg bw per day NaBr during GD6-15 Equal to 0, 78, 233, 776 mg Br <sup>-</sup> /kg bw per day	Dams: Clinical signs of neurotoxicity, reduced feed intake at high dose. Reduced bw gain at the top two doses. Fetuses: No deaths or effects on bw or sex ratio. Increased skeletal anomalies at the top two doses, and visceral malformations at the top dose.	NOAEL = 78 mg Br <sup>-</sup> /kg bw per day LOAEL = 233 mg Br <sup>-</sup> /kg bw per day	Study Report (1995)
NaBr No info on source or purity	SD rat Pregnant F (18 treated) 9 pups/dam	Drinking water 0, 2500 mg/L Equivalent to 175 mg Br <sup>-</sup> /kg bw per day <sup>c</sup> GD5-15, pups observed up to PND 30 Br <sup>-</sup> in basal diet not reported	Decreased pup weight, brain weight and protein content of the brain, indicating delays in postnatal development. The size of olfactory glomeruli was consistently increased. Histopathological changes in the brain (details not provided)	LOAEL: 175 mg Br <sup>-</sup> /kg bw per day (the only dose tested)	Disse et al. (1996)
NH <sub>4</sub> Br No info on source or purity	SD rat 24/group F OECD TG 414	Gavage 0, 100, 300, 1000 mg/kg bw per day NH <sub>4</sub> Br Equal to 0, 82, 245, 816 mg Br <sup>-</sup> /kg bw per day GD6-19	Dams: Signs of severe neurotoxicity at the high dose. No effects at low and mid dose Fetuses: Decreased fetal body weight at the high dose. Increased visceral abnormalities at the top dose. Dose-related increased skeletal abnormalities starting at the low dose.	LOAEL = 82 mg Br <sup>-</sup> /kg bw per day (fetal toxicity)	Study Report (2000b)
NH <sub>4</sub> Br Purity: 99.94% No info on source	SD rat 10/sex/group	Diet 0, 1600, 3200, 6400 mg/kg in feed. Equal to 0, 127, 242 and 503 (M) and 0, 228, 454 and 651 (F) mg /kg bw per day NH <sub>4</sub> Br Equal to 0, 104, 197, 410 (M) and 0, 186, 370, 531 mg Br <sup>-</sup> /kg bw per day 2 weeks prior to mating through to PND77.	Parental generation: Signs of neurotoxicity at the top two doses in both M and F. Decreased bw gain (M + F) and feed consumption (M) at the top two doses. Decreased fertility at the top two doses. Changes in absolute but not relative organ weights at the top two doses Offspring: increased mortality at top two doses (100% at the top dose). Decreased mean body weight at mid-dose.	NOAEL = 104 mg Br <sup>-</sup> /kg bw per day LOAEL = 197 mg Br <sup>-</sup> /kg bw per day	Study report, 2001 in (ECHA RAC, 2020)

(Continues)

TABLE 2 (Continued)

Compound Purity	Species Number of animals Sex and Age	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
NaBr No info on purity	Wistar rat 5/group F 8–10 weeks old prior to mating	Drinking water 0, 1000, 5000 mg Br <sup>-</sup> /L for 28 days from PND2 Equivalent to 0, 90, 450 mg Br <sup>-</sup> /kg bw per day <sup>c</sup>	Dose-related decrease in maternal feed and water consumption, maternal body weight, milk production and pup survival.	LOAEL = 90 mg Br <sup>-</sup> /kg bw per day	Vobecký et al. (2005)
NH <sub>4</sub> Br No info on source or purity	SD rat 22/group F OECD TG 414	Gavage 0, 50, 300, 600, 800 mg/kg bw per day NH <sub>4</sub> Br during GD6-19 0 and 300 mg/kg bw per day NH <sub>4</sub> Br allowed to litter and rear young to PND21 without further treatment. Equal to 0, 41, 245, 490, 653 mg Br <sup>-</sup> /kg bw per day Additional groups at 0 and 300 mg/kg bw per day continued as recover groups for littering phase	Dams: Clinical signs of neurotoxicity at the top two doses. Maternal bw gain was decreased at the top dose and increased at the two mid-doses. Duration of gestation shorter than controls at 300 mg/kg bw per day. Fetuses: No effects on fetal weight or mortality. Increased incidences of skeletal anomalies at doses ≥245 mg/kg bw per day. Incidence of abnormalities were similar to controls in the weaned pups.	NOAEL = 41 mg Br <sup>-</sup> /kg bw per day LOAEL = 245 mg Br <sup>-</sup> /kg bw per day	Study Report (2007)
NaBr Purity 99.5% No info on source	CrI:CD(SD) rat 24/sex/ group OECD TG 416	Gavage 0, 50, 175, 350 (M)/500 (F) mg/kg bw per day NaBr Equal to 0, 39, 136, 272 (M)/388 (F) mg Br <sup>-</sup> /kg bw per day Commencing 10 weeks before mating through PND21 of F2 generation	Parental (P): Severe toxicity, decreased bw gain, decreased fertility and increased abnormalities in the reproductive organs at the top two doses, particularly in males. F1: Pups of top dose P generation were culled due to poor condition of P generation and low viability of pups. No adverse effects on mating or fertility at mid-dose. Decreased body weight and weights of reproductive organs in males. No effects at 50 mg/kg bw per day. No effects on the F2 litters	NOAEL = 39 mg Br <sup>-</sup> /kg bw per day LOAEL = 136 mg Br <sup>-</sup> /kg bw per day	Study Report (2016a)
<b>Rabbit – Developmental</b>					
NaBr No info on source or purity	Rabbit, New Zealand White 6/group F	Gavage 0, 100, 200, 400 mg/kg bw per day during GD3-28 Equal to 0, 78, 155, 310 mg Br <sup>-</sup> /kg bw per day Dose range finding study	Dams: Ataxia at top dose, no adverse maternal effects at lower doses. Fetuses: No indications of adverse effects at any dose	Maternal NOAEL = 155 mg Br <sup>-</sup> /kg bw per day Maternal LOAEL = 310 mg Br <sup>-</sup> /kg bw per day	Study report (2008) in (ECHA RAC, 2020)
NaBr No info on source or purity	Rabbit, New Zealand White 30/group F OECD TG 414	Gavage 0, 25, 75, 250 mg/kg bw per day during GD6-28 Equal to 0, 20, 61, 204 mg Br <sup>-</sup> /kg bw per day	Dams: No treatment-related effects Fetuses: No treatment related effects	NOAEL = 204 mg Br <sup>-</sup> /kg bw per day	Study Report (2008)

<sup>a</sup>Based on default conversion factor for subacute mouse study (EFSA, 2012).<sup>b</sup>Based on default conversion factor for subacute rat study (EFSA, 2012).<sup>c</sup>Based on default conversion factor for subchronic rat study (EFSA, 2012).



**TABLE 3** Summary of toxicity studies in experimental animals reporting effects on the thyroid.<sup>26</sup>

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
<b>Rat – Adult</b>					
NaBr JT Baker Chemicals 99.5%	Wistar rat 10/group M, F 50–60 g	Diet 0, 75, 300, 1200, 4800, 19,200 ppm NaBr Equivalent to 0, 5, 21, 84, 337, 1348 mg Br <sup>-</sup> / kg bw per day <sup>a</sup> (Br <sup>-</sup> in basal diet not measured) 13 weeks	Decreased BW gain in week 3. Clinical signs of CNS effects at top dose. Increased feed consumption in females at top 2 doses. No consistent changes in haematological or biochemical parameters, except for decreased aminopyrine demethylase in males at the top dose. Dose-related increase in relative thyroid weight from 1200 ppm in females and at top dose in males. Changes in some other organ weights (thymus, spleen, adrenals, prostate) at higher doses. Histopathological changes in the pituitary (cysts, only males) and thyroid (reduced follicle size, increased activity) at two top doses in females but only at the top dose in males. Decreased spermatogenesis at top dose.	NOAEL: 21 mg Br <sup>-</sup> /kg bw per day LOAEL: 84 mg Br <sup>-</sup> /kg bw per day Based on increased relative thyroid weight in females	van Logten et al. (1974)
NaBr JT Baker Chemicals 99.5%	Wistar rat 10/group M, F 50–60 g	Diet 0, 75, 300, 1200, 4800, 19,200 ppm NaBr with normal chloride (8 g/kg Cl <sup>-</sup> ) diet Equivalent to 0, 5, 21, 84, 337, 1348 mg Br <sup>-</sup> / kg bw per day <sup>a</sup> 0, 8, 31, 125, 500 and 2000 ppm NaBr with low chloride (1 g/kg Cl <sup>-</sup> ) diet Equivalent to 0, 0.56, 2.2, 8.8, 35 and 140 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> (Br <sup>-</sup> in basal diets not measured) 13 weeks	<b>Normal chloride diet:</b> Signs of neurotoxicity at the top dose. Terminal body weight was decreased in top dose males. Also, at the top dose, relative weights of thyroid were increased in both sexes and of pituitary and ovaries were decreased (females), and of adrenals were increased (males). Evidence of thyroid activation based on histopathological changes in the top two doses. Histopathological changes at the top dose in pituitary (cysts), adrenals, ovaries and testes (inhibition of spermatogenesis) <b>Low chloride diet:</b> Signs of neurotoxicity, decreased terminal body weight at the top dose and 3 males and 3 females died. Also at the top dose, relative weights of pituitary were decreased in females, and of adrenals were increased in males. Evidence of thyroid activation, and changes also noted in the adrenals and pancreas in the top two doses. Cl <sup>-</sup> was replaced by Br <sup>-</sup> in brain (25%) and kidneys (50%) at the top 2 doses with both normal and low chloride diet.	With normal chloride diet: NOAEL = 84 mg Br <sup>-</sup> /kg bw per day LOAEL = 337 mg Br <sup>-</sup> /kg bw per day Based on organ weights, thyroid effects With low chloride diet: NOAEL = 8.8 mg Br <sup>-</sup> /kg bw per day LOAEL = 35 mg Br <sup>-</sup> /kg bw per day	van Logten et al. (1976)

(Continues)

TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
NaBr	Sprague Dawley rat 10/group Male 125–150g	Diet 0, 200, 2000 mg/kg Equivalent to 0, 18.6, 186 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> 4 weeks	Statistically significant increase of tT4 level (57%) in serum of male rats at the highest dose after 28 days	NOAEL: 18.6 mg Br <sup>-</sup> /kg bw per day LOAEL 186 mg Br <sup>-</sup> /kg bw per day	Newsome et al. (1978)
NaBr JT Baker Chemicals 99.5%	Wistar rat 10 per group Male 60–100 g	Diet 0, 20, 75, 300, 1200, 19,200 mg/kg NaBr Equivalent to 0, 1.9, 6.8, 28, 112, 1797 mg Br <sup>-</sup> /kg bw per day 4 weeks <sup>b</sup> 0, 1.4, 5, 21, 84, 1348 mg Br <sup>-</sup> /kg bw per day 12 weeks <sup>a</sup> (Br <sup>-</sup> in basal diet not measured)	Increased relative thyroid weight, stimulation of the thyroid, decreased spermatogenesis, decreased tT4 and increased TSH, increased FSH, decreased testosterone, increased insulin and decreased growth hormone in serum, mainly at the top dose. Decreased body weight at the top dose after 4 and 12 weeks. Increased relative thyroid weight and decreased serum tT4 (28%, 58%) at the top two doses after 4 weeks, and only at the top dose (62%) after 12 weeks. Increased serum TSH at the top dose after 4 (3-fold) and 12 weeks (5-fold). Increased serum FSH at the top dose after 4 weeks and the top 2 doses after 12 weeks. Increased serum insulin at the top dose after 4 and 12 weeks. Histopathological changes in the thyroid (increased number of follicles and decreased follicular size) at the top dose, at 4 and 12 weeks. Effects at 4 weeks are of unclear relevance as they are transient and not accompanied by histopathological changes.	NOAEL: 84mg Br <sup>-</sup> /kg bw per day LOAEL: 1348 mg Br <sup>-</sup> /kg bw per day Based on increased relative thyroid weight and decrease of serum tT4 after 12 weeks	Loeber et al. (1983)
NaBr No info on source or purity	Wistar rat, 8/group Male 200-300g	Diet Control and 19,000 mg NaBr/kg Equivalent to 1768 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> 2 weeks	Decrease of body weight Decrease of absolute and relative thyroid weights Decrease of tT4 (56%), increase of TSH (2-fold), decrease of I uptake. Decreased TPO activity, increase of Guaiacol-TPO. Increased NADPH-cyt.c reductase in thyroid	LOAEL: 1768 mg Br <sup>-</sup> /kg bw per day (the only dose tested)	van Leeuwen et al. (1988)

TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
NaBr No info on source or purity	Sprague Dawley rat 12/sex/group M, F 10 weeks old	Diet (low iodine diet) 0, 4000, 8000, 16,000 mg NaBr/kg in low iodine diet (Altromin C-1042, 0.060 mg iodine/kg) Equivalent to 0, 372, 745, 1490 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> (Br <sup>-</sup> in basal diet not measured) Two control groups: normal or Low iodine diet 2 weeks acclimation to the diet and 4 weeks NaBr treatment	All bromide-treated animals were fed iodine-deficient diets and effects of bromide were assessed compared to low-iodine control group. Effects of iodine deficiency in control rats were compared to effects in the control group fed normal diet. Moribund and dead animals found after 26 days at the two highest Br <sup>-</sup> doses, leading to termination of the top dose group at the end of week 5. Hypoactivity observed at the top two dose groups. No clinical signs in the low-dose group. Dose-related decrease in serum fT4 (> 50% at top two doses) and increase in serum TSH levels at all doses (from 30% up to 70%). Dose-related trend of increasing relative and absolute thyroid weights. except at the highest dose which was toxic. No statistical analysis is presented. Trends of tT4 were roughly the same as those of fT4. No sex difference in serum tT4, fT4 and TSH. Tri-substituted bromo/iodothyronines were detected in all thyroids of bromide-treated groups, with lower levels of tT3, and tT4 compared to control.	LOAEL: 372 mg Br <sup>-</sup> /kg bw per day Based on serum fT4 and thyroids wet weights in iodine-deficient rats	Buchberger et al. (1990)
KBr Analytic grade	Wistar rat 6/group Male 41 days old	Drinking water 0, 10, 50, 100 mg Br <sup>-</sup> /L for 16 days Equivalent to 0, 1.2, 6, 12 mg/kg bw per day <sup>b</sup> 0,10, 50, 100 mg Br <sup>-</sup> /L for 66 days Equivalent to 0, 0.9, 4.5, 9 mg/kg bw per day <sup>a</sup> Content of diet: 10.04 mg Br <sup>-</sup> /kg (equivalent to 1.2 mg/kg bw) and 0.52 mg I <sup>-</sup> /kg	Dose-related decrease (≤ 25%) in plasma level of tT4 after 16 and 66 days in all animals. tT3 decreased after 66 days at all doses (< 20%), but not after 16 days. No statistically significant effect on TSH ( <i>p</i> > 0.05). Decrease of the I/Br molar concentration ratio with increasing bromide intake and/or duration. Reported histological observations included growth of the follicular epithelial component, mitoses and microfollicular reorganisation, with lower amount of colloid in the tissue, follicular cells featured multiple PAS positive spherical vacuoles. There was no clear dose dependence for the changes.	NOAEL: 0.9 mg/kg bw per day LOAEL: 4.5 mg/kg bw per day Based on tT4 plasma levels after 66 days	Velický, Titlbach, Dusková, et al. (1997)

(Continues)

TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
KBr Analytic grade	Wistar rat 10/group (3–4 per time point) Male 41 days old	Drinking water 0, 10, 50, 100mg Br <sup>-</sup> /L for 16 days or 66 days Equivalent to 0, 1.2, 6, 12 mg/kg bw per day <sup>b</sup> after 16 days and 0, 0.9, 4.5, 9 mg/kg bw per day <sup>a</sup> after 66 days 0, 100, 200, 400 mg Br <sup>-</sup> /L for 133 days Equivalent to 0, 9, 18, 36 mg/kg bw per day <sup>a</sup>	Microfollicular rearrangement in thyroids of exposed rats with reduction of the number of colloids. Number of PCNA-positive nuclei (PCNA-LI index) higher in Br-treated animals and increased with increasing bromide dose, although not clearly dose related at 16 days. Changes are evidence of sustained TSH stimulation. Values of PCNA-LI in rats exposed to bromide decreased with exposure, indicating that the changes are not progressive.	NOAEL: 1.2 mg/kg bw per day LOAEL: 6 mg/kg bw per day Based on histological feature	Velický, Titlbach, Lojda, et al. (1997)
KBr Analytic grade	Wistar rat 10/group Male 41 days old	Drinking water 0, 100, 200, 400mg Br <sup>-</sup> /L Equivalent to 0, 9, 18, 36 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> (133 days) 19 weeks Content of diet: 10.04 mg Br <sup>-</sup> /kg and 0.52 mg I <sup>-</sup> /kg	Increased numbers of microfollicles with increased height of follicular cells and decrease in colloid, indicating thyroid follicular cell hypertrophy. Decrease of Tg immunoreactivity Complete loss of Tg immunoreactivity. Electron microscopy indicated changes in the localisation of Golgi apparatus, rough ER, lysosomes and microvilli of thyrocytes starting at 9 mg/kg bw per day. Authors reported a dose-related decrease of tT4 for all treated animals (≤20%). The Scientific Committee noted problems with the statistical analysis. No significant increase in TSH. Bromine level decreased I in the thyroid, with increasing concentration of bromide.	LOAEL: 9 mg Br <sup>-</sup> /kg bw per day Based on the decrease of tT4	Velický et al. (1998)
KBr Analytic grade	Wistar rats 10/group Male 41 days old	Drinking water 0, 10, 50, 100mg Br <sup>-</sup> /L For 16 days, equivalent to 0, 1.2, 6, 12 mg/kg bw per day <sup>b</sup> 2 weeks For 66 days, equivalent to 0, 0.9, 4.5, 9 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> 9.5 weeks 0, 100, 200, 400 mg Br <sup>-</sup> /L For 133 days, equivalent to 0, 9, 18, 36 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> 19 weeks Content of diet: 10.04 mg Br <sup>-</sup> /kg and 0.52 mg I <sup>-</sup> /kg	Enlargement of tubular structures (endoplasmic reticulum) associated with an increased number of subapical granules, and possible microvilli elongation and surface pits increase, particularly at 100 and 200 mg Br/L and above possibly increasing in severity with time. Features compatible with the morphological characterisation of microfollicles are noted, mostly at 100 mg and 200 Br/L. At 400 mg Br/L, there is no corresponding increase in the severity of the lesion, rather a decreased severity of the lesions is reported by the study author, with no details.	NOAEL 0.9 mg Br <sup>-</sup> /kg bw per day LOAEL 4.5 mg Br <sup>-</sup> /kg bw per day (ultrastructural changes in thyrocytes)	Velický et al. (2004)

TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
KBr No info on source of purity	Female Wistar rats 5 per group 190-230g	Drinking water 0, 10, 50, 100 mg/L 16 or 66 days Equivalent to 0, 1.2, 4, 8 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> Equivalent to 0, 0.9, 3, 6 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> Br <sup>-</sup> in basal diet not measured	Thyroids were examined by scanning electron microscopy. All treated rats presented an increased density and number of meshes in the capillary network of the follicle. Capillary meshes denser and more diffused with increasing dose and time. Peripheral vessels showed flattening of the walls and in the central portion of follicle. Altered follicles received less blood. Presence of angiogenic sprouts in the follicular capillary networks of animals that ingested potassium bromide.	Not possible to determine (qualitative observations)	Cozzolino et al. (2005)
Br <sup>-</sup> (Compound not specified) No info on purity	Wistar rats 10/group Male 250-290g	Drinking water 0, 500, 5000 mg/L Br <sup>-</sup> (14 days experiment) Equivalent 0, 60, 600 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> 2 weeks 0, 3000, 5000 mg/L Br <sup>-</sup> (56 days for tT4 determination) Equivalent 0, 270, 450 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> 8 weeks Two diets: iodine sufficient or low iodine Content of iodine sufficient diet (1.2 mg I <sup>-</sup> /kg): 3.8 mg Br <sup>-</sup> /kg Content of low iodine diet (0.06 I mg/kg): 1 mg/kg Br <sup>-</sup> 14 days (time course) 56 days (TPO and tT4 levels in sera)	<sup>131</sup> Iodide uptake depended on the diets. Enhanced bromide intake produced inhibitory effect on iodide uptake by the thyroid (after 24 h application of <sup>131</sup> iodide), decrease of iodide was more pronounced in the low I diet only at the highest concentration. Biphasic effect of bromide on TPO activity in thyroid observed, only the highest concentrations of bromide exerted inhibitory effect of microsomal TPO regardless of diet. Decrease of serum tT4 (55%) in male rats after 56 days treatment at the top dose in normal diet No statistics	LOAEL: 60 mg Br <sup>-</sup> /kg bw per day in an iodine-sufficient diet (2 weeks) Based on decreased iodide uptake NOAEL: 270 mg/kg bw per day LOAEL: 450 mg Br <sup>-</sup> /kg bw per day (8 weeks) Serum tT4 (iodine normal diet)	Pavelka (2012b)

(Continues)



TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
NaBr Purity 100%	CrI:CD(SD) rat 10/sex/group M, F OECD TG 408	Gavage 0, 60, 175, 500 mg/kg bw per day NaBr Sodium chloride comparator group received 284 NaCl mg/kg bw per day Equal to 0, 47, 136, 388 mg Br <sup>-</sup> /kg bw per day 13 weeks	<p>Clinical signs of neurotoxicity, reduced body weight gain, feed intake and water consumption, generally more severe in males, at top two doses. Changes in functional observation battery and in motor activity were reported at the top dose, and to a lesser extent at the mid-dose.</p> <p>Statistically significant increase of the relative thyroid weight in female at the highest dose</p> <p>Serum thyroid hormones were analysed only in week 4.</p> <p>Statistically significant decrease of tT3 at higher doses in males only, (28% and 37%) at 136, and 388 mg/kg bw per day, respectively).</p> <p>Statistically significant decrease of tT4 in males (28% and 52%) at 136, and 388 mg/kg bw per day, respectively and in females (26%, 34% and 47%) at 47, 136, and 388 mg/kg bw per day, respectively.</p> <p>Increases in TSH, 36% and 74% higher than controls (male rats) at 136–388 mg/kg bw per day, respectively not statistically significant (but wide variation in individual results).</p> <p>Levels at the low and mid-dose were within the historical control range.</p> <p>Depletion of colloid (mild–moderate) observed at 136 mg/kg bw per day and 388 mg/kg bw per day.</p> <p>In the absence of effects on thyroid weight and histopathology, the authors concluded that the changes at the low dose were not adverse.</p> <p>NaCl had no effects, demonstrating that the effects observed with NaBr were due to Br<sup>-</sup></p>	NOAEL = 47 mg Br <sup>-</sup> /kg bw per day LOAEL = 136 mg Br <sup>-</sup> /kg bw per day Serum tT4 and T3	Study Report (2016b)

TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
Rat – Developmental NaBr No info on source or purity	Wistar rat 10/sex/group F0: M, F	Diet 0, 75, 300, 1200, 4800, 19,200 ppm NaBr in F0. 0, 75, 300, 1200, ppm NaBr in F1 and F2. Equivalent to 0, 5, 21, 84, 337, 1348 mg Br <sup>-</sup> /kg bw per day (Br <sup>-</sup> in basal diet not measured) <sup>a</sup> 3-generation study	Complete infertility at 19200 ppm. Reduced fertility and live pups at 4800 ppm. No effects on reproductive performance, pup viability or BW at doses up to 1200 ppm in any generation. BW decreased in F2 males and females at 1200 ppm. No change in relative thyroid weight in any of the F0, F1 or F2 dose groups Dose-related decrease in serum tT4 (10, 16, 25, 40, 60%) at all doses in F0 males and at the top two doses (20, 35%) in F0 females after 6 weeks. 'Less pronounced' at the lower dose levels after 12 weeks and in the F1 and F2 generations. (data not shown)	LOAEL: 5 mg Br <sup>-</sup> /kg bw per day Based on decreased serum tT4	van Leeuwen et al. (1983)
Unclear, refers only to Br <sup>-</sup>	Wistar rat 5-10/group Pregnant F 200g	Drinking distilled water 14 days before mating and until PND 16 Group A: 0, 1000, 5000 mg/L during lactation only. Group B: 1000 mg/L from 14 days before mating to PND0 followed by 0, 1000, 5000 mg/L during lactation. Equivalent to 0, 120, 600 mg Br <sup>-</sup> /kg bw per day (group A) <sup>b</sup> Equivalent to 0, 90, 450 mg Br <sup>-</sup> /kg bw per day (group B) <sup>a</sup> Bromide content in diet: 3.8 mg Br <sup>-</sup> /kg diet, equivalent to 0.3 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> and 1.2 mg iodine/kg	Dams: dose-related decrease in tT4 (by about 57% at top dose) and in tT3 (by up to 35%). Decreased milk production at top dose. No other effect on dams. Pups: Dose-related decreased BW and increased relative but not absolute thyroid weight. Decreased tT4 (by up to 70%) and tT3 (by up to 65%).	LOAEL: 120 mg Br <sup>-</sup> /kg bw per day (Group A) LOAEL: 90 mg Br <sup>-</sup> /kg bw per day (Groups B) Based on decreased serum tT4 and tT3 in pups	Pavelka et al. (2002)

(Continues)

TABLE 3 (Continued)

Compound Purity	Species Number of animals Age and gender/ Weight	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
Br <sup>-</sup> (Compound not specified) No info on purity	Wistar rat 12 dams, each with 8 pups (lactation and hypothyroid status experiments) M 8–10 weeks (Goitrogenic experiment) 6/group per time point	Drinking water Lactating dams: 5000 mg Br <sup>-</sup> /L Exposed PND 0–15 Males: 5000 mg Br <sup>-</sup> /L Exposed 56 days Equivalent to 450 mg/kg bw per day <sup>a</sup> Females: 1000 and 5000 mg Br <sup>-</sup> /L Exposed PND 0–17 (For hypothyroid status in pups <sup>1</sup> experiment) Equivalent to 120 and 600 mg Br <sup>-</sup> /kg bw per day <sup>b</sup> Content of bromide in iodine-sufficient diet (1.2 mg I <sup>-</sup> /kg): 3.8 mg Br <sup>-</sup> /kg diet, equivalent to 0.3 mg Br <sup>-</sup> /kg bw per day <sup>a</sup> Content of bromide in low iodine diet (0.06 mg I <sup>-</sup> /kg): 1 mg Br <sup>-</sup> /kg diet, equivalent to 0.09 mg Br <sup>-</sup> /kg bw per day <sup>a</sup>	Hypothyroid effect in pups at 5000 mg Br <sup>-</sup> /L Significant increase in the relative weight of thyroids of pups at 5000 mg Br <sup>-</sup> /L on PND 17. Dose dependent hypothyroxinaemia in dams and pups, with decrease in both tT4 (46, 52% in dams; 35–69% in pups) and in tT3 for pups (24, 54%) High bromide intake (5000 mg/L) in lactating dams caused a decrease in the iodide transfer into the pups. Increased relative thyroid weight in adult male rats in a standard diet. Effect more pronounced with low iodine diet. Effect increased with time of exposure. No statistics	LOAEL: 120 mg Br <sup>-</sup> /kg bw per day Based on serum tT4 levels (dams and pups)	Pavelka (2012a)

<sup>a</sup>Based on default conversion factor for subchronic rat study (EFSA, 2012).

<sup>b</sup>Based on default conversion factor for subacute rat study (EFSA, 2012).

### 3.1.4 | Observations in humans

#### 3.1.4.1 | Biomarkers of exposure to bromide

Bromide concentration in human biological samples (blood, saliva or urine)<sup>27</sup> is used to monitor bromide exposure, particularly to detect unusually and potentially adverse high concentrations due to ingestion of sedative-hypnotic drugs, foods treated with pesticides or other occupational and environmental sources of exposure (Lascu et al., 2019). For example, the mean concentration of bromide in human blood of 183 randomly collected blood specimens from healthy individuals in the State of Queensland (Australia) was  $5.3 \pm 1.4$  mg/L and ranged from 2.5 to 11.7 mg/L (Olszowy et al., 1998). Bromide blood concentrations were suggested to vary with age and sex (Olszowy et al., 1998), but such associations have not been detected in other studies (Allain et al., 1990; de Jong & Burggraaf, 1983; Michigami et al., 1989; Nusair et al., 2019).

Bromide blood concentrations were determined in blood samples collected from 34 child patients with epilepsy at least 3 weeks after the last change in dosage of bromide (Ernst et al., 1988). In this group, the average dosage, body weight and blood concentrations ( $\pm$ SD) were 1520.2 ( $\pm$ 674.7) mg/day, 33.1 ( $\pm$ 19.2) kg and 75.8 ( $\pm$ 23.5) mg/L, respectively.

The correlation between bromide intake and blood (i.e. serum) bromide concentrations has also been reported in a later study (Braam et al., 2006). These authors showed that subjects ( $n=8$  in each group) taking 5, 24 and 30 mg/day of KBr daily for 20 weeks had a dose-dependent increase in blood bromide concentrations over time. Baseline bromide concentrations for the 5, 24 and 30 mg KBr/day groups were (mean  $\pm$  SD)  $5.6 \pm 0.32$ ,  $5.6 \pm 1.6$  and  $5.6 \pm 1.6$  mg/L, respectively. Steady state was reached after 6–10 weeks with bromide concentrations of  $11.2 \pm 2.4$ ,  $16.0 \pm 3.2$  and  $20.8 \pm 5.6$  mg/L, respectively. Four weeks after the end of the KBr supplementation, blood concentrations returned to the baseline concentrations. There was considerable inter-individual variability in blood concentrations of KBr, likely due to variability in absorption and clearance among individuals. This suggests that the use of blood  $\text{Br}^-$  concentrations as a biomarker of exposure could be more useful to differentiate between groups than between individuals. The authors observed that taking into account body weight could improve the correlation between dose and serum bromide concentration (Braam et al., 2006).

Little information is available about the suitability of urinary bromide concentrations to reflect exposure, thus precluding a comprehensive assessment of the reliability of this biomarker with reference to bromide dietary intake, while for occupational exposure urinary bromide has been shown to reflect a high level of exposure (Hanley et al., 2006, 2010; Kawai et al., 2001). Tubular reabsorption of bromide is faster than that of chloride, thus excretion of bromide can be increased or decreased by administering a salt-deficient diet or an excess of chloride ions, respectively (Vaiseman et al., 1986). This makes urinary concentration less reliable as biomarker of bromide exposure.

Among the limited information available on the relation between dietary and urinary bromide, one study has assessed the correlation between dietary patterns, in terms of food consumption, and urinary bromide concentration in East Asia. Bromide concentration in spot urines was positively correlated with consumption of various food groups at 10 survey sites, with correlation coefficients greater than 0.5 for fruits, algae, fish and shellfish intake (Kawai et al., 2002).

#### 3.1.4.2 | Adverse health effects of therapeutic application of bromide

Bromide has been used as an antiepileptic medicine and sedative at doses as high as 31 g/day, but the usual administered dose does not exceed 6 g/day (100 mg/kg bw per day) (EMA, 1997). Bromism is the term used to describe symptoms associated with elevated blood bromide concentrations. Symptoms can be mild (tiredness, lack of concentration and drowsiness). Large doses of bromide cause nausea and vomiting, abdominal pain, coma and paralysis. Doses of bromide giving blood concentrations of 959 mg/L produce bromism (the chronic state of bromide intoxication), and plasma concentrations greater than 3196 mg/L can be fatal (EMA, 1997). Bromism is associated with effects on the nervous, dermal, endocrine and gastrointestinal systems (van Leeuwen & Sangster, 1987). Effects on the nervous system include restlessness, headache, delirium and dementia. Other neurologic changes, such as diminished deep tendon reflexes, loss of pupil reflexes, papilledema, increased cerebrospinal fluid pressure, slowing of the delta waves on electroencephalogram, loss of the gag reflex and anorexia may occur (Ryan & Baumann, 1999).

Generally, therapeutic use of bromide is associated with serum bromide concentrations of 5–50 mg/L. Toxic concentrations range from 700 to 4100 mg/L and concentrations  $> 2000$  mg/L may be fatal. Cases of bromism have been reported at concentrations as low as 40 mg/L (Health Council of the Netherlands, 2005). Lugassy & Nelson (2009) considered toxic concentrations of bromide in blood to be  $> 500$  mg/L, and severe systemic toxicity can occur at concentrations  $> 2000$  mg/L. However, these authors also noted that lower serum bromide concentrations were associated with adverse health effects, indicating that other factors, such as chronicity of exposure, age, blood volume and renal function can alter the effect for a given serum bromide concentration (Lugassy & Nelson, 2009).

An acute overdose of bromide salts can result in nausea and vomiting due to the irritating effect of bromides on the gastrointestinal tract. Poisoning or high blood bromide serum concentrations is due to chronic repeated exposure during weeks to months or years (Lugassy & Nelson, 2009). Adverse effects on the skin caused by a high exposure to bromide include acneiform rashes and granulomatous lesions. Patients with elevated bromide concentrations may have a loss of appetite and, if continued, become underweight.

<sup>27</sup>The blood bromide concentrations that were reported in other units in the literature were converted to mg/L for direct comparison. 1 mEq/L = 79.9 mg/L; molecular weight bromide: 79.9045.

### 3.1.4.3 | *Experimental studies in humans of bromide effects on the thyroid*

Variability in thyroid hormones levels within (during the day) and between individuals is frequent and common. An evaluation of the variation in TSH and T4 (free and total) was carried out in two different cohorts by monthly blood sampling of 35 persons for 1 year (Andersen et al., 2022). Participants were included based on tT4 within the reference range and TSH either within (euthyroid;  $n=15$ ) or above (subclinical hypothyroidism;  $n=20$ ) the laboratory reference range. In the euthyroid and subclinical hypothyroid groups, the mean TSH was 1.27 and 7.19 mIU/L, respectively, and the mean tT4 was 106 and 85 nmol/L, respectively. The subclinical hypothyroidism state deviated from the euthyroid by 20% for tT4 and by 466% for TSH. There was no confidence interval overlap of the estimated AUC between participant groups for TSH while there was a considerable overlap for tT4 (Andersen et al., 2022).

Experimental human studies are described in Table 4. These studies were appraised for RoB and the outcome is summarised in Appendix B.

Sangster et al. (1982) carried out a study with human volunteers following the findings in two 90-day rat toxicological studies with bromide by van Logten et al. that had shown changes in the endocrine system (for males changes in pituitary gland, thyroid, adrenals, testes and prostate and in females thyroid, adrenals and ovaries were affected) (van Leeuwen et al., 1976; van Logten et al., 1974). Sodium bromide at 1 mg Br<sup>-</sup>/kg bw per day was administered orally by capsules to 20 healthy volunteers (10 females not using oral contraceptives and 10 males) during 8 weeks (Sangster et al., 1982). In the females, bromide was administered during two full menstrual cycles. There were no differences observed in physical examinations before and after the intakes; haematological, biochemical and urine parameters did not change. Plasma bromide concentrations ( $\pm$ SD) rose in females and males from  $6.39 \pm 0.8$  mg/L to  $77.5 \pm 14.4$  mg/L and from  $6.39 \pm 0.8$  mg/L to  $66.3 \pm 7.19$  mg/L, respectively. Because the concentration of hormones in blood can vary significantly throughout the day, blood sampling of the subjects always took place between 9:00 and 10:00 in the morning. No changes were observed in the serum concentrations of tT4, fT4, TBG,<sup>28</sup> tT3, cortisol, testosterone, oestradiol or progesterone. There were also no changes in the serum concentrations of TSH, prolactin, LH and FSH measured before as well as 20 and 60 min after the administration of thyrotropin-releasing hormone (TRH)<sup>29</sup> and luteinising hormone releasing hormone (LHRH) (Sangster et al., 1982).

In another experimental study, healthy volunteers were given sodium bromide at oral bromide doses of 0, 4 or 9 mg/kg bw per day (Sangster et al., 1983).<sup>30</sup> For each treatment regimen, groups of seven males received the treatment for 12 weeks, and groups of seven females (not using oral contraceptives) received it over three full menstrual cycles. At the beginning and end of the study, a full medical history, the results of physical examination, haematological studies, standard clinical chemistry and urine analyses were recorded for each subject. Except for incidental nausea ( $n=0$  in control group,  $n=2$  in 4 mg group and  $n=5$  in 9 mg group; nausea disappeared when bromide capsules were taken with a meal), no changes were observed. Mean plasma bromide concentrations at the end of treatment were 6.39, 171 and 344 mg/L for males and 5.59, 244 and 394 mg/L for females in the 0, 4 and 9 mg/kg bw per day bromide dose groups, respectively. Only for the females receiving bromide at 9 mg/kg bw per day, there was a statistically significant increase in serum fT4 ( $p < 0.05$ ), tT4 and tT3 ( $p < 0.01$ ) at the end compared to concentrations at the start of the study. The tT3, fT4 and tT4 serum concentrations did not change in the 0 mg and 4 mg groups and increased from  $1.8 \pm 0.2$  to  $2.1 \pm 0.2$  nmol/L,  $22 \pm 2$  to  $25 \pm 2$  pmol/L and from  $115 \pm 11$  to  $131 \pm 15$  nmol/L, respectively, in the 9 mg group (Sangster et al., 1983). No changes were observed in serum concentrations (determined by radioimmunoassay) of fT4, TBG, cortisol, oestradiol, progesterone or testosterone, TSH, prolactin, LH and FSH before or after the administration of TRH and LHRH. To assess the activity of the central nervous system, the spontaneous electroencephalogram (EEG) and evoked cerebral activity of each subject were recorded and analysed quantitatively at the start and end of the trial. A decrease in  $\delta_1$ - and  $\delta_2$ -activities and increases in  $\beta$ -activities and mean frequency (Mobility parameter) were observed in the groups on 9 mg Br<sup>-</sup>/kg bw per day (Sangster et al., 1983). Although all findings were, according to the authors, within normal limits, changes in thyroid hormones can lead to disturbances or imbalances of the thyroid function. Furthermore, even a reversible change in thyroid hormone homeostasis, can be sufficient to affect the developing brain (Hall et al., 2023; Korevaar et al., 2016).

In 1986, these researchers carried out a randomised, double-blind study to examine whether the results reported in 1982 and 1983 were reproducible (Sangster et al., 1986). Three groups of 15 female healthy volunteers (not taking oral contraceptives, 20–28 years old) each were given 0, 4 or 9 mg Br<sup>-</sup>/kg bw per day (as NaBr) during three full menstrual cycles followed by three cycles without bromide supplementation. Nausea was not reported in the control group; it was reported by three persons in the 4 mg group and by 11 persons in the 9 mg group. Plasma bromide concentrations were unchanged for the placebo group and rose from 4.0 mg/L at the start of the administration period (baseline) to 257.3 mg/L in the 4 mg/kg group and from 4.0 to 638.4 mg/L in the 9 mg/kg group. At the end of the experiment, thus after six menstrual cycles with the last three cycles without additional NaBr, serum concentrations had returned to baseline concentrations (7.2, 8.8 and 8.0 mg/L) for the 0, 4 and 9 mg/kg bw groups, respectively. This study did not show effects on serum concentrations of fT4, tT4, T3 and TBG. Analysis of the EEGs showed small, reversible effects for the 4 mg group and a marginal effect in females receiving bromide at 9 mg/kg bw per day, similar to the effects observed in Sangster et al. (1983), Sangster et al. (1986).

<sup>28</sup>Thyroxine-binding globulin (TBG) is a transport protein, which binds and transports thyroid hormones to the tissues.

<sup>29</sup>Hypothalamic thyrotropin-releasing hormone (TRH) stimulates thyroid-stimulating hormone (TSH) secretion from the anterior pituitary.

<sup>30</sup>Volunteers were administered NaBr capsules daily according to weight class. From the information in the paper, it can be calculated that the mean intake per day of NaBr from the capsules was for males 5.12 and 11.45 mg/day in the 4 and 9 mg/kg bw group and for females 5.43 and 11.78 mg/day in 4 and 9 mg/kg bw group.



The Scientific Committee noted possible errors in the paper by Sangster et al. (1986)/van Gelderen et al. (1993), namely in the concentrations of fT4 and TSH for the 0 mg group. The mean concentrations ( $\pm$ SD) according to the individual concentrations reported in Sangster et al. (1986) were at the start of the experiment for fT4 24.5 ( $\pm$ 1.8) and after three menstrual cycles 26.0 ( $\pm$ 3.3) pmol/L instead of 24.2 and 25.9, respectively. For TSH, the concentrations should read 2.0 ( $\pm$ 0.7) and after three menstrual cycles 1.8 ( $\pm$ 0.8). They were reported as 2.0 ( $\pm$ 0.7) and 2.8 ( $\pm$ 0.8), respectively. The (correct) data show an increase in TSH in the 9 mg group (from 1.8 to 2.1 mIU/L). In the 9-mg group, 11 women had an increased TSH concentration after three menstrual cycles and four had a decreased TSH concentration.

When comparing the results of these studies, the Scientific Committee notes that the serum bromide concentrations in the group of women who received 9 mg Br<sup>-</sup>/kg bw per day in the study by Sangster et al. (1986)/van Gelderen et al. (1993) were higher than the concentrations in women receiving the same amount of bromide in the study by Sangster et al. (1983): 638 compared to 394 mg/L, respectively. Serum bromide concentrations in these studies (Sangster et al., 1982; Sangster et al., 1983) increased more in women than in men following NaBr administration per kg bw. The possible reasons for these differences in bromide serum concentrations were not discussed by the authors.

The Scientific Committee also notes that the doses in these studies did not take into account background exposure from food and drinking water. The typical daily dietary intake of bromide in the United States of America was reported as 2–8 mg (Nielsen & D. M., 2009) from grains, nuts and fish. The average bromide intake from dietary sources in the Netherlands was reported as 8.4–9.4 mg/day (EMEA, 1997), which represents a minimal addition to the administered doses of 4 and 9 mg/kg bw per day (corresponding to approximately 240 and 540 mg/day).

### *Thyroid hormones in pregnancy and breastfeeding*

Suboptimal thyroid function is associated with infertility, miscarriage and poor growth and neurodevelopment of the fetus (Griebel-Thompson et al., 2023). The fetal thyroid is not fully functional until mid-pregnancy (18–20 weeks) and the fetus depends on the maternal thyroid hormone. Thus, placental transfer of maternal thyroid hormones during early pregnancy is crucial, as is the maternal iodine status (Hall et al., 2023; Korevaar et al., 2016). Decrease of maternal serum T4 is the principal factor leading to poorer neurodevelopment of the child regardless of TSH increase (Morreale de Escobar et al., 2000). Thyroid hormone insufficiency in humans, even when it is mild, can produce adverse effects in specific neuropsychological functions, depending on the developmental timing of the deficiency and the brain region, including impaired visual processing development (Mirabella et al., 2005), learning and memory deficits (Henrichs et al., 2010; Zoeller & Rovet, 2004). For example, thyroid hormone deficiency early in pregnancy is associated with reduced visual attention, visual processing (i.e. acuity and strabismus) and gross motor skills in the offspring. If it occurs later in pregnancy, children are at additional risk of subnormal visual (i.e. contrast sensitivity) and visuospatial skills, as well as slower response speeds and fine motor deficits. Finally, if thyroid hormone insufficiency occurs after birth, language and memory skills are most predominantly affected (Zoeller & Rovet, 2004). Even modest degrees of thyroid hormone disruption experienced in utero can result in neuropsychological deficits in children despite normal thyroid status at birth (Finken et al., 2013; Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Soldin, 2004; Zoeller, 2003; Zoeller & Crofton, 2000).

A population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, The Netherlands), showed that fT4 and TSH serum concentrations in pregnant women (<18 weeks pregnant) higher or lower than the optimal ranges for the cohort were associated with adverse outcomes of child neurodevelopment, measured as mean total grey matter volume, mean cortex volume, and IQ at the age of 6–8 years (Jansen et al., 2019; Korevaar et al., 2016). Based on these data, U.S. EPA estimated that a 10%–20% decrease in maternal serum fT4 during the first trimester was associated with a 0.6–1.1-point decline in child IQ at age 6–8 years (U.S. EPA, 2020).

Because of the importance of thyroid function during pregnancy, measuring the effect of bromide on thyroid hormones in young women is relevant for risk assessment.

When the Collaborative Perinatal Project (Klebanoff, 2009) had monitored 50,282 mother–child pairs, 986 had been exposed to bromides in the first trimester of pregnancy and 2610 at any time during pregnancy (Heinonen et al., 1977). There was no firm evidence to suggest a relationship to malformations. Case reports are described in literature of two male infants with intrauterine growth restriction from a mother who chronically ingested a product containing bromides (Bromo-Seltzer) (Opitz et al., 1972). One infant also had congenital heart disease. Another case reported on a woman who chronically ingested tablets containing bromides throughout gestation. The female infant growth was restricted at birth and at 2.5 years of age had a persistent developmental delay (Rossiter & Rendle-Short, 1972). Bromide intoxication in neonates following intake of bromide-containing medications or being exposed to bromides by the pregnant mothers has been described in another four infants (Finken & Robertson, 1963; Mangurten & Ban, 1974; Mangurten & Kaye, 1982; Pleasure & Blackburn, 1975). All infants had symptoms of bromism (poor suck, weak cry, diminished Moro reflex, lethargy and hypotonia). Bromide concentrations in the three infants whose mothers took bromide-containing medication were 3650, 2000 and 2420 mg/L on days 6, 5 and 5, respectively (Finken & Robertson, 1963; Mangurten & Ban, 1974; Pleasure & Blackburn, 1975). The serum concentration 18 days after birth of the infant of the mother who was occupationally exposed was 150 mg/L (Mangurten & Kaye, 1982).

Mean bromide concentrations in cord serum of 1267 newborn infants born in Rochester, New York, in 1984 were low: 8.6 mg/L (range: 3.1–28.5 mg/L) (Miller et al., 1987). None of the mothers had taken bromide-containing drugs and the concentrations in cord serum were thought to have resulted from occupational exposure to photographic chemicals or from the low levels encountered in food and water. The bromide concentrations in cord serum were not related to indices of fetal health including Apgar scores, neonatal condition or presence of congenital abnormalities (Miller et al., 1987).

Bromide is excreted into breast milk. A report from as early as 1938 reviewed this topic and demonstrated the presence of bromide in milk in 10 mothers (Tyson et al., 1938). A 1935 report measured milk concentrations of 1666 mg/L in two patients treated with 5 g daily during 1 month (Kwit & Hatcher, 1935). Rash and sedation of varying degrees in nursing infants have been reported as a result of maternal consumption of bromide during lactation. The American Academy of Pediatrics classified bromide as compatible with breastfeeding only until May 2010 when the Policy Statement was retired (Committee on Drugs, 2001).

**TABLE 4** Experimental studies on bromide in humans.

Reference	Study type	Source	Age, gender	Route, dose, duration	Outcome/main findings	Br <sup>-</sup> concentration	Remark
Sangster et al. (1982)	Experiment	NaBr capsules	10 M + 10 F (not using contraceptives and not pregnant), 20–26 years	Oral, 1 mg Br <sup>-</sup> /kg bw per day during 8 weeks or 2 full cycles	No changes observed in the serum concentrations of T4, fT4, TBG, T3, cortisol, testosterone, oestradiol, progesterone, TSH, prolactin, LH and FSH	Plasma Br <sup>-</sup> concentration (mean ± SD) in females rose from 6.39 ± 0.80 mg/L to 77.5 ± 14.4 mg/L and in males from 6.39 ± 0.80 mg/L to 66.3 ± 7.19 mg/L. Mean excretion in urine rose for females from 9.8 ± 2.9 mg to 90.6 ± 30.2 mg NaBr/24 h ( <i>n</i> = 7; mean daily dose administered: 85 ± 10 mg NaBr); for males from 9.5 ± 4.2 to 79.7 ± 18.5 mg NaBr/24 h ( <i>n</i> = 9; mean daily dose: 95 ± 9 mg NaBr)	
Sangster et al. (1983)	Experiment	NaBr capsules	42 M + F (7 M and 7 F per group), 19–31 years	Oral administration during 12 weeks (M) or 3 full menstrual cycles (F). 3 groups: 0 mg Br <sup>-</sup> /kg bw per day, 4 mg Br <sup>-</sup> /kg bw per day, 9 mg Br <sup>-</sup> /kg bw per day	Female subjects taking 9 mg Br <sup>-</sup> /kg per day: significant increase ( <i>p</i> < 0.01) in serum T4 and T3 and in serum fT4 ( <i>p</i> < 0.05). No significant changes were observed in females receiving 4 mg Br <sup>-</sup> /kg bw per day or in males given either 4 or 9 mg Br <sup>-</sup> /kg bw per day. Electroencephalogram (EEG) and evoked cerebral activity showed a decrease in δ1- and δ2-activities and increases in β-activities and in mean frequency (Mobility parameter) for the 9 mg group	Mean plasma Br <sup>-</sup> (mg/L, ±SD) concentrations at start for men in the 0, 4, and 9 mg Br <sup>-</sup> /kg bw per day groups were: 5.59 ± 0.80, 5.59 ± 0.80, 6.39 ± 0.80 respectively. For women: 4.79 ± 0.80, 5.59 ± 1.60, 5.59 ± 0.80, respectively. After 12 weeks plasma concentrations for men 6.39 ± 1.60, 171 ± 57.5, 344 ± 56.7 respectively and for women: 5.59 ± 0.80, 244 ± 65.5, 394 ± 85.5 respectively	Nausea: <i>n</i> = 0 in control group, <i>n</i> = 2 in 4 mg and <i>n</i> = 5 in 9 mg groups. 5 M in the 4 mg group and 1 M and 1 F in 9 mg group mentioned decreased ability to concentrate and increase in sleepiness. Results of only four females in the group receiving 4 mg Br <sup>-</sup> /kg bw per day and of six F in the group receiving 9 mg Br <sup>-</sup> /kg bw per day evaluated
van Gelderen et al. (1993)/ Sangster et al. (1986)	Experiment	NaBr capsules	48 healthy F, 20–28 y not taking oral contraceptives; <i>n</i> = 3 withdrew	Oral daily administration of 0, 4 and 9 mg Br <sup>-</sup> /kg bw ( <i>n</i> = 15 per group) during 3 menstrual cycles, followed by 3 cycles without Br <sup>-</sup> administration	No differences between dosage groups of serum concentrations of T4, FT4, TBG, T3. Increase of TSH in 9 mg group. Reversible small effects on EEG for the 4 and 9 mg groups	Plasma Br <sup>-</sup> concentrations: control group: no change; increase from 4.00 ± 0.80 to 257 ± 74.3 mg/L in the 4 mg/kg group and from 4.00 ± 0.80 to 638 ± 151 mg/L in the 9 mg/kg bw group	Complaints of nausea ( <i>n</i> = 0 in control group, <i>n</i> = 3 in 4 mg group and <i>n</i> = 11 in 9 mg group)

#### 3.1.4.4 | *Observational studies in humans on bromide effects*

Observational human studies on bromide are described in [Table 5](#).

Wong et al. (1984) carried out a cohort study investigating mortality among 3579 white male workers employed between 1935 and 1976 at three manufacturing plants and one research establishment in US. These workers were potentially exposed to brominated chemicals, including various organic bromides. As of 31 December 1976, 2806 (79%) of the workers were still living and 578 (16%) had died. For 541 deaths (94%), death certificates could be obtained. Mortality in this cohort was compared with mortality in US white men adjusted for age and calendar time and specific mortality rates were used to calculate expected deaths. Based on the standardised mortality ratio (SMR), more deaths in the cohort were observed for cancer of the digestive system (cancer of the stomach), diseases of the circulatory system and diabetes mellitus. However, overall mortality for the entire cohort and several subgroups was lower than expected. The workers were exposed to several brominated compounds in addition to sodium bromide and potassium bromide, and therefore the mortality from specific causes could not be linked to specific brominated compounds. Finally, no information on potential confounders such as smoking, diet, physical activity, exposure to asbestos or other chemicals, was available and accounted for in the analysis (Wong et al., 1984).

Nusair et al. (2019) determined serum bromide concentrations in two populations living in the Dead Sea area and located either close to or far from a bromine factory (a factory extracting liquid bromine from the Dead Sea water): Ghor As-safi and Deir Alla, respectively, and assessed potential correlation between bromide exposure with genotoxicity and apoptosis in human (Nusair et al., 2019). The study used the comet assay to measure DNA damage in peripheral leucocytes (i.e. T%DNA), enzyme-linked immunosorbent assay was used to determine fortilin level as an apoptosis marker and specific analytical method to measure serum bromide concentration. The serum Br<sup>-</sup> concentrations were much higher in Ghor As-safi (16.35 ± 0.40 mg/L; *n* = 197) than in Deir Alla (8.01 ± 0.21 mg/L; *n* = 200), as were the genotoxicity biomarkers. In contrast, serum fortilin did not differ significantly between the two regions (*p* > 0.05). T%DNA was strongly and statistically significantly correlated (*r* = 0.886, *p* < 0.01) with serum Br<sup>-</sup> concentrations. In this study, however, no significant apoptosis levels due to bromide exposure were found (Nusair et al., 2019). No information in the paper is available on (the source of) exposure to bromide, other than serum concentration, or other chemicals and a causal relationship between serum bromide concentration and DNA damage cannot be assumed without taken possible confounders into account. It is possible that bromine release from the factory resulted in bromination disinfection products in water, and therefore the findings of this study cannot be attributed to dietary exposure to bromide.

**TABLE 5** Observational studies on bromide in humans.

Reference	Study type	Source	Age, gender	Route, dose, duration	Outcome/main findings	Br <sup>-</sup> concentration	Remark
Wong et al. (1984)	Cohort	Exposure to organic and inorganic brominated chemicals	3579 white male workers	Between 1935 and 1976 potentially exposed to brominated compounds including 1,2-dibromo-3-chloropropane (DBCP), Tris (2,3-dibromopropyl) phosphate, polybrominated biphenyls (PBB), various organic and inorganic bromides, and DDT	The vital status as of 31 December 1976 was determined for 3384 (95%) of these workers: 2806 (79%) were still living and 578 (16%) had died. Death certificates were obtained for 541 deaths (94% of all deaths). Overall mortality for the entire cohort and several subgroups was significantly lower than expected	Not measured	Lack of accurate historical exposure information and many workers were potentially exposed to a multitude of chemicals
Miller et al. (1987)	Observational/ cross-sectional		1267 newborn babies born in Rochester, New York from 1 January 1984 to 30 June 1984	No mothers were taking significant amounts of bromide-containing drugs during pregnancy	Highest cord concentration found was still below the minimal bromide concentration associated with toxic effects (720 mg/L). No association between the cord serum bromide concentration and indices of fetal health including Apgar scores, presence of congenital malformations, and neonatal disposition	Normal distribution of cord serum bromide concentration: 3.1–28.5 mg/L; mean ± SD: 8.6 ± 2.6 mg/L	3 mothers used bromide-containing drugs during pregnancy. Second highest cord serum bromide concentration (21.4 mg/L): amateur photographer developing her own film, using chemicals containing bromide
Nusair et al. (2019)	Cross-sectional	Proximity to bromine factory			Residence in the region with higher serum bromide concentrations was associated with higher DNA damage in peripheral leukocytes ( $\beta$ 0.703, $p < 0.001$ ) and serum Br <sup>-</sup> concentrations (Pearson correlation coefficient 0.886, $p < 0.01$ )	Serum Br <sup>-</sup> (mg/L): 16.35 ± 0.40 vs. 8.01 ± 0.21	Cross-sectional associations between serum bromide concentrations and a biomarker of genotoxicity, but limited control of confounding



### 3.1.4.5 | Human case reports on bromide intake

Table B.3.1 in Appendix B gives an overview of case reports identified after EFSA's literature search. From these case reports it can be summarised that infants ( $\leq 12$  months) treated with KBr for seizures developed bromoderma or other adverse effects at intakes 495–720 mg/day resulting in serum bromide concentrations of 890–1230 mg/L. A similar pattern was seen for older children. Adults experienced adverse health effects at high intakes, such as on the nervous system (drowsiness) and the skin (cutaneous rash), and anorexia but survived intakes of 6.25 g NaBr/day (serum bromide: 12,224 mg/L) or more than 10 g KBr/day (equivalent to 143 mg/kg bw per day). On the other hand, one case report mentioned the occurrence of reversible effects such as drowsiness and myoclonic jerks in all extremities following suicidal administration of 4500 mg of bromovalerylurea (corresponding to 1.6 g of bromide) and subsequent bromide intoxication, with serum bromide concentrations of 81 mg/L (Lin et al., 2008). However, such circulating concentrations of bromide do not appear to be consistent with the amount of bromide acutely ingested, being apparently too low when taking into account the relation between bromide intake and blood concentrations found after controlled dietary bromide administration in humans (Sangster et al., 1983). Bromovalerylurea may not release all bromide ions, thus raising some uncertainties about the intake of bromide calculated and whether bromide is responsible for the adverse health effects.

Psychiatric abnormalities of acute or chronic bromide intoxication include confusion, self-neglect, fatigue, sluggishness, impairment of memory and concentration, irritability or emotional instability, depression, hallucinations, and schizophrenic-like psychotic behaviour (Lin et al., 2008). Common adverse reactions to bromide containing products in Canada included headache, bronchitis, nausea, tachycardia, chest pain, abdominal pain, flushing, vomiting, diarrhoea, rhinitis, hypertension, dizziness, drowsiness and restlessness (Lin et al., 2019; Thornton & Haws, 2020).

### 3.1.4.6 | Summary

In the main human experimental studies, increases of TSH (Sangster et al., 1986), T<sub>3</sub>, T<sub>4</sub> and fT<sub>4</sub> (Sangster et al., 1983) were found in women receiving 9 mg Br<sup>-</sup>/kg bw per day. No changes in thyroid hormone concentrations were observed after administering 4 mg Br<sup>-</sup>/kg bw per day. In males, no effect was apparent at either of the two doses tested. With regard to the activity of the central nervous system, analysis of the electroencephalogram (EEG) and evoked cerebral activity showed small effects in both men and women receiving 9 mg Br<sup>-</sup>/kg bw per day (Sangster et al., 1983, 1986).

The few non-experimental (observational) studies, all rated as of high RoB, did not provide reliable evidence to assess potential effects of bromide exposure.

Finally, a number of mild to severe adverse health effects on the nervous system, the skin and other organs have been documented following high exposure to bromide, e.g. 20–80 mg/kg bw per day up to 10–15 and 31 g/day, generally for medical therapeutic purposes.

## 3.1.5 | Toxicity of bromide in food-producing and non-food-producing animals

The studies on effects in food-producing and non-food-producing animals are summarised in Appendix C.

### Horses

The pharmacokinetics of bromide were studied in six mares given a single oral dose of 120 mg KBr/kg bw (corresponding to 80 mg Br<sup>-</sup>/kg bw) by stomach tube (Raidal & Edwards, 2008). Another six mares received a loading dose of 120 mg KBr/kg bw per day (corresponding to 80 mg Br<sup>-</sup>/kg bw per day and also to 3520 mg Br<sup>-</sup>/kg diet), by stomach tube for 5 days, followed by 40 mg KBr/kg bw per day (corresponding to 26.8 mg Br<sup>-</sup>/kg bw per day and also to 1180 mg Br<sup>-</sup>/kg diet) in feed for 7 days. Four mares were used as an untreated control group. A single dose of KBr was well tolerated by all mares, and there was no evidence of adverse effects, such as loss of appetite or neurological deficits. In the second dosing group, each horse remained well throughout the duration of the study and no horse had a reduced appetite. However, during the administration of loading doses, two horses demonstrated mild ataxia and proprioceptive deficits in all four limbs and on neurological examination on days 3 and 4 from the start of dosing. These signs had abated by day 7, 2 days after commencing the lower 'maintenance' dose of KBr. However, considering its design and short duration, the Scientific Committee could not use this study to establish a reference point for horses.

Bromide intoxication was reported in a 3-year-old thoroughbred filly, that had been administered an unknown dose of oral KBr for behavioural modification over several months (Sacks et al., 2022). The horse presented a several months history of weight loss, polydipsia and polyuria, intermittent diarrhoea and behavioural changes and intermittently uncoordinated gait. Neurological examination revealed hyperexcitability, bilaterally reduced pupillary light reflexes and quadrilateral ataxia with proprioceptive deficits more obvious in the forelimbs than in the hindlimbs. Serum bromide concentration (1.17 mg Br<sup>-</sup>/mL) confirmed bromide intoxication. Clinical signs resolved within 20 days following the last bromide administration, without specific medical intervention. However, considering that the study reported data for a single animal, and dose and duration of the bromide administration are unknown, the Scientific Committee could not use this study to establish a reference point for horses.

## Cattle

The effects of NaBr on production and health of cattle for fattening were evaluated in 13 Holstein-Friesian steers and one heifer (body weight: 136–234 kg), fed a pelleted diet supplemented with NaBr at 170, 511, 1062, 2633 and 4650 mg Br<sup>-</sup>/kg diet (corresponding to 2.3–3.3, 6.3–8.2, 15.6–19.6, 32.7 and 50.5–73.6 mg Br<sup>-</sup>/kg bw per day, respectively) (Knight & Reina-Guerra, 1977). The five treatments used 2, 3, 4, 3 and 2 cattle, respectively. The duration of the treatment period was 49 days, followed by a recovery period from day 50 to day 91. Four cattle in total [1 cattle from group 170 mg Br<sup>-</sup>/kg diet (day 49), 1 cattle from group 2633 mg Br<sup>-</sup>/kg diet (day 63, culled due to pneumonia) and 2 cattle from group 4650 mg Br<sup>-</sup>/kg diet (days 49 and 91)] were euthanised and tissues (kidney, liver, muscle) were collected to determine the bromide content. Groups fed the diet containing the highest concentration of bromide (4650 mg Br<sup>-</sup>/kg diet) developed signs of motor incoordination after 10–12 days of supplementation. The signs of incoordination were observed at serum bromide concentrations of 2400 mg/L<sup>31</sup> or more. Serum bromide concentrations and associated neurologic signs subsided markedly 14 days after feeding of the bromide-containing feeds was discontinued. However, considering the small number of cattle per treatment (1–4), the absence of a control group and lack of statistical analysis for the reported data, the Scientific Committee could not use this study to establish a reference point for cattle.

In a study performed to determine the efficacy of KBr as a sedative medical agent in cattle for fattening, 22 Belgian White and Blue double-musled male cattle (bw: 241.5 ± 6.2 kg; age: 7 months) were divided in two groups (11 cattle/treatment, group penned) and fed diets supplemented with KBr at 0 (control) or 736 mg KBr/kg diet DM (corresponding to 495 mg Br<sup>-</sup>/kg diet DM, 435 mg Br<sup>-</sup>/kg diet and 9.5 mg Br<sup>-</sup>/kg bw per day) (Genicot et al., 1991). The duration of the experiment was 221 days, and the treatment was ended 60 days before the slaughtering day. The treatment with KBr resulted in a significant reduction in the rear engagements during the whole trial period (221 days), in direct attacks during the period from day 1 to 53 and in side-on attacks during the period from day 54 to 167. The daily weight gains were not significantly different between the two groups. Although no statistical analysis was performed, feed utilisation was lower in treated bulls. The time spent for hay intake and the frequency of water intake were reduced and the time during which the bulls were standing was prolonged in the group fed the bromide-containing diet. However, considering the lack of statistical replicates, the lack of statistical analysis for feed to gain ratio, and the reporting of only behavioural data and body weight gain, the Scientific Committee could not use this study to establish a reference point for cattle.

Another study was conducted to evaluate effects of dietary sodium bromide on bromide transfer to milk and deposition in tissues of dairy cattle (Vreman et al., 1985). Nine dairy cows in early lactation were allocated to three treatments (3 cows/treatment, group penned) and fed on a total mixed ration (18.8 kg diet DM/cow per day) supplemented with NaBr at 0, 46.5 and 93.1 mg Br<sup>-</sup>/kg diet DM, and, considering the basal dietary bromide content, corresponding to 22 (control), 69 and 115 mg Br<sup>-</sup>/kg diet DM (corresponding to 19 (control), 61 and 101 mg Br<sup>-</sup>/kg diet and also to 0.7, 2.1 and 3.6 mg Br<sup>-</sup>/kg bw per day). The duration of the experiment/treatment period was 35 days, followed by a recovery period from day 36 to 56. The initial body weight and milk production of cows, as well as the method of animal distribution to treatments, were not reported. At the start of the study, the milk bromide concentration was 2.8 mg/kg. At the end of the dosing period, two cows of each group were slaughtered, and tissue samples taken to determine bromide. The daily milk production (14.9, 27.5 and 21.8 kg, respectively) and milk bromide concentration (6.1, 17.4 and 30.5 mg/kg, respectively) increased with dietary supplementation of bromide. However, considering the small number of cows used per treatment, the lack of individual feed intake data in the study, as well as of a statistical analysis for feed efficiency, and the poor reporting of the data, the Scientific Committee could not use this study to establish a reference point for dairy cows.

## Sheep

A pharmacokinetics study of bromide in sheep used eight Merino sheep (49.5–67.0 kg bw), administered with a single dose of KBr at 178.8 mg/kg bw (corresponding to 120 mg Br<sup>-</sup>/kg bw), via an orogastric tube (Quast et al., 2015). Sheep did not present any adverse reactions, including neurological signs, or changes in rumen motility and feed and water intake. However, considering the single dose used and the lack of a control group, the Scientific Committee could not use this study to establish a reference point for sheep.

## Pigs

The effect of a bromide salt mixture was studied on pig performance (Barber et al., 1971). Large White pigs (initial bw 20 kg, 10 weeks of age) were used in four treatments, with two replicate pens/treatment and four pigs/pen. The bromide salt mixture, consisting of equal parts of ammonium, potassium and sodium bromides was supplemented to diet at a level of 0 or 200 mg/kg diet (corresponding to 151 mg Br<sup>-</sup>/kg diet, and also to 6.5 mg Br<sup>-</sup>/kg bw per day). The bromide salt mixture was added to the basal diet alone or in combination with copper sulfate at 0 or 1000 mg/kg diet (corresponding to 250 mg Cu/kg diet). The experiment lasted until pigs reached 90 kg of body weight. Copper sulfate significantly increased the growth rate and improved feed to gain ratio, whereas the bromide salts had no effect on either of these two variables. However,

<sup>31</sup>Reported as 30 mEq/L (1 mEq/L = 79.9 mg/L).

considering the insufficient number of replicate pens used per treatment, and the reporting of performance data only, the Scientific Committee could not use this study to establish a reference point for pigs.

### Chicken

The effect of dietary NaBr supplementation on the chick growth was studied in four separate experiments (Bosshardt et al., 1956). The study used 1- to 3-day-old cockerels of various New Hampshire strains, and one to two replicate pens per treatment (15 cockerels/replicate pen) for a 31-day experimental period. In Experiment 1, diet was supplemented with NaBr at 0 (control), 8 and 15 mg Br<sup>-</sup>/kg diet, or with 10.0 g Trace Element Sea Salt (TESS)/kg diet that provided 15 mg Br<sup>-</sup>/kg diet. In Experiments 2 and 3, diet was supplemented with NaBr at 0 (control), and 15 mg Br<sup>-</sup>/kg diet, and in Experiment 4, diet was supplemented with NaBr at 0 (control), and 8 mg Br<sup>-</sup>/kg diet. In all four experiments, feed intake and feed to gain ratio of cockerels were not reported. A significant increase in final body weight was measured in three of four experiments by about 8%–11% in the bromide-supplemented groups (average body weight of control animals about 460 g). No other endpoints were reported. It is noted that modern broiler chicken breeds reach that body weight after 14 days. Considering the small number of replicates used in the study and the lack of reporting feed intake and feed to gain ratio, the Scientific Committee could not use this study to establish a reference point for chicken.

Three experiments were conducted to determine the effect of dietary bromide, fluoride and fat levels on the chick growth, using New Hampshire × Delaware broiler chicken, and two to four replicate pens per treatment (5 males and 5 females per pen) for 4-week experimental periods (days 1–28 of age) (Doberenz et al., 1965). In Experiment 1, diet was supplemented with NaBr at 0 (control), 2500, 5000, 10,000 and 20,000 mg Br<sup>-</sup>/kg diet (corresponding to 0, 333, 682, 1382 mg Br<sup>-</sup>/kg bw per day, but no intake could be calculated for the top concentration due to 100% mortality). Performance and mortalities were not affected among treatments up to the dietary level of 5000 mg Br<sup>-</sup>/kg diet, but the feeding of 10,000 mg Br<sup>-</sup>/kg diet resulted in a significant decrease in growth rate and the 20,000 mg Br<sup>-</sup>/kg diet resulted in 100% mortality by 2 weeks of age. In Experiment 2, diet was supplemented with NaBr at 0 (control), and 10,000 mg Br<sup>-</sup>/kg diet (corresponding to 0 and 1307 mg Br<sup>-</sup>/kg bw per day), without or with 2000 mg F<sup>-</sup>/kg diet. Performance and mortalities were adversely affected in the bromide groups, compared to the control. In Experiment 3, diet was supplemented with NaBr at 0 (control), 5000 and 10,000 mg Br<sup>-</sup>/kg diet (corresponding to 0, 680 and 1364 mg Br<sup>-</sup>/kg bw per day), without or with 1000 and 2000 mg F<sup>-</sup>/kg diet or fat (at 100 g/kg diet). Performance was adversely affected for both bromide groups, compared to the control. It is noted that, in all three experiments, the body weight of the control broiler chicken was very low (approximately 411–440 g) when compared to the one the modern breeds reach at day 28 of age (Doberenz et al., 1965). Any conclusions from this old study could not be extrapolated to current farming conditions, where birds grow at a much faster rate and are expected to be more sensitive to any disturbance. Consequently, the Scientific Committee could not use this study to establish a reference point for chicken.

The iodine (I) toxicity in young chicks and its amelioration by supplemental bromide was studied in four chicken bioassays (Baker et al., 2003). The research was done with male New Hampshire × Columbian broiler chicken (90 g bw, 8 days of age) over a 13-day growth period (days 8–21 of age), using four treatments, with four replicate pens per treatment and four birds per pen. In two of the assays, the diet was supplemented with NaBr at 0, 50 (assay 1) or 100 (assays 1 and 2) mg Br<sup>-</sup>/kg diet (for assay 1 corresponding to 0, 5.1 and 10.1 mg Br<sup>-</sup>/kg bw per day, and for assay 2 corresponding to 0, and 10.1 mg Br<sup>-</sup>/kg bw per day), and with KI at 1000 (assay 1) or 1500 (assay 2) mg I<sup>-</sup>/kg diet. Supplemental iodine levels of 1000–1500 mg/kg caused severe growth depressions that could be totally reversed by dietary addition of 50 or 100 mg Br<sup>-</sup>/kg diet. Performance was not affected among control and bromide treatments. However, considering the short duration of the study, the high dietary iodine supplementation as a confounding factor, the Scientific Committee could not use this study to establish a reference point for chicken.

The effects of bromide in drinking water were studied on the performance of broiler chicken (du Toit & Casey, 2010). The study used mixed Ross broiler chicken over a 42-day post-hatch growth period, and six treatments in a 3 × 2 factorial design, with bromide and iodine delivered via drinking water (three levels of bromide as NaBr and two levels of iodine as KI), and three replicate pens per treatment with 30 birds per pen. The six treatments were T1: 0 mg Br<sup>-</sup>/L and 0 mg I<sup>-</sup>/L; T2: 1 mg Br<sup>-</sup>/L and 0 mg I<sup>-</sup>/L; T3: 3 mg Br<sup>-</sup>/L and 0 mg I<sup>-</sup>/L; T4: 0 mg Br<sup>-</sup>/L and 0.7 mg I<sup>-</sup>/L; T5: 1 mg Br<sup>-</sup>/L and 0.7 mg I<sup>-</sup>/L; and T6: 3 mg Br<sup>-</sup>/L and 0.7 mg I<sup>-</sup>/L (corresponding to 0.017, 0.178, 0.502, 0.017, 0.178 and 0.527 mg Br<sup>-</sup>/kg bw per day). Bromide administered at 1 and 3 mg Br<sup>-</sup>/L decreased water intake (267.8 vs. 250.2 and 241.9 mL/bird per day) and feed intake (120.3 vs. 116.2 and 113.6 g/bird per day) significantly, for 0, 1 and 3 mg Br<sup>-</sup>/L treatments respectively. The interaction of bromide and I had no significant effect on intake of water or feed. Iodine was effective in ameliorating the effect of bromide. Average daily gains, feed to gain ratios and mortalities were not affected among treatments.

A subsequent companion publication (du Toit & Casey, 2012) reported additional data on blood and tissues of chicken. At days 16 and 42, blood samples were taken from five birds of each replicate. The thyroid, liver and kidneys from two chicken per replicate pen were collected for analysis and histopathology (only the 2 groups with high bromide supplementation). The effect of bromide on T3 and T4 levels overall was non-significant, but T3 and T4 levels decreased between weeks 4 and 6 with a significant effect at week 6 on T3. Bromide in water for drinking resulted in a dose-dependent increase of bromide residues in the three organs analysed with lower levels in the groups with added I. The I residue was not influenced by iodine or bromide in water for drinking. Bromide residues were highest in the kidneys, followed by liver and thyroid gland. Histopathological assessment showed explicit damage to the livers that received the bromide treatments. Hepatocellular hypertrophy and vacuolar degeneration due to swelling of the intracytoplasmic endoplasmic reticulum

were observed to be more severe in groups without added I. Both publications by du Toit and Casey (2010, 2012) reported results from the same study. In principle, only the treatments without added I should be used to examine possible adverse effects of Br. The replication (3 replicate pens/treatment) is rather limited, and the main shortcoming is that, due to rather confusing reporting, it is not possible to know certainly which was the level of exposure of the birds to bromide in each treated group. This limitation makes the study unsuitable to establish a reference point for chicken.

A study was conducted to determine the quality and safety of eggs obtained from laying hens after their experimental poisoning with NaBr, for 28 days, followed by a 14-day period of birds' recovery period (Kutsan et al., 2020). Sixty Hisex White cross laying hens (365 days of age, body weight: 1.4 kg) were allocated to four dietary treatments (15 hens/treatment, group penned), and supplemented with NaBr at 0 (control) or 10, 50 and 250 mg Br<sup>-</sup>/kg diet (corresponding to 0, 0.6, 3.0 and 15.0 mg Br<sup>-</sup>/kg bw per day). The background bromine content of the compound feed was 2.0 mg/kg. Egg production and quality was determined, and the bromine content was determined separately in egg white, yolk and shell. Clinical manifestations of poisoning in hens were not observed. No significant deviation from the control group was observed in productivity, egg mass, white to yolk mass ratios and pH values of yolk and white. However, considering the low number of replicate pens used per treatment, the lack of reporting of laying rate, feed intake and feed to egg mass ratio, the Scientific Committee could not use this study to establish a reference value for chicken.

Another study was conducted to determine chicken embryo sensitivity to a range of bromide treatments (Lucht et al., 2018). A NaBr solution was injected into Ross-308 eggs in three phases: (1) five eggs injected with 0.002 mg Br<sup>-</sup>/egg; (2) 45 eggs divided into groups and injected with 0, 0.0002 and 0.001 mg Br<sup>-</sup>/egg; (3) 148 eggs divided into groups injected with 0, 0.000002, 0.00001, 0.0001, and 0.0002 mg Br<sup>-</sup>/egg. The mass of the embryo and of the heart, liver and brain was measured at day 20. The results showed: (1) 0.002 mg Br<sup>-</sup>/egg is toxic; (2) Br<sup>-</sup> is lethal to embryos at concentrations > 0.0002 mg Br<sup>-</sup>/egg and toxic at 0.0002 mg Br<sup>-</sup>/egg; and (3) embryo survival was significantly and inversely correlated with increasing Br<sup>-</sup> concentrations. Concentrations > 0.0001 mg Br<sup>-</sup>/egg showed greater risk on differential development. Concentrations > 0.000002 mg Br<sup>-</sup>/egg showed potentially severe effects on developing embryos. The heart showed the greatest relative growth response followed by the brain. However, considering that in ovo bromide treatments were used, the Scientific Committee could not use this study to establish a reference point for chicken.

## Dogs

Rosenblum (Rosenblum, 1958) conducted a study to produce experimental bromide intoxication in dogs. Adult mongrel dogs of both sexes (4–8 dogs per group) were used in six treatments, with a duration of 4–26 weeks, depending on the dose. Dogs received NaBr, in capsules wrapped in dog food balls, at doses of 100, 200, 300, 400, 500 and 600 mg NaBr/kg bw per day (corresponding to 78, 156, 234, 312, 390 and 468 mg Br<sup>-</sup>/kg bw per day and also to 4038, 8076, 12,114, 16,152, 20,190 and 24,228 mg Br<sup>-</sup>/kg diet). Bromide intoxication included signs of neurotoxicity, gastrointestinal toxicity, and toxicity to the skin. Dogs given 78 mg/kg bw per day experimentally for 6 weeks had minimal adverse effects (i.e. emaciation and weight loss of 15%), whereas those given the drug at dosages of 156 to 390 mg Br<sup>-</sup>/kg bw per day for 4–26 weeks developed shivering, ataxia, skin lesions, salivation, vomiting, diarrhoea, haematochezia, stupor, emaciation and weight loss, coma, and in some cases, death. In a follow-up publication, Rosenblum and Hawkins Jr. (1958) reported for the same experimental animals a decrease in the volume of the extracellular space and haemoconcentration, and/or anaemia and leucocytosis, during the bromide intoxication of dogs.

In another publication, Rosenblum et al. (1960) studied the chronic effects of inorganic bromide in dogs. Beagle dogs (initial body weight: 5.4–6.1 kg, 6–12 weeks of age) were used as the controls (3 males and 3 females) and the treated group (3 males and 1 female). Dogs received NaBr, in capsules wrapped in meat balls, at doses of 0 and 128 mg NaBr/kg bw per day (corresponding to 0 and 100 mg Br<sup>-</sup>/kg bw per day, and to 0 and 5176 mg Br<sup>-</sup>/kg diet), for 12 months. Body weight and feed intake were similar between the two groups. Occasional salivation and diarrhoea were noted in the treated group. No significant effects were noted in the dogs on haemoglobin, haematocrit, white and red cell counts, serum proteins or blood urea nitrogen. One dog died during the course of the experiment in the treated group, but pneumonia was diagnosed as the cause of death. Histological examination of the various organs (brain, lung, heart, liver, kidneys, spleen, testes, adrenals and thyroids) gave predominantly normal results, and there were no changes that could be attributed to bromide intoxication.

Bromide secretion by the canine prostate was studied, using four dogs (11–14 kg bw) with surgically produced prostatic fistulas that were given single oral doses of 1130 mg NaBr/day (corresponding to 881 mg Br<sup>-</sup>/day and 70.5 mg Br<sup>-</sup>/kg bw per day and also to 3650 mg Br<sup>-</sup>/kg diet), for five consecutive days (Smith & Ilievski, 1985). The bromide secreted in prostatic fluid, given that it may impair sperm motility in vitro, potentially could adversely affect reproduction. However, considering the lack of a control group and the single dose used, the Scientific Committee could not use this study to establish a reference point for dogs.

The pharmacokinetics of KBr in dogs was studied, using six healthy adult Beagle dogs (3 males and 3 females, mean body weight: 11.3 kg) (March et al., 2002). Dogs received KBr, with canned food, at 60 mg KBr/kg bw per day (corresponding to 40 mg Br<sup>-</sup>/kg bw per day and to 2070 mg Br<sup>-</sup>/kg diet), for a period of 115 days. The study lacked an untreated control group. High-dose KBr administration was well tolerated and resulted in minimal adverse side effects. Dogs showed minimal to no neurologic signs during all phases of the study. At the highest serum bromide concentrations of approximately 400 mg/dL, two dogs exhibited mild to moderate caudal paresis and ataxia.



A placebo-controlled experiment was performed to evaluate the effect of potassium bromide on the canine thyroid gland (Paull et al., 2003). The trial was conducted with 10 adult, sexually intact, hound dogs (1–2 years of age) and used two treatment groups (2 male and 3 female dogs/treatment), a group of dogs treated with KBr, and another one which remained untreated. Dogs were assigned such that baseline tT<sub>4</sub>, TSH and sex were comparable between control and experimental groups. Treated dogs received a loading dose of KBr at 200 mg KBr/kg bw per day (corresponding to 134 mg Br<sup>-</sup>/kg bw per day) for 2 days, and this was followed by a maintenance dose of KBr at 30 mg KBr/kg bw per day (corresponding to 20 mg Br<sup>-</sup>/kg bw per day and to approximately 1035 mg Br<sup>-</sup>/kg diet) for 180 days. The five control dogs received an equivalent loading dose volume of distilled water for 2 days, followed by an equivalent maintenance dose volume for 180 days. Potassium bromide, or distilled water, was administered daily in a treat ('meatball' of white bread) with canine maintenance diet. Basal tT<sub>4</sub>, fT<sub>4</sub> and basal TSH serum concentrations were evaluated over the 6-month period in potassium bromide-treated and control dogs. A TRH-releasing hormone stimulation test was also performed in all dogs at the beginning and conclusion of the study. Thyroid histopathology was compared between treated and control dogs at the end of the study. No difference was detected in any parameter between the two groups at the end of the study. A decline in thyroid hormone concentrations over the course of the study did occur in both groups of dogs. KBr did not appear to have a significant effect on canine thyroid function or morphology. Administration of KBr did not affect the canine thyroid function or morphology. From the study of Paull et al. (2003), the value of 1035 mg Br<sup>-</sup>/kg diet or 20 mg Br<sup>-</sup>/kg bw per day can be considered as the NOAEL of dogs for effects on the thyroid (Paull et al., 2003).

Piperisova et al. (Piperisova et al., 2009) reported a bromide toxicosis of a male Cavalier King Charles Spaniel dog (6.7 kg bw, 5-years old), after an inadvertent use of KBr (239 mg Br<sup>-</sup>/capsule) (corresponding to 35.7 mg Br<sup>-</sup>/kg bw per day, and also to 1848 mg Br<sup>-</sup>/kg diet), reportedly for 3 weeks, instead of potassium citrate to acidify the urine due to an earlier history of urolithiasis. The dog presented a progressive paresis, a marked hyperchloraemia and a decreased anion gap on blood electrolyte analysis, accompanied with elevated serum bromide concentration (400 mg/dL). However, considering the reporting of data in only one dog and the short duration of the study, the Scientific Committee could not use this study to establish a reference point for dogs.

A case of bromide toxicity in a castrated male Shetland sheepdog (9-years old) was reported (McConkey et al., 2012), following a fivefold compounding error in the concentration of potassium bromide. The dog had been treated with KBr and phenobarbital for idiopathic epilepsy for 6 years prior to presentation for the compounding error. The dog was receiving a KBr solution at 27 mg KBr/kg bw per day (corresponding to 18 mg Br<sup>-</sup>/kg bw per day and also to 935 mg Br<sup>-</sup>/kg diet) and 8 mg phenobarbital/kg bw per day, at the time of the compounding error. Five days after the owner renewed the KBr prescription at a local pharmacy, the dog fell down the stairs and appeared to have a subdued demeanour, sore neck and delayed proprioception in both forelimbs. Within a few days, his signs progressed to depression, inability to walk, mild abdominal discomfort and bradycardia (heart rate 60 beats/min). Bromine toxicity was attributed to compounding error during the refilling of the KBr prescription at the local pharmacy, as, after a sample of the compounded drug was sent to Diagnostic Services, the KBr concentration in the solution was found to be 225 mg/mL (corresponding to 90 mg Br<sup>-</sup>/kg bw per day and also to 4675 mg Br<sup>-</sup>/kg diet), instead of the 200 mg/5 mL that had been prescribed and written on the label. However, considering the reporting of data in only one dog (case report), the short duration of the study, the uncertainty on the dose level (a mistake), and administration together with phenobarbital, the Scientific Committee could not use this study to establish a reference point for dogs.

## Cats

A controlled experimental study on the pharmacokinetics of KBr administration was performed in seven healthy adult male cats (mean body weight: 6 kg, 1.5–2 years old) (Boothe et al., 2002). Cats received KBr, into capsules, at 30 mg KBr/kg bw per day (20 mg Br<sup>-</sup>/kg bw per day), which is estimated to be approximately 880 mg Br<sup>-</sup>/kg diet, until bromide steady-state concentrations were reached. Health status of cats, by clinical examination and body weight, serum biochemical parameters and a routine urinalysis, was determined. Mean C<sub>max</sub> of 1.1 ± 0.2 mg Br<sup>-</sup>/mL occurred at 8 weeks for all cats. Steady-state concentrations, C<sub>max</sub>, occurred at a mean of 5.3 ± 1.1 weeks. All cats tolerated KBr administration well with no evidence of adverse effects, including loss of appetite. However, considering the lack of an untreated control group and the short duration of the study, the Scientific Committee could not use this study to establish a reference point for cats.

### 3.1.5.1 | Studies in food producing animals fed with diets containing seaweeds

#### Studies in cattle using seaweeds

Ruminants are an important source of methane emitted to the atmosphere. Recent studies have shown that the inclusion of certain microalgae in the diets of ruminants can result in a reduction of methane emissions by ruminants (Abbott et al., 2020). Such use could lead to increases in bromide exposure to food producing animals. The effects of dietary supplementation of the microalgae *Asparagopsis taxiformis* (AT) and oregano leaves were studied on methane emission, rumen fermentation and lactational performance of dairy cows (Stefenoni et al., 2021). A total of 20 Holstein cows (2.6 lactations, 95 days in milk, 42.2 kg of milk yield/day) were used in a replicated 4 × 4 Latin square design with four 28-days periods (21 days for adaptation and 7 days for data and samples collection), with four dietary treatments. Basal diet was supplemented with 0 (control), 2.5 g AT (LowAT), 5.0 g AT (HighAT) or 17.7 g oregano (*Origanum vulgare* L.) leaves/kg diet DM.



The study lacks reporting of the bromide content of the microalga *A. taxiformis* or of the diets. HighAT decreased average daily CH<sub>4</sub> emission and CH<sub>4</sub> yield by 65% and 55%, respectively, in the first two 28-days periods, but had no effect in the last two 28-days periods. The differential response to AT among experimental periods was likely a result of a decrease in CHBr<sub>3</sub> concentration in AT over time. Compared with the control, HighAT decreased DM intake, milk yield and energy corrected milk yield. Milk composition was not affected by treatment, except lactose percentage and yield were decreased by HighAT. Concentrations of bromide and iodine in milk were increased by HighAT compared with the control (5.1 vs. 40.4 mg Br<sup>-</sup>/kg milk, 8 times higher, and 575 vs. 2966 ng I<sup>-</sup>/mL (μg I<sup>-</sup>/L) milk, 5 times higher, respectively). Both bromide and iodine concentrations were lower (by 27% and 20%, respectively) in milk from the last two 28-days periods than in milk from the first two 28-days periods. Milk CHBr<sub>3</sub> concentration and its organoleptic characteristics were not different between control and HighAT.

The effects of dietary supplementation of microalga *Asparagopsis taxiformis* (AT) were determined on milk production and quality, methane (CH<sub>4</sub>) production and rumen microbiome of dairy cows (Krizsan et al., 2023). Six Nordic Red cows (611 kg bw, 122 days in milk) were assigned to an extra-period Latin-square change-over design comprising two dietary treatments. The dietary treatments were a diet supplemented with 0 (control) or 5.0 g AT/kg on an organic matter intake basis. The study lacks reporting of the bromide content of the microalga *A. taxiformis* or of the diets. Daily CH<sub>4</sub> production, CH<sub>4</sub> yield and CH<sub>4</sub> intensity decreased by 60%, 54% and 58%, respectively, in cows fed the diet supplemented with AT. Furthermore, hydrogen gas emitted by cows fed diets supplemented with AT increased by more than five times compared with cows fed a non-AT-supplemented diet. Feed intake was decreased and milk production altered, reflecting a decreased yield of milk fat in cows fed an AT-supplemented diet, but feed efficiency increased. The most prominent change in milk quality was an increase in bromine (5.1 vs. 43.2 mg Br<sup>-</sup>/L milk, more than a 8-fold increase) and iodine (139 vs. 2105 μg I<sup>-</sup>/L milk, more than a 15-fold increase) when the diet was supplemented with AT.

### Studies in chicken using seaweeds

The effects of dietary supplementation of the seaweed *Ulva lactuca* (UL) were studied on broiler chicken performance and meat quality (Costa et al., 2022). Sixty 22-day-old male Ross 308 broilers (initial body weight: 758 g) were allocated to two dietary treatments, with 10 replicate pens per treatment, and 3 chicken per pen, in a 14-day experimental period. Diets were supplemented with 0 (control) or 150 g UL/kg diet. The bromine content of UL was 694 mg Br<sup>-</sup>/kg DM. The bromine content in control and UL diets were reported to be 4.1 and 211 mg Br<sup>-</sup>/kg diet DM, respectively (corresponding to 3.6 and 185.7 mg Br<sup>-</sup>/kg complete feed and to average doses of 0.4 and 18.3 mg Br<sup>-</sup>/kg bw per day). Feed intake (124 vs. 103 g/bird/day), final body weight (1763 vs. 1621 g), daily bw gain (77.4 vs. 68.1 g/bird/day) and feed to gain ratio (1.68 vs. 1.72) were unaffected with the UL diet compared to the control, but relative liver weight (20.30 vs. 17.73 g/kg bw) decreased. Bromine (0.12 vs. 0.30 mg/100 g fw) content in meat increased.

### 3.1.5.2 | Studies in non-food-producing animals using bromide salts as antiepileptic treatment

Ten review articles on canine and feline epilepsy including its treatment by bromide were identified in the literature search (Baird-Heinz et al., 2012; Baka & Polizopoulou, 2019; Bergman & Coates, 2005; Bhatti et al., 2015; Boothe, 1998; Chandler, 2006; Goiz-Márquez et al., 2008; Muñana, 2013; Platt, 2003; Thomas, 2000). Epilepsy is the most common chronic neurological disorder in dogs, and bromide has gained use as a sole antiepileptic therapy in dogs, either as a first-line drug or in dogs with intolerable side effects from phenobarbital. The initial therapy with KBr is a daily oral dose of 20–40 and 10–20 mg/kg bw per day as maintenance dosage for dogs and cats, respectively (Bergman & Coates, 2005; Boothe, 1998). The target serum concentration for monotherapy is 2–3 mg/mL (Trepanier et al., 1998). Clinical experience indicates that bromide is effective as monotherapy.

Possible adverse effects observed in dogs (Baird-Heinz et al., 2012) and cats (Baka & Polizopoulou, 2019) treated with bromide as an antiepileptic drug have been reported in some, but not all, related studies; notably, neurologic signs, such as sedation, irritability, restlessness, depression, ataxia, hind limb paresis, mydriasis, stupor and coma (Baird-Heinz et al., 2012; Bhatti et al., 2015). Most adverse reactions to bromide tend to be dose-dependent and appeared to be reversible (Baird-Heinz et al., 2012; Boothe, 1998). Bromide toxicosis in dogs was most frequently associated with high serum bromide concentrations (Baird-Heinz et al., 2012). Most adverse reactions occur in the initial weeks of treatment and subside (partly or completely) once KBr steady-state concentrations are reached (Baird-Heinz et al., 2012; Bhatti et al., 2015).

Therapeutic administration of KBr in dogs was not found to affect thyroid weight or serum tT4, fT4, T3 and TSH concentrations or to cause histologic changes in the thyroid (Baird-Heinz et al., 2012).

In cats, bromide use as an anticonvulsant has been associated with life-threatening idiosyncratic allergic pneumonitis (Boothe et al., 2002), or the development of moderate to severe bronchoalveolitis/pulmonary fibrosis (Baka & Polizopoulou, 2019). Due to the idiosyncratic response to bromide in cats, the Scientific Committee could not establish a reference value for this species.

For additional information on the use of bromide therapeutically see Appendix C, Section C.1.

### 3.1.6 | Modes of action of bromide effects

#### 3.1.6.1 | Adverse outcome pathways related to thyroid and downstream effects

Several adverse outcome pathways (AOPs) have been proposed supporting the biological plausibility of associations between impairment of HPT homeostasis and downstream adverse effects including neurodevelopment, cardiovascular diseases or cancer (Crofton et al., 2019; Marty et al., 2021; Meek et al., 2014; Rolaki et al., 2019). A network of multiple proposed AOPs is depicted in Figure 1 which includes a series of molecular initiating events (MIEs) related to HPT homeostasis, key events (KEs), adverse outcomes (AOs) and their putative relationships (Noyes et al., 2019).

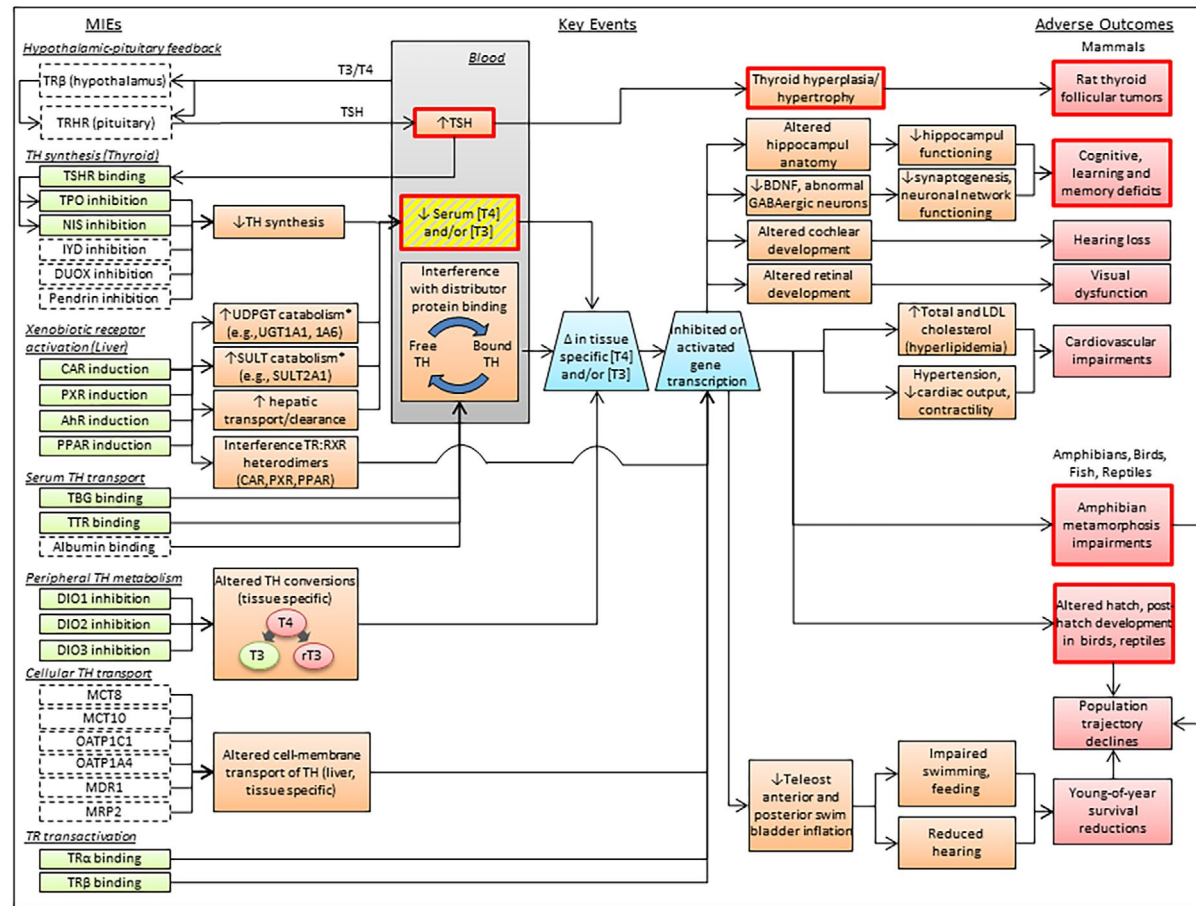
Disruption of HPT homeostasis may take place via several MOA with different MIEs. If modified by multiple stressors concurrently, their combined impact may converge on multiple effects on thyroid function (Crofton, 2008). Disruption of HPT homeostasis may occur via the following MOA (points A-G) (Bartsch et al., 2018; EFSA, 2019c, 2024).

- A. Inhibition of thyroid hormone synthesis via impairment of the sodium iodide symporter (NIS) (membrane transporter implicated in iodide uptake into follicular cells), thyroid peroxidase (TPO), deiodinases (DIOs), thyroglobulin synthesis or TSH receptor.
- B. Inhibition of thyroid hormone release (e.g. via inhibition of colloid droplet formation in rodents).
- C. Disruption of thyroid hormone transport, via inhibition of, or competitive displacement of thyroid hormone from TH transport proteins, e.g. T4 from serum thyroid binding proteins.
- D. Increased degradation and elimination of hormones due to induction or inhibition of conjugating enzyme activities (uridine diphosphate glucuronosyltransferases, UGTs, or sulfotransferases, SULTs). In rats, glucuronidation of T3 (dominant pathway in rat) leads to decreased serum tT4, increased serum TSH and proliferation of follicular cells (Hood et al., 2003; Klaassen & Hood, 2001).
- E. Competitive displacement of thyroid hormone from their specific receptors (TRs), e.g. T3 from TR $\beta$ 1 in the thyrotropic cells by some drugs.
- F. Indirect interference via nuclear receptor crosstalk, e.g. RXR agonist is known to play a role in hypothyroidism (Nakanishi, 2008).
- G. Alteration of TSH homeostasis, because of decreased T3 formation, followed by an increase of TSH-altered gene expression of proteins/enzymes/receptors or change in T3, T4 uptake into target cells (e.g. via membrane transporters) in turn alters hormone homeostasis, in a negative feedback loop as demonstrated with some pesticides (EFSA, 2019c). Impairment of TSH receptors may also result in altered TSH homeostasis.

Other MIEs include activation of xenobiotic-dependent nuclear receptors in the liver (e.g. CAR, PXR, PPAR alpha, AhR), TBG and TTR binding in serum, iodothyronine deiodinases and TR $\alpha$  and TR $\beta$  binding (Noyes et al., 2019).

For additional evidence on the role of thyroid homeostasis during development and potential downstream effects of thyroid perturbation, see Appendix D.

The available evidence indicates that points A and G are MOAs of bromide (see Section 3.1.6.2).



**FIGURE 1** Network of multiple proposed adverse outcome pathways associating thyroid homeostasis with downstream effects. From Noyes et al. (2019) with permission. Items marked with red borders represent in vivo endpoints targeted by US EPA and OECD test guidelines.

### 3.1.6.2 | Evidence of mode of action for bromide effects on the thyroid

The available evidence indicates possible MOA of bromide on the thyroid based on experimental animal studies. These are presented in the following paragraphs and in [Table 6](#) and [Figure 2](#) in relation to MIE and key events (KE). Evidence from human studies is not sufficient to support a MOA consistent with these AOPs.

#### MOA point A – Inhibition of thyroid hormone synthesis

##### *Iodide uptake in thyroid epithelial cells*

Bromine, due to its chemical similarity to iodine, is a goitrogen. van Leeuwen et al. (1983, 1987) showed that bromide inhibits iodine uptake by the thyroid gland in rats, a rate-limiting step for thyroid hormone synthesis, with subsequent increased TSH secretion. Increased bromide intake in the rat markedly reduced iodide accumulation in the thyroid (Pavelka, Babický, Vobecký, Lener, & Svandová, 2000; Buchberger et al., 1990; van Leeuwen et al., 1988), as well as in the skin (Pavelka et al., 2001). Furthermore, Pavelka, Babický, Vobecký, Lener, and Svandová (2000) and Vobecký et al. (2000) observed that in rats treated with increasing bromide doses, bromide replaced iodide in the thyroid, whereas bromide replaces chloride in other tissues. Even though bromide replaces iodide in the thyroid, increases of  $^{131}\text{I}$  uptake in the thyroid of bromide-treated rats relative to controls were observed by van Leeuwen et al. (1983) with a biphasic pattern: in rats maintained on a chloride-free diet for 90 days, the uptake of iodide was measured at 6, 24 and 48 h using  $^{131}\text{I}$  as a tracer.  $^{131}\text{I}$  uptake by the thyroid was increased significantly at 35 mg  $\text{Br}^-/\text{kg}$  bw per day (middle dose), but not significantly at 9 and 139 mg  $\text{Br}^-/\text{kg}$  bw per day. Serum tT4 was also significantly decreased at all doses in males and at the two highest doses in females after 42 days of bromide exposure. The authors postulated that the increased  $^{131}\text{I}$  uptake was consistent with thyroid stimulation via a TSH feedback mechanism because of reduced serum tT4, but that at the highest concentration serum bromide concentration was sufficiently high to compete with the uptake of  $^{131}\text{I}$  (van Leeuwen & Sangster, 1987). A statistical significant inhibition of  $^{131}\text{I}$  uptake in the thyroid of rats was also reported after 2-week treatment at a high dose (1768 mg  $\text{Br}^-/\text{kg}$  bw per day) (van Leeuwen et al., 1988).

##### *Bromide effect on Na<sup>+</sup>/I<sup>-</sup> symporter (NIS) (a Molecular Initiating Event)*

Bromide competition with iodide for binding and/or transport sites of NIS resulting in weak inhibition of iodide uptake was shown in HEK293 cells stably transfected with hNIS (Lecat-Guillet et al., 2007, 2008). These data are consistent with previous data of Jones et al. (Jones et al., 1996) demonstrating in cultured porcine thyrocytes that anions smaller than  $\text{I}^-$ , such as  $\text{Br}^-$ , are weak inhibitors of NIS, and spherical shape anions are more likely to be concentrated in the thyroid in contrast to linear/planar molecules. More recently, Hallinger et al. (2017), using a screening approach in vitro in the hNIS-HEK293T-EPA cell line identified an inhibitory effect of bromide on iodide uptake only when extending NaBr concentrations up to 500 mM, with an  $\text{IC}_{50}$  of NaBr of 8112 $\pm$ 10  $\mu\text{M}$ .

##### *Bromide effect on Thyroid Peroxidase (TPO) (a Molecular Initiating Event)*

TPO catalyses the peroxidation of iodide in a step that is critical for the incorporation of iodide in de novo biosynthesis of thyroid hormones. van Leeuwen et al. (1988) investigated TPO activity in thyroid homogenates from NaBr-treated rats. Their findings suggested that bromide strongly inhibited the oxidation of iodide to iodine by hydrogen peroxide and, to a lesser degree, inhibited iodinated tyrosine residue coupling to thyronine. Buchberger et al. showed that bromide can also replace iodide on TPO active site such that bromination reactions take place, with formation of bromo/iodo-substituted thyronines in the gland (Buchberger, 1988; Buchberger et al., 1990). Taurog and Dorris reported evidence against the hypothesis of TPO inhibition and iodination of thyroglobulin by bromide in vitro, even at a 200-fold excess concentration relative to iodide (Taurog & Dorris, 1991). To explain the data reported by Buchberger et al., a non-specific bromination of thyronines occurring extra-thyroidally and transported to the thyroid, under conditions of excess bromide levels for an extended time period was proposed. Earlier reports suggested that bromide oxidation by TPO is not possible (Yagi et al., 1953) due to differences in redox potential (Hosoya, 1963).

Later, Pavelka (2012a) demonstrated a biphasic effect on TPO activity, in rat microsomal fractions after 56 days of exposure, with a dose-dependent activation of TPO at lower dose levels (starting at 120 mg  $\text{Br}^-/\text{kg}$  bw per day) and an inhibitory effect only at the highest dose (600 mg  $\text{Br}^-/\text{kg}$  bw per day with a normal diet, and at 360 mg  $\text{Br}^-/\text{kg}$  bw with an iodine-deficient diet), regardless of iodine supplementation of the diets ( $\text{I}^-$  sufficient or deficient). However, in the absence of data on cytotoxicity, the inhibitory effect at high concentration of  $\text{Br}^-$  could be secondary to toxicity.

#### MOA point G – Effect on the pituitary axis and increase TSH secretion.

Alteration of pituitary gland activity due to thyroid hormone homeostasis feedback mechanisms (Loeber et al., 1983; van Leeuwen et al., 1983; van Leeuwen et al., 1988) was observed in rats exposed to bromide. In rats fed with a semisynthetic purified diet, a high dose of bromide (1768 mg  $\text{Br}^-/\text{kg}$  bw per day) was associated with decreased body weight and increased absolute and relative thyroid weights, decreased serum tT4 accompanied by increased TSH (van Leeuwen

et al., 1988). Increased TSH was also reported in iodine-deficient rats when treated with NaBr (372–1490 mg Br<sup>-</sup>/kg bw per day) for 4 weeks (Buchberger et al., 1990), while in another study, histopathological changes were noted in pituitaries of rats treated with similar NaBr dose levels (337–1348 mg Br<sup>-</sup>/kg bw per day) (van Leeuwen et al., 1976).

The homeostatic feedback mechanism of thyroid regulation via the pituitary–thyroid axis, whereby decreased peripheral thyroid hormone stimulates pituitary production and release of TSH is the principal mechanism of the pituitary effects of bromide (van Leeuwen et al., 1976). Interestingly, some experiments suggested that, in bromide-treated rats, the pituitary gland functions at its maximum capacity and cannot compensate for a further decrease in serum tT4, with an additional increase in release of TSH. Indeed, it has been shown that higher doses of bromide do not increase further the <sup>131</sup>Iodide uptake in the thyroid in response to compensatory stimulation of the gland by TSH that is observed at lower doses of bromide.

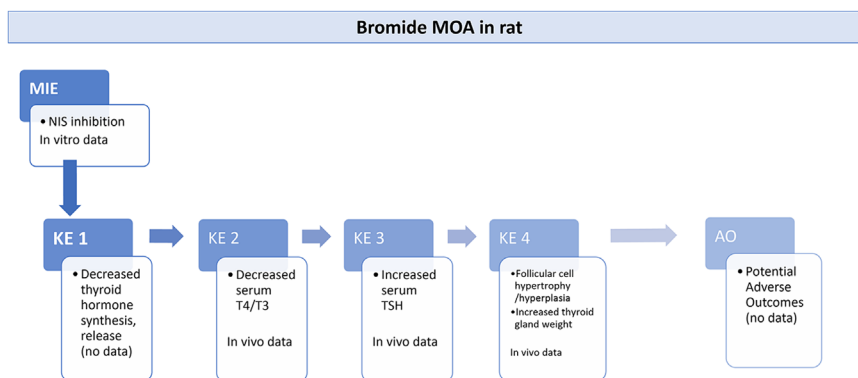
Hence, at severe bromide-induced thyroid impairment, pituitary stimulation cannot further compensate to restore adequate thyroid physiological function. A lack of sufficient stimulation of the thyroid by TSH release from the pituitary gland in bromide-treated animals may indicate that maximal pituitary response has been reached. This is suggested by the small TSH increase after thyrotropin-releasing hormone (TRH) administration in high dose bromide treated rats (1348 mg Br<sup>-</sup>/kg bw per day) that was of similar magnitude to animals not stimulated with TRH (Dollahide et al., 2002; Loeber et al., 1983; van Leeuwen & Sangster, 1987).

Thyroid gland stimulation may also result from mechanisms other than increased TSH activity resulting from a decrease in peripheral thyroid hormones (Gaitan et al., 1991; Gaitan & Dunn, 1992). Indeed, growth factors such as immunoglobulin-stimulating thyroid growth factor (ITGF), epidermal growth factor (EGF), insulin-like growth factors (IGF) and transforming growth factor β (TGFβ), fibroblast growth factor (FGR) and insulin are associated with thyroid stimulation (Maciel et al., 1988; Wenzel & Bottazo, 1991) and have shown mitogenic activity of the follicular thyroid epithelial cells, in vitro (Logan et al., 1992; Maciel et al., 1988; Zerek-Meleń et al., 1987).

Regarding other MIE and KE of the AOP, there is no further evidence for bromide effects except for effects on PPAR alpha (Shi et al., 2019).

Some evidence indicates an impact of bromide on fertility, but no neurodevelopmental studies have been identified.

Furthermore, little if any information is available regarding the effects of bromide on conversions of T4 and T3, catabolism, half-life or turnover in peripheral tissues. However, bromide is not metabolised and is not expected to be an inducer of xenobiotic metabolising enzymes (Figure 2).



**FIGURE 2** Proposed mode of action for bromide (adapted from Foster et al., 2021).

**TABLE 6** Overview of evidence on thyroid-mediated effects of bromide according to MIE, KE and AO in relevant AOPs.

AOP	AOP node	Target	Evidence of bromide effect*	Dose (mg/kg bw per day)	Reference
54, 134	MIE	<b>NIS</b>	<b>Yes</b> (in vitro)	NA	Lecat-Guillet et al. (2007, 2008), Hallinger et al. (2017)
		<b>Iodide uptake in thyroid</b>	22%–50%	1768 (14 days)	van Leeuwen et al. (1988)
		<b>↓ I/Br</b>		0.9–9 (66 days)	Velický, Titlbach, Dusková, et al. (1997)
				9–36 (133 days)	Velický et al. (1998)
				1.2–12 (15 days)	Vobecký and Babický (1994), Vobecký et al. (2000)
				0.9–9 (57 days)	
				60–600 (14 days; time course after 24 h)	Pavelka (2012a)

(Continues)



TABLE 6 (Continued)

AOP	AOP node	Target	Evidence of bromide effect*	Dose (mg/kg bw per day)	Reference
42, 54	KE	<b>T4 Significant ↓ (serum, plasma)</b>	56%	1768 (14 days)	van Leeuwen et al. (1988)
			10%–16%	5, 21, 84, 337, 1348 (M); 337–1348 (F) (42 days)	van Leeuwen et al. (1983)
			25, 40, 60% (F0–M). 20% and 35% (F0–F)		
			23%, 58% (4 weeks) 62% (12 weeks)	112–1797 (4 weeks) 1348 (12 weeks)	Loeber et al. (1983)
			> 50% (28 days)	372–1490 (iodine deficient diet) FT4	Buchberger et al. (1990)
			< 25%	0.9–9 (66 days) 9–36 (133 days)	Velický, Titlbach, Dusková, et al. (1997), Velický et al. (1998)
			46, 52% (dams) 35, 69% (pups) 55% (adult M)	120–600 (dams and PND17 pups) 450 (adult M)	Pavelka (2012a, 2012b), Pavelka et al. (2002) (no statistics performed in 2012)
			28, 52% (M) 34, 47% (F)	136–388 (M) 136–388 (F)	Study Report (2016b)
	KE	<b>T3 Significant ↓</b>	28, 37%	136–388 (M)	Study Report (2016b)
			< 20%	0.9–9 (66 days)	Velický, Titlbach, Dusková, et al. (1997)
18.5–48% (pups)			120–600 (dams and pups)	Pavelka et al. (2002)	
		24–54% (pups) no stats performed	120–600 (dams and pups)	Pavelka (2012b)	
KE	<b>TSH ↑</b>	3-fold (4weeks) 5-fold (12 weeks)	≥ 1348	Loeber et al. (1983)	
		30%–70%	≥ 372 (iodine deficient diet)	Buchberger et al. (1990)	
		Slight increase (not stat. sign)	0.9–9 (66, 133 days)	Velický, Titlbach, Dusková, et al. (1997), Velický et al. (1998)	
		2-fold %	1768 (14 days)	van Leeuwen et al. (1988)	
		36–74% higher (not stat. sign)	136–388 (M)	Study Report (2016b)	
KE	<b>Thyroid histology change</b>	<b>Yes</b>	11,348 (M) (4 and 12 weeks) 337-1348 (F) 1348 (M)	Loeber et al. (1983) van Logten et al. (1974, 1976)	
			35–140 (low Cl <sup>-</sup> diet)	van Logten et al. (1976)	
			1.2–12 (M) 0.9–36 (M) 9–36 (M)	Velický, Titlbach, Dusková, et al. (1997), Velický et al. (1998, 2004), Velický, Titlbach, Lojda, et al. (1997)	
			136–388 (M, F)	Study Report (2016b)	
KE	<b>Thyroid weight</b>	<b>Significant ↑</b>	≥ 372 (I-deficient diet) ≥ 84 mg (F) 1348 (M)	Buchberger et al. (1990) van Logten et al. (1974, 1976)	
			≥ 112 (M, after 4 weeks) 1348 (M, after 12 weeks)	Loeber et al. (1983)	
			120–600 PND17 pups 600 (M, after 56 days)	Pavelka (2002, 2012b)	
			1768	van Leeuwen et al. (1988)	
			388 (F)	Study Report (2016b)	
AO	Neuro-development	<b>No</b>		No studies available	

Abbreviation: ND, not determined.

### Summary on AOPs for thyroid-mediated effects

In summary, there is evidence that bromide alters thyroid hormone homeostasis (i.e. disrupts the HPT axis) in the rat. A decrease of serum T4 concentration, a critical effect with clear dose dependency, appears to be the most sensitive endpoint of bromide in the rat (see Table 3). A plausible MOA appears to involve competitive inhibition of iodide uptake, via the NIS, a direct mechanism of action (followed by decreased thyroid hormone synthesis (KE) and associated increase in TSH (KE)). NIS inhibition is a MIE in AOP 54 and 134 leading to neurodevelopmental adverse outcomes (AO), indicating a potential impact of bromide exposure on neurodevelopment. Decreased serum T4 concentration is a key event in AOP 42 and 54. TSH is the relevant parameter that indicates compensatory response of the HPT feedback loop.

According to the AOPs, the observed plasma decreases in thyroid hormone activate the feedback mechanism of the HPT axis, resulting in TRH release from the hypothalamus which in turn stimulates hypophyseal TSH release (KE). Sustained thyroid stimulation by TSH in response to reduced thyroid hormone levels may result in hypertrophy of thyroid follicles (increases size of follicles), which further result in thyroid hyperplasia (increased number of follicles), accompanied by colloid depletion with granular appearance, and increase in the colloid vacuolation in thyroid glands. Altered circulating levels of T3 and T4 without histopathological finding may still present sufficient evidence for a potential concern for neurodevelopment (EFSA-ECHA et al., 2018), and decreased serum T4 is considered as a biomarker of effect for neurodevelopment as an adverse outcome.

#### 3.1.6.3 | Species and sex differences of thyroid endpoints

##### Species differences

Dogs appeared less sensitive to thyroid effects of bromide (Paull et al., 2003) and overall, to thyroid disruptive chemicals when compared to rats. The young adult rat is considered a sensitive species, and several substances disrupt the HPT axis in this species. This is mainly due to the faster decline of the hormone reservoir in rats, which occurs within days compared to the more stable reservoir in humans. The half-lives of T3 and T4 in rats are 6 h and 12–24 h, respectively, compared to half-lives of 1 and 7 days, respectively, in humans. As a result, the homeostatic upregulation of TSH and related changes are more immediate in the rat and serve as sensitive indicators of a disturbance. In addition, there are species differences in thyroid hormone binding proteins, where thyroid binding globulin (TBG) is the main transporter in humans whereas transthyretin (TTR; a.k.a. prealbumin) is the predominant protein in rats (and a secondary binding and transport protein in humans). TBG acts also as a reservoir for thyroid hormone, due to its high affinity for the thyroid hormone. Only the free hormones (about 0.3% or even less for T3) are biologically active at the tissue and cellular level (Bartsch et al., 2018; Foster et al., 2021). In humans, about 75% of T4 is bound to TBG, 20% to transthyretin (TTR) and 5% to albumin while in the young adult rat, TTR is the predominant serum-binding protein where 75% of the T4 is bound to TTR and 25% to albumin.

However, in the neonatal rat, T4 is primarily bound to TBG as in humans, and thus although this species-difference is often highlighted, it is based only on data from adult animals.

In young adult rats, a 10-fold higher tT4 supplementation (20 mg/kg bw) is needed to maintain health in the absence of a functional thyroid compared to humans (2.2 mg/kg bw) (Capen, 1997). The tT4 half-life is significantly shorter in young adult rodents (12–24 h in rat, 12–18 h in mouse) compared to humans (5–9 days) due to higher reserves of thyroid hormone in humans in the form of TBG which is essentially absent in the young adult rodents. This, however, is not the case in the developing rodent where TBG also functions as a transport protein (Dohler et al., 1979). In contrast, TBG in humans, monkeys and dogs, has a 1000-fold higher affinity for T4 compared to TTR. These differences result in thyroid hormone kinetic differences, higher turnover, higher clearance rates with higher rate of thyroid hormone production, smaller reserve capacity of thyroid hormones in adult rodents compared to humans and by extension higher basal TSH level, a more active thyroid gland and consequently higher sensitivity of rodents to thyroid hormone inhibition compared to humans (Bartsch et al., 2018; Lewandowski et al., 2004; McClain et al., 1989). Distinct histological differences of the thyroid gland are observed between rats and other species, including humans and non-human primates (McClain, 1995). In rodents, unlike humans, the follicles have a tall cuboidal epithelium lining, contain smaller amounts of thyroglobulin colloid and have higher hormone synthesis and secretion activity (Suttie et al., 2017). The quantitative morphological and physiological differences observed in rat support a faster rate of thyroid hormone synthesis and turnover in response to perturbations compared to humans (U.S. EPA, 1998).

Nevertheless, despite the low level of TBG, mice appear less sensitive than rats (Kato et al., 2003) to the impact of T3 glucuronidation on decreased serum T4, increased serum TSH and proliferation of follicular cells (Hood et al., 2003; Klaassen & Hood, 2001). Furthermore, rats and mice showed a different pattern of T4 and T3 binding proteins in blood with a greater binding of thyroid hormone to prealbumin in rats (transthyretin) and to postalbumin in mice (Capen, 1997; Capen, 1999).

Species differences have been demonstrated *in vitro* for NIS activity, with rat NIS being more efficient/effective in I-uptake than human NIS (Dayem et al., 2008; Heltemes et al., 2003). In addition, species differences have been observed in TPO activity, with non-human primates, humans, guinea pigs and chicken being more resistant to inhibition than rats (Capen, 1999).

Substantial species differences have also been reported with respect to thyroid hormone availability to the brain, as a result of differences in cell type and expression of different thyroid hormone transmembrane transporters, including their

regulation, especially during development but also in adult brain (Wirth et al., 2014). The implications of these differences have not been fully assessed.

TSH serum concentrations differ between males and females in the rat and mouse, with threefold higher TSH concentrations in male compared to female rats (Foster et al., 2021; Kieffer et al., 1976). The histology of the female rat thyroid gland displays a greater number of large colloids filled follicles and a flattened epithelial lining and is more like non-human-primates (Foster et al., 2021). In addition, the binding capacity of TTR for thyroid hormones in female rats is lower than in male rats due to oestrogen binding (Emerson et al., 1990).

#### 3.1.6.4 | Modes of action related to neurotoxicity

There is limited information on possible MOAs of bromide other than those mediated via the thyroid.

Bromide is thought to exert its antiepileptic activity by passing through neuronal chloride ion channels associated with  $\gamma$ -aminobutyric acid (GABA) receptors, which hyperpolarises neuronal membranes, leading to the seizure threshold being raised, and neurons stabilised against excitatory input. Due to the smaller size of the hydrated bromide, it can passively cross these neuronal channels more readily than chloride ions. As a result, bromides are distributed into the CSF and interstitial tissues of the brain. Removal from the CNS is via an active transport mechanism that is overwhelmed at pharmacological doses (Baird-Heinz et al., 2012). In a systematic review of the safety of potassium bromide in dogs, Baird-Heinz et al. found that neurologic signs were the most reported adverse events associated with bromide administration in dogs and in other species in clinical and experimental studies. Thus, it is likely that the neurotoxicity of bromide can be a direct effect of its pharmacological effects, in addition to neurodevelopmental toxicity mediated by effects on thyroid homeostasis.

It has been suggested that high concentrations of bromide inhibit its active transport from the CSF thereby increasing its concentration in the brain (van Leeuwen & Sangster, 1987).

Bromide seems to mimic some of the neurotrophic or neuroplastic effects of the neurotransmitter GABA. Bromide and GABA induced the same dendritic changes in the principal ganglion cells of the superior cervical ganglion of adult rats (Joó et al., 1979; Wolff et al., 1978). In cultured mouse neuroblastoma cells both sodium bromide and GABA induced plastic changes affecting the shape of the dendrites with non-innervated or free postsynaptic thickenings and desmosome-like contact between dendrites and morphological changes suggestive of maturation of presynaptic elements and primitive stages of synaptogenesis (Eins et al., 1983; Spoerri, 1983; Spoerri & Wolff, 1982).

In a study in which foreign nerves were implanted into the superior cervical ganglion of adult rats, prior administration of 2800 mg/L sodium bromide in drinking water for 12 days (equivalent to about 260 mg Br<sup>-</sup>/kg bw per day) promoted synaptogenesis analogous to GABA (Toldi et al., 1986). When rats were given 2.16 mg Br<sup>-</sup>/L sodium bromide in drinking water for periods of time from 1 day to 1 month (equivalent to about 200 mg Br<sup>-</sup>/kg bw per day), there was no effect on GABA binding, uptake, metabolism or tissue concentration (Balcar et al., 1987).

Bromide decreased acetylcholine release from rat presynaptic cells *in vitro* in a manner independent of the GABA receptors. *In vivo*, perfusion of the exposed superior cervical ganglion of the anaesthetised rat depressed the amplitude of the potentials evoked by preganglionic nerve stimulation in the superior cervical ganglion of the rat (Kása et al., 1987). However, the relevance of these data is open to question since the studies were conducted at a relatively high concentration of NaBr (1 mM).

In conclusion, bromide seems to have similar actions to GABA, but there is little information on the mechanisms of bromide neurotoxicity.

### 3.1.7 | Consideration of critical effects and reference values

#### 3.1.7.1 | Establishment of reference values for human health

##### 3.1.7.1.1 | Critical effects

As described above (Section 3.1.3), studies in experimental animals (mainly rats) have shown that bromide has effects on the thyroid and other endocrine organs, CNS, kidneys, reproductive system and on growth (body weight gain) and fetal development. The effects seen at the lowest doses involve the thyroid and CNS. Reports of neurotoxicity were generally related to clinical signs, such as abnormal gait, at doses in excess of 100 mg Br<sup>-</sup>/kg bw per day. It is possible that more subtle effects could occur at lower doses, but there are no data available to assess this. Similarly, effects on reproduction and development have generally been reported at doses in excess of 100 mg Br<sup>-</sup>/kg bw per day (Table 2).

A large number of studies have reported adverse effects of bromide on levels of thyroid hormones (particularly tT4) or on morphology of the thyroid gland, but the dose response is not well defined. Most of the studies published in the scientific literature were performed in a small number of laboratories and were not compliant with OECD guidelines. However, the overall weight of evidence supports the activation of the HPT axis following oral exposure to bromide.

Studies performed with administration of bromide salts in the diet for 4–13 weeks have shown dose-related increases in thyroid weight, decreased serum levels of tT4 and increased TSH generally at doses of 84 mg Br<sup>-</sup>/kg bw per day or higher, with no reported effects at tested doses of 1–21 mg Br<sup>-</sup>/kg bw per day for 2–13 weeks (van Leeuwen et al., 1976; Loeber et al., 1983; van Logten et al., 1974). One study (van Leeuwen et al., 1988) noted a dose-dependent decrease in serum tT4

in males after 6 weeks starting from the lowest dose, equivalent to 5 mg Br<sup>-</sup>/kg bw per day. A significant decrease was also seen in female rats at higher doses, starting from 337 mg Br<sup>-</sup>/kg bw per day. However, the authors noted that other studies from their laboratory (Loeber et al., 1983) had not confirmed effects on thyroid hormones at the low doses seen in males in this study after 13 weeks.

The majority of the studies were conducted with administration of bromide salts in the drinking water for varying periods of time. The studies of Pavelka and colleagues (Pavelka, 2012a, 2012b; Pavelka et al., 2002) reported observations such as decreased iodide uptake, decreased serum tT4 (and in some instances T3) and increased thyroid gland weight in adult males at 60 mg Br<sup>-</sup>/kg bw per day and in dams exposed at 120 mg Br<sup>-</sup>/kg bw per day and their pups, but lower doses were not tested. In contrast, Velicky and colleagues (Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997) administered lower concentrations in drinking water and found significantly decreased serum tT4 and morphological changes in the thyroid at administered doses as low as around 1 mg Br<sup>-</sup>/kg bw per day. This observation was cast into doubt by poor reporting and lack of biological significance and by a subsequent study (Velický et al., 1998) which reported no marked effect on serum tT4 levels at doses of 9–36 mg Br<sup>-</sup>/kg bw per day.

Thus, there is consistency in the observations relating to effects on the thyroid but not in the doses at which these are observed. The differences between the dose levels reported to have effects in the different Velicky studies, together with the high risk of bias in these studies (see Appendix A), lead to the conclusion that these studies do not provide a suitable basis for identification of reference points.

The doses cited in all of these studies relate to supplemental bromide exposure, i.e. they do not take into account total exposure from the background concentrations in the feed and drinking water. Most studies did not include data on these background concentrations. The studies of Velicky and colleagues (Velický et al., 1998; Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997) cited a concentration of 10.04 mg Br<sup>-</sup>/kg in the feed, adding in the region of 1 mg Br<sup>-</sup>/kg bw per day, which has a minor impact on most of the studies performed with doses of 60 mg Br<sup>-</sup>/kg bw per day and above, but needs to be taken into account in the dose response modelling for the studies of Velicky and colleagues, performed with lower administered doses. None of the studies reported concentrations of bromide in drinking water, but it could be up to 0.5 mg/L (see Section 1.3.3), which could add in the region of 0.05 mg Br<sup>-</sup>/kg bw per day<sup>32</sup> and have a minor impact on the total dose in the toxicological studies.

Mode of action studies suggested that bromide competitively inhibits iodide uptake into the thyroid, via the NIS, which leads to decreased thyroid hormone synthesis and associated increase in hypophyseal TSH. Sustained thyroid stimulation by TSH as compensatory response to reduced thyroid hormone levels may result in hypertrophy of thyroid follicles, thyroid hyperplasia, accompanied by colloid depletion and increased peripheral colloid vacuolation in thyroid glands. Changes in thyroid hormone levels, depending on magnitude, the windows of exposure and time length, present a potential concern for adults and for pre- and post-natal neurological development (EFSA-ECHA et al., 2018). According to the guidance, changes in thyroid hormone levels in the rats are considered a sensitive indicator of the potential of chemical compounds for thyroid disruption and a concern for the developing brain.

The Scientific Committee also reviewed the human observations related to bromide exposure. The case studies provided evidence of adverse effects on the CNS, skin and GI tract, but did not provide adequate information on dose–response. The observational studies were insufficient to indicate specific associations.

A few experimental studies in healthy volunteers were available with oral administration of NaBr by capsule for up to 12 weeks. The studies by Sangster et al. (1982), Sangster et al. (1983) and Sangster et al. (1986)/ van Gelderen et al. (1993) examining the effect of bromide on endocrinological parameters, indicated a NOAEL of 4 mg Br<sup>-</sup>/kg bw per day for women. At 9 mg/kg bw per day, there was a statistically significant increase in serum tT4 ( $p < 0.01$ ), fT4 ( $p < 0.05$ ) and tT3 ( $p < 0.01$ ) at the end of the intervention compared to concentrations at the start of the study of Sangster et al. (1983), whereas an increase in TSH but no change in T4 was reported in Sangster et al. (1986)/van Gelderen et al. (1993). In addition, the spontaneous electroencephalogram (EEG) and evoked cerebral activity of each subject showed a decrease in  $\delta 1$ - and  $\delta 2$ -activities and increases in  $\beta$ -activities and in mean frequency (Mobility parameter) at the end compared to the start of the study (Sangster et al., 1983). Overall, these studies provide evidence of effects of bromide on the CNS and on thyroid hormones at supplemental exposures of 9 mg Br<sup>-</sup>/kg bw per day in females. The Scientific Committee noted that there was no explanation for the increase in mean tT4 concentration in one of these studies, which was not replicated in another, but that the increase in mean TSH concentration is indicative of effects on the HPT axis.

There is no information on health effects of bromide for children, adults > 31 years, pregnant or lactating women, or after long-term intake.

An intake of 4 mg Br<sup>-</sup>/kg bw per day, above intake of bromide that is naturally present in the diet (8–9 mg/day, i.e. about 0.1 mg/kg bw per day for a 70-kg adult), resulted in plasma bromide concentrations of 244 and 258 mg/L for females in two studies (Sangster et al., 1983; Sangster et al., 1986; van Gelderen et al., 1993), and 171 mg/L for males (Sangster et al., 1983). The background intake from the diet is minimal compared to the doses administered in these studies, and therefore, the NOAEL of 4 mg/kg bw per day does not require adjustment to total intake.

Therefore, the Scientific Committee concludes that altered thyroid hormone concentrations is an early critical effect of bromide and that the human data do not provide a suitable basis for identification of a reference point. Most studies in rats had reported on serum tT4 concentrations, although there was inconsistency between the dose levels at which changes

<sup>32</sup>Taking into account the EFSA default conversion factors of 0.05 to 0.12, depending on the age of rat.



occur. By developing a reference dose based on the critical effect of decreased serum tT4, it is expected that all subsequent potential adverse effects will be prevented. Therefore, benchmark dose modelling was performed on the tT4 data from the more reliable studies in order to provide a potential reference point.

### 3.1.7.1.2 | Dose response modelling

The Scientific Committee performed benchmark dose (BMD) modelling according to the 2022 EFSA Guidance on the use of the BMD approach in risk assessment (see Section 2.6) (EFSA Scientific Committee, 2022).

The results of the BMD modelling for the critical studies identified above on disturbance of thyroid homeostasis in rats after oral exposure to bromide are summarised in Table 7. The individual reports of the modelling are shown in Appendix E.

#### Selection of the BMR

The EFSA guidance on BMD (2022) recommends that the BMR should reflect the onset of a human-relevant adverse effect, meaning that a response above the BMR is considered adverse. In rats, a 10%–17% decrease in T4 during pregnancy and lactation is associated with neurodevelopmental toxicity in rat offspring (Gilbert, 2011; Gilbert et al., 2016). Heterotopia, an abnormal cluster of neurons within the normal neurons, sparse white matter of the corpus callosum have been observed in fetuses of dams with serum T4 decrements of approximately 20% (Hassan et al., 2017). In humans, a 25% decrease in T4 (either tT4 or fT4) during pregnancy (during second trimester) results in neurodevelopmental and cognitive deficits in children (Haddow et al., 1999).

Therefore, the Scientific Committee selected a BMR of 20% for blood tT4 level decrease.

#### BMD analysis

BMD modelling was performed on animal studies reporting blood tT4 level changes after oral exposure to bromide (sub-chronic), including at least three doses and a control group (cf. part 3.1.3.5, Table 3). Details of the modelling are in Appendix E.

Loeber et al. (1983) observed a tT4 level decrease in serum at the two highest doses after 4 weeks and only at the highest dose after 12 weeks. BMD modelling is done using exposure time as a covariate. BMD analysis of tT4 levels after 12 weeks is not considered relevant as the 90% credible interval is too wide (BMDU/BMDL > 100).

van Leeuwen et al. (1983) measured serum tT4 levels of male and female rats exposed to bromide for 6 weeks. BMD modelling is done using sex as covariate.

In a 13-week study in which serum thyroid hormone levels were measured in week 4 (study report 2016b), a tT4 level decrease is reported in both male and female rats. BMD modelling is done using sex as covariate.

**TABLE 7** Benchmark dose (BMD) modelling for the critical change of plasma tT4 levels (BMR 20%) (all results calculated using bridge sampling<sup>a</sup>).

Reference	Animal dosing	BMDL <sub>20</sub> (mg Br <sup>-</sup> /kg bw per day)	BMD <sub>20</sub> (mg Br <sup>-</sup> /kg bw per day)	BMDU <sub>20</sub> (mg Br <sup>-</sup> /kg bw per day)
Loeber et al. (1983)	Adult M rats (Wistar, <i>n</i> = 10) 0, 1.9, 6.8, 28, 112 mg Br <sup>-</sup> /kg bw per day for 4 weeks	58	98	153
Van Leeuwen et al. (1983)	Adult M rats (Wistar, <i>n</i> = 10) 0, 5, 21, 84, 335, 1341.89 mg Br <sup>-</sup> /kg bw per day for 6 weeks	39	79	154
Van Leeuwen et al. (1983)	Adult F rats (Wistar, <i>n</i> = 10) 0, 5, 21, 84, 335, 1341.89 mg Br <sup>-</sup> /kg bw per day for 6 weeks	54	157	434
Study report (2016b)	Adult M rats (Sprague Dawley, <i>n</i> = 10) 0, 47, 136, 388 mg Br <sup>-</sup> /kg bw per day for 13 weeks, with analysis of plasma tT4 at 4 weeks	52	86	144
Study report (2016b)	Adult F rats (Sprague Dawley, <i>n</i> = 10) 0, 47, 136, 388 mg Br <sup>-</sup> /kg bw per day for 13 weeks, with analysis of plasma tT4 at 4 weeks	13	47	164

<sup>a</sup>All analyses using a covariate were performed Laplace approximation. Extended dose range assumption was not applied in order to avoid confidence intervals falling outside of the dose range tested.

### 3.1.7.1.3 | Health-based guidance values

The range of BMDL<sub>20</sub> values is of 13–58 mg Br<sup>-</sup>/kg bw per day. The Scientific Committee noted that the lowest of these values was for female rats in a study in which the BMDL<sub>20</sub> for male rats was 51.6 mg Br<sup>-</sup>/kg bw per day (Study Report, 2016b). In contrast, modelling of the data of Van Leeuwen et al. (1983) resulted in higher BMD<sub>20</sub> and BMDL<sub>20</sub> values for female rats than for males. Furthermore, male rats are generally found to be more sensitive to changes in thyroid hormone levels



than female rats (Foster et al., 2021; Kieffer et al., 1976). The greater sensitivity of the males was also apparent in the 2016b study in which serum tT3 was decreased only in males but not females. Taking into account also the higher uncertainty in the BMD analysis of the females in the 2016b study (BMDU/BMDL ratio of 12.8 in females compared to 2.8 in males), the Scientific Committee concluded that the BMDL<sub>20</sub> of females of 13 mg/kg bw per day was not a robust reference point and identified the BMDL<sub>20</sub> of 40 mg Br<sup>-</sup>/kg bw per day as the reference point (RP).

The Scientific Committee established a tolerable daily intake (TDI) of 0.4 mg/kg bw for bromide by applying an UF of 100 to the RP of 40 mg Br<sup>-</sup>/kg bw per day to allow for inter- and intra-species differences. In principle, a lower UF might be proposed because humans are considered to be no more sensitive than rats to effects on the thyroid (EFSA-ECHA et al., 2018), suggesting that the default factor of 2.5 for inter-species variability in toxicodynamics (EFSA Scientific Committee, 2012) is not required and an overall uncertainty factor of 40 would be sufficiently protective for human health. The reproductive and developmental studies that have been performed with bromide give conflicting reports regarding the sensitivity of the offspring. Van Leeuwen et al. (1983) reported effects on the parental generation at doses not associated with changes in thyroid hormones in the pups, whereas Pavelka et al. (2002), Pavelka (2012b) reported that effects on thyroid hormones were more pronounced in pups. However, these studies did not assess the range of endpoints that would be expected in neurodevelopmental studies and the studies of Pavelka et al. were judged to be of low reliability. The Scientific Committee noted the additional uncertainty with respect to the possibility of neurodevelopmental effects in neonates and followed an EKE process to determine the size of uncertainty factor required to allow for these uncertainties (see Section 3.9). By expert group judgement, a factor of 2.5 was considered sufficient to allow for all additional uncertainties. Therefore, an overall uncertainty factor of 100 was applied.

This TDI is supported by the NOAEL of 4 mg Br<sup>-</sup>/kg bw per day from the study in humans of Sangster et al. (1983) including an uncertainty factor of 10 for inter-individual variability.

From the case reports it can be summarised that infants ( $\leq 12$  months) treated with KBr had intakes of 495–720 mg/day resulting in serum bromide concentrations of 890–1230 mg/L. A similar pattern was seen for older children. Case reports for adults reported serum bromide concentrations from 407.5 to 3520 mg/L. These serum bromide concentrations are all considerably higher than those estimated to result from the TDI.

Overall, and based on a comprehensive assessment of the literature and assessment of serum bromide levels in the case reports, a TDI of 0.4 mg Br<sup>-</sup>/kg bw is considered to be sufficiently protective for the general human population, including the offspring of pregnant and lactating women.

The Scientific Committee also considered whether there is a need for establishment of an acute reference dose (ARfD). Bromide is of low acute toxicity in rodents, and effects other than on thyroid hormones (e.g. neurological, gastrointestinal or skin reactions) are observed following repeated exposure to doses of 100 mg/kg bw per day and higher. With respect to effects on thyroid hormones, for adult humans, a decrease in tT4 is not an apical endpoint and hypothyroxaemia will not generally cause an immediate clinical manifestation because of the hormone functional reserve (most of T4 is protein bound) and because of the feedback mechanism on the pituitary axis (the level of serum TSH increases due to TRH stimulation).

However, if the thyroid hormone deficiency occurs early in pregnancy, the offspring may suffer from visual attention deficits, visual processing and gross motor skills. If it occurs later in pregnancy, children are at additional risk of subnormal visual and visuospatial skills, as well as slower response speeds and fine motor deficits (Zoeller & Rovet, 2004). The most sensitive window for thyroid hormone disturbance is the first trimester of pregnancy during which neuron proliferation, migration and differentiation occur (e.g. the GABA switch). Even modest degrees of thyroid hormone disruption experienced in utero can result in neuropsychological deficits in children despite normal thyroid status at birth (U.S. EPA, 2020; Finken et al., 2013; Haddow et al., 1999; Korevaar et al., 2016; Pop et al., 1999, 2003). In rats, a 20% reduction in maternal serum T4 is associated with a 35% reduction in fetal serum T4 (Hassan et al., 2017). Therefore, the Scientific Committee concluded that there is a need for an ARfD to protect against neurodevelopmental effects arising from short-term elevated exposure to bromide that results in > 20% reduction in maternal serum T4 at a critical stage in pregnancy. In the absence of short-term studies assessing the effects of bromide on thyroid hormones to provide a Reference Point as a basis for the ARfD, the Scientific Committee considered that the TDI should also be applied as an ARfD. Therefore, the Scientific Committee established an ARfD of 0.4 mg Br<sup>-</sup>/kg bw per day.

This assessment on bromide effects on the thyroid applies to conditions of iodine-sufficient diets. Individuals who are iodine deficient may not be adequately protected by the TDI and ARfD. The impact of iodine deficiency is out of the scope of this assessment and warrants attention of public health authorities.

#### 3.1.7.1.4 | Reference values for animal health

As described above (see Section 3.1.6., and Appendix C), studies in dogs have shown that bromide has effects on the survival, the nervous system, the skin, the digestive organs and the appetite of animals.

In dogs fed on sodium or potassium bromide for periods from 30 up to 360 days, dogs developed shivering, paresis, ataxia, bradycardia, skin lesions, salivation, vomiting, diarrhoea, haematochezia, stupor, and emaciation and weight loss, at doses higher than 40 mg Br<sup>-</sup>/kg bw per day, and, in some cases, coma and death at doses higher than 156 mg Br<sup>-</sup>/kg bw per day (March et al., 2002; Rosenblum, 1958, 1960; Rosenblum & Hawkins Jr., 1958). Potassium bromide at the dose of 20 mg Br<sup>-</sup>/kg bw per day did not appear to have a significant effect on canine thyroid function or morphology (Paull et al., 2003) and on feline body weight, appetite and blood and urine parameters (Boothe et al., 2002).

The Scientific Committee also reviewed other studies in food producing and non-food producing animals, such as a pharmacokinetic study in horses (Raidal & Edwards, 2008), a case report of bromide toxicosis in horses (Sacks et al., 2022), a study to determine effects of sodium bromide on production and health of cattle for fattening (Knight & Reina-Guerra, 1977) a study to determine the efficacy of potassium bromide, as a sedative medical agent, in cattle for fattening (Genicot et al., 1991), a study to determine effects of dietary sodium bromide on bromide deposition to milk and tissues of dairy cattle (Vreman et al., 1985), a pharmacokinetic study in sheep (Quast et al., 2015), a study to determine the effect of a bromide salt mixture in pig performance (Barber et al., 1971), performance studies in chicken for fattening (Baker et al., 2003; Bosshardt et al., 1956; Doberenz et al., 1965; du Toit & Casey, 2010), a study to determine the quality and safety of eggs obtained from laying hens after their experimental poisoning with sodium bromide (Kutsan et al., 2020), a chicken embryo sensitivity study (Lucht et al., 2018), a canine prostate secretion study (Smith & Ilievski, 1985), and two case reports of bromide toxicosis in dogs (McConkey et al., 2012; Piperisova et al., 2009). However, none of these studies were considered appropriate for establishing reference values for these target species due to several study design and other limitations, including any or a combination of the following: the dose and duration of Br<sup>-</sup> ion administration were not reported; the duration of the study was short; a single bromide dose was used; confounding of other trace mineral supplementation (i.e. iodine) present; data were reported in only one animal or with low replication; poor reporting of studies; or in ovo bromide treatments.

In addition, three studies in food producing animals with seaweeds were identified but were not considered for the assessment due to the following limitations: in the two studies in dairy cows (Krizsan et al., 2023; Stefanoni et al., 2021), the bromide content of the seaweed or the diet was not reported; in the study in chicken for fattening (Costa et al., 2022), the duration of the study was short (i.e. 14 days) and the final body weight at day 35 of age was lower than the respective standards of the breed implying unknown factors that impacted the study.

Based on the data considered for the assessment, the Scientific Committee established a NOAEL of 20 mg Br<sup>-</sup>/kg bw per day for dogs (Paull et al., 2003), with the approximate concentration in feed of bromide being 1035 mg Br<sup>-</sup>/kg complete feed for dogs, and when applying an uncertainty factor of 10 for intra-species differences within dogs, the maximum safe concentration in feed of bromide being 103 mg Br<sup>-</sup>/kg complete feed for dogs. However, the Scientific Committee could not establish a reference value for cats due to the idiosyncratic response to bromide in this species and for any of the other target species due to the limitations in the database outlined above.

In such cases, toxicological data derived from subchronic studies in experimental animals are used for establishing reference values for food-producing and non-food-producing species for which data are lacking. Based on the weight of evidence available for bromide, from experimental animal studies, a reference point of 40 mg/kg bw per day was identified (see Section 3.1.7.1.4). Applying an uncertainty factor (UF) of 100 to the reference point of 40 mg/kg bw, the maximum safe intake for the food- and non-food-producing species (other than dogs and cats) was derived for bromide. According to the EFSA Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017), the maximum safe feed concentration which can be considered safe for the food- and non-food-producing animals can be derived from the lowest no observed adverse effect level (NOAEL) or benchmark dose level (BMDL<sub>10</sub>) identified, if suitable data are available. Thus, the maximum safe bromide feed concentration was calculated as shown in Table 8.

**TABLE 8** Maximum safe concentration in feed for bromide for food and non-food producing animals (other than dogs and cats).

	Daily feed intake <sup>a</sup> (g DM/kg bw)	Maximum safe bromide concentration in feed (mg Br <sup>-</sup> /kg complete feed) <sup>b</sup>
Chicken for fattening	79	4.5
Laying hen	53	6.6
Turkey for fattening	59	6.0
Piglet	44	8.0
Pig for fattening	37	9.6
Sow lactating	30	11.7
Veal calf (milk replacer)	19	20.0
Cattle for fattening	20	17.6
Dairy cow	31	11.4
Sheep/goat	20	17.6
Horse	20	17.6
Rabbit	50	7.0
Salmon	18	20.1
Ornamental fish	5	78.2

<sup>a</sup>Default values according to EFSA FEEDAP Panel (2017).

<sup>b</sup>Complete feed containing 88% dry matter (DM), milk replacer 94.5% DM.

## 3.2 | Occurrence data

An initial number of 57,497 analytical results on bromide in food ( $n=57,440$ ) and feed ( $n=57$ ) were available in the EFSA database. The data on food matrices included both raw food commodities collected via monitoring programmes for pesticide residue levels and food items collected via monitoring programmes for food contaminants. Data were reported from 25 EU countries, Norway, Switzerland, the UK,<sup>33</sup> Northern Ireland<sup>34</sup> and Bosnia-Herzegovina. The major contributor of data on bromide was Germany who reported 61% of the data, followed by Poland (8%). Other European countries contributed with  $\leq 5\%$  of data. It should be noted that the origin of the samples was not always the European country reporting the data, i.e. the data set also contained samples originating from North and South America, Australia, Africa, and Asia. All these food products were available on the EU market and were therefore subject to legal requirements applicable in the EU. The analytical results were obtained between 2009 and 2022. The raw occurrence dataset on bromide in food and feed as extracted from the EFSA datawarehouse is available at the EFSA Knowledge Junction community in Zenodo (<https://doi.org/10.5281/zenodo.14699804>).

The occurrence data were carefully evaluated, and a list of validation steps was applied before being used to compare with the current MRLs (see [Annex D](#), Table D.1 for further details). In total, 471 analytical results were obtained through suspect sampling and therefore excluded from further evaluation. Out of these, four analytical results reported for food category 'Fish, seafood, amphibians, reptiles and invertebrates' including samples on canned mackerel and unspecified canned seafood, were the only data for fish reported. Following the validation steps as described in [Annex D](#), Table D.1, the final data set comprised 46,965 analytical results, obtained between 2013 and 2022, for food and drinking water (out of these only 23 analytical results were available for drinking water; all below LOQ) and 57 analytical results for feed.

In total, 45% of occurrence data were obtained through the official control activities on pesticide residues carried out in the EU Member States and 55% of data were submitted through a call for annual collection of chemical contaminant occurrence data in food and feed. Approximately 97% of the data were obtained from samples collected within official national and EU monitoring programmes, 3% from industry/private programmes, and  $<0.001\%$  from a combination of programmes.

In the final data set, 45% of the data were reported as 'Objective sampling', 52% as 'Selective sampling', while the remaining 3% were reported as other undefined sampling.

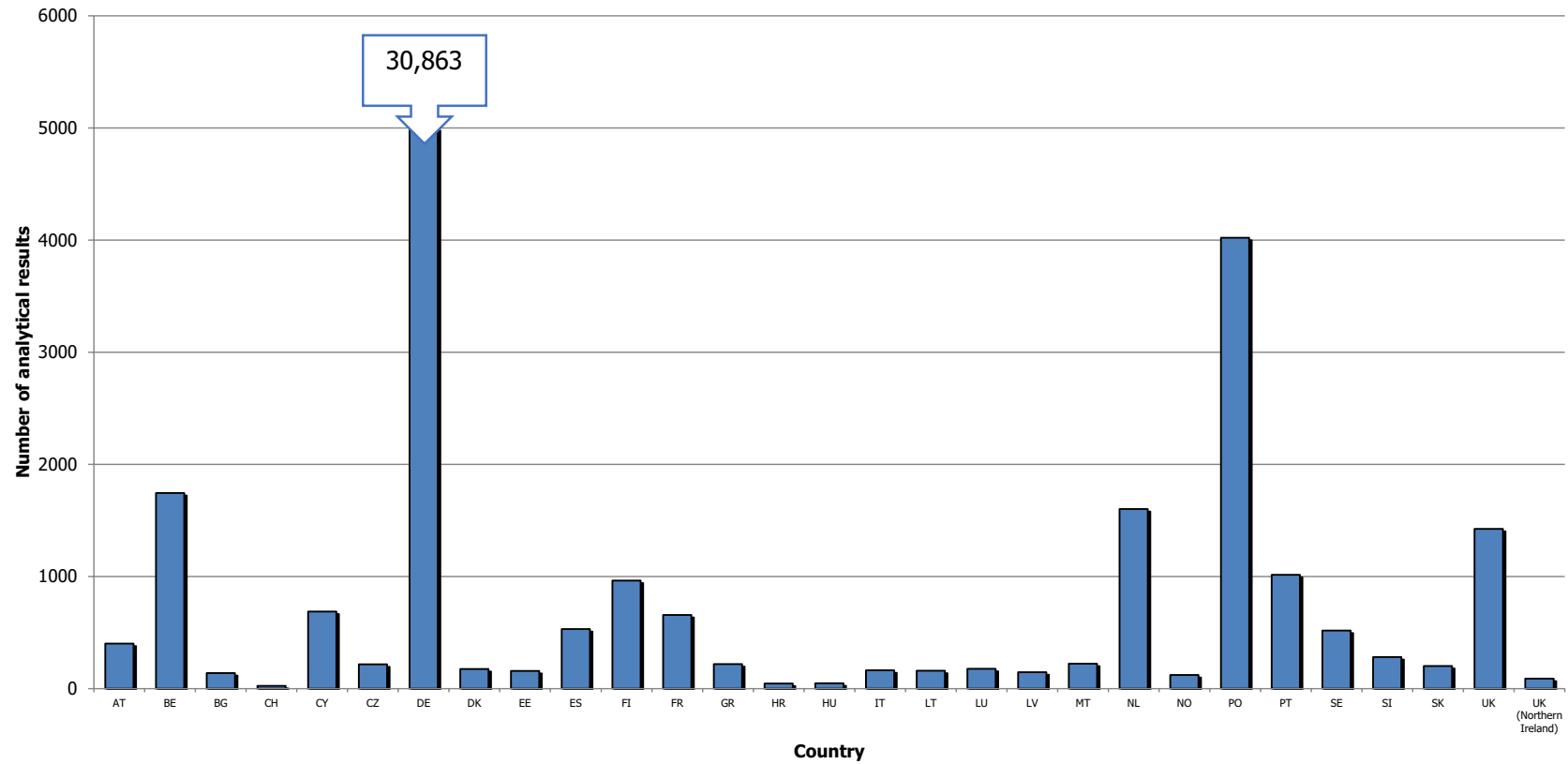
The results for which information on analytical results was reported were obtained by the LC-based methods (19%; almost all were MS methods) GC-based methods (12%; out of these majority were GC-ECD and only 18% were MS methods) and ICP-based methods (3%; almost all were MS methods). For the remaining data, no information on analytical methods was reported. Data analysis showed that the reported bromide concentrations without reference to analytical methods were consistent with those measured by valid methods of analysis and based on this, the Scientific Committee decided to consider the data for which no information on the analytical method was provided in the assessment.

### *Occurrence data of bromide in food and drinking water submitted to EFSA*

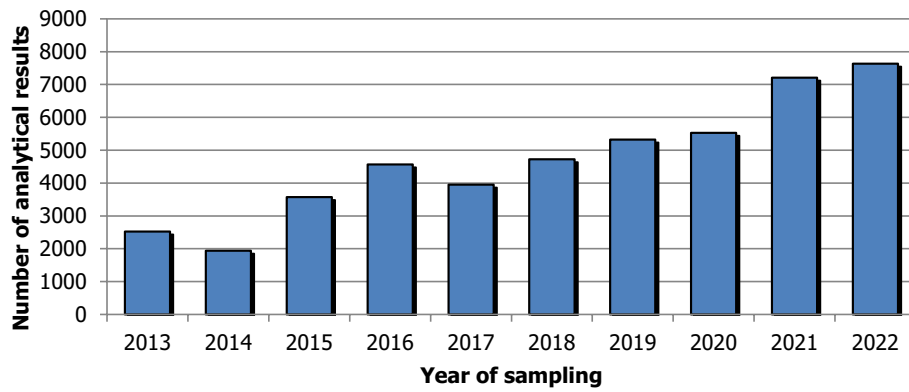
The analytical results included in the final data set ( $n=46,965$ ) and considered for the comparison with the current MRLs in EU were collected in different European countries, most of them in Germany (66% of analytical results), while other countries contributed far less data ([Figure 3](#)). The data were for samples collected between 2013 and 2022 ([Figure 4](#)).

<sup>33</sup>Only occurrence data submitted to EFSA when the UK was a member of the EU were included in the assessment.

<sup>34</sup>Analytical data in 2021 reported separately pursuant to Article 5(4) and Section 24 of Annex 2 of the Protocol on Ireland/Northern Ireland.



**FIGURE 3** Distribution of analytical results reported for bromide across different European countries (final cleaned data set).



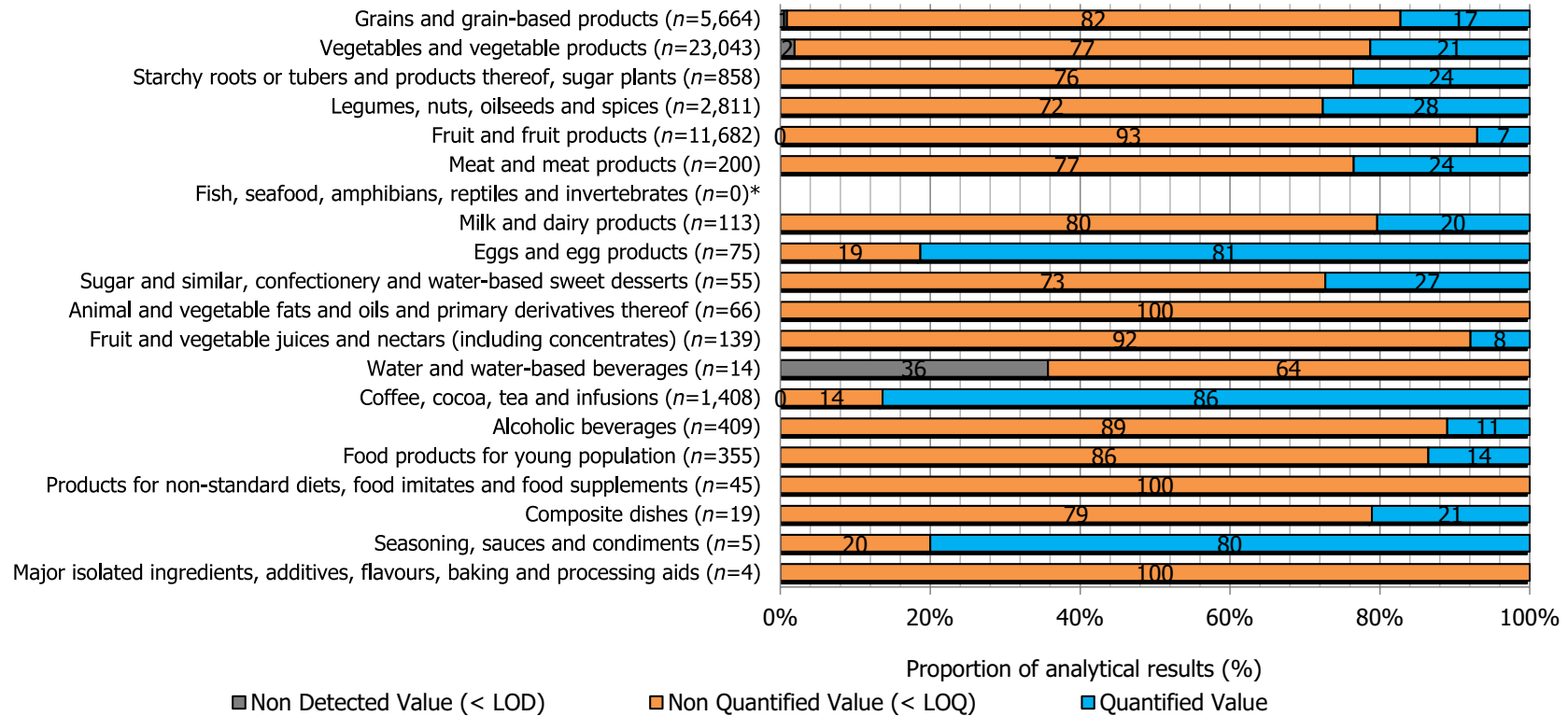
**FIGURE 4** Distribution of analytical results reported for bromide by year (final cleaned data set).

Overall, the LCD accounted for 80% of the analytical results for food. For drinking water, only limited data were available ( $n = 13$ ); all being reported as non-quantified. Among the FoodEx2 Level 1 food categories, the highest percentage of quantified data was found in food categories 'Coffee, cocoa, tea and infusions' and 'Eggs and egg products' with proportion of LCD at level of 14% and 19%, respectively.

Based on the FoodEx2 classification, 19 food categories at FoodEx2 Level 1 were represented (Figure 5). 'Vegetables and vegetable products' was the most represented food category with 23,043 occurrence values reported, followed by 'Fruit and fruit products' with 11,682 occurrence values, and 'Grains and grain-based products' with 5664 occurrence values. Proportions of non-detected, non-quantified and quantified analytical results by FoodEx2 Level 1 food category are presented in Figure 5.

More details with regard to proportion of LCD up to FoodEx2 Level 3 food category are presented in Annex D, Table D.2.





**FIGURE 5** Percentage of analytical results below LOD, below LOQ and quantified values in the final data set across the different food categories (FoodEx2 Level 1).

When considering only the FoodEx2 Level 1 food categories with a substantial number of data available ( $n > 5$ ) the highest mean bromide concentration levels were measured in 'Coffee, cocoa, tea and infusions', in particular in dry forms of flowers used for herbal infusions and herbal infusion materials from leaves and herbs. The second FoodEx2 Level 1 food category with the highest mean bromide concentration levels reported was 'Legumes, nuts, oilseeds and spices', in particular in different types of spices (e.g. dried herbs, seed spices, fruit spices) and tree nuts (e.g. pistachios, Brazil nuts).

When considering the food categories at lower FoodEx2 level, very high bromide concentrations were found in algae and prokaryotes organisms and salt, but only very limited number of data were available for these food products. This limitation needs to be borne in mind when interpreting the results.

A more detailed overview of the number of data points, the proportion of LCD as a percentage and statistical description according to FoodEx2 levels (up to Foodex2 level 4) for all food categories are reported in [Annex D](#), Tables D.2–D.5.

#### *Occurrence data considered for the comparison with the current MRLs in EU*

Regarding the food categorisation system as defined in Annex I of Regulation (EC) No 396/2005, the Scientific Committee considered only occurrence data relevant in the context of pesticide residues and existing MRLs. A total number of 44,468 analytical results reported for 10 food categories at level 1 was available for the evaluation. The most frequently analysed food categories were 'Vegetables, fresh or frozen' ( $n = 23,541$  data) and 'Fruits, fresh or frozen; tree nuts' ( $n = 12,211$  data). A substantial amount of data was also available for other food categories while others, e.g. 'Hops', 'Sugar plants' were much less represented. It should be noted that the Annex I of Regulation (EC) No 396/2005 defines the part of the product to which the MRL applies (e.g. whole product after removal of stems), but from the data description it was not clear whether these requirements were respected when analysing the samples collected through the call for chemical food contaminants.

An overview of the number of data points, the proportion of LCD as a percentage, the mean and 95th percentile (P95) concentration values of selected food categories as defined in Annex I of Regulation (EC) No 396/2005 is presented in [Table 9](#). A more detailed overview of the number of data points, the proportion of LCD as a percentage and statistical description according to food categorisation system as defined in Annex I of Regulation (EC) No 396/2005 (up to level 4) for all food categories are reported in [Annex D](#), Tables D.6–D.9. The highest percentage of quantified data was observed for the food category 'Teas, coffee, herbal infusion materials, cocoa and carobs' (dry forms of these food products) with 20% of LCD data comprised. This was also the level 1 food category with the highest bromide mean concentration levels observed, in particular for 'Herbal infusions from flowers' with the mean LB and UB concentrations around 30 mg/kg (the highest concentrations measured for hibiscus infusion flowers) and 'Herbal infusion materials from leaves and herbs' with the mean LB and UB concentrations about 20 mg/kg (the highest concentrations measured for strawberry infusion leaves and herbs).

When considering the level 1 food categories, the next highest mean bromide concentrations were measured for 'Spices' with the mean LB and UB levels of 7.08 and 8.02 mg/kg, respectively, for 'Hops' with the mean LB and UB mean levels of 3.86 and 7.27 mg/kg, respectively and 'Cereals' with the mean LB and UB mean levels of 1.43 and 6.20 mg/kg, respectively. For 'Pulses', similarly high mean bromide concentration was observed for the UB (7.72 mg/kg), but this was not confirmed when considering the LB mean concentration (1.09 mg/kg).

Attention was paid to analysis of levels measured in different food categories belonging to level 1 categories 'Fruits, fresh or frozen; tree nuts' (mean LB = 0.54 mg/kg; mean UB = 3.61 mg/kg) and 'Vegetables, fresh or frozen' (mean LB = 0.86 mg/kg; mean UB = 4.66 mg/kg). Within the first one, the highest mean bromide levels were measured for 'Tree nuts' with the mean LB and UB at level of 7.29 and 10.9 mg/kg, respectively (for Brazil nuts the mean LB and UB concentration was around 48 mg/kg), while the mean bromide concentration were much lower for other food categories, including 'Citrus fruits', 'Pome fruits', 'Berries and small fruits', 'Stone fruits' and 'Miscellaneous fruits' with the mean LB less than 1.0 mg/kg and the UB mean around 3.0 mg/kg. Among the level 2 food categories belonging to 'Vegetables, fresh or frozen', the highest bromide concentration levels were measured in 'Algae and prokaryotes organisms' with the LB and UB mean of 54.2 mg/kg, followed by 'Leaf vegetables, herbs and edible flowers' with the mean LB level of 1.50 mg/kg an mean UB level of 5.61 mg/kg and 'Stem vegetables' with the mean LB level of 1.40 mg/kg an mean UB level of 4.69 mg/kg. For the remaining food categories, including 'Brassica vegetables', 'Bulb vegetables', 'Fruiting vegetables', 'Fungi, mosses and lichens', 'Root and tuber vegetables' and 'Legume vegetables', the mean bromide concentrations were rather low with the mean LB below 1.0 mg/kg and mean UB around 4.0 mg/kg.

Other level 1 food categories had low mean concentrations as follows: 'Oilseeds and oilfruits' with the mean LB and UB mean levels of 1.07 and 3.53 mg/kg respectively, 'Products of animal origin – terrestrial animals' with the mean LB and UB mean levels of 0.58 and 0.80 mg/kg respectively and 'Sugar plants' with only five analytical available, all left-censored.

**TABLE 9** Summary of the bromide occurrence data by food category according to the food categorisation system as defined in Annex I of Regulation (EC) No 396/2005 (mg/kg).

Food category, level 1	Food category, level 2	N	%LCD	Mean		P95 <sup>a</sup>	
				LB	UB	LB	UB
<b>Cereals</b>		4971	82	1.43	6.20	4.80	20.0
<b>Sugar plants</b>		5	100	0.00	0.01	–	–
<b>Pulses</b>		743	74	1.09	7.72	5.70	20.0
<b>Oilseeds and oilfruits</b>		634	74	1.07	3.53	5.40	17.7
<b>Spices</b>		173	35	7.08	8.02	21.3	21.3
<b>Fruits, fresh or frozen; tree nuts</b>		12,211	92	0.54	3.61	0.45	5.00
	Tree nuts	752	81	7.29	10.9	51.9	51.9
	Citrus fruits	1652	87	0.09	3.10	0.63	5.00
	Pome fruits	1750	100	0.00	3.16	0.00	5.00
	Berries and small fruits	3601	95	0.03	3.11	0.00	5.00
	Stone fruits	1862	99	0.02	3.06	0.00	5.00
	Miscellaneous fruits (generic)	2594	85	0.30	3.23	1.40	5.00
<b>Products of animal origin – terrestrial animals</b>		359	59	0.58	0.80	2.80	2.80
	Milk	47	51	1.11	1.34	–	–
<b>Vegetables, fresh or frozen</b>		23,541	79	0.86	4.66	4.50	10.7
	Brassica vegetables (excluding brassica roots and brassica baby leaf crops)	1876	83	0.47	3.67	2.70	5.00
	Bulb vegetables	558	82	0.26	3.16	1.80	5.00
	Fruiting vegetables	8466	79	0.49	4.56	2.50	11.4
	Fungi, mosses and lichens	542	97	0.24	3.42	0.00	5.00
	Algae and prokaryotes organisms	3	0	54.2	54.2	–	–
	Stem vegetables	1641	71	1.40	4.69	9.00	10.0
	Root and tuber vegetables	2170	77	0.45	3.59	2.40	5.00
	Leaf vegetables, herbs and edible flowers	7555	78	1.50	5.61	9.00	20.0
	Legume vegetables fresh	730	91	0.18	3.60	1.10	5.00
<b>Teas, coffee, herbal infusion materials, cocoa and carobs</b>		1809	20	22.6	23.1	71.7	71.7
<b>Hops</b>		22	68	3.86	7.27	–	–

Abbreviations: % LCD, proportion of left-censored data; N, number of analytical results; LB, lower bound; P95, 95th percentile; UB, upper bound.

<sup>a</sup>The 95th percentile obtained for food categories with fewer than 59 observations may not be statistically robust (EFSA, 2011b) and are therefore not included in this table.

### 3.2.1 | Comparison of the occurrence data with the current MRLs in EU

The maximum occurrence levels collected for each food commodity was compared with the respective MRL to which it is applied. The occurrence level exceeded the MRLs in tree nuts,<sup>35</sup> apricots, gooseberries, figs, tomatoes, sweet peppers, Lamb's lettuces, escaroles, Roman rocket, spinaches and similar leaves, herbs and edible flowers, celeries, wild fungi, algae and prokaryotes, poppy seeds, sesame seeds, rice, herbal infusions, hops, bovine fat and liver, milk and eggs. The highest residue levels were detected in rice, up to 378 mg/kg compared to the MRL of 50 mg/kg, however, less than 1% of the samples exceeding the MRL (23 out of 2459). High occurrences above 150 bromide mg/kg were also detected in some leafy crops (herbal infusions, Roman rocket/rucola). With few exceptions (Brazil nuts, animal products), exceedance of the MRLs occurred at low frequency (< 10% of samples) for commodities having more than five samples analysed.

With respect to commodities of animal origin, the MRLs are set at the LOQ of 0.05 mg/kg, which was frequently exceeded. It is noted that the limit of quantification of the analytical method used for liver, eggs, milk and honey was in some cases higher than 0.05 mg/kg, whereas for pig meat/muscle it was higher in all samples analysed. For this reason, the number of samples exceeding the MRLs for these commodities were higher for the upper bound levels compared to the lower bound. Only three samples of occurrence data were available in algae and mosses, and two of them exceeded the MRL

<sup>35</sup>Tree nuts' include: Brazil nuts, chestnuts, pistachios, walnuts.

of 5 mg/kg (occurrence level: 78 and 83 mg/kg). The occurrence data exceeding the existing MRL for bromide across food commodities considering the lower bound and the upper bound levels is presented in [Table 10](#).

In citrus fruits, pome fruits, root and tuber vegetables, Brassica vegetables, bulb vegetables, and legume vegetables the respective MRLs were not exceeded.

For the following food product categories, the comparison of the MRLs were not possible as no occurrence data were available: pine nut kernels, loquats, mulberries, azaroles/Mediterranean medlars, table olives, jambuls, American persimmons, breadfruits, soursops/guanabanas, yams, arrowroots, red mustards, laurel/bay leaves, cardoons, bamboo shoots, palm hearts, mosses and lichens, lupins/lupini beans, cotton seeds, safflower seeds, borage seeds, castor beans, olives for oil production, oil palms fruits, kapok, sorghum, dill, Sichuan pepper, vanilla, tamarind, ginger, horseradish, capers, saffron, mace, sugar canes, chicory roots, products of animal origin (including fish), except bovine fat, liver, pig fat and meat, cattle milk, chicken eggs and honey. In addition, for the commodities with less than five samples the data may not be sufficient to derive a robust conclusion.

The detailed comparison of the occurrence levels to the individual MRL it applies to is presented in [Appendix F](#).

**TABLE 10** Food products in which the occurrence levels exceeded the existing MRL for bromide.

Food commodities to which the MRLs apply	MRL (mg/kg)	LB Max level reported (mg/kg)	UB Max level reported (mg/kg)	N	LB N exceeding the MRL	UB N exceeding the MRL	LB Samples exceeding the MRL (%)	UB Samples exceeding the MRL (%)
<b>Brazil nuts</b>	50	120	120	93	35	35	38	38
<b>Chestnuts</b>	50	71	71	46	1	1	2	2
<b>Pistachios</b>	50	180	180	40	2	2	5	5
<b>Walnuts</b>	50	69	69	125	1	1	<1	<1
<b>Apricots</b>	20	24	24	294	1	1	<1	<1
<b>Gooseberries</b>	5	5.7	5.7	59	1	1	2	2
<b>Figs</b>	20	35	35	122	4	4	3	3
<b>Tomatoes</b>	50	154	154	3525	1	1	<1	<1
<b>Sweet peppers/bell peppers</b>	30	47	47	2733	1	1	<1	<1
<b>Lamb's lettuces/corn salads</b>	50	74	74	608	3	3	<1	<1
<b>Escaroles/broad-leaved endives</b>	50	59	59	332	1	1	<1	<1
<b>Roman rocket/rucola</b>	50	177	177	544	6	6	1	1
<b>Spinaches and similar leaves</b>	50	82	82	709	2	2	<1	<1
<b>Herbs and edible flowers</b>	50	53	53	718	2	2	<1	<1
<b>Celeries</b>	30	31	31	658	2	2	<1	<1
<b>Wild fungi</b>	30	34	34	134	1	1	<1	<1
<b>Algae and prokaryotes organisms</b>	5	83	83	3	2	2	67	67
<b>Poppy seeds</b>	20	28	28	16	1	1	6	6
<b>Sesame seeds</b>	20	64	64	102	3	3	3	3
<b>Rice</b>	50	378	378	2459	23	23	<1	<1
<b>Herbal infusions from Hibiscus/roselle (dry)</b>	100	216	216	803	4	4	<1	<1
<b>Herbal infusions from strawberries leaves (dry)</b>	100	213	213	180	14	14	8	8
<b>Hops (dry)</b>	20	32	32	22	1	1	5	5
<b>Fat (bovine)</b>	0.05*	0.62	0.62	44	19	19	43	43
<b>Fat (pig)</b>	0.05*	0.82	0.82	43	5	5	12	12
<b>Fat (poultry)</b>	0.05*	0.85	0.85	22	3	3	14	14
<b>Muscle<sup>a</sup> (pig)</b>	0.05*	1	1	31	0	31	0	100
<b>Liver (bovine)</b>	0.05*	5.8	5.8	42	19	27	45	64
<b>Cattle milk</b>	0.05*	7.5	7.5	47	23	30	49	64
<b>Chicken eggs</b>	0.05*	4.7	4.7	75	61	69	84	95
<b>Honey</b>	0.05*	1.1	10	55	15	39	27	71

Note: For food commodities in **bold**, the number of samples exceeding the MRLs differs between lower bound and upper bound levels.

Abbreviations: LB, lower bound; Max, maximum; MRL, Maximum residue level; N, number of analytical data; UB, upper bound.

\*MRL set at the limit of quantification for enforcement of pesticide residues.

<sup>a</sup>Monitoring data for meat considered.



### 3.2.2 | Occurrence data of bromide in feed submitted to EFSA

As mentioned above, only very limited occurrence data of bromide were available in the EFSA database. In total, 57 analytical results were reported by three European countries, the UK ( $n=44$ ), the Netherlands ( $n=10$ ) and Finland ( $n=3$ ). The samples were obtained between 2009 and 2021 with majority of them being sampled in 2009.

The analytical results covered three FoodEx2 Level 1 feed categories, including 'Cereal grains and products derived thereof' ( $n=53$ ; LCD=85%); 'Oil seeds, oil fruits, and products derived thereof' ( $n=3$ ; LCD=67%); and 'Legume seeds and products derived thereof' (one quantified analytical result).

The limited data did not allow to perform a robust analysis. Bearing in mind this limitation, among the feed categories belonging to the three feed categories, the highest LB concentration levels of bromide were measured in barley grain (only three analytical results reported) and sunflower seed meal (only one analytical result reported).

An overview of the number of data points, the proportion of LCD as a percentage, the mean concentration values of an appropriate FoodEx2 feed category is presented in Table 11. More details on statistical description and according to lower FoodEx2 levels are reported in Annex D, Tables D.2–D.5.

**TABLE 11** Summary of the bromide occurrence data by feed category (mg/kg).

	N	%LCD	Mean	
			LB	UB
<b>FoodEx2 Level 1</b>				
<b>FoodEx2 Level 2</b>				
<b>Cereal grains and products derived thereof</b>	53	85	0.75	9.1
Barley grain	3	0	7.87	7.87
Wheat grains	31	97	0.06	9.74
Rice protein	1	100	0.00	2.00
Wheat feed	18	78	0.78	8.56
<b>Oil seeds, oil fruits and products derived thereof</b>	3	67	2.37	2.37
Soya (bean) meal	2	100	0.00	0.001
Sunflower seed meal	1	0	7.10	7.10
<b>Legume seeds and products derived thereof</b>	1	0	3.90	3.90
Pea protein	1	0	3.90	3.90

Abbreviations: % LCD, proportion of left-censored data; LB, lower bound; N, number of analytical results; UB, upper bound.

### 3.2.3 | Previously reported occurrence data in the open literature

Published data on occurrence in food were sought for foods lacking monitoring data for the purpose of their comparison with the existing MRLs, as requested in the mandate. The additional screening performed in this opinion was also based on these foods; hence, no additional data were reviewed in this opinion. The very few reliable data retrieved from the literature related to foods with available occurrence data in the EFSA database, with which they were compatible (hence no additional value). Should a standard (refined) dietary exposure assessment be conducted following this opinion, the identified data gaps will be subject to comprehensive data collection.

Very few data on the occurrence of bromide in animal feedingstuffs have been identified, and routine bromide analysis of feedingstuffs does not appear to be a common practice. Widely used feed databases in Europe or the USA do not list bromide as a constituent, and where concentrations have been reported, these have frequently been in feeds which have been fumigated with methyl bromide or grown on soils to which methyl bromide has been applied as a soil fumigant. An exposure assessment for animals was requested in the mandate, and therefore a thorough review of the literature was performed to identify relevant the published data on occurrence in feed.

Hill and Thompson (Hill & Thompson, 1973) analysed almost 1000 samples of feed imported into the UK between 1968 and 1973, including cereal grains and cereal by-products and oilseed products. Of these, 84% had bromide concentrations of < 100 mg/kg, but the authors concluded that for many of these samples, and particularly for those with higher concentrations, methyl bromide had been used as a fumigant prior to importation.

Underwood (1971) cited several publications in which the bromide contents up to 25 mg Br<sup>-</sup>/kg in non-forage feeds (whole cereal grains) had been reported and where no fumigant had been used. For green forages, bromide concentrations were generally lower (up to 11 mg/kg DM), although in one report concentrations of up to 8400 mg/kg were found in grass hay which had been cut from a field previously treated with methyl bromide (Knight and Costner, 1977). Lynn et al. (1963) also reported low (< 10 mg/kg) concentrations of bromide in forage samples from a few sites in the USA.

In contrast, Van Paemel et al. (2010) reported lower bromide contents in non-forage feeds (typically < 3 mg/kg) than in forages (26 mg/kg DM in fresh grass, 8–9 mg/kg DM grass hay, 4–12 mg/kg DM alfalfa). An exception to this was fishmeal,

with a concentration of 12.6 mg/kg. Data from a commercial UK feed laboratory<sup>36</sup> suggests that there may be greater variation in the bromide levels in grasses (17–119 mg/kg DM), but overall levels in non-forage feeds tend to be lower (21–33 mg/kg DM).

### 3.3 | Food and feed processing

#### 3.3.1 | Food processing

Bromide is negatively charged and readily dissolves in water. It is stable and not subject to degradation. It can therefore be assumed to migrate from food when it is cooked in water, assuming that the concentration in the food is greater than in the water that is used for cooking. If water is lost from food as it is cooked or processed, then it can be assumed that bromide will be lost with that water, but if fats or oils are lost during cooking or processing, then the bromide may remain in the food and hence the concentration could increase.

Cunningham and Warner investigated bromine concentration as an indication of pre-baking bromination of bread products, related to the use (in some parts of the world) of potassium bromate as a strong oxidiser that is commonly used in the production of bread products as a flour maturing and dough conditioning agent to strengthen the gluten of strong or high-protein flour (Cunningham & Warner, 2000). The bromate reduces to bromide in the final products because of the reductive properties of bread dough. Reduction begins when ingredients are mixed and continues during baking. As a result, when potassium bromate is used, the amount of bromide is elevated in bread products. Bromate is typically added at concentrations equivalent to 10–36 mg/kg bromide and this will typically be converted to similar concentrations of bromide in the cooking process. Similar results were reported by Osborne et al. (Osborne et al., 1988) and Thewlis (Thewlis, 1977). Bromate is no longer used in bread production in Europe.

Kim and Ha reported that brominated disinfection by-products such as tri-halomethanes (THMs) and haloacetic acids (HAAs) may be generated in high concentrations during the chlorinated washing of brined kimchi cabbage during manufacture as a result of the presence of bromide in the salts used for the brine (Kim & Ha, 2023). The average bromide content in 22 salt products used to produce the brine sourced from various regions of Korea was  $1600 \pm 468$  mg/kg. Increasing bromide content shifted the speciation of disinfection by-products from chlorinated to mixed bromochloro to brominated species. Formation of these products during the washing of brined kimchi at average bromide levels was influenced by the brine salinity, salting temperature and disinfectant type.

#### 3.3.2 | Feed processing

The manufacture of feeds for food- and non-food producing animals may involve several different processes, including crushing and grinding, exposure to heat, pressure or steam, micronisation or oil extraction. A literature search failed to identify any effects of these processes on levels of bromide in feeds for food- and non-food-producing animals.

### 3.4 | Screening of existing MRLs

In response to the terms of reference, a screening of MRLs has been performed based on the MRLs as currently set in the EU, using the PRIMo 3.1 model. The TMDI calculation was performed assuming that residues are present at the level of the MRLs in all food commodities consumed and a lifelong exposure which is not expected to occur in practice (for details on the tool and the methodology, see Section 2.7). This approach is defined as a high-level screening method and cannot be considered as a dietary exposure assessment.

The calculated levels ranged from 0.16 mg/kg bw per day (for the Irish child diet) to 2.11 mg/kg bw per day (for the Dutch toddler diet) when considering a lifetime consumption (see Appendix G). The main contributors with regard to estimated diets were maize, bananas, wheat grain, apples, coffee beans, rye and potatoes. In the scenario based on short time of consumption, the estimated levels for adults ranged from the minimum of 0.003 mg/kg bw for hops/beer to the maximum of 2 mg/kg bw for boiled beetroots.

Appendix G shows that the MRLs used as input values for the screening are in most of the cases much higher compared to the bromide levels measured in the framework of the monitoring analytical data collection in the EU.

### 3.5 | Screening of monitoring data

As explained in Section 2.8; to obtain a more realistic assessment, the Scientific Committee performed an additional screening based on the monitoring data submitted to EFSA (for details on methodology, see Section 2.8). A detailed overview

<sup>36</sup>NRM Technical Information Advice Sheet 31: Plant Tissue analysis for Undesirables, 2021.

of the number of data points and statistical description according to food categorisation system as defined in Annex I of Regulation (EC) No 396/2005 according to level as used for the estimation for all food categories are reported in Annex D, Tables D.10 and D.11.

#### *Scenario based on a lifetime consumption*

Among different diets, the calculated levels ranged from 0.02 to 0.51 mg/kg bw per day for the lower bound, whereas for the upper bound, the estimated levels ranged between 0.06 and 0.75 mg/kg bw per day. In both scenarios, the major contributors with regard to estimated diets were milk and coffee beans. For more details, see Appendix G.

#### *Scenario based on a short time of consumption*

Among all commodities for which occurrence data allow to derive the percentiles, in the lower bound scenario, the estimated levels for children ranged from 0.00002 mg/kg bw for thyme to a maximum of 1 mg/kg bw for pistachios. For adults, the estimated levels ranged from 0.00002 mg/kg bw for cumin seeds to 0.6 mg/kg bw for chard leaves.

In the upper bound scenario, the estimated levels for children ranged from 0.0004 mg/kg bw for fenugreek to a maximum of 2.45 mg/kg bw for watermelons. For adults, the estimated levels ranged from 0.000002 mg/kg bw for juniper berries to 0.8 mg/kg bw for watermelons. It is underlined that the calculations reported above are affected by the following limitations:

- PRIMo 3.1 does not include consumption data for drinking water, infant formulae, fish, seafood and algae (relevant for both the lifetime and the short time calculations).
- The lifetime calculations are based on the highest reliable percentile of the monitoring data which is very conservative (the calculated mean of the occurrence data is usually considered for the estimation of the long-term exposure).
- For some food commodities (see Section 3.2), monitoring data were not available or not sufficient to derive concentration levels (relevant for both the lifetime and the short time calculations).
- Only very limited occurrence data with the LOQs ranging from to 0.5 to 10 mg/kg were available, which did not allow any robust estimation of the exposure to bromide from drinking water.
- The upper bound calculation is very conservative as the analytical methods used for the generation of the occurrence data were not always sufficiently sensitive. In particular, for watermelons, head cabbages and pumpkins, the exceedance of the ARfD in the upper bound scenario (see Section 3.8) is clearly driven by results at the LOQs of 20 and 10 mg/kg. Although these LOQs are below the existing MRL for these commodities (30 mg/kg), they are significantly higher than the upper confidence interval of the 95th percentile calculated based on the measured values only (2.6 mg/kg for watermelons, 1.7 mg/kg for head cabbages and 1.6 mg/kg for pumpkins).

### 3.6 | Previously reported dietary exposure in humans

The typical daily dietary intake of bromide in the United States of America has been reported to be 2–8 mg (Nielsen & D. M., 2009; WHO, 2009) with the majority coming from grains, nuts and fish. The average bromide intake from dietary sources in the Netherlands was reported as 8.4–9.4 mg/day (EMEA, 1997).

### 3.7 | Dietary exposure assessment for food-producing and non-food-producing animals

No previously reported estimates of dietary exposure for food- and non-food-producing animals have been identified. These animals consume a wide range of feedingstuffs; for ruminants and horses, forages may comprise part or all of their diet, but diets for non-ruminants, fish and companion animals may include cereal grains, cereal by-products, protein supplements, co-products from food and drink industries, vegetable oils and feed additives (including mineral and vitamin supplements). While some diets may consist of a few ingredients, most consist partly or completely of manufactured compound or complete feeds, which may consist of 20 or more ingredients (Van der Aar et al., 2016). However, as illustrated in Table 8, insufficient data have been identified with which to estimate exposure to bromide by food-producing and non-food-producing animals.

### 3.8 | Screening of MRL safety for human health

In line with the TOR, a risk assessment for human health was not conducted. Instead, the safety of current MRLs for human health was assessed based on a TMDI calculation. This involved the comparison of the (theoretical) maximum daily intake estimates based on the MRLs for bromide to the TDI and ARfD established for bromide in this opinion. This approach assumes that all commodities contain residues at the MRL which is not expected to occur in practice. In this theoretical calculation (MRL screening), the TDI was exceeded in 29 out of the 34 diets assessed by the model, with highest exceedance

calculated for the Dutch toddler, up to 528% of the TDI. The main contributors with regard to estimated diets were the following: maize up to 88% of TDI (Dutch toddler), bananas up to 67% (Dutch toddler), wheat up to 90% (GEMS/Food G06), apples up to 62% (German child), coffee beans up to 97% (Finnish adult), rye up to 69% (Danish child), potatoes up to 67% (Portugal general population). In the context of a short time period assessment, only the adult population is considered as relevant because the ARfD is set to protect during the pregnancy (see Section 3.1.7.1.4). For adults, the ARfD was exceeded for 54 raw commodities and for 31 processed commodities, with the highest exceedance calculated for boiled beetroots (486% of the ARfD) (see Appendix G).

In the case of the additional scenario of screening using the lower bound concentrations of available monitoring data and considering a lifetime consumption, the calculated level was up to 127% of the TDI (Dutch toddler), while for the upper bound concentrations, this was up to 188% of the TDI (Dutch toddler). In both the LB and the UB scenarios, the main contributors among the food categories for which the monitoring data were available were milk, accounting for 96% of TDI (Dutch toddler) and coffee beans, accounting for 77% of TDI (Finnish adult).

When considering a short time period of consumption using lower bound concentrations from occurrence data, the highest estimates for adults were calculated for chards (151% of the ARfD), pistachios (120% of the ARfD), boiled celeries (121% of ARfD) and boiled chards (100% of ARfD). In the upper bound scenario, the highest relevant estimates were calculated for watermelons (203% of the ARfD), chards (151% of the ARfD), pistachios (120% of the ARfD), head cabbages (105% of the ARfD), boiled pumpkins (138% of ARfD), boiled celeries (121% of ARfD) and boiled chards (100% of ARfD) (see Appendix G).

### 3.9 | Risk characterisation for animal health

A risk characterisation of food-producing and non-food-producing animals was not feasible due to lack of data for exposure assessment.

### 3.10 | Uncertainty analysis

Uncertainty analysis for this opinion was conducted according to the EFSA Guidance (EFSA Scientific Committee, 2018a, 2018b) in order to identify and assess the impact of uncertainties on the conclusions of the assessment. The sources of uncertainty associated with all areas of the assessment of bromide were identified and prioritised (Appendix H, Tables H.1 and H.2). The impact of the prioritised uncertainties was then individually examined (Impact summary in Appendix H). Quantification of the uncertainty of hazard assessment was based on expert judgement of the sources and impact of all uncertainties, through a semi-formal Expert Knowledge Elicitation (EKE) method. The EKE protocol on the Uncertainty of the Risk Assessment of bromide in food and feed, including the evidence considered and the EKE results are provided in Appendix H.

#### *Uncertainty of hazard assessment*

The purpose of the analysis was to assess the overall uncertainty of the TDI for human health.

The calculation of the TDI is based on a selected reference point of 40 mg Br<sup>-</sup>/kg bw per day and application of standard extrapolation factors of 10 for intra-species extrapolation, and four for inter-species differences in toxicokinetics, which are not subject to further uncertainty analysis. An additional factor of 2.5 was proposed to account for residual uncertainties due to limitations in the body of evidence. Hence, the EKE session was refocused on assessing additional uncertainties in the body of evidence.

The EKE group concluded that (a) although there is uncertainty about the sensitivity of the fetus to plasma tT4 decreases, the maternal adaptive response to small changes in T4 (up to 20%) is expected to maintain thyroid homeostasis and not impact the functional T3 levels in the brain of the fetus; (b) since measurements of hormones were made in adult animals, the LOD is not a limitation. In addition, the variability of the assays leads to a lower BMDL, which compensates for uncertainties in the impact that the effect level (20%) may have on fetal brain T3 (BMDL more protective). Overall, there is larger uncertainty in the body of evidence suggesting that the true reference point is more likely to be lower than 40 mg/kg bw per day. It is less likely that the reference point is higher than 40 mg/kg bw per day.

The EKE group estimated that the plausible range of the multiplicative factor of the reference point due to the uncertainty in the evidence base was 0.56–1.72 (with 90% certainty, the reference point may be 0.56 times lower or 1.72 times higher; or 22.4–68.8 mg/kg bw per day), while the median estimate of the true reference point remained nearly unchanged (factor 0.98). Hence, the additional extrapolation factor due to limitations of the evidence base is approximately 1.02 with a 90% certainty range from 0.58 to 1.78. Therefore, the TDI may be lower by a factor of up to 2 (1.78), in addition to the applicable uncertainty factors of 4 for inter-species toxicokinetics differences and 10 for inter-individual variability. By expert group judgement, an additional factor of 2.5 in the extrapolation of the reference point to the TDI is considered sufficient to cover all additional uncertainties of limited study design, which are not covered by the standard factors (an overall

uncertainty factor of 100 is therefore sufficient for establishing the TDI). The Scientific Committee is 90% certain<sup>37</sup> that the established TDI is conservative.

The uncertainty analysis of the chronic effects was applied also to the ARfD, since the endpoint used for the chronic assessment is sensitive enough to be relevant to potential acute effects, such that the ARfD in this assessment is equal to the TDI. There is uncertainty about the length of bromide exposure that may lead to sufficient thyroid hormone disturbance during pregnancy to result in neurodevelopmental effects. There is considerable uncertainty about whether the short period of bromide exposure assumed in the calculation is sufficient to trigger such an effect and therefore the ARfD is conservative.

#### *Uncertainties related to animal health*

There is considerable uncertainty about the doses of bromide resulting in toxicological effects in animals, due to the limitations of available studies and lack of relevant data.

#### *Uncertainties related to screening of safety of MRLs*

Uncertainty assessment is not performed for the screening of the MRL safety as these values are set by regulation.

#### *Uncertainty related to screening of safety based on monitoring data*

There is considerable uncertainty related to the occurrence of bromide in foods and drinking water, due to data gaps for sources that may be potentially important contributors of consumer exposure to bromide. These data gaps were considered too large for a quantitative analysis to be performed.

#### *Uncertainties about bromide exposure in animals*

Uncertainty related to animal exposure cannot be characterised due to the lack of data for exposure assessment. Uncertainty related to transfer of bromide from animal feed to food of animal origin has not been assessed due to lack of relevant data.

## 4 | CONCLUSIONS

### 4.1 | Background

- Bromide can be present in food and feed as a result of natural occurrence, environmental contamination from anthropogenic activity, use of certain biocidal products, use in veterinary medicinal products in food-producing animals and possibly from the use of bromide-containing pesticides outside of the EU.
- When measuring bromide in food and feed, it is not possible to determine the contributions from these different sources.

### 4.2 | Analysis of bromide in food and feed and effects of cooking and processing

- Chromatographic methods coupled to mass spectrometry are sufficiently specific and sensitive for measuring total elemental bromine in food and feed; they can distinguish between bromide and bromine-containing compounds.
- Bromide is assumed to migrate from food when it is cooked in water, if the concentration in the food is greater than in the water that is used for cooking.

### 4.3 | Toxicokinetics

- Bioavailability in humans, rodents and sheep is almost complete ( $96.6 \pm 6\%$ ) and is much lower in dogs and horses (46% and 38%).
- Elimination half-life in humans ( $285 \pm 34$  h) is longer than in rodents ( $198 \pm 22$  h) and horses ( $75 \pm 14$  h), shorter than in dogs (365 h) and sheep ( $347 \pm 94$  h), and similar to cats ( $270 \pm 34$  h).
- In all species, bromide is widely distributed and follows renal excretion, although specific tissue distribution data are limited.

<sup>37</sup>Probabilities assessed by the uncertainty analysis are reported in conclusions as % certainty.



#### 4.4 | Transfer from feed to food of animal origin

- There is evidence that bromide can transfer from feed to food of animal origin but from the limited data, it is not possible to quantify the transfer rate.
- The impact of feeding macroalgae to ruminants on bromide levels in milk or meat is not known, as is the contribution of possible conversion of bromoform to bromide.

#### 4.5 | Toxicity in experimental animals and model systems

- Bromide has low acute toxicity in experimental animals.
- In repeat dose studies, mainly in rats, bromide has shown evidence of effects on the CNS, kidneys, thyroid and other endocrine organs, and on bodyweight gain. The effects occurring at the lowest doses are on thyroid hormone homeostasis and the CNS.
- The available evidence does not support genotoxic or carcinogenic potential.
- Reports of neurotoxicity were generally related to clinical signs, such as abnormal gait, at doses in excess of 100 mg Br<sup>-</sup>/kg bw per day.
- The most sensitive effect on the rat thyroid is decreased serum total thyroxine.
- Bromide toxicity to the thyroid depends upon the iodine status and is exacerbated in rats by an iodine deficient diet.

#### 4.6 | Observations in humans

- Evidence in women indicates bromide supplementation increased thyroxine and thyroid stimulating hormone and resulted in changes in the nervous system (EEG and visual evoked response) at 9 mg Br<sup>-</sup>/kg bw per day. No effects were observed at 4 mg Br<sup>-</sup>/kg bw per day.
- High doses of bromide, generally taken as medical treatment (20–80 mg/kg bw per day up to 10–15 and 31 g/day) are associated with adverse health effects on the nervous system, the skin and other organs.

#### 4.7 | Mode of action

- Bromide may competitively inhibit iodine uptake into the thyroid via the sodium iodide symporter.
- Based on its MOA, bromide may have downstream effects subsequent to impaired thyroid function (e.g. neurodevelopmental effects, cardiovascular toxicity), although data are lacking.
- Bromide also has direct neurotoxic effects, possibly mediated by mimicking the neurotransmitter  $\gamma$ -aminobutyric acid.

#### 4.8 | Reference values for human health assessment

- Altered serum thyroid hormone levels (total thyroxine) in rats is an early critical effect of bromide. Benchmark dose modelling performed on the data for a 20% decrease in blood tT4 (BMR) of relevant studies with iodine-sufficient diets in order to provide a reference point, resulted in BMDL20 values ranging from 13 to 58 mg Br<sup>-</sup>/kg bw per day. Based on a weight of evidence approach, the Scientific Committee selected a reference point of 40 mg/kg bw per day.
- The Scientific Committee established a TDI of 0.4 mg Br<sup>-</sup>/kg bw for bromide by applying an UF of 100 to the RP of 40 mg Br<sup>-</sup>/kg bw per day to allow for inter- and intra-species differences and taking into account deficiencies in the database.
- Thyroid hormone disruption in utero can result in neuropsychological deficits in children. In order to protect against elevated short-term bromide exposures that could result in decreases in serum total thyroxine in pregnant women, the Scientific Committee concluded that the TDI should also be applied as an ARfD. Therefore, the Scientific Committee established an ARfD of 0.4 mg Br<sup>-</sup>/kg bw per day.
- The Scientific Committee concluded with greater than 90% certainty that the TDI and ARfD are conservative.

#### 4.9 | Toxicity in food-producing and non-food-producing animals

- At bromide doses higher than 40 mg Br<sup>-</sup>/kg bw per day, dogs developed shivering, paresis, ataxia, bradycardia, skin lesions, salivation, vomiting, diarrhoea, haematochezia, stupor and emaciation and weight loss.
- A bromide dose of 20 mg Br<sup>-</sup>/kg bw per day was considered as a NOAEL for dogs based on thyroid function and morphology.
- Cats may present an idiosyncratic response to bromide; therefore, no NOAEL could be identified.
- For food-producing and non-food-producing animals, other than dogs, the identified studies could not be considered for the current assessment, due to several limitations.

## 4.10 | Maximum safe concentrations in complete feed for animals

- A maximum safe concentration of 103 mg Br<sup>-</sup>/kg complete feed for dogs was derived from a NOAEL of 20 mg Br<sup>-</sup>/kg bw per day in dogs, using an UF of 10 for intra-species variability.
- The reference point of 40 mg Br<sup>-</sup>/kg bw per day from the rat studies was used with an UF of 100 for inter- and intra-species variability to establish maximum safe concentrations of bromide in complete feed for food-producing and non-food producing species (other than dogs and cats) for which data are lacking, as follows (all in mg Br<sup>-</sup>/kg complete feed):
- 4.5 mg/kg for chicken for fattening
- 6 mg/kg for turkeys for fattening
- 6.5 mg/kg for laying hens
- 7 mg/kg for rabbits
- 8 mg/kg for piglets
- 9.5 mg/kg for pigs for fattening
- 11 mg/kg for lactating sows and dairy cows
- 17.5 mg/kg for cattle for fattening, sheep/goats and horses
- 20 mg/kg for veal calves and salmon
- 78 mg/kg for all ornamental fish
- In cats, due to the idiosyncratic response to bromide in this species, no maximum safe concentration in feed for bromide can be established.

## 4.11 | Occurrence and screening of safety of existing MRLs

### 4.11.1 | Occurrence in food

- A total of 46,965 bromide analytical results collected in 29 European countries between 2013 and 2022 were considered in the assessment.
- According to FoodEx2 classification, the highest mean bromide concentration levels were measured in 'Coffee, cocoa, tea and infusions', 'Flowers used for herbal infusions' (i.e. herbal infusions from flowers) and 'Herbal infusion materials from leaves and herbs'.
- The MRLs were exceeded in some food commodities, usually at low frequencies (< 10% of samples). The MRLs were exceeded with higher frequency in Brazil nuts (38% of samples) and in the animal commodities (up to 100% of samples for pig meat).
- No or insufficient monitoring data were available for some potentially important food groups, i.e. fish and seafood, infant formulae, drinking water.

### 4.11.2 | Occurrence in feed

- In total, 57 analytical results reported by three European countries obtained between 2009 and 2021 covering only three FoodEx2 Level 1 feed categories were available, and these limited data did not allow to perform a robust analysis.

## 4.12 | Screening of existing MRLs

- In line with the terms of reference, the screening of existing MRLs was performed using the Pesticide Residue Intake Model (PRIMo) version 3.1. The results of this high-level screening cannot be considered as a dietary exposure assessment. The calculated levels ranged from 0.16 mg/kg bw per day to 2.11 mg/kg bw per day across various diets when considering a lifetime consumption. In the scenario based on short time of consumption, the estimated levels for adults ranged from the minimum of 0.003 mg/kg bw for hops/beer to the maximum of 2 mg/kg bw for boiled beetroots.

## 4.13 | Screening of monitoring data

- The calculated levels ranged from the minimum LB of 0.02 to maximum UB of 0.75 mg/kg bw per day when considering a lifetime consumption. The major contributors were milk and coffee beans.
- In the scenario based on a short time of consumption, the estimated levels for adults ranged from the minimum UB of 0.000002 mg/kg bw for juniper berry to the maximum UB of 0.8 mg/kg bw for watermelons.

#### 4.14 | Dietary exposure assessment for food-producing and non-food-producing animals

- Insufficient data on levels of bromide in feed materials and compound feed for food-producing and non-food-producing animals were available to allow an assessment of exposure to be made.

#### 4.15 | Safety screening of MRLs for human health

- According to the screening of the safety of the existing MRLs, the TDI was exceeded in 29 out of the 36 diets assessed by the model, with the highest exceedance, up to 528% of the TDI. The main contributors among the food commodities for which MRLs are set were maize, bananas, wheat grain, apples, coffee beans, rye and potatoes. The ARfD was exceeded for adults 54 raw commodities and for 31 processed commodities, with the highest exceedance calculated for boiled beetroots (486% of the ARfD).
- Exceedances of the TDI and ARfD were seen also with the additional screening performed with the available monitoring data.
- The Scientific Committee could not conclude on uncertainties in the risk to human health because an exposure assessment was not included in this opinion.

#### 4.16 | Risk characterisation for animal health

- The Scientific Committee could not assess the risk to animal health or conclude on related uncertainties due to limitations in the toxicity data and the lack of data for exposure assessment.

### 5 | RECOMMENDATIONS

Data providers should be requested to submit further occurrence data generated using methods with suitable sensitivity in:

- food, in particular in fish and seafood, infant formulae and drinking water
- all types of feed materials, in particular in algae, fish and other aquatic animals, and products derived thereof.

A dietary exposure assessment for humans and animals with inclusion of relevant food (e.g. fish, seafood, infant formulae and drinking water) and feed is needed to perform a more accurate risk assessment when the occurrence data are available.

Data should be generated in relation to transfer of bromide from feed/water to food of animal origin.

All in vivo studies with oral exposure to bromide should consider intake from feed/diet and water.

Uncertainties in the risk assessment could be reduced by performing an in vivo developmental neurotoxicity study, following OECD TG 426, at a wide range of Br<sup>-</sup> doses, measuring serum tT4 and fT4, TSH and thyroid iodine/Br<sup>-</sup> ratio along with established neurodevelopment assessments. Measurement of other indicators of thyroid-mediated effects in the same study are encouraged.

Further research is encouraged to better understand the MOA of bromide and indicate other possible adverse outcomes.

Well-designed observational and experimental human studies should also be performed to assess the long-term effect of low-dose bromide exposure through diet and drinking water, on a number of health endpoints and in sex- and age-specific subgroups.

#### ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
ADME	adsorption, distribution, metabolism, excretion
ADI	Acceptable Daily Intake
ArfD	Acute reference Dose
AO	Adverse Outcome
AOP	Adverse Outcome Pathway
bw	Body weight
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower bound
BMR	Benchmark Response
BPC	Biocidal Products Committee
CAR	Constitutive Androstane Receptor
CNS	Central Nervous System
CSF	Cerebrospinal Fluid

DAR	Draft Assessment Report
DBDCB	2-bromo-2-(bromomethyl)pentanedinitrile
DBNPA	2,2-dibromo-2-cyanoacetamide
DNT	Developmental neurotoxicity
ECHA	European Chemical Agency
EEG	Electroencephalogram
EGF	Epidermal Growth Factor
EMA	European Medicines Agency
FGR	Fibroblast Growth Hormone
FSH	Follicle Stimulating Hormone
ft4	Free Thyroxine
GABA	$\gamma$ -aminobutyric acid
GD	Gestational Day
GI-Tract	Gastro-intestinal Tract
GH	Growth Hormone
HBGV	Health-Based Guidance Value
HPT	Hypothalamic–pituitary–thyroid axis
IGF	Insulin like Growth Factor
IPCS	International Programme on Chemical Safety (World Health Organization)
ITGF	Immunoglobulin Stimulating Thyroid Growth Factor
KE	Key Event
LH	Luteinising Hormone
LOAEL	Lowest Observed Adverse Effect Level
LOE	Line of evidence
MRL	Maximum Residue Level
MOA	Mode of Action
MIE	Molecular Initiating Event
NIS	Sodium/Iodide Symporter
NOAEL	No Observed Adverse Effect Level
PCNA	Proliferating cell nuclear antigen
PND	Postnatal day
PPAR	Peroxisome proliferator activated receptor
PXR	Pregnane X Receptor
RAC	Risk Assessment Committee
rT3	Reverse T3
RP	Reference point
RXR	Retinoid X Receptor
SCF	Scientific Committee on Food
STOT	Specific Target Organ Toxicity
SULT	Sulfotransferase
TBG	Thyroid Binding Globulin
TDI	Tolerable Daily Intake
TGF $\beta$	Transforming Growth Factor $\beta$
TH	Thyroid hormone
TPO	Thyroid Peroxidase
T3	Triiodothyronine
tT3	Total Triiodothyronine
T4	Thyroxine
tT4	Total Thyroxine
TTR	Transthyretin
TRH	Thyrotropin-Releasing Hormone
TSH	Thyroid Stimulating hormone or Thyrotropin
UF	Uncertainty factor
UGT	Uridine Glucuronosyl Transferase
WHO	World Health Organization

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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## APPENDIX A

## Appraisal of evidence of bromide thyroid effects in experimental animal studies

TABLE A.1 Heat map of quality appraisal.

CRITERIA	van Logten et al., 1974	van Logten et al., 1976	Newsome et al., 1978	van Leeuwen et al., 1983	Loeber et al.1983	Van Leeuwen et al., 1988	Buchberger et al., 1990	Velicky, Titlbach, Dusková, et al., 1997	Velicky, Titlbach, Lojda, et al., 1997	Velicky et al., 1998	Pavelka et al., 2002	Velicky et al., 2004	Cozzolino et al., 2005	Pavelka 2012a	Pavelka, 2012b	Study report* 2016b in RAC 2020 and CLH report 2022
<b>Experimental design</b>																
Randomisation of animals in treatment groups	YES	unclear	NO	unclear	YES	NO	YES	unclear	NO	NO	unclear	unclear	NO	YES	unclear	unclear
Test substance source, preparation and administration well described	YES	YES	NO	NO	YES	NO	NO	YES	YES	YES	unclear	NO	NO	unclear	unclear	YES
Was the number of animals sufficient	YES	YES	NO	YES	YES	NO	YES	NO	YES	YES	NO	YES	NO	NO	NO	YES
Both sexes tested	YES	YES	NO	YES	NO	NO	YES <sup>5</sup>	NO	NO	NO	NO	NO	NO	YES	NO	YES
Diet content reported	NO	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES	YES	NO	YES	YES	NO
Water content reported	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO <sup>1</sup>	NO	NO	NO	NO	NO
Statistics performed and appropriate	YES	YES	YES	YES	YES	YES	YES	YES <sup>2</sup>	YES	YES <sup>2</sup>	YES <sup>2</sup>	NO	NA	NO	NO	YES
Dose response T4	NA	NA	NO	YES	NO	NO <sup>3</sup>	YES	YES/NO <sup>4</sup>	NA	NO	YES	NA	NA	YES	YES	YES
<b>Endpoints assessed - method and results reliability</b>																
serum tT4 change	NA	NA	L <sup>6</sup>	M	H	M	M**	L	NA	L	L	NA	NA	L	L	M
TSH increase	NA	NA	NA	NA	H	M	M	L	NA	L	NA	NA	NA	NA	NA	H
Histological changes	L	L	NA	NA	H	NA	NA	M	M	M	NA	M	NA	NA	NA	H
Morphometry (imaging and/or EM)	NA	NA	NA	NA	M	NA	NA	M	NA	M	NA	M	M	NA	NA	NA
Relative thyroid weight increase	L	L	M	M	M	M	M	NA	NA	NA	M	NA	NA	L	NA	H
additional hormonal modalities	YES	YES	NA	YES	YES	NA	NA	NA	NA	NA	NA	NA	NO	NA	NA	YES
Outcome assessment with reliable methods	YES/NO <sup>4</sup>	YES/NO <sup>4</sup>	NO	YES	YES	NO	YES <sup>5</sup>	YES/NO <sup>4</sup>	YES/NO <sup>4</sup>	YES/NO <sup>4</sup>	YES/NO <sup>4</sup>	YES/NO <sup>4</sup>	NO	YES/NO <sup>4</sup>	NO	YES
<b>Overall quality</b>	L	L	L	M	M	L	M	L	L	L	L	L	L	L	L	H

The table presents responses to study quality criteria indicating if they were met (YES) or not (NO), or if this was equivocal (YES/NO). The reliability of results assessed in each study is presented as high (H), medium (M) or low (L), as is the overall study quality. NA: not applicable, if not reported in the study; unclear, if not enough information was provided. Colour coding is for visual overview: 'Yes' or 'High', green; 'No' or 'Low', red; 'Yes/No', orange; 'Medium', blue; 'NA' no colour.

\*The only study according to OECD TG408; performed by gavage.

\*\*T4 measured in thyroid (tT4) and serum.

1: Distilled water (if not mentioned: Tap water); 2: Some experiments; 3: Only one dose tested; 4: Methods not completely reliable, with some drawbacks; 5: Iodine deficient conditions; 6: Increase.



## A.1 | APPRAISAL OF ANIMAL STUDIES

A detailed assessment of study quality is provided below for selected relevant studies (Loeber et al., 1983; Study Report, 2016b; Velický et al., 1998, 2004; Velický, Titlbach, Dusková, et al., 1997; Velický, Titlbach, Lojda, et al., 1997).

**TABLE A.2** Details on study quality and reliability of Loeber et al. (1983).

Experimental setting		
Element	Authors	EFSA comments
<b>Test system</b>	Inbred male Wistar rats (Riv: TOX[M]), weighing 60–100 g	It is recognised that thyroid morphology is more variable in control male rats than females (see also results).
<b>Animal welfare</b>	It is stated that, during the experiments, the rats were handled daily to diminish possible stress-related effects, quoting another publication (Döhler et al., 1977).	The study has been carried out before the 'European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes' (Strasbourg, 1986). No information on internal approval of the protocol is provided
<b>GLP</b>	–	Research study.
<b>Experimental design</b>	Main study: 2 control groups; 4 dose levels; 10 rats/group treated for 4 or 12 weeks Satellite study: 1 control group and a HD group, 5 rats/group for release test following TRH after 12-week treatment	Research study, no standardised protocol used. A separate control was used for the high dose, no justification is provided.
<b>Diet</b>	Semi-synthetic, purified diet (Muracon SSP-Tox standard flour) obtained from Trouw and Co. (Putten).	No detailed information is available on diet composition. Generally, laboratory rodent diets are balanced, with detailed information on relevant micronutrients, including iodine. The laboratory rat iodine requirement is 150 µg/kg diet (NRC. Nutrient Requirements of Laboratory Animals: Fourth Revised Edition, 1995. Washington (DC): 2, Nutrient Requirements of the Laboratory Rat). Available from: <a href="https://www.ncbi.nlm.nih.gov/books/NBK231925/">https://www.ncbi.nlm.nih.gov/books/NBK231925/</a> Standard chows (e.g. Purina 5002) contain 1 ppm iodine. In the conditions of this study, lack of reporting on bromide and iodide content in the diet is a bias.
<b>Test substance, doses, and formulation</b>	Sodium bromide (purity 99.5%) supplied by J. T. Baker Chemicals (Deventer) mixed with the diet to give final concentrations of 0, 20, 75, 300, 1200 and 19,200mg/kg (diet)	No information on the actual dose levels in mg/kg/body weight per day is provided; the same study was assessed in the CHL document, with doses corresponding to 1.5, 5.6, 22.5, 90 and 1440 mg NaBr/kg bwper day.
<b>Pathology procedures</b>		
<b>Method of euthanasia</b>	Decapitation and exsanguination (main and satellite groups)	This is considered adequate for the scope.
<b>Randomisation of pathology procedures</b>	All animals were killed between 9:00 and 11:00 am	The defined slot allows for controlling circadian rhythms differences in T4. Slides randomised and read blindly.
<b>Materials and methods – Tissue sampling, processing and staining</b>	Thyroid dissected, weighed, fixed in 4% formalin and embedded in paraffin. Staining: H&E; immunohistochemistry Other organs: pituitary and testes. Immunohistochemistry on pituitary (TSH, GH, ACTH), thyroid (T4) and testes (testosterone).	Considered appropriate.

(Continues)

TABLE A.2 (Continued)

Experimental setting		
Element	Authors	EFSA comments
<b>Biochemistry and hormonal analysis</b>	Radioimmunoassay (serum): T4, TSH, GH, LH and FSH; insulin, testosterone, corticosterone	There is no mention on how the method was validated, no calibration curve and no LOD and LOQ are reported. Despite these limitations, the method, per se, is appropriate. The inclusion of a positive control would have been highly beneficial to understand the dynamic range of the changes observed in the study for T4 and TSH.
<b>Pathologist/peer review</b>	No information available.	–
<b>Results</b>		
<b>Body weight</b>	Decreased as compared to respective controls at both time points.	Body weight at term differs between the two control groups, on week 4 (control B 32% higher than control A); the statistical analysis did not take this into account.
<b>Organ weight</b>	In the thyroid weight in the 1200-mg/kg group after 4 weeks but not after 12 weeks. In the 19,200-mg/kg group, however, a statistically significant increase was observed after both 4 and 12 weeks	<p>The results on thyroid weight should be tackled with care, in particular as regards groups other than the high dose.</p> <ul style="list-style-type: none"> <li>– Thyroid weight is reported as relative to the body weight only</li> <li>– Considering the above comments on body weight, the relevance of the statistical outcome at 1200 ppm at week 4 is doubtful.</li> <li>– It is also noted that histopathology examination considered 20 controls (merging the two control groups)</li> <li>– In general, for groups other than the high dose a trend to increase in the relative thyroid weight is noted in week 4, however with no clear dose relationship; this was not confirmed at week 12.</li> </ul> <p>No information is available on absolute thyroid weight or thyroid weight relative to brain weight.</p>
<b>Histopathology</b>	<p>After exposure of rats to 19,200 mg NaBr/kg diet for 4 weeks, histopathological changes were observed, characterised by an increase of follicles and a decrease in their size.</p> <p>The follicular epithelium was greatly heightened while the colloid was decreased in amount and more granular in appearance. This was also seen after an exposure time of 12 weeks. No marked changes in the histological picture of the thyroid were detected in the lower dosage groups, irrespective of the exposure time.</p>	<p>The information reported include a description, 4 microphotographs from control and high dose group (H&amp;E and T4) and a summary table of histopathology.</p> <p>The <u>narrative description</u> points to follicular cell hypertrophy, increased in incidence and severity in the high dose only. Follicular epithelial cells are described as increased in height; follicles show smaller lumen with pale colloid, granular. No features indicative of epithelial hyperplasia are described (no epithelial cell piling up or projections into the follicular lumen). The description ‘increase in follicles and decrease in size’ is not supported by morphometric investigations; therefore, it should be interpreted as qualitative and likely related to the follicular epithelial hypertrophy. It is noted that there is no harmonised score classification for follicular cell hypertrophy, and no criteria are provided in this paper.</p> <p>The <u>pictures</u> confirm follicular cell hypertrophy in the thyroid at high dose; though it is acknowledged that similar changes can be seen in control Wistar rat in the central part of the thyroid (see also below). In the absence of severity score criteria defined by the author and considering that only one image at high magnification is provided, it is difficult to conclude on the severity score of this finding; the qualitative score proposed in the paper could correspond to a minimal/mild condition based on the descriptive pathology and reported images. Of note, no features indicative of hyperplasia are identified in the proposed picture.</p>

TABLE A.2 (Continued)

Experimental setting		
Element	Authors	EFSA comments
		<p>The <a href="#">summary tables</a> indicate 'degree of activation' slight to strong to describe histopathological findings. A clear increase in the incidence and severity is seen at the high dose (19,200ppm), with almost all the animals affected up to 'strong' score on week 4, without apparent progression on week 12. It is noted also that 'degree of activation' is described in a few control animals (2/20 at week 4 and 12) and in some animals throughout groups other than the high dose; however, these were a few and described as slight. It is, therefore, confirmed that histopathological findings are present at the high dose only, while there are no differences between controls and groups at 20, 75, 300 and 1200 ppm in thyroid gland histology. To substantiate the severity score of 'strong' activation, criteria should have been included or the score should have been substantiated with more appropriate reporting of the pictures with example of 'slight' and 'strong'. In addition, it is known that the size of the thyroid follicles can vary in normal rats and it is not homogeneously distributed. Inactive 'cold' follicles are present in the periphery of the gland. These are considered to be a reserve of thyroglobulin and are activated when higher amount of thyroid hormones is necessary. These follicles are large, with a flat to cuboidal epithelium and contain a densely and homogeneously stained colloid. Smaller follicles, with cuboidal epithelium and less amount of paler colloid are present in the centre of the gland. The selected high magnification picture should also indicate from where (central or periphery part of the organ) in the thyroid gland they were taken and representative of. Therefore, without a dose related effect in the severity of the finding, without a positive control indicative of the dynamic range of the histological changes, without a clear geographic description of the sampling included in the picture, the histological changes described in the study should be considered of minimal/mild severity and are expected to be reversible following a recovery period.</p> <p>At <a href="#">immunohistochemistry analysis (IHC)</a> a more rarefied and paler colloid accompanies an apparent decrease in T4 immunohistochemical (IHC) staining at the top dose; this possibly indicates a less functional or a reduced amount of thyroglobulin in the lumen of thyroid follicles. It is noted that the authors describe that no definitive conclusions can be drawn from this analysis.</p> <p>IHC assessment of the pituitary was reported in a tabulated summary and using a selective picture; no objective counting of the positive cells was done, and the analysis was conducted for the top dose animals only. The tabulated summary indicates a time related increase in the number of TSH positive cells in the pituitary gland.</p> <p>Overall, histopathological findings suggest thyroid activation at the high dose group (19,200ppm). Corroborating morphological evidence of a likely follicular cell hypertrophy should have been the increase in thyroid weight, but with only the reporting of thyroid weight relative to body weight, this evidence remains uncertain.</p>
<b>Hormones and TSH</b>	<p>There was a statistically significant decrease of T4 both after the 4- and 12-week treatment with the 19,200 mg NaBr/kg diet. Also in the 1200 mg/kg diet group, the T4 level was significantly reduced after the 4-week exposure period. TSH levels were significantly increased in the highest dose group. TRH had no effect on the T4 level, but as might be expected, it caused an increase in the TSH levels both in the control group and in the bromide group</p>	<p>Overall, histopathological changes are consistent with a drop in T4 and increase in TSH at the high dose, which was not overactivated by TRH treatment. The decrease in T4 and the increase in TSH were considered of a biologically relevant magnitude.</p>

**TABLE A.3** Details on study quality and reliability of Velický, Titlbach, Lojda, et al. (1997).

Experimental setting		
Element	Authors	EFSA comments
<b>Test system</b>	41-day old male Wistar rats (TOP VELAZ Prague CR)	Only male rats were used in the study. Male rats are known to have a more reactive thyroid gland with a higher number of micro follicles located in the central part of the gland and less evident inactive large follicles located in the periphery of the organ. The number of animals included in each group ( $n = 10$ ) is considered adequate.
<b>Animal welfare</b>	Standard procedures are reported	Considered sufficient.
<b>GLP</b>	Not mentioned	No reference to any internal SOP is reported
<b>Experimental design</b>	10 animals for group/dose Doses of 10, 40 and 100 mg/L in drinking water for 16 and 66 days or 100, 200 and 400 mg/L in drinking water for 133 days	There is no mention of animal randomisation or how animals were allocated in the treatment groups (3 plus control). The number of animals is considered adequate.
<b>Diet</b>	The content of Iodine and Bromide in the diet was adequately reported	Considered adequate.
<b>Test substance, doses and formulation</b>	Test substance is administered through drinking water.	There is no mention of the stability of the substance in the water and how often the solution is changed along the study. However, it is likely that KBr is not going to any degradation process, but oxidation cannot be excluded. Number of doses is considered adequate. Source and purity of the substance is not given.
<b>Pathology procedures</b>		
<b>Method of euthanasia</b>	By ether anaesthesia, but the exsanguination methods is not reported. Randomisation of animals at killing is not mentioned	More details should be given, though the time of killing is unlikely to have impact on the measured endpoint.
<b>Randomisation of pathology procedures</b>	Not reported.	PCNA positive nuclei were manually counted; therefore, lack of blinding is considered a bias.
<b>Materials and methods – Tissue sampling, processing and staining</b>	Reported	Considered adequate for the standard histopathology and for the IHC methodology. The blank is mentioned but a positive control e.g. intestinal mucosa, was not included in the assay. This is however expected to be of low impact because of the clear positivity of nuclei in the PCNA stained sections.
<b>Pathologist/peer review</b>	Not reported	
<b>Results</b>		
<b>Body weight</b>	Not reported	• No information on systemic toxicity is given
<b>Organ weight</b>	Not reported	
<b>Histopathology</b>	<b>Light microscopy:</b> descriptive pathology in the text complemented by descriptive pathology in a limited number of pictures. <b>IHC:</b> description is given and a picture of a treated and a control sample is included in the paper.	<b>Light microscopy:</b> the descriptive pathology is not in line with the current standard (not following INHAND 2018 recommendations). However, by combining the text in the paper and in the figure legend of microscopic pictures, the descriptive pathology is clear. The number of pictures is limited. There is no incidence table for the histopathological changes, and no scoring is given to quantify the changes, and this is compromising the understanding of the dose relationship. <b>IHC:</b> description is adequate and reported in a tabulated format. The statistical analysis is complemented by a graphic format. The reporting of the PCNA is considered adequate.

**TABLE A.4** Details on study quality and reliability of Velický, Titlbach, Dusková, et al., 1997).

<b>Experimental setting</b>		
<b>Element</b>	<b>Authors</b>	<b>EFSA comments</b>
<b>Test system</b>	41-day old male Wistar rats (TOP VELAZ Prague CR)	Only male rats were used in the study. Male rats are known to have a more reactive thyroid gland with a higher number of micro follicles located in the central part of the gland and less evident inactive large follicles located in the periphery of the organ. The number of animals included in each group ( $n = 10$ ) is considered adequate.
<b>Animal welfare</b>	Standard procedures are reported	Considered sufficient.
<b>GLP</b>	Not mentioned	No reference to any internal SOP is reported
<b>Experimental design</b>	6 animals for group/dose Doses of 0, 10 50 and 100 mg/L in drinking water for 16 and 66 days	There is no mention of animal randomisation or how animals were allocated in the treatment groups (3 plus control). The number of animals is considered low and below the current standard for these studies.
<b>Diet</b>	The content of iodine and bromide in the diet was adequately reported	Considered adequate.
<b>Test substance, doses and formulation</b>	Test substance is administered through drinking water. Analytical grade. 3 doses are included in the study.	There is no mention of the stability of the substance in the water and how often the solution is changed along the study. However, it is likely that KBr is not going to any degradation process, but oxidation cannot be excluded. Number of doses is considered adequate. The producer of substance is mentioned but the analytical grade can only be inferred. Considered sufficient.
<b>Pathology procedures</b>		
<b>Method of euthanasia</b>	By ether anaesthesia, but the exsanguination methods is not reported. Randomisation of animals at killing is not mentioned	More details should have been given. Lack of randomisation is a relevant bias because also time of killing is not given, and this can compromise thyroid hormone assessment (T4).
<b>Randomisation of pathology procedures</b>	Not reported. This is true for all methodologies; standard histopathology assessment, immunohistochemistry assessment, ultrastructural analysis and morphometry.	While is generally accepted that standard histopathological assessments are not performed blindly or following a randomisation procedure (STP position paper exist on this), morphometric analysis should be; this is mainly because while histopathology cannot be separate by expert judgement, morphometry should be agnostic. This is considered a relevant bias.
<b>Materials and methods – Tissue sampling, processing and staining</b>	Reported	Considered adequate for the standard histopathology. For the IHC analysis, the methodology is adequate but reporting of the positive control and of the blank is lacking.
<b>Biochemistry and hormonal analysis</b>	No plasma/blood biochemistry was done. TSH, T3 and T4 were analysed by RIA. Blood sample collected by cardiac puncture.	Lack of time recording for the time of blood sampling and animals' randomisation is a relevant bias (T4 levels in the blood is following a circadian fluctuation). RIA methodology is adequate, but no reference is given on kit validation, positive control, calibration curve is not given, LOQ and LOD are not given and no references are given. Overall, the methodology of hormonal assessment is considered not adequate

(Continues)



TABLE A.4 (Continued)

Experimental setting		
Element	Authors	EFSA comments
<b>Tissue and diet Br and I concentration</b>	Analysis considered adequate. Bromine and iodine levels in the thyroid gland dry weight were determined by instrumental neutron activation analysis (INAA) in a short-term irradiation regime applied to dried thyroid glands in a nuclear reactor. The bromine level in the diet was assessed by INAA in a long-term irradiation regime using the <sup>82</sup> Br radionuclide and the iodine level by kinetic photometry	The reviewer (A. Terron) has no experience on the described analytical methodology. The methods seem however be adequate and the outcome is reported in a tabulated format
<b>Pathologist/peer review</b>	Not reported	
<b>Results</b>		
<b>Body weight</b>	Not reported	No information on systemic toxicity is given.
<b>Organ weight</b>	Not reported	
<b>Histopathology</b>	<p><b>Light microscopy:</b> Descriptive pathology in the text complemented by descriptive pathology in a limited number of pictures.</p> <p><b>Electron microscopy:</b> Description is given and only one picture (no control) is reported. The number of animals and a tabulated summary is not given.</p> <p><b>IHC:</b> Description is given and few picture of treated and control are included in the paper.</p> <p><b>Morphometry:</b> The results are descriptive and no data on measures is reported in a tabular format. Colloid volume and distribution are reported in a graphic.</p>	<p><b>Light microscopy:</b> the descriptive pathology is not in line with the current standard (not following INHAND 2018 recommendations). However, by combining the text in the paper and in the figure legend of microscopic pictures, the descriptive pathology is clear. The number of pictures is adequate. There is no incidence table for the histopathological changes, and no scoring is given to quantify the changes, and this is compromising the understanding of the dose relationship. Dimension of thyroid follicular cell is reported as increase in height, which can be however considered adequate as a synonym of cell hypertrophy.</p> <p><b>Electron microscopy:</b> the descriptive pathology is adequate but selective reporting (only one picture from a treated animal) is representing a bias.</p> <p><b>IHC:</b> description is adequate and the IHC was used to perform the morphometry. Overall, it is considered sufficiently reported.</p> <p><b>Morphometry:</b> only the volume of the follicle's lumen was measured by using the colloid volume and colloid volume distribution (also by IHC staining of the thyroglobulin). The combination of the insufficient details given in the methods, lack of blind procedures, lack of measure reporting, lack of statistical analysis reporting and with the only reporting of mean plus/minus S.E.M. only for the colloid volume, the morphometric analysis is considered as of risk of bias.</p>
<b>Hormone analysis</b>	Data are not tabulated. Only a graphic illustration is given for T4, T3 and TSH levels, reporting mean and S.E.M. The statistical analysis is included in the text.	The reporting is not considered sufficient and with the bias reported for the methodology, hormonal analysis overall should be considered as a risk of bias.
<b>Bromine and iodine tissue concentrations</b>	Data are reported in a tabulated format	Reporting is considered adequate and with an increased administration in Bromide concentration there is an increase in bromine in thyroid tissue.

**TABLE A.5** Details on study quality and reliability of Velický et al. (1998).

<b>Experimental setting</b>		
<b>Element</b>	<b>Authors</b>	<b>EFSA comments</b>
<b>Test system</b>	43-day old male Wistar rats (TOP VELAZ Prague CR)	Only male rats were used in the study. Male rats are known to have a more reactive thyroid gland with a higher number of micro follicles located in the central part of the gland and less evident inactive large follicles located in the periphery of the organ. The number of animals included in each group ( $n = 10$ ) is considered adequate.
<b>Animal welfare</b>	Standard procedures are reported	Considered sufficient.
<b>GLP</b>	Not mentioned	Research study. No reference to any internal SOP is reported
<b>Experimental design</b>	10 animals for group/dose Doses of 100, 200 and 400 mg/L in drinking water for 133 days	There is no mention of animal randomisation or how animals were allocated in the treatment groups (3 plus control). The number of animals is considered adequate.
<b>Diet</b>	The content of iodine and bromide in the diet was adequately reported	Considered adequate.
<b>Test substance, doses and formulation</b>	Test substance is administered through drinking water. Analytical grade. 3 doses are included in the study.	There is no mention of the stability of the substance in the water and how often the solution is changed along the study. However, it is likely that KBr is not going to any degradation process, but oxidation cannot be excluded. Number of doses is considered adequate. The substance is considered analytical grade, though high level of purity can be inferred. Considered sufficient.
<b>Pathology procedures</b>		
<b>Method of euthanasia</b>	By ether anaesthesia, but the exsanguination method is not reported. Randomisation of animals at killing is not mentioned	More details should have been given. Lack of randomisation is a relevant bias because also time of killing is not given, and this can compromise thyroid hormone assessment (T4).
<b>Randomisation of pathology procedures</b>	Not reported. This is true for all methodologies; standard histopathology assessment, immunohistochemistry assessment, ultrastructural analysis and morphometry. No blind examination is reported.	While is generally accepted that standard histopathological assessments are not performed blindly or following a randomisation procedure (STP position paper exist on this), morphometric analysis should be; this is mainly because while histopathology cannot be separate by expert judgement, morphometry should be agnostic. This is considered a relevant bias.
<b>Materials and methods – Tissue sampling, processing and staining</b>	Reported	Considered adequate for the standard histopathology. For the IHC analysis, the methodology is adequate but reporting of the positive control and of the blank is lacking.
<b>Biochemistry and hormonal analysis</b>	No plasma/blood biochemistry was done. TSH, T3 and T4 were analysed by RIA. Blood sample collected by cardiac puncture.	Lack of time recording for the time of blood sampling and animals' randomisation is a relevant bias (T4 levels in the blood is following a circadian fluctuation). RIA methodology is adequate, but no reference is given on how the method was validated, positive control is no mentioned, calibration curve is not given, LOQ and LOD are not given, and no references are given. Overall, the methodology of hormonal assessment is considered not adequate.
<b>Tissue and diet Br and I concentration</b>	Analysis considered adequate. Bromine and iodine levels in the thyroid gland dry weight were determined by instrumental neutron activation analysis (INAA) in a short-term irradiation regime applied to dried thyroid glands in a nuclear reactor. The bromine level in the diet was assessed by INAA in a long-term irradiation regime using the $^{82}\text{Br}$ radionuclide and the iodine level by kinetic photometry	The reviewer (A. Terron) has no experience on the described analytical methodology. The methods seem however be adequate and the outcome is reported in a tabulated format

(Continues)

TABLE A.5 (Continued)

Experimental setting		
Element	Authors	EFSA comments
Pathologist/peer review	Not reported	-
<b>Results</b>		
Body weight	Not reported	No information on systemic toxicity is given
Organ weight	Not reported	
Histopathology	<p><b>Light microscopy:</b> descriptive pathology in the text complemented by descriptive pathology in a limited number of pictures.</p> <p><b>Electron microscopy:</b> Description is given and only one picture (no control) is reported. The number of animals and a tabulated summary is not given.</p> <p><b>IHC:</b> Description is given and few pictures of treated and control are included in the paper.</p> <p><b>Morphometry:</b> The results are descriptive and no data on measures is reported in a tabular format. Colloid volume and distribution are reported in a graphic.</p>	<p><b>Light microscopy:</b> the descriptive pathology is not in line with the current standard (not following INHAND 2018 recommendations). However, by combining the text in the paper and in the figure legend of microscopic pictures, the descriptive pathology is clear. The number of pictures is limited and not all the aspects considered in the descriptive pathology are highlighted in the pictures (mitosis, capillary dilation). The authors report a striking microfollicular rearrangement as main finding, with microfollicles presented in foci, in the centre and at the periphery of the gland. However, a more comprehensive set of images, showing the central and peripheral portions of the thyroid, should have been provided for an independent interpretation; it is well recognised that micro follicles are normally present in the internal portion of thyroids, while large follicles are at the periphery of the gland. There is no incidence table for the histopathological changes, and no scoring is given to quantify the changes, and this is compromising the understanding of the dose relationship. Dimension of thyroid follicular cell is reported as increase in height, which can be however considered adequate as a synonym of cell hypertrophy.</p> <p><b>Electron microscopy:</b> The descriptive pathology is adequate but selective reporting (only one picture from a treated animal) is representing a bias.</p> <p><b>IHC:</b> Description is adequate and the IHC was used to perform the morphometry. Overall, it is considered sufficiently reported.</p> <p><b>Morphometry:</b> Only the volume of the follicle's lumen was measured by using the colloid volume and colloid volume distribution (also by IHC staining of the thyroglobulin). The combination of the insufficient details given in the methods (selection of the areas to measure), lack of blind procedures, lack of measure reporting, lack of statistical analysis reporting and with the only reporting of mean plus/minus S.E.M. only for the colloid volume, the morphometric analysis is considered to have a high risk of bias.</p>
Hormone analysis	Data are not tabulated. Only a graphic illustration is given for T4 levels, reporting mean and S.E.M. The statistical analysis is included in the text and with a limited description. Neither data nor graphics are reported for T3 and TSH.	The reporting is not considered sufficient and with the bias reported for the methodology, hormonal analysis overall should be considered to have a high risk of bias.
Bromine and iodine tissue concentrations	Data are reported in a tabulated format	Reporting is considered adequate, and with an increased administration in Bromide concentration, there is an increase in Bromine in thyroid tissue.

**TABLE A.6** Details on study quality and reliability of Velicki et al. (2004).

<b>Experimental setting</b>		
<b>Element</b>	<b>Authors</b>	<b>EFSA comments</b>
<b>Test system</b>	Inbred male Wistar rats (TOP Velaz Ltd), 41-day old, weighing 100–120 g	It is recognised that thyroid morphology is more variable in control male rats than females
<b>Animal welfare</b>	Acclimation (7 days), study conditions: 20 + 1°C, relative air moisture 55 – + 5%, 13 h light and 11 h dark period)	Considered adequate.
<b>GLP</b>	–	Research study.
<b>Experimental design</b>	12 groups (3 controls and 9 treated), 10 rats/group, multiple time points/ KBr administered via drinking water: 10, 50, 100 mg Br <sup>-</sup> /L for 16 days 10, 50, 100 mg Br <sup>-</sup> /L for 66 days 100, 200, 400 mg Br <sup>-</sup> /L for 133 days, 0 mg Br <sup>-</sup> /L 16, 66, and 133 days, respectively. Rats drank 15 mL water/day, approximately. Electron microscopy investigation (thyroid gland) only.	Research study, no standardised protocol used. The study is intended to explore thyroid ultrastructural changes only, complementing histopathology described in previous studies (Velicki et al. 1997a,b; 1998) (above described). The study is likely the same conducted in 1998, and the EM analysis should be considered as supplementary arm. It is however not clear if all animals in the study, or only a proportion of them, went through the EM processing and analysis. If animals were selected, it is not clear how they were selected. It is indeed a common practice to execute the EM analysis only on a proportion of selected animals and selection is generally using the outcome of the light microscopy analysis. Without any specification, it should be assumed that all animals were assessed for EM.
<b>Diet</b>	Standard pellet diet KS-ST-1 (TOP) VELAZ Ltd., Prague, CR. The mean content of bromide and iodine in the diet (analysed in seven samples) was 10.04 mg Br <sup>-</sup> /kg and 0.52 mg I <sup>-</sup> /kg respectively. The amount of food consumed by the animals was approximately 20 g/animal per day.	No detailed information is available on diet composition, however Br and I content is analytically determined and described. For the records, standard diets for laboratory rodents are nutritionally balanced, i.e. formulated according to nutrient requirements; the laboratory rat iodine requirement is 150 µg/kg diet (0.15 ppm) (NRC. Nutrient Requirements of Laboratory Animals, Fourth Revised Edition, 1995. Washington (DC): 2, Nutrient Requirements of the Laboratory Rat. Available from: <a href="https://www.ncbi.nlm.nih.gov/books/NBK231925/">https://www.ncbi.nlm.nih.gov/books/NBK231925/</a> ) Standard chows (e.g. Purina 5002) contain around 1 ppm iodine. In this Velicki study the amount is lower (0.52 ppm), nevertheless above the amount covering rat needs. No information is generally available for the bromide content in standard rodent chows.
<b>Test substance, doses, and formulation</b>	KBr analytical grade; AR Lachema, Brno, CR	No information on the purity of the test substance. No information on the stability of the substance in the water and how often the solution is changed along the study. Although KBr is unlikely to degrade, oxidation cannot be excluded. Number of doses is considered adequate. It is assumed that the total amount of iodine and bromide intake is the sum of that introduced by diet and administered by drinking water.
<b>Pathology procedures</b>		
<b>Method of euthanasia</b>	Overdose of ether.	The method per se is adequate but for the EM analysis, perfusion fixation is generally recognised as a gold standard. However, overall, fixation by immersion in the appropriate fixatives, as described in the paper, is considered adequate to guarantee a sufficient quality of the samples.
<b>Randomisation of pathology procedures</b>	No information	Randomisation of necropsy and in general pathology procedures is particularly important in morphological studies on the thyroid gland (circadian rhythm). This represents an uncertainty, also for the type of investigation (TEM) on subcellular morphology (to check at results level). In addition, is not clear if all or selected animals were evaluated for the EM analysis. Lacking any consideration on animal selection, we assume that all animals were evaluated. However, in this case, with this numerosity, a summary incidence table would have been beneficial for a correct interpretation of the observed changes.

(Continues)

TABLE A.6 (Continued)

Experimental setting		
Element	Authors	EFSA comments
<b>Materials and methods – Tissue sampling, processing and staining</b>	Thyroid glands were dissected free of fibrous fatty tissue and muscles; small pieces of tissue (approx. 1 mm <sup>3</sup> ) were fixed in 2.5% glutaraldehyde and post-fixed in 2% osmium tetroxide dehydrated in ethanol, embedded in plastic and processed for electron microscopy.  Semithin and ultrathin sections were cut using ultramicrotomes; semithin sections (1 µm) stained in aqueous solution of Azur B, ultrathin sections (60–90 nm) were contrasted using uranyl-acetate and lead-citrate and examined using ZEISS EM 109 electron microscope.	There is no detailed information on the sampling protocol (how many samples per animal/thyroid, region of the thyroid). This is considered a significant limitation. The processing and staining procedures are adequate.
<b>Biochemistry and hormonal analysis</b>	Not performed	–
<b>Pathologist/peer review</b>	No information available.	–
<b>Results</b>		
<b>Body weight</b>	Not reported	This could provide information on systemic toxicity, the lack of information is a limitation.
<b>Organ weight</b>	Not reported	The study is intended to explore thyroid ultrastructural changes only, complementing histopathology described in previous studies. The lack of information on thyroid weight in the current study is considered a significant limitation for the interpretation of the study in the regulatory context.
<b>Histopathology</b>	Not reported.	Ultrastructural studies are generally carried out to support the interpretation of histopathological results and has the objective to clarify histopathological effects at subcellular level, i.e. clarifying which subcellular structure is affected. This is why the rationale for animal selection, and thyroid area selection is so important; because the EM analysis is intended to corroborate what was observed at light microscopy and provide a description of events at organelles rather than cellular level. The use of EM information should therefore be considered complementary to the histopathological assessment
<b>Ultrastructural studies</b>	12 images reported, and detailed descriptions provided.	Narrative descriptions in the paper often refer to conditions that are generally captured at light microscopy examination (e.g. small follicles, microfollicles). Considering the limited set of pictures available, the results specifically referring to ultrastructural features (i.e. related to subcellular structures) are considered relevant to discuss. Overall, dilation of tubular structures (e.g. endoplasmic reticulum, rough and smooth, increased subapical granules are noted.) As a caveat, the distension of tubular structures is described as artefacts in transmission electron microscopy. Control animal, 66 days (1 picture, X14,000). The quality is acceptable, although not outstanding (mitochondrial cristae not well defined). The lumen with colloid is visible, although in a limited portion. Capillary vessel on the left side, ER, nucleus and lysosomes identifiable.



TABLE A.6 (Continued)

Experimental setting		
Element	Authors	EFSA comments
		<p>As compared to the control, the most relevant features in treated rats were dilated tubular structures (endoplasmic reticulum) and increased number of subapical granules. Elongated microvilli and increasingly evident coated pits are also noted; however, the limited view on follicle lumen in the control picture does not allow a proper comparison. Some intraluminal debris (Figure 7). Figures 11 and 12 show swollen mitochondria with broken cristae, while the outer membrane is preserved. Bizarre nuclei in Figure 8 are of unclear significance. It difficult to separate these last two observations from the occurrence of technical artefact, possibly of fixative nature.</p> <p>The authors report of small/microfollicles, that can be identified in Figures 6 and 10. Note that the authors define Figure 6 as presenting a neoplastic condition, unclear on which basis. The author is also quoting hyperplastic conditions but there is no mention of mitotic activity in the gland. Therefore, both neoplastic as well as hyperplastic definitions are likely referring to the increased number of newly formed microfollicles. The author describes two different types of thyrocytes, which are likely representing the morphological dynamic state of cells producing thyroglobulin.</p> <p>The author is describing changes in the nuclei as increase density of the chromatin and incisions. Although artefacts (see above) cannot be excluded, these changes, if real, are more suggestive of apoptosis, while the author is claiming that necrotic thyrocytes and/or cellular debris were occasionally observed. This is a contradicting observation. In addition, the overall pattern is suggestive of cell activation; in this case it would be expected to see less condensed euchromatin, indicative of increase in DNA synthesis. These aspects are therefore representing an uncertainty.</p> <p>The author is quoting an increase in the number of microfollicles. Although no proper morphometric analysis was performed, the author is quoting an average dimension of follicles in control animals of 30–50 µm and of 8–20 µm. How to interpret the assessment of the microfollicles is difficult without proper sampling and statistics and remains uncertain because the measure of 8 µm corresponds to the measure of an erythrocyte (diameter).</p> <p>No obvious change in the colloid ultrastructural characteristics (tinctorial properties, homogeneity), beside the presence of some debris.</p> <p>Because it is not clear how many animals were assessed for the EM, assuming that all animals in the study were included, an incidence table summarising the frequency of the reported ultrastructural changes should have been included and should be considered for the interpretation of the findings</p>
Hormones and TSH	Not reported	The study is intended to explore thyroid ultrastructural changes only, complementing histopathology described in previous studies.

**TABLE A.7** Details on study quality and reliability of Unpublished repeat dose 90-day toxicity study in rats, 2016 (Study report, 2016b).

<b>Experimental setting</b>		
<b>Element</b>	<b>Authors</b>	<b>EFSA comments</b>
<b>Test system</b>	Rat, CrI:CD(SD)	Considered adequate.
<b>Animal welfare</b>	Standard procedures are reported	Considered sufficient.
<b>OECD/GLP</b>	OECD TG 408 (1998)	Assumed to be GLP
<b>Experimental design</b>	10/sex/group (+10 sex Group control, sodium chloride and top dose)	In line with OECD TG 408, considered sufficient.
<b>Diet</b>	No information	No information on iodine and bromide content in the diet is available in the summary
<b>Test substance, doses and formulation</b>	Test substance is administered through gavage. Doses of 0, 60,175 and 500 mg sodium bromide /kg bw day; 284 mg/kg bw day sodium chloride)	No information on stability is provided in the summary.
<b>Pathology procedures</b>		
<b>Method of euthanasia</b>	Not reported	The lack of randomisation is a relevant bias because also time of killing is not given, and this can compromise thyroid hormone assessment (T4). Information not available in the summary.
<b>Randomisation of pathology procedures</b>	Not reported. This is true for all methodologies.	Information not available in the summary.
<b>Materials and methods – Tissue sampling, processing and staining</b>	Not reported	Information not available in the summary.
<b>Biochemistry and hormonal analysis</b>	Not reported.	Information not available in the summary.
<b>Pathologist/peer review</b>	Not reported	Information not available in the summary.
<b>Results</b>		
<b>Body weight</b>	No significant effect of treatment at 60 or 175 mg/kg per day on body weight or body weight gain in males and females, although values at 175 mg/kg per day were slightly lower than controls. Relevant changes at 500 mg/kg bw per day.	The top dose overcomes the MTD.
<b>Organ weight</b>	There were no statistically significant differences in absolute thyroid weight and increases relative to body weight were only significant ( $p \leq 0.05$ ) in females treated at 500 mg/kg per day.	No details reported (figures)
<b>Histopathology</b>	Data not tabulated. Mild/moderate depletion of colloid (noted when the majority of follicles in the thyroid contained no identifiable colloid) was observed in 2 males and 2 females in the groups treated at 175 and 500 mg/kg per day. It is, however, noteworthy that there was no correlation between these findings and decreased T3 and T4 levels in individual animals. These changes were not apparent at 60 mg/kg per day	The findings could be consistent with thyroid activation at 175 and 500 mg/kg bw per day. The reduced colloid looks associated with a situation of follicles diffusely devoid of colloid. Declaring lack of correlation is misleading and should be ignored as the hormonal analysis was conducted at week 4 while the histological analysis was done at termination (Day 90).

TABLE A.7 (Continued)

Experimental setting		
Element	Authors	EFSA comments
<b>Hormone analysis</b>	<p>Data are not tabulated. Thyroid hormone analysis in serum was conducted on a single occasion in Week 4. High number of values below the LOQ. Apparent reduction (<math>p \leq 0.01</math>) in T3 (males only) and in T4 (males and females) at 500 mg/kg per day. At 175 mg/kg per day, differences from control in T3 (<math>p \leq 0.05</math>, males) and T4 (<math>p \leq 0.01</math>, males and females) were less marked and values were comparable to historical control values.</p> <p>Although not statistically significant (probably due to wide variation in individual results) mean TSH levels were 36% and 74% higher than controls in the 175 and 500 mg/kg per day male groups, respectively. All mean values, including controls were, however, markedly higher (~2 to 6-fold) than the historical control range. There was no significant effect on TSH in females.</p> <p>Questionable toxicological significance of decreases in T3 and T4 at 60 mg/kg per day.</p>	<p>The reported information does indicate a drop in T3 and T4 and increased TSH at 175 mg/kg bw per day. No effects at 60mg/kg bw per day. More details are needed (figures). No HCD were provided in the summary.</p>

## APPENDIX B

## Appraisal of evidence of bromide health effects from human studies

TABLE B.1 Heat map of RoB appraisal\*.

Risk of bias domain	Sangster et al., 1982	Sangster et al., 1983	Van Gelderen et al., 1993/ Sangster et al., 1986	Wong et al., 1984	Miller et al., 1987	Nusair et al., 2019
Selection bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Performance bias	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
Attrition bias	Low risk	Low risk	Low risk	High risk	Low risk	Unclear
Detection bias-outcome	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
Detection bias-exposure	Low risk	Low risk	Low risk	High risk	High risk	High risk

\*Colour-coding is for visual overview: 'Low risk', green; 'High risk', red; 'Unclear', orange.

TABLE B.2 Appraisal of human experimental studies.

Sangster et al. (1982)			
A	Selection bias	Rating	Rationale for rating
A1	Adequate description inclusion/exclusion	Partially	Exclusion criteria mentioned
A2	Adequate methods	Yes	
A3	Adequate participation	Yes	Only males and females, aged 20–26 y
Was selection bias present? RoB:		Low	
B	Performance bias	Rating	Rationale for rating
B1	Clear definition intervention	Yes	NaBr in capsules
B2	Blinding of participants	No	
B3	Blinding of assessors	Yes	
Was performance bias present? RoB:		Low	
C	Attrition bias	Rating	Rationale for rating
C1	Adequate participation by eligible persons	Yes/No	
C2	Adequate availability of outcome data	Yes/No	21 selected; 20 participants (10M, 10F); serum concentrations for 9M, 9F
C3	Results equally available for the test and placebo	Yes	Outcome data available for all participants for the baseline and at end
Was attrition bias present? RoB:		Low	
D	Detection bias - outcome	Rating	Rationale for rating
D1	Appropriate length of follow-up	Unclear	Males may have not reached steady-state
D2	Precise definition of outcome	Yes	
D3	Valid method for outcome assessment	Yes	
D4	Blinding of outcome assessors	No?	
Was detection bias present in relation to the outcome? RoB:		Unknown/unclear	
E	Detection bias - exposure	Rating	Rationale for rating
E1	Amount bromide known	Yes	Background intake not assessed
E2	Amount consistent	Yes	
E3	Amount consistent across individuals	Yes	Given per kg bw
E4	Initial dose, dose intervals and dose range appropriate for diagnosis	Yes	
Was detection bias present in relation to the exposure? RoB:		Low	
F	Overall assessment of validity	-	Low, possible detection bias

TABLE B.2 (Continued)

<b>Sangster et al. (1983)</b>			
<b>A</b>	<b>Selection bias</b>	<b>Rating</b>	<b>Rationale for rating</b>
A1	Adequate description inclusion/exclusion	Yes	42 subjects (males and females, 19–31 years); health assessment and exclusion criteria described
A2	Adequate methods	?	The population from which subjects were recruited is unclear; volunteers
A3	Adequate participation	Yes	
Was selection bias present? RoB:		Low	
<b>B</b>	<b>Performance bias</b>	<b>Rating</b>	<b>Rationale for rating</b>
B1	Clear definition intervention	Yes	
B2	Blinding of participants	Yes	
B3	Blinding of assessors	Yes	
Was performance bias present? RoB:		Low	
<b>C</b>	<b>Attrition bias</b>	<b>Rating</b>	<b>Rationale for rating</b>
C1	Adequate participation by eligible persons	Yes	4 F dropped out – with reasons not related to the study
C2	Adequate availability of outcome data	Yes	
C3	Results equally available for the test and placebo	Yes	
Was attrition bias present? RoB:		Low	
<b>D</b>	<b>Detection bias - outcome</b>	<b>Rating</b>	<b>Rationale for rating</b>
D1	Appropriate length of follow-up	Yes	12 weeks for M and 3 full menstrual cycles for F
D2	Precise definition of outcome	Yes	
D3	Valid method for outcome assessment	Yes	
D4	Blinding of outcome assessors	Yes	
Was detection bias present in relation to the outcome?		Low	
<b>E</b>	<b>Detection bias - exposure</b>	<b>Rating</b>	<b>Rationale for rating</b>
E1	Amount bromide known	Yes/No	Groups receiving 0, 4 or 9 mg NaBr per kg bw per day. This was not calculated on individual basis but according to weight classes. Likely subjected received more NaBr per kg bw per day
E2	Amount consistent across sessions	Yes	
E3	Amount consistent across individuals	Yes	
E4	Initial dose, dose intervals and dose range appropriate for diagnosis	Yes	
Was detection bias present in relation to the exposure?		Low	
<b>F</b>	<b>Overall assessment of validity</b>	–	
<b>Sangster et al. (1986)/Van Gelderen et al. (1993)</b>			
<b>A</b>	<b>Selection bias</b>	<b>Rating</b>	<b>Rationale for rating</b>
A1	Adequate description inclusion/exclusion	Yes	
A2	Adequate methods	Yes	
A3	Adequate participation	Yes	
Was selection bias present? RoB:		Low	
<b>B</b>	<b>Performance bias</b>	<b>Rating</b>	<b>Rationale for rating</b>
B1	Clear definition diagnostic intervention	Yes	
B2	Blinding of participants	Yes	
B3	Blinding of assessors	Yes	
Was performance bias present? RoB:		Low	
<b>C</b>	<b>Attrition bias</b>	<b>Rating</b>	<b>Rationale for rating</b>
C1	Adequate participation by eligible persons	Yes	48 (n = 3 withdrew): 45 F (n = 15 in 3 dosage groups), 20–28 years

(Continues)



TABLE B.2 (Continued)

Sangster et al. (1986)/Van Gelderen et al. (1993)			
C2	Adequate availability of outcome data	Yes	Outcome data available for all participants
C3	Results equally available for the test and placebo	Yes	
Was attrition bias present? RoB:		Low	
<b>D</b>	<b>Detection bias - outcome</b>	<b>Rating</b>	<b>Rationale for rating</b>
D1	Appropriate length of follow-up	Yes	
D2	Precise definition of outcome	Yes	
D3	Valid method for outcome assessment	Yes	
D4	Blinding of outcome assessors	Yes	
Was detection bias present in relation to the outcome? RoB:		Low	
<b>E</b>	<b>Detection bias - exposure</b>	<b>Rating</b>	<b>Rationale for rating</b>
E1	Amount of bromide known	Partially	Not exactly; F in groups according to weight; weight difference of max 10 kg, receiving same dose of NaBr
E2	Amount consistent across sessions	Yes	
E3	Amount consistent across individuals	Yes	
E4	Initial dose, dose intervals and dose range appropriate for diagnosis	Yes	
Was detection bias present in relation to the exposure? RoB:		Low	
<b>F</b>	<b>Overall assessment of validity</b>	–	Possible mistake in calculated mean concentrations of FT4 and TSH for 0 mg group

Abbreviation: RoB, Risk of bias.

### Evidence overview from case reports

In total 61 papers were identified by EFSA; 24 were not relevant or were reviews. A few other relevant papers were found and this resulted in 28 publications with descriptions of 41 cases of effects of bromide.

**TABLE B.3** Description of case reports on bromide intake.

Source	Age, gender	Route, dose, duration	Outcome	Serum bromide	Remark	Reference
Cordial de Monell (Dominican Republic, elixer for colic with KBr)	22 days, F	Elixer added to each meal during 12 days; contained potassium bromide: 0.3 g/100 mL	Bromism; physical exam findings included lethargy, hypotonia, and slightly diminished reflexes		Healthy, normal infant	Lugassy and Nelson (2009)
Syrup containing sodium bromide (Medictral)	2 months, F	1 months	Vegetant bromoderma			Bel et al. (2001)
Syrup for abdominal colic containing calcium bromide	5 months, M	From age 1 months	Bromoderma for 3 months			Hoefel et al. (2016)
Colic medication (syrup) containing CaBr	8 months, F	CaBr, 3 months	Vegetating bromoderma			Nofal et al. (2020)
KBr therapy (in combination with other medicines)	1 months, F	20–80 mg/kg bw per day, 20 days	Reduction in occurrence of epileptic seizures with no apparent side effects	Bromide blood: 196 mg/L	Malignant migrating partial epilepsy of infancy	Horesh et al. (2013)
	2 months, F	20–80 mg/kg bw per day	Reduction in occurrence of epileptic seizures with no apparent side effects	Bromide blood (at discharge): 110 mg/L	Ohtahara syndrome	
KBr therapy	5 months, M	KBr 60 mg/kg bw per day, 4 weeks	Bromoderma		Patient with migrating partial seizures in infancy	Nabatame et al. (2010)
KBr therapy	6 months, F	260 mg KBr twice daily; 1 months	Bromoderma	Serum bromide: 930 mg/L		Paloni et al. (2013)

(Continues)

TABLE B.3 (Continued)

Source	Age, gender	Route, dose, duration	Outcome	Serum bromide	Remark	Reference
KBr as medicine (plus other antiepileptic drugs)	6–12 months at introduction, 4 M + 2 F	30 mg/kg bw per day KBr, 4 years	Seizure free	710 mg/L	Infancy epilepsy with migrating focal seizures (EIMFS); introduction to KBr at 6–12 mo old; 4 boys, 2 girls; mental retardation and language impairment; all had daily seizures before start treatment	Caraballo et al. (2014)
		80 mg/kg bw per day KBr, 0.5 years	No response Drowsiness	1230 mg/L		
		65 mg/kg bw per day KBr, 5 years	Monthly seizures Vomiting	1140 mg/L		
		70 mg/kg bw per day KBr, 0.5 years	No response Skin rash	1150 mg/L		
		60 mg/kg bw per day KBr, 1 years	Weekly seizures	950 mg/L		
		55 mg/kg bw per day KBr, 2.5 years	Monthly seizures	890 mg/L		
KBr in combination with several anti-epileptic drugs	1 years, M		Bromoderma: rash after 5 months		Was born with severe asphyxia and had Apgar scores of 1 and 1 at 1 and 5 min, respectively. Thereafter he developed hypoxic–ischaemic encephalopathy; severe epilepsy	Nakagawa et al. (2019)
KBr treatment (+ ketogenic diet)	14 months, M	KBr, 80 mg/kg bw per day	Seizures stopped	Br <sup>-</sup> : 1100 mg/L	Patient with malignant migrating partial seizures in infancy	Okuda et al. (2000)
KBr therapy	14 months, F	KBr, 3 weeks	No seizures and recovery of neurological development		Patient with malignant migrating partial seizures in infancy	
KBr therapy (+ other therapy)	15 months, F	80 mg/kg bw per day	No serious side effects except for spurious hyperchloremia (143 mEq/L) and mild somnolence. Seizures recurred after 4 months	Br <sup>-</sup> blood concentration: 2400 mg/L	Developmental retardation as the sequelae of severe neonatal asphyxia; seizures	Takayanagi et al. (2002)
Dibromide in combination with other anti-epileptics	5 years, M	Dibromide		Serum bromide level was after 3 days decreased from 2092 to 1255 mg/L (105.0 mg/L)	Patient with Dravet syndrome and refractory epilepsy	Sarkis et al. (2021)
Treatment with triple bromide elixir	17 years, F	60.1 mg/kg bw per days, 6–7 years	Bromism	Serum bromide: 3907 mg/L	Patient with intractable epilepsy; used also other medication	James et al. (1997)
Bromovalerylurea administration	23 years, F	45 tablets, 100 mg/ tablet (overdose)	Drowsiness, myoclonic jerks in all extremities	Serum Br <sup>-</sup> : 81 mg/L after patient underwent emergent gastric lavage	Complete recovery after 2 months	Lin et al. (2008)

TABLE B.3 (Continued)

Source	Age, gender	Route, dose, duration	Outcome	Serum bromide	Remark	Reference
NaBr and KBr (suicide attempt)	22 years, F	Approx. 10 g NaBr and KBr	Bromide-induced hypothyroidism; coma. Thyroid follicular cells revealed the presence of significant amounts of bromine and an absence of iodine		Patient treated for schizophrenia	Mizukami et al. (1988)
NaBr	44 years, M	Up to 25 pills/day Normgastryl® (250 mg NaBr/pill, 6.25 g/day)	Confusion, hallucinations, disorientation. Bromism	Serum Cl <sup>-</sup> was decreased to 91 mM (normal=98–108) with an increased anion gap of 25.2 mM (normal=10–18). Serum Br <sup>-</sup> : 12,224 mg/L (toxic 1500 mg/L), 3235 mg/L in urine and 11,842 mg/L in CSF	Encephalopathy, duodenal ulcer, smoking of 20 cigarettes/day and chronic but moderate alcohol intake	Robe et al. (2004)
NaBr compound tablets	34 years, F	NaBr compound tablets, 6 months		Serum Cl <sup>-</sup> concentration: 112–130 mmol/L, serum bromide: 4.89 mmol/L (407.5 mg/L)	Patient with epilepsy for 11 years	Jiang et al. (2022)
KBr therapy	3 years, F	KBr dose: 0.5–0.8 g/day	Lesions on back and face	Serum bromide concentration: 43.7 mEq/L (normal, 0–5 mEq/L) on May 25, increased to 114 mEq/L (912 mg/L) on June 14. After withdrawal of KBr and treatment decreases to 56.8 mEq/L on July 6	Patient with severe epilepsy	Anzai et al. (2003)
KBr (+ other medication)	5 years, M	KBr: DIBROBE mono® 850 mg 1–0–1 ¼/days, 3 years	Bromoderma		Epilepsy	Scola et al. (2012)
KBr monotherapy	8 years, M	86 mg/kg bw per day	Seizures ceased after 18 days for 2.5 months; no serious side effects except for spurious hyperchloremia (129 mEq/L)		Psychomotor retardation since the age of 2 months; seizures at age 4 months	Takayanagi et al. (2002)
KBr therapy and methsuximide	8 years, F	4 months	Clinically a diagnosis of bromoderma tuberosum was made, but histologically it was a necrotising panniculitis	Plasma bromide concentration: 1650 mg/L	Mentally retarded with severe generalised epilepsy with generalised tonic clonic seizures	Diener et al. (1998)

(Continues)

TABLE B.3 (Continued)

Source	Age, gender	Route, dose, duration	Outcome	Serum bromide	Remark	Reference
KBr therapy	9 years, F	1700 mg/day, 16 months	Bromoderma		Single vegetating plaque of bromoderma on the leg; presence of pustules at the periphery of the plaque	Maffei et al. (2008)
KBr therapy (plus valproate)	10 years, F		Halogen panniculitis		Retarded with severe generalised epilepsy with generalised tonic-clonic seizures	Diener et al. (1998)
KBr therapy in combination with other AED	12 years, M	KBr, 2 weeks	Multiple erythematous vegetating plaques (painful nodular plaques) on the lower legs. Diagnosis: Halogenoderma, in this case vegetating bromoderma (or bromoderma tuberosum)		Patient with a developmental retardation and a severe seizure disorder that had been difficult to control	Schwieger-Briel et al. (2015)
KBr therapy (combined therapy)	14 years, M	8 years	Folliculitis followed by abscesses with deep ulcerations all over the skin; fever. Nodular panniculitis: diagnosis Weber-Christian syndrome		Patient with severe myoclonic epilepsy in infants	Diener et al. (1998)
KBr therapy (in combination with other drugs)	15 years, M	10 years	Skin lesions, fever, unable to walk		Severely retarded with symptomatic focal epilepsy and drug-resistant secondarily generalised tonic-clonic seizures	Diener et al. (1998)
KBr therapy plus phenytoin	15 years, F	1 months	Skin nodules; signs of colitis and an enlarged spleen. Diagnosis of necrotising panniculitis	Plasma bromide concentration: 1500 mg/L	Handicapped with partial duplication of the short arm of chromosome; suffered from severe generalised tonic-clonic seizures	Diener et al. (1998)
KBr, medicine	20 years, M	2125 mg KBr/day	Acne pustulosa and cognitive side effects evident and attributed to treatment with potassium bromide		Patient with cystic fibrosis (CF) at the age of 3 months developed febrile seizures at the age of one and at the age of three, afebrile seizures	Schmalbach et al. (2013)
KBr therapy	27 years, F	850 mg 4 times a day, 14 months	Diffuse vegetating bromoderma		Lafora epilepsy	Didona et al. (2020)



TABLE B.3 (Continued)

Source	Age, gender	Route, dose, duration	Outcome	Serum bromide	Remark	Reference
KBr therapy	33 years epileptics	10 g/day	Several cases who became seizure-free but also had both psychological and neurological symptoms			Otto (1874) in (Lund, 1997)
	4 cases	11–15 g/day	Became seizure-free but developed psychoses			Wendt (1875) in (Lund, 1997)
	26 years, M	31 g	Patient died 18 days later			Wright (1898) in (Lund, 1997)
Br derivative	49 years, M	Sedative	Global confusion and outbursts of aggression	Blood bromide level 1 week later was 1230 mg/L (> 500 mg/L is toxic level)	History of an excessive intake of bromide derivative sedative preparation during the previous 2 weeks	Jenkins and Chaleby (1987)
Sedative medication containing KBr	74 years, F	Mixture menopause: 15 mL containing 1 g potassium bromide – 60 mL/day for 4 weeks	Bromide intoxication: confusion, disorientation, auditory and visual hallucinations and loss of short-time memory after 4 weeks	Serum chloride: 176 mEq/L (spurious hypercloraemia), negative anion gap (–60 mEq/L). Serum bromide: 3520 mg/L (44 mEq/L)	Patient with spinal stenosis caused by posterolateral L.-S fusion.	Vasuyattakul et al. (1995)

Abbreviations: F, female; M, male.

## APPENDIX C

## Evidence of bromide health effects in food-producing and non-food-producing animals

TABLE C.1 Quality assessment of studies in food-producing and non-food-producing animals.

	Raidal and Edwards (2008)	Sacks et al. (2022)	Knight and Reina-Guerra (1977)	Genicot et al. (1991)	Vreman et al. (1985)	Quast et al. (2015)	Barber et al. (1971)	Bosshardt et al. (1956)	Doberenz et al. (1965)	Baker et al. (2003)	du Toit and Casey (2010, 2012)	Kutsan et al. (2020)	Lucht et al. (2018)	Rosenblum (1958) and Rosenblum and Hawkins (1958)	Rosenblum et al. (1960)	Smith and Iljevski (1985)	March et al. (2002)	Paul et al. (2003)	Piperisova et al. (2009)	McConkey et al. (2012)	Boothe et al. (2002)
<b>CRITERIA</b>																					
Sufficient number of animals?	Yes	No (CR)	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No (CR)	No (CR)	Yes
Randomisation?	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Appropriate control?	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No
Measurements at baseline?	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Sufficiently characterised exposure or dosing?	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Assessment methods well described and appropriate?	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes
Time between exposure and assessment sufficient?	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No
Statistical analysis appropriate?	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No
<b>Overall quality*</b>	M	L	M	M	M	L	M	L	M	L	M	L	L	M	M	L	M	M	L	L	M

\*L: Low, M: Medium, H: High. Colour coding is for visual overview: 'Yes' or 'H', green; 'No' or 'L', red; 'M', blue.

\*\*CR, case report.

**TABLE C.2** Studies reporting effects in food producing and non-food producing animals.

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
<b>Horses</b>						
Mares Two treatment groups (6 mares each), plus one untreated group (control, 4 mares). Duration: 1 or 5 + 7 days.	In first group, horses received a single oral dose of 120 mg KBr/ kg BW (corresponding to 80 mg Br <sup>-</sup> /kg bw) by stomach tube.  In second group, horses received a loading dose of 120 mg KBr/kg bw per day (corresponding to 80 mg Br <sup>-</sup> /kg bw per day and also to 3520 mg Br <sup>-</sup> / kg diet) by stomach tube for 5 days, followed by 40 mg KBr/kg bw per day (corresponding to 26.8 mg Br <sup>-</sup> /kg bw per day and also to 1180 mg Br <sup>-</sup> / kg diet) for 7 days.	Single dose of KBr was well tolerated by all mares, with no evidence of adverse effects, including loss of appetite or neurological deficits.  In the second group, each horse remained well throughout the duration of the study and no horse had a reduced appetite. Two horses demonstrated mild ataxia and proprioceptive deficits in all four limbs on days 3 and 4 from the start of dosing. These signs had abated by day 7, two days after commencing the lower 'maintenance' dose of KBr.	No pathology was investigated.	LOAEL: 3520 mg Br <sup>-</sup> /kg diet or 80 mg Br <sup>-</sup> /kg bw per day, due to motor incoordination signs developed	Study to determine the pharmacokinetics of bromide in horses.  Single oral dose by stomach tube and a loading dose by stomach tube for 5 days, followed by a maintenance dose in feed for 7 days.  Short duration of study.	Raidal and Edwards (2008)
3-year-old Thoroughbred filly. Duration: several months (reported).	The filly had been administered oral KBr for behavioural modification over several months.	Weight loss, polydipsia and polyuria, intermittent diarrhoea and behavioural changes and intermittently uncoordinated gait.  Neurological examination revealed clinical signs more obvious in the forelimbs than in the hindlimbs.  Serum bromide concentration (15 mmol Br/L, corresponding to 1.17 mg Br/mL) confirmed bromide intoxication.  Clinical signs of bromide intoxication resolved within 20 days following the last bromide administration.	No pathology was investigated.		Case report of bromide toxicosis in horses.  The dose and duration of KBr administration were not reported.  Data reported in one horse.	Sacks et al. (2022)

(Continues)

TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
<b>Cattle</b> 13 Holstein-Friesian steers and 1 heifer (bw 136.1–233.6 kg). Five treatments, with 2, 3, 4, 3(1), and 2 cattle, respectively. Duration: 49 days, followed by a recovery period from day 50 to day 91.	Diet supplemented with NaBr at 170, 511, 1062, 2633 and 4650 mg Br <sup>-</sup> / kg diet (corresponding to 2.3–3.3, 6.3–8.2, 15.6– 19.6, 32.7, and 50.5–73.6 mg Br <sup>-</sup> /kg bw per day, for the five treatments, respectively).	1 cattle from group 170 mg Br <sup>-</sup> / kg diet (day 49), 1 cattle from group 2633 mg Br <sup>-</sup> / kg diet (day 63), and 2 cattle from group 4650 mg Br <sup>-</sup> / kg diet (days 49 and 91) were euthanized and tissues (kidney, liver, muscle) were collected. Groups fed the 4650 mg Br <sup>-</sup> / kg diet developed signs of motor incoordination after 10 to 12 days of supplementation. The sign of incoordination correlated with serum bromide concentrations of 2400 mg/L or more. Serum bromide concentrations and associated neurologic signs subsided markedly 14 days after feeding of the bromide-containing feeds was discontinued.	Tissue (kidney, liver, muscle) and serum bromide concentration increased with increasing the bromide feed supplementation dose.	LOAEL: 4650 mg Br <sup>-</sup> /kg diet or 50.5 mg Br <sup>-</sup> / kg bw per day, due to motor incoordination signs developed.	Study to determine effects of sodium bromide on production and health of cattle for fattening. No control group was used, a small number of cattle used (1–4 per treatment), and no statistical analysis was performed. Results for treatment 2633 mg Br <sup>-</sup> /kg diet were based on 1 cattle, as two animals were culled.	Knight and Reina-Guerra (1977)
22 Belgian White and Blue double- muscled cattle (bw: 241.5 ± 6.2 kg; age: 7 months) Two dietary treatments (11 cattle/ treatment, group penned). Duration: 221 days (until 60 days before the slaughtering day).	Diet was supplemented with KBr at 0 (control) or 736 mg KBr/kg diet DM (corresponding to 495 mg Br <sup>-</sup> /kg diet DM, 435 mg Br <sup>-</sup> /kg diet and 9.5 mg Br <sup>-</sup> /kg bw per day).	The treatment with KBr induced a significant reduction in the rear engagements during the whole trial period (221 days), in direct attacks (from day 1 to 53) and in side-on attacks (from day 54 to 167). The daily weight gains were not significantly different between the two groups, and feed utilisation was numerically lower in treated bulls.	No pathology was investigated.		Study to determine the efficacy of potassium bromide, as a sedative medical agent, in cattle for fattening. Cattle were group penned, and statistical analysis was not performed for feed efficiency. Behavioural data and body weight gain were only reported.	Genicot et al. (1991)

TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
9 dairy cows in early lactation. Three treatments (3 cows/treatment, group penned). 7 days preliminary period. Duration: 35 days, followed by a recovery period from day 36 to 56.	Diet supplemented with NaBr at 0, 46.5 and 93.1 mg Br <sup>-</sup> /kg diet DM, and, considering the basal dietary bromide content, corresponding to 22 (control), 69, and 115 mg Br <sup>-</sup> /kg diet DM (corresponding to 19.4 (control), 60.7, and 101.2 mg Br <sup>-</sup> /kg diet and also to 0.68, 2.14 and 3.56 mg Br <sup>-</sup> /kg bw per day).	At the end of the dosing period, two cows of each group were slaughtered, and samples of blood and urine, and of muscles, liver and kidney were taken to determine bromide their content. Daily milk production and tissue bromide concentration increased with increasing dietary bromide.	The milk and tissue bromide concentrations increased linearly with increasing dietary bromide.		Study to determine effects of dietary sodium bromide on bromide deposition to milk and tissues of dairy cattle. Low number of cows used per treatment, lack of reporting initial bw and milk production of cows, as well as the method of animal distribution to treatments.	Vreman et al. (1985)
<b>Sheep</b> Eight Merino sheep (49.5–67.0 kg bw). Duration: 14 days.	Sheep were administered with a single dose of KBr at 178.8 mg KBr/kg bw (corresponding to 120 mg Br <sup>-</sup> /kg bw), via an orogastric tube.	Blood samples were collected to determine Br <sup>-</sup> serum concentration. No adverse reactions (neurological signs, rumen motility, feed and water intake) reported to sheep. The oral bioavailability (F) of bromide was 92%.	No pathology was investigated.		Study to determine the pharmacokinetics of bromide in sheep. A single oral dose was used and no control group.	Quast et al. (2015)
<b>Pigs</b> Large White pigs (initial bw 20 kg, 10 weeks of age). Four treatments in total (two relevant treatments), two replicate pens/treatment, and 4 pigs/pen. Duration: until pigs reached the BW of 90 kg.	Bromide salt mixture, consisting of equal parts of ammonium, potassium and sodium bromides, supplemented to diet at 0 or 200 mg/kg diet (corresponding to 151 mg Br <sup>-</sup> /kg diet, and also to 6.5 mg Br <sup>-</sup> /kg bw per day). CuSO <sub>4</sub> was added at 0 or 1000 mg/kg diet (corresponding to 250 mg Cu/kg diet).	The bromide salts had no effect on rate of growth and feed to gain ratio.	No pathology was investigated.		Study to determine the effect of a bromide salt mixture, consisting of equal parts of ammonium, potassium and sodium, in pig performance. Insufficient number of replicate pens. Performance data were only reported	Barber et al. (1971)

(Continues)



TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
<b>Chicken</b>						
Four experiments 1–3 day-old New Hampshire strain cockerels. One (Exp. 1) to two (Exp. 2, 3, and 4) replicate pens/treatment (15 cockerels/pen). Duration: 31 days.	In Exp. 1, diet was supplemented with NaBr at 0 (control), 8, and 15 mg Br <sup>-</sup> /kg diet, or with 10.0 g Trace Element Sea Salt (TESS)/kg diet that provided 15 mg Br <sup>-</sup> / kg diet. In Exp. 2 and 3, diet was supplemented with NaBr at 0 (control), and 15 mg Br <sup>-</sup> /kg diet, and in Exp. 4, diet was supplemented with NaBr at 0 (control), and 8 mg Br <sup>-</sup> /kg diet.	In Exp. 1, 2, and 3, significant growth increases were reported for the bromide added treatments compared to the control, but in Exp. 4 no significant growth response was registered.	No pathology was investigated.		Study to determine the effect of dietary bromide on the chick growth. In all 4 experiments, only one or two replicates were used per treatment, and feed intake and feed to gain ratio of cockerels were not reported.	Bosshardt et al. (1956)
Three experiments New Hampshire × Delaware broiler chicken. Two to four replicate pens/ treatment (5 males and 5 females/pen). Duration: 4 weeks (days 1–28 of age).	In Exp. 1, diet was supplemented with NaBr at 0 (control), 2500, 5000, 10,000, and 20,000 mg Br <sup>-</sup> /kg diet (corresponding to 0, 333, 682, 1382, and n.d. mg Br <sup>-</sup> /kg bw per day). In Exp. 2, diet was supplemented with NaBr at 0 (control), and 10,000 mg Br <sup>-</sup> /kg diet (corresponding to 0 and 1307 mg Br <sup>-</sup> /kg bw per day), without or with 2000 mg F <sup>-</sup> /kg diet. In Exp. 3, diet was supplemented with NaBr at 0 (control), 5000, and 10,000 mg Br <sup>-</sup> /kg diet (corresponding to 0, 680, and 1364 mg Br <sup>-</sup> /kg bw per day), without or with 1000 and 2000 mg F <sup>-</sup> / kg diet or fat (at 100 g/ kg diet).	In Exp. 1, performance and mortalities were not affected among treatments up to the dietary level of 5000 mg Br <sup>-</sup> /kg diet, but the feeding of 10,000 mg Br <sup>-</sup> /kg diet resulted in a significant decrease in growth rate and the 20,000 mg Br <sup>-</sup> /kg diet produced a definite sedative effect and resulted in 100% mortality by 2 weeks of age. In Exp. 2, performance and mortalities were adversely affected in the bromide groups, compared to the control. In Exp. 3, performance was adversely affected for both bromide groups, compared to the control.	No pathology was investigated.	LOAEL: 5000 mg Br <sup>-</sup> /kg diet or 680 mg Br <sup>-</sup> / kg bw per day, due to increased mortalities and decreased performance indices.	Study to determine the effect of dietary bromide, fluoride and fat levels on the chick growth. Short duration of the study, and insufficient number of replicate pens used per treatment.	Doberenz et al. (1965)

TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
Two assays relevant (out of totally four) Male New Hampshire × Columbian broiler chicken (90 g bw, 8 days of age). Four treatments in both assays (4 replicate pens/treatment and 4 birds/pen). Duration: 13 days (days 8–21 of age).	In two of the assays, diet was supplemented with NaBr at 0, 50 (as. 1) or 100 (as. 1 and 2) mg Br <sup>-</sup> /kg diet (for as. 1 corresponding to 0, 5.1 and 10.1 mg Br <sup>-</sup> /kg bw per day, and for as. 2 corresponding to 0, and 10.1 mg Br <sup>-</sup> /kg Bw per day), and with KI at 1000 (as. 1) or 1500 (as. 2) mg I <sup>-</sup> /kg diet.	Supplemental I levels of 1000–1500 mg/kg caused severe growth depressions that could be totally reversed by dietary addition of 50 or 100 mg Br <sup>-</sup> /kg diet. Performance was not affected among control and bromide treatments.	No pathology was investigated.		Study to determine iodine (I) toxicity in young chicken and its amelioration by supplemental bromide. Short duration of the study, and the high dietary iodine supplementation in both assays served as a confounding factor.	Baker et al. (2003)
Mixed Ross broiler chicken. Six treatments in 3 × 2 factorial design, with bromine and iodine delivered via drinking water (three levels of bromide as NaBr and two levels of iodine as KI, and three replicate pens/treatment with 30 birds/pen). Duration: 42 days.	Six treatments: T1: 0 mg Br <sup>-</sup> /L and 0 mg I <sup>-</sup> /L; T2: 1 mg Br <sup>-</sup> /L and 0 mg I <sup>-</sup> /L; T3: 3 mg Br <sup>-</sup> /L and 0 mg I <sup>-</sup> /L; T4: 0 mg Br <sup>-</sup> /L and 0.7 mg I <sup>-</sup> /L; T5: 1 mg Br <sup>-</sup> /L and 0.7 mg I <sup>-</sup> /L; and T6: 3 mg Br <sup>-</sup> /L and 0.7 mg I <sup>-</sup> /L (corresponding to 0.017, 0.178, 0.502, 0.178, 0.178 and 0.527 mg Br <sup>-</sup> /kg bw per day, respectively).	Bromine administered at 1 and 3 mg Br/L decreased water and feed intake significantly. The interaction of Br and I had no significant effect on intake of water or feed. Iodine had an effective ameliorating effect on Br. Performance and mortalities were not affected among treatments.	Detrimental effects were reported on the liver, kidneys and thyroid and the thyroid hormones T <sub>3</sub> and T <sub>4</sub> . Br had an overall effect on the thyroid gland, liver and kidney, and had accumulated in these three organs. Histopathological assessment showed explicit damage to the livers that received the bromide treatments (i.e. hepatocellular hypertrophy, vacuolar degeneration).		Study to determine possible detrimental effects of bromide in drinking water on the performance and blood and tissue parameters of broiler chicken. Insufficient number of replicate pens used per treatment, insufficient number of chicken examined for histopathology per treatment, and poor reporting.	du Toit and Casey (2010, 2012)

(Continues)

TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
			The kidney and thyroid gland appeared similar without any specific pathological changes among treatments. Iodine (I) may alleviate the potential hazardous effect of Br.			
Sixty Hisex White cross laying hens (365 days of age, body weight: 1.4 kg). Four dietary treatments (15 hens/treatment). Duration: 28 days, followed by a 14 days period of birds' recovery period.	Diet was supplemented with NaBr at 0 (control) or 10, 50 and 250 mg Br <sup>-</sup> /kg diet (corresponding to 0, 0.6, 3.0 and 15.0 mg Br <sup>-</sup> /kg bw per day).	Egg production and quality was determined, and the bromine content was determined separately in egg white, yolk, and shell. Clinical manifestations of poisoning in hens were not observed. No significant deviation from the control group was observed in productivity, egg mass, white to yolk mass ratios and pH values of yolk and white. Bromine content in eggs increased with increasing dietary bromide.	No pathology was investigated.		Study to determine the quality and safety of eggs obtained from laying hens after their experimental poisoning with sodium bromide. Insufficient number of replicate pens used per treatment, and feed intake and feed to gain egg mass ratio were not reported.	Kutsan et al. (2020)
Fertilised Ross-308 eggs. Duration: 20 days.	Br <sup>-</sup> treatments injected into fertilised Ross-308 eggs in three phases: (1) five eggs injected with 0.002 mg Br <sup>-</sup> /egg; (2) 45 eggs divided into groups and injected with 0, 0.0002 and 0.001 mg Br <sup>-</sup> /egg; (3) 148 eggs divided into groups injected with 0, 0.000002, 0.00001, 0.0001, and 0.0002 mg Br <sup>-</sup> /egg.	Incubation was at standard conditions. The mass of the embryo and of the heart, liver and brain was measured at day 20.	The results showed: (1) 0.002 mg Br <sup>-</sup> /egg is toxic; (2) Br <sup>-</sup> is lethal to embryos at concentrations > 0.0002 mg Br <sup>-</sup> /egg and toxic at 0.0002 mg Br <sup>-</sup> /egg; and (3) embryo survival was inversely correlated with increasing Br <sup>-</sup> concentrations.		Study to determine chicken embryo sensitivity to a range of bromide treatments into fertilised eggs. In ovo bromide treatments were used.	Lucht et al. (2018)

TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
<b>Dogs</b>						
Adult mongrel dogs of both sexes. Six treatments (4–8 dogs/ treatment). Duration: 4 to 26 weeks, depending on the dose.	Dogs received NaBr, in capsules wrapped in dog food balls, at doses of 100, 200, 300, 400, 500 and 600 mg NaBr/kg bw per day (corresponding to 78, 156, 234, 312, 390 and 468 mg Br <sup>-</sup> /kg bw per day and also to 4038, 8076, 12,114, 16,152, 20,190, and 24,228 mg Br <sup>-</sup> /kg diet).	Bromide intoxication included signs of neurotoxicity, gastrointestinal toxicity, and toxicity to the skin. Dogs given NaBr (78 mg Br <sup>-</sup> /kg bw per day) experimentally for 6 weeks had minimal adverse effects (i.e. emaciation and weight loss of approx. 15%). Dogs given the drug at 156 to 390 mg Br <sup>-</sup> /kg bw per day for 4 to 26 weeks developed neurological and gastrointestinal signs, skin lesions, weight loss, coma, and in some cases, death. During the bromide intoxication, dogs exhibited decreased volume of the extracellular space and haemoconcentration and/or anaemia and leucocytosis.	No pathology was investigated.	LOAEL: 4038 mg Br <sup>-</sup> /kg diet or 78 mg Br <sup>-</sup> /kg bw per day, based on moderate emaciation and weight loss of dogs.	Study to produce experimental bromide intoxication in dogs.	Rosenblum (1958) and Rosenblum and Hawkins (1958)
Beagle dogs (6–12 weeks of age, initial bw 5.4–6.1 kg, final bw 10.7–12.6 kg). Six Beagle dogs (3 males and 3 females) as the controls and four Beagle dogs (3 males and 1 female) as the treated group. Duration: 12 months.	Dogs received NaBr, in capsules wrapped in meat balls, at doses of 0 and 128 mg NaBr/kg bw per day (corresponding to 0 and 100 mg Br <sup>-</sup> /kg bw per day, and also to 0 and 5176 mg Br <sup>-</sup> /kg diet).	Body weight and feed intake was similar between the two groups. Occasional salivation and diarrhoea were noted in the treated group. No significant effects were noted in the dogs on haemoglobin, haematocrit, white and red cell counts, serum proteins or blood urea nitrogen. One dog died during the course of the experiment in treated group, but pneumonia was diagnosed as the cause of death.	Histological examination of the various organs (brain, lung, heart, liver, kidneys, spleen, testes, adrenals and thyroids) gave predominantly normal results, and there were no changes that could be attributed to bromide intoxication.	LOAEL: 5176 mg Br <sup>-</sup> /kg diet or 100 mg Br <sup>-</sup> / kg bw per day, based on salivation and diarrhoea noted in the treated group.	Study to determine the chronic effects of inorganic bromide in dogs.	Rosenblum et al. (1960)

(Continues)

TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
Four dogs (11–14 kg bw) with surgically produced prostatic fistulas. Duration: 30 days.	Dogs were given single oral doses of 1130 mg NaBr/day (corresponding to 881 mg Br <sup>-</sup> /day and to 70.5 mg Br <sup>-</sup> /kg bw per day and also to 3650 mg Br <sup>-</sup> /kg diet), for five consecutive days.	Prostatic fluid and blood samples were collected. The bromide secreted in prostatic fluid, given that it may impair sperm motility in vitro, potentially could adversely affect reproduction.	No pathology was investigated.		Study to determine the bromide secretion by the canine prostate. A single oral dose was used. No control group was used.	Smith and Ilievski (1985)
Six healthy adult Beagle dogs (3 males and 3 females, mean bw 11.3 kg). Duration: 115 days.	Dogs received KBr, with canned food, at 60 mg KBr/kg bw per day (corresponding to 40 mg Br <sup>-</sup> /kg bw per day and also to 2070 mg Br <sup>-</sup> /kg diet), for a period of 115 days.	High dose KBr administration was well tolerated and resulted in minimal adverse side effects. Dogs showed minimal to no neurologic signs during all phases of the study. At the highest serum bromide concentrations of approximately 400 mg/dL, two dogs exhibited mild to moderate caudal paresis and ataxia.	No pathology was investigated.	LOAEL: 2070 mg Br <sup>-</sup> /kg diet or 40 mg Br <sup>-</sup> /kg bw per day, based on mild to moderate caudal paresis and ataxia presented in two of the treated dogs.	Study to determine the pharmacokinetics of potassium bromide in dogs. Lack of an untreated control group.	March et al. (2002)
10 adult, sexually intact, hound dogs (approx. 1 to 2 years of age). Two treatment groups (5 dogs/treatment), treated dogs (2 male and 3 female), and control (2 male and 3 female). Duration: 182 days.	Treated dogs received, with food, a loading dose of KBr at 200 mg KBr/kg bw per day (corresponding to 134 mg Br <sup>-</sup> /kg bw per day) for 2 days, and followed by a maintenance dose of KBr at 30 mg KBr/kg bw (corresponding to 20 mg Br <sup>-</sup> /kg bw per day and also to 1035 mg Br <sup>-</sup> /kg diet) for 180 days. The five control dogs received an equivalent loading dose of distilled water for 2 days followed by an equivalent maintenance dose volume for 180 days.	No difference was detected in any parameter (basal tT4, fT4, basal TSH, and TRH serum concentrations) between the two groups at the end of the study. A decline in thyroid hormone concentrations over the course of the study did occur in both groups of dogs.	Thyroid histopathology was determined. KBr did not appear to have a significant effect on canine thyroid function or morphology.	NOAEL: 1035 mg Br <sup>-</sup> /kg diet or 20 mg Br <sup>-</sup> /kg bw/day.	A placebo-controlled experiment was performed to evaluate the effect of potassium bromide on the canine thyroid gland.	Paull et al. (2003)



TABLE C.2 (Continued)

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
A male Cavalier King Charles Spaniel dog (6.7 kg bw, 5-years old). Duration: 3 weeks (reported).	Dog received an inadvertent use of KBr (239 mg Br/capsule) (corresponding to 35.7 mg Br <sup>-</sup> /kg bw per day and also to 1848 mg Br <sup>-</sup> /kg diet), reportedly for 3 weeks, instead of potassium citrate to acidify the urine due to an earlier history of urolithiasis.	Dog had a progressive paresis, a marked hyperchloraemia and a decreased anion gap on blood electrolyte analysis, accompanied with elevated serum bromide concentration (400 mg/dL).	No pathology was investigated.		Case report of bromide toxicosis in dogs. Data reported in one dog. Short duration of the study.	Piperisova et al. (2009)
A castrated male Shetland sheepdog (9-years old). Duration: 5 days (reported).	A 5-fold compounding error in the concentration of KBr occurred. The dog was receiving, for idiopathic epilepsy for 6 years, a KBr solution at 27 mg KBr/kg bw per day (corresponding to 18.1 mg Br <sup>-</sup> /kg bw per day and also to 935 mg Br <sup>-</sup> /kg diet) and 8 mg phenobarbital/kg bw per day, the time of the compounding error.	Five days after the prescription renewal, the dog presented progressive depression, inability to walk, mild abdominal discomfort and bradycardia. Bromine toxicity was attributed to compounding error during the refilling of the KBr prescription at the pharmacy, as the KBr concentration in the solution was found to be 225 mg/mL (corresponding to 90.5 mg Br <sup>-</sup> /kg bw per day and also to 4675 mg Br <sup>-</sup> /kg diet), instead of the 200 mg/5 mL that had been prescribed.	No pathology was investigated.		Case report of bromide toxicosis in dogs. Data reported in one dog. Short duration of the study.	McConkey et al. (2012)
<b>Cats</b>						
Seven healthy male adult cats (mean bw 6 kg, 1.5–2 years old). Duration: 56 days, followed by a recovery period from day 57 to 77.	Cats received KBr, into capsules, at 30 mg KBr/kg bw per day (corresponding to 20 mg Br <sup>-</sup> /kg bw per day and also to approximately 880 mg Br <sup>-</sup> /kg diet), until bromide steady-state concentrations were reached.	Health status of cats, by clinical examination and body weight, serum biochemical parameters and a routine urinalysis, was determined. Mean C <sub>max</sub> of 1.1 ± 0.2 mg Br <sup>-</sup> /mL occurred at 8 weeks for all cats. Steady-state concentrations, C <sub>max</sub> , occurred at a mean of 5.3 ± 1.1 weeks. All cats tolerated KBr administration well with no evidence of adverse effects, including loss of appetite.	No pathology was investigated.		Study to determine the pharmacokinetics of potassium bromide in cats. Lack of an untreated control group, and short duration of the study.	Boothe et al. (2002)

**TABLE C.3** Studies in food producing animals fed with seaweeds.

Study design Breed, age, gender, exposure period, animal weight	Doses or feed concentrations	Clinical signs/biochemical changes	Pathological findings	NOAEL/LOAEL and endpoint	Remarks	Reference
<b>Cattle</b>						
20 Holstein cows (2.6 lactations, 95 days in milk, 42.2 kg of milk yield/day) (Exp. 3). Four dietary treatments, 4 × 4 Latin square design with four 28-day periods (21 days for adaptation and 7 days for data and samples collection). Duration: 112 days (28 days each period).	Diets were supplemented with 0 (control), 2.5 g (LowAT), and 5.0 g (HighAT) <i>Asparagopsis taxiformis</i> (AT) or 17.7 g oregano ( <i>Origanum vulgare</i> L.) leaves/kg diet DM.	Compared with the control, HighAT decreased DM intake, milk yield and energy corrected milk yield. Milk composition was not affected by treatment, except lactose percentage and yield were decreased by HighAT. Concentrations of bromide and iodine in milk were increased by HighAT compared with the control (8 and 5 times higher, respectively).	No pathology was investigated.		Study to determine effects of the microalga <i>Asparagopsis taxiformis</i> (AT) and oregano leaves on CH <sub>4</sub> emission, rumen fermentation, and lactational performance of dairy cows. The bromide content of the microalga <i>A. taxiformis</i> or of the diets was not reported.	Stefenoni et al. (2021)
Six Nordic Red cows (611 kg bw, 122 days in milk). Two dietary treatments, extra-period Latin-square change-over design, with three 21-day periods (14 days for adaptation and 7 days for data and samples collection). Duration: 63 days (21 days each period).	Diets were supplemented with 0 (control) or 5.0 g <i>Asparagopsis taxiformis</i> (AT)/kg diet organic matter.	Feed intake was decreased and milk production altered, reflecting a decreased yield of milk fat in cows fed an AT-supplemented diet, but feed efficiency increased. Increase in milk bromine (more than an 8-fold increase) and iodine (more than a 15-fold increase) concentration, when the diet was supplemented with AT.	No pathology was investigated.		Study to determine the effects of dietary supplementation of microalga <i>Asparagopsis taxiformis</i> (AT) on milk production and quality, methane (CH <sub>4</sub> ) production and rumen microbiome of dairy cows. The bromide content of the microalga <i>A. taxiformis</i> or of the diets was not reported.	Krizsan et al. (2023)
<b>Chicken</b>						
Sixty 22-day-old male Ross 308 broilers (initial bw 758 g). Two treatments (10 replicate pens/treatment, 3 chicken/pen). Duration: 14 days (days 22–35 of age).	Diets were supplemented with 0 (control) or 150 g <i>Ulva lactuca</i> (UL)/kg diet. The bromine content of UL was 694 mg Br <sup>-</sup> /kg DM, and of control and UL diet 4.1 and 211 mg Br <sup>-</sup> /kg diet DM, respectively (corresponding to 3.6 and 185.7 mg Br <sup>-</sup> /kg diet and also to 0.4 and 18.3 mg Br <sup>-</sup> /kg bw per day).	Feed intake, final bw, daily body weight gain and feed to gain ratio were unaffected with the UL diet compared with the control. Total minerals and bromine content in meat increased.	Relative liver weight (20.30 vs. 17.73 g/kg bw) decreased with UL dietary supplementation.		Study to determine the effects of dietary supplementation of the seaweed <i>Ulva lactuca</i> to broiler chicken' performance and meat quality.	Costa et al. (2022)

## C.1 | Studies in non-food producing animals using bromide salts as antiepileptic treatment

There are 10 review articles on canine and feline epilepsy including its treatment by bromide identified by the literature search (Baird-Heinz et al., 2012; Baka & Polizopoulou, 2019; Bergman & Coates, 2005; Bhatti et al., 2015; Boothe, 1998; Chandler, 2006; Goiz-Márquez et al., 2008; Muñana, 2013; Platt, 2003; Thomas, 2000). There are no relevant differences between these publications concerning the effect, tolerability and side effects of potassium/sodium/ammonium bromide in dogs and cats. The brief summary below is based on these publications without attribution to specific articles.

Epilepsy is the most common chronic neurological disorder in dogs, and the prevalence is estimated to be from 0.5% to 5.7%. The anticonvulsive properties of bromide have been known since the mid-1800s, although its use in veterinary medicine has experienced a resurgence after a report in 1986 of the concurrent use of bromide and phenobarbital to control refractory epilepsy in dogs. Bromide was originally described as an add-on treatment for epileptic dogs that were poorly controlled with phenobarbital. More recently, bromide has gained use as a sole antiepileptic therapy in dogs, either as a first-line drug or in dogs with intolerable side effects from phenobarbital.

The mechanism of antiepileptic activity is unclear, although it is often stated that it is due to hyperpolarisation of neurons caused by bromide entry through chloride channels. Recent evidence shows that it increases GABAergic inhibition.

The initial therapy with KBr is a daily oral dose of 20–40 and 10–20 mg/kg bw per day as maintenance dosage for dogs and cats, respectively. The amounts should be corrected for an equivalent bromide level when other salts are used instead (Bergman & Coates, 2005; Boothe, 1998). If seizure control is needed more rapidly, a loading dosage (400–600 mg/kg bw divided into 5 doses over 24–48 h) could be administered. The elimination half-life ranges from 25 to 46 days in dogs (and 1 day in cats). Accordingly, it can take 3–4 months to reach steady-state concentrations. The target serum concentration for monotherapy is 2–3 mg/mL. Trepanier et al., in their study with the participation of 122 dogs with epilepsy, reported that the therapeutic range for serum bromide concentrations is 0.88 to 3.00 mg/mL for KBr treatment alone (Trepanier et al., 1998).

Clinical experience indicates that bromide is effective as monotherapy, and some veterinary neurologists consider it to be the initial drug of choice for any dog with idiopathic epilepsy. The addition of bromide improves seizure control of dogs with idiopathic epilepsy refractory to phenobarbital. It is also applied together with phenobarbital.

Some published studies have reported possible adverse effects observed in dogs (Baird-Heinz et al., 2012) and cats (Baka & Polizopoulou, 2019) treated with bromide as an antiepileptic drug. It is worth mentioning that there are also studies not showing any adverse drug events in bromide-treated dogs and cats (Baird-Heinz et al., 2012).

Baird-Heinz et al. published a comprehensive review on the safety of KBr in dogs (Baird-Heinz et al., 2012). Neurologic signs were the most consistently reported adverse drug events, such as sedation, irritability, restlessness, depression, ataxia, hind limb paresis, mydriasis, stupor and coma (Baird-Heinz et al., 2012; Bhatti et al., 2015). Most adverse reactions to bromide tend to be dose-dependent and appeared to be reversible (Baird-Heinz et al., 2012; Boothe, 1998). Bromide toxicosis in dogs was most frequently associated with high serum bromide concentrations; although very sensitive dogs may also develop signs of toxicosis (Baird-Heinz et al., 2012). The adverse reactions may be magnified when KBr is administered in combination with phenobarbital. Baird-Heinz (Baird-Heinz et al., 2012) reviewed other publications with descriptive information on adverse drug reactions in other farm animals (rabbits, cattle, goats, horses), and concluded that the information reported was limited to clearly attribute such effects to bromide administration.

Vomiting, transient diarrhoea, and bloody faeces have been also reported in dogs but do not appear to require cessation of KBr treatment for resolution. Other typical side effects observed occasionally in dogs treated with KBr have been polyphagia with weight increase (up to 10%), salivation, polydipsia, polyuria or anorexia and weight loss (Baird-Heinz et al., 2012; Bhatti et al., 2015). Uncommon idiosyncratic reactions of KBr in dogs include personality changes (aggressive behaviour, irritability, hyperactivity), but there is insufficient information to assess the effects of KBr on behavioural changes (Baird-Heinz et al., 2012). Most adverse reactions occur in the initial weeks of treatment and subside (partly or completely), once KBr steady-state concentrations are reached (Baird-Heinz et al., 2012; Bhatti et al., 2015).

In some cases, bromide toxicity has been reported secondary to renal insufficiency, and, therefore, it has been suggested that the initial dose of bromide should be reduced when renal function is impaired (Nichols et al., 1996). Nichols et al. attributed a bromide toxicosis of a 8-year old Labrador Retriever dog, treated for epilepsy at standard doses with 29 mg KBr/kg bw per day (corresponding to 19.5 mg Br<sup>-</sup>/kg bw per day) and 3.8 mg phenobarbital/kg bw per day, to renal insufficiency, which reduced the bromide elimination by the kidneys. The dog developed hind limb weakness, ataxia and stupor, following a high serum bromide concentration (3120 mg/L), while a therapeutic range is between 1000 and 2000 mg/L. After only 24–48 h of intravenous saline diuresis, serum bromide concentration decreased to 1980 and 1480 mg/L, respectively, while the hind limb weakness and disorientation resolved rapidly.

Dermatologic reactions (non-suppurative, macular and scaly dermatitis) are rare and not of concern with clinical KBr use in dogs, while respiratory disease is unlikely (Baird-Heinz et al., 2012).

Some studies have suggested increased risk of pancreatitis in KBr treated dogs, although it could be also related to polyphagia and garbage ingestion (Baird-Heinz et al., 2012). Therapeutic administration of KBr in dogs was not found to affect thyroid weight or serum tT4, fT4, T3 and TSH concentrations or to cause histologic changes in the thyroid (Baird-Heinz et al., 2012).

A further publication (Charalambous et al., 2016) reported the results of a systematic review and meta-analysis of adverse effects by antiepileptic drugs in dogs. Ninety studies, including six conference proceedings, reporting clinical outcomes of adverse effects of various antiepileptic drugs were identified. Direct comparisons suggested a better safety for imepitoin,

levetiracetam, and phenobarbital, compared to potassium bromide. However, none of these comparisons showed a statistically significant difference. Individual drug assessments placed the potassium bromide also behind the three drugs mentioned above, supported with a strong level of evidence. Adverse effects usually appeared mild for all antiepileptic drugs and disappeared when doses/serum levels were monitored or after the drug was withdrawn.

Twenty-one studies presented data about the safety of KBr either as monotherapy (8 studies) or adjunctive therapy to phenobarbital and/or other drugs (16 studies), giving a combined sample size of 1940 dogs. Fifteen studies reported adverse effects, including neurological signs; from these, 7/15 (47%) and 10/15 (67%) studies reported adverse effects for potassium bromide monotherapy and adjunctive therapy, respectively. Specifically, in all the studies, the adverse effects most commonly reported were ataxia followed by sedation, polyuria, polydipsia, polyphagia, paraparesis, hyperactivity, vomiting, increased serum ALP and ALT activity.

In cats, bromide use as an anticonvulsant has been associated with life-threatening idiosyncratic allergic pneumonitis (Boothe et al., 2002), or the development of moderate to severe bronchoalveolitis/pulmonary fibrosis (Baka & Polizopoulou, 2019). In their retrospective study, Boothe et al. (2002) associated the reported coughing in 6 out of 17 cats to allergic reactions, rather than concentration (dose) or duration of bromide administration dependent relationship, also noting that allergic responses to bromide have been reported in the human literature. Bromide-associated lower airway disease with mild-to-moderate cough and/or dyspnoea was observed in some cats after starting bromide (NaBr) therapy (Bertolani et al., 2012; Klang et al., 2012). The onset of respiratory signs started between 1 month and 8 years of initiating bromide therapy. The airway disorders seem to be the result of a hypersensitivity or allergic reaction without any dose (serum bromide concentration range for coughing cats was 1.0 to 3.2 mg/mL) or time dependence (duration of treatment). Significant clinical improvements were evident after ceasing bromide therapy (Bertolani et al., 2012). Other adverse effects reported in cats included polydipsia, polyuria, vomiting or weight gain or grogginess (Baird-Heinz et al., 2012; Boothe et al., 2002). Due to the idiosyncratic response to bromide in cats, the Scientific Committee could not establish a reference value for this species.

## APPENDIX D

### Thyroid effects in humans and animals

#### Thyroid-mediated downstream adverse outcomes

##### Neurodevelopment

It is recognised that thyroid function is essential for brain development, maturation, and function, they play a major role during neurogenesis, cell migration, proliferation, myelination and glial and neuronal differentiation (Brent, 2012), although the levels of thyroid hormones and the specific impact during critical windows of development are still debated (Foster et al., 2021).

##### *Role of thyroid hormones during pregnancy in animals*

The fetus is fully dependent on maternal thyroid hormone until the fetal thyroid gland is developed, which occurs between gestational days 17–20 in rats (Perez-Castillo & Ferreiro, 1985).

Indeed, maternal hypothyroidism affects neurodevelopment in Wistar rats (Mafikandi et al., 2019) and development of the auditory tissues is shown to be a critical target of thyroid hormone activity associated with TR $\beta$  receptor (Mustieles et al., 2022). Regarding auditory system cochlea is a major target of thyroid hormones, specifically by promoting terminal differentiation of a variety of cells in mice (Ng et al., 2009). Experimental evidence indicates that changes in T4 in the range of 50% reduction are sufficient to permanently impair the auditory system (Crofton, 2004; Gilbert & Sui, 2008). This was confirmed in a later publication where regulatory developmental neurotoxicity endpoints were affected by a decrease of tT4 in a similar range of magnitude (Marty et al., 2021). Additional evidence from experiments conducted in rats treated with perchlorate under conditions of iodine deficiency indicate that a drop in tT4 of around 28% can induce changes in hippocampal neurotransmission (Gilbert & Sui, 2008). The experimental observations of impaired thyroid function in the suckling pups of dams exposed to high bromide levels (with more pronounced decreases of tT4 and T3 in serum, compared to reduced thyroid hormone levels of the dams), suggests potential hypothyroidism, with implications for associated neurodevelopmental deficits.

Furthermore, several studies in rodents, used in support of the KER444 (AOP 54), have demonstrated that thyroid hormone can regulate the expression of the brain derived neurotrophic factor (BDNF), which may play a critical role in CNS development and brain function through regulation of synaptic transmission, dendritic structure and synaptic plasticity in adulthood. Lower thyroid hormone levels during fetal and/or neonatal periods resulted in a trend of reduced BDNF expression (mRNA and proteins) in the developing brain (mostly affecting the hippocampus and cortex, the key brain areas for learning and memory function). However, there is inconsistent evidence in the literature and the impact of thyroid hormone disturbance on BDNF expression and its role in thyroid-mediated effects on brain development is debated (Gilbert & Lasley, 2013). In AOP 54, reduced BDNF (KE) results in abnormal GABAergic neurons and synaptogenesis (KEs) leading to impairment of learning and memory. Alteration of GABAergic function is associated with bromide exposure (see below), although it is not known if this relationship is mediated via BDNF. Goodman and Gilbert (Goodman & Gilbert, 2007) induced maternal thyroid hormone insufficiency in rats by exposing pregnant dams to the goitrogenic propylthiouracil (PTU) at doses of 0, 1, 2, 3 and 10 ppm in the drinking water from gestational day 6 through weaning on postnatal day 30. Administration of PTU reduces thyroid hormone production by inhibiting thyroperoxidase (TPO). Brain sections of the offspring at day 23 were examined and showed a bilateral cellular malformation, a heterotopia, positioned within the white matter of the corpus callosum of both hemispheres. This heterotopia consisted of neurons emerging between gestational days 17–19 and showed a dose-dependent increase in size with decreases in thyroid hormone concentrations. The malformation was formed at modest maternal thyroid hormone insufficiency (45% reduction in T4 and no change in T3) and persisted in adult offspring. It was reduced in size with prenatal thyroid hormone replacement. Cortical heterotopias are associated with neurodevelopmental disorders such as learning disorders and epilepsy (O'Shaughnessy & Gilbert, 2020). Furthermore, treating a pregnant rat for 5 days with propylthiouracil during the perinatal period (GD19–PN2) induced heterotopia in all offspring (O'Shaughnessy & Gilbert, 2020). Sharlin et al. gradually decreased serum tT4 concentrations in rats using PTU and increased serum TSH, type 2 deiodinase mRNA expression and enzyme activity in the brain, and the expression of the mRNA encoding the tri-iodothyronine (T3) transporter MCT8 in the postnatal day (P) 15 cortex (Sharlin et al., 2010). A target of T3 action, the mRNA encoding RC3/neurogranin showed a strong negative linear correlation with serum total T4 despite the adaptive responses. The researchers conclude that these findings do not support the hypothesis that the developing rat brain is able to compensate for low T4 (Sharlin et al., 2010). The absence of thyroid compensatory abilities that are not yet developed in early life makes fetal/neonatal population particularly sensitive (Sharlin et al., 2010).

## APPENDIX E

### Benchmark Dose (BMD) modelling

#### INTRODUCTION

##### Selection of the BMR

The EFSA guidance on BMD (2022) recommends that the BMR should reflect the onset of a human-relevant adverse effect, meaning that a response above the BMR is considered adverse. In rats, a 10%–17% decrease in T4 during pregnancy and lactation, is associated with neurodevelopmental toxicity in rat offspring (Gilbert, 2011; Gilbert et al., 2016). In humans, a 25% decrease in T4 during pregnancy (during second trimester) results in neurodevelopmental and cognitive deficits in children (Haddow et al., 1999).

Therefore, the Scientific Committee selected a BMR of 20% for blood tT4 level decrease.

##### Software used

Results are obtained using the EFSA web-tool for Bayesian BMD analysis, which uses the R-package [BMABMDR] version 0.0.0.9077 for the underlying calculations.

##### Specification of deviations from default assumptions

All analyses using a covariate were performed by Laplace approximation.

Extended dose range assumption was not applied in order to avoid confidence intervals falling outside of the dose range tested.

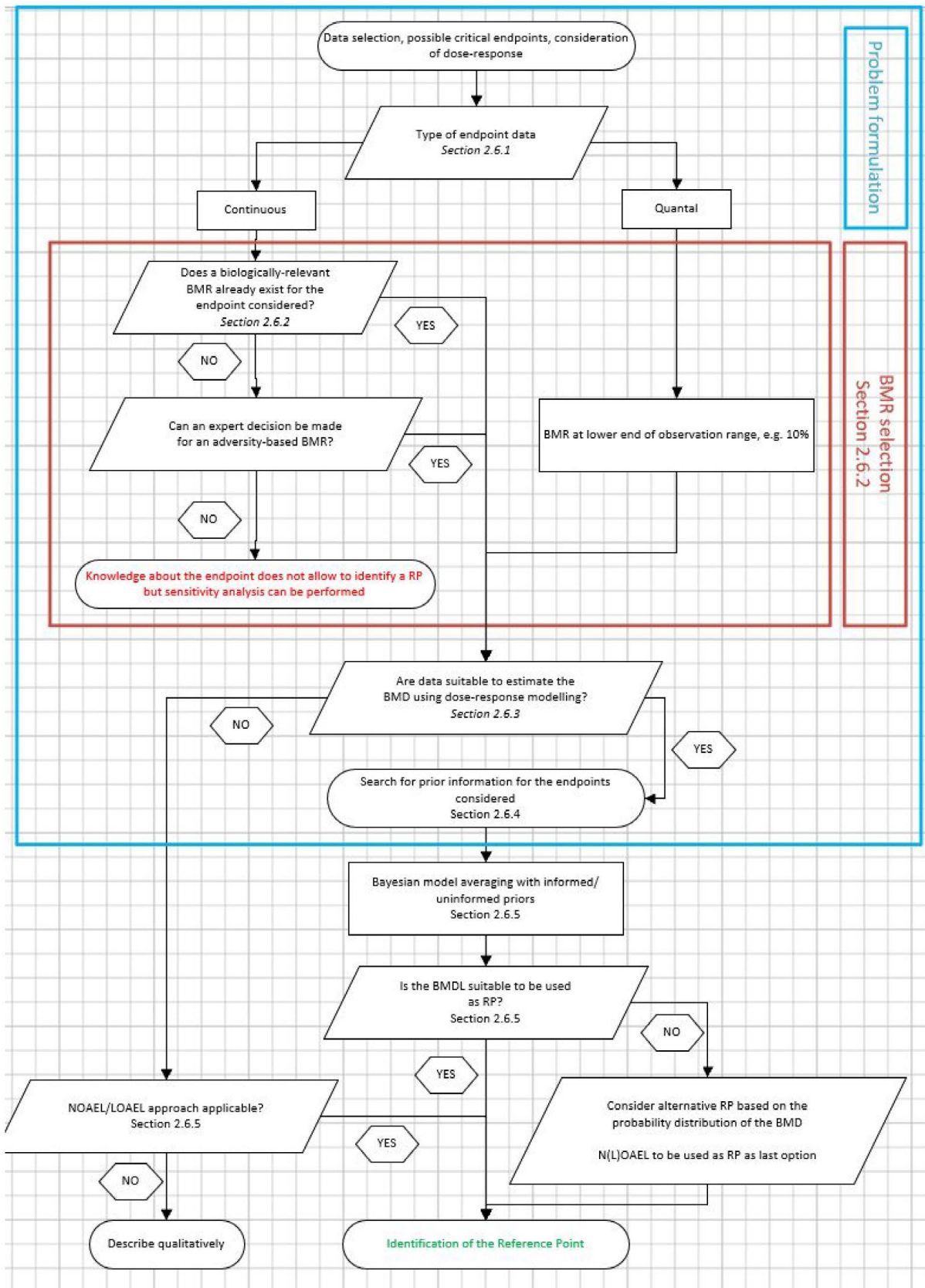
##### Default set of fitted models

Family	Model	$y x \sim N(\mu(x), \sigma^2)$	$y x \sim \text{LOGN}(\mu(x), \sigma^2)$
		Dose-response function ( $\mu(x)$ )	Dose-response function ( $e^{\mu(x)}$ )
1a	Exponential <sup>(i)</sup>	$a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x^d}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x^d}\right)\right)}$
	Inverse Exponential	$a \cdot \left(1 + (c-1) \cdot e^{-b \cdot x^d}\right)$	$e^{a \cdot \left(1 + (c-1) \cdot e^{-b \cdot x^d}\right)}$
	Hill <sup>(ii)</sup>	$a \cdot \left(1 + (c-1) \cdot \left(1 - \frac{b}{b + x^d}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - \frac{b}{b + x^d}\right)\right)}$
	Log-Normal	$a \cdot \left(1 + (c-1) \cdot \Phi(\log(b) + d \cdot \log(x))\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \Phi(\log(b) + d \cdot \log(x))\right)}$
1b	Gamma <sup>(iii)</sup>	$a \cdot \left(1 + (c-1) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}\right)}$
	LMS-two stage	$a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)\right)}$
2	Probit increasing	$a \cdot \Phi(c + b \cdot x^d)$	$e^{a \cdot \Phi(c + b \cdot x^d)}$
	Probit decreasing	$a \cdot (1 + \Phi(c)) - a \cdot \Phi(c + b \cdot x^d)$	$e^{a \cdot (1 + \Phi(c)) - a \cdot \Phi(c + b \cdot x^d)}$
	Logistic increasing	$a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}$	$e^{a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}}$
	Logistic decreasing	$a \cdot \left(1 + \frac{e^c}{1 + e^c}\right) - a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}$	$e^{a \cdot \left(1 + \frac{e^c}{1 + e^c}\right) - a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}}$



**Procedure for selection of BMDL**

Flowchart to derive a Reference Point (RP) from a dose–response data set of a specified endpoint, using BMD analysis



## SELECTED STUDIES

### Loeber et al. (1983) – tT4 serum level in male Wistar rats exposed to NaBr for 4 or 12 weeks

#### Data description

The endpoint to be analysed is: tT4 serum level after 4 weeks or 12 weeks of treatment (time as covariate).

#### Data used for analysis

Dose (mg Br <sup>-</sup> /kg bw per day)	tT4 (nmol/L)	SD	n	Time
0.000	103	12	10	12 weeks
1.398	116	23	10	12 weeks
5.242	111	9	10	12 weeks
20.967	125	18	10	12 weeks
83.868	114	20	10	12 weeks
1341.894	42	9	5	12 weeks
0.000	141	21	10	4 weeks
1.864	133	24	10	4 weeks
6.989	143	18	10	4 weeks
27.956	125	14	10	4 weeks
111.825	109	22	10	4 weeks
1789.192	54	9	5	4 weeks

## RESULTS

### Estimated BMDs per model

Model	Weight	Submodel	Submodel weight	Covariate	BMDL	BMD	BMDU
E4_N	0.002	All	0.997	4 weeks	61.098	98.445	157.901
E4_N	0.002	All	0.997	12 weeks	22.638	507.656	11156.108
IE4_N	0.000	All	0.973	4 weeks	98.355	112.468	128.561
IE4_N	0.000	All	0.973	12 weeks	7.600	161.655	3481.941
H4_N	0.001	All	0.994	4 weeks	54.021	96.348	171.285
H4_N	0.001	All	0.994	12 weeks	107.034	508.891	2420.768
LN4_N	0.000	a_sigma2	1.000	4 weeks	103.862	112.596	122.311
LN4_N	0.000	a_sigma2	1.000	12 weeks	103.862	112.596	122.311
G4_N	0.001	All	0.990	4 weeks	63.654	99.037	153.890
G4_N	0.001	All	0.990	12 weeks	76.405	345.245	1550.263
QE4_N	0.000	None	1.000	4 weeks	103.851	189.829	348.111
QE4_N	0.000	None	1.000	12 weeks	103.851	189.829	348.111
P4_N	0.003	All	0.998	4 weeks	65.693	100.620	154.001
P4_N	0.003	All	0.998	12 weeks	7.815	656.543	56253.189
L4_N	0.002	All	0.997	4 weeks	65.877	100.537	153.984
L4_N	0.002	All	0.997	12 weeks	12.803	593.067	27275.438
E4_LN	0.349	All	0.997	4 weeks	55.288	93.122	156.432
E4_LN	0.349	All	0.997	12 weeks	19.276	402.170	8760.210
IE4_LN	0.040	All	0.952	4 weeks	99.265	110.773	123.589
IE4_LN	0.040	All	0.952	12 weeks	23.615	138.781	793.669
H4_LN	0.121	All	0.991	4 weeks	54.968	93.970	159.756
H4_LN	0.121	All	0.991	12 weeks	70.232	449.243	2858.855
LN4_LN	0.002	a_sigma2	1.000	4 weeks	104.070	111.434	119.187
LN4_LN	0.002	a_sigma2	1.000	12 weeks	104.070	111.434	119.187
G4_LN	0.168	All	0.992	4 weeks	59.724	94.513	150.354

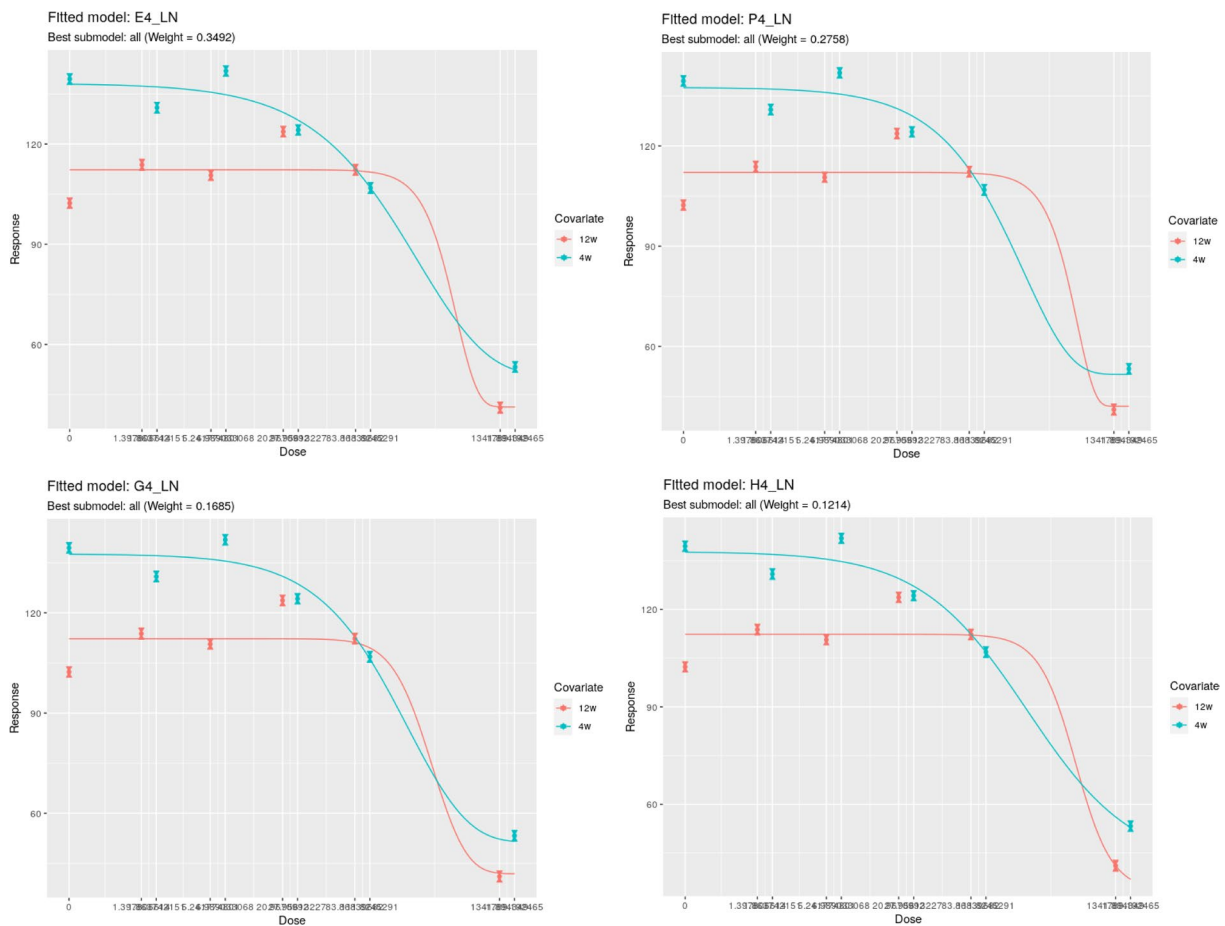
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Model	Weight	Submodel	Submodel. weight	Covariate	BMDL	BMD	BMDU
G4_LN	0.168	All	0.992	12 weeks	80.157	262.058	871.319
QE4_LN	0.007	All	0.959	4 weeks	59.650	91.314	140.938
QE4_LN	0.007	All	0.959	12 weeks	151.630	253.723	421.896
P4_LN	0.276	All	0.996	4 weeks	60.938	95.432	148.965
P4_LN	0.276	All	0.996	12 weeks	29.647	460.874	7359.558
L4_LN	0.027	All	0.994	4 weeks	54.965	92.532	154.485
L4_LN	0.027	All	0.994	12 weeks	33.007	434.962	6015.223

**Model averaged BMD**

Group	BMDL	BMD	BMDU
4 weeks	57.989	95.731	153.305
12 weeks	32.665	349.000	5568.892

**Visualisation**



**van Leeuwen et al. (1983) – tT4 serum level in male and female Wistar rats exposed to NaBr for 6 weeks**

**Data description**

The endpoint to be analysed is: tT4 serum level in males and females after 6 weeks of treatment (sex as covariate).

## Data used for analysis

Dose (mg Br <sup>-</sup> /kg bw/day)	tT4 (nmol/L)	SD	N	Sex
0.00	63.5	7.4	10	f
5.24	56.9	12.0	10	f
20.97	56.9	10.9	10	f
83.87	54.2	17.6	10	f
335.47	42.9	10.9	10	f
1341.89	29.1	5.9	10	f
0.00	95.5	13.0	10	m
5.24	85.2	6.2	10	m
20.97	80.4	10.2	10	m
83.87	72.3	6.3	10	m
335.47	56.9	7.9	10	m
1341.89	34.1	7.2	10	m

## Results

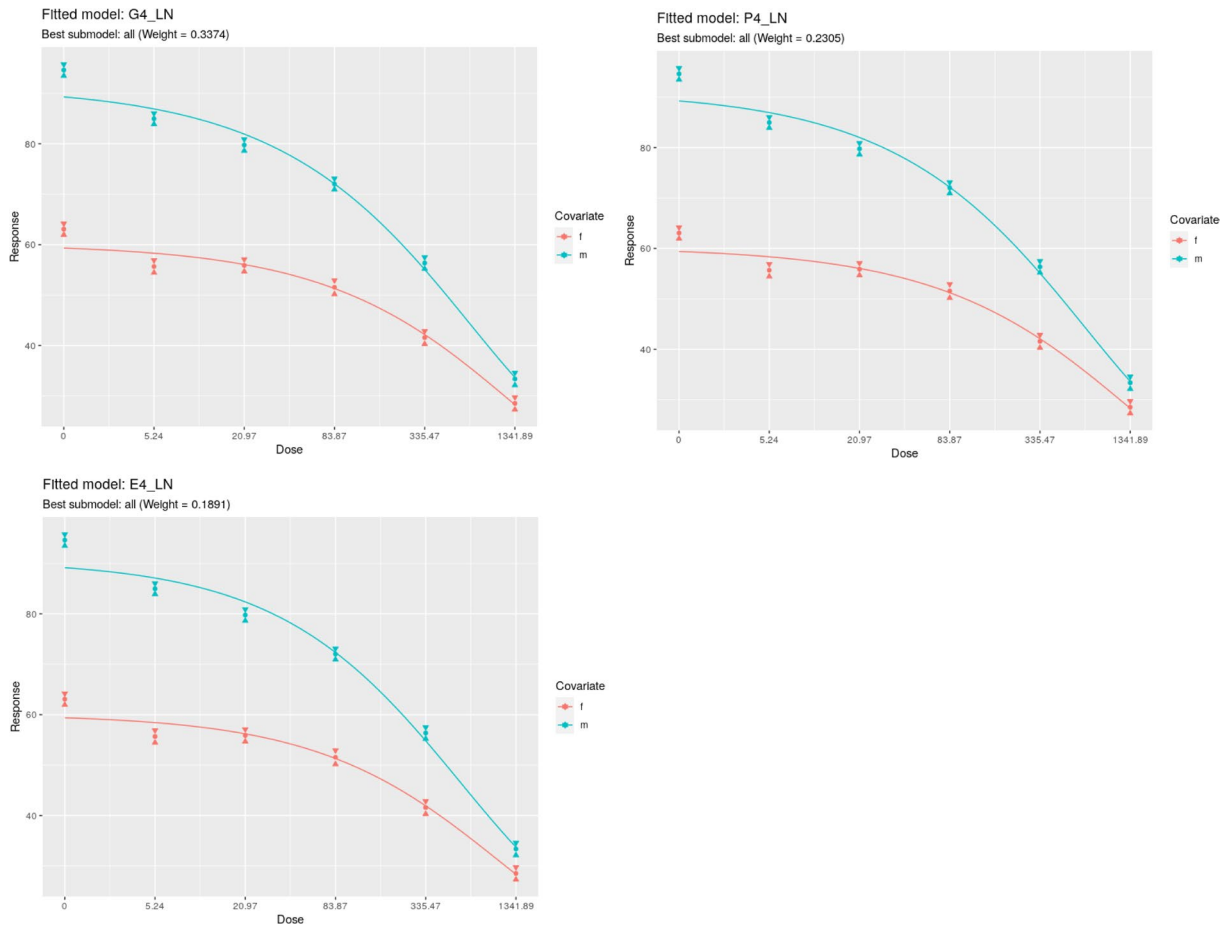
### Estimated BMDs per model

Model	Weight	Submodel	Submodel. weight	Covariate	BMDL	BMD	BMDU
E4_N	0.017	All	0.814	f	70.665	185.447	478.914
E4_N	0.017	All	0.814	m	31.327	57.962	106.924
IE4_N	0.000	All	0.840	f	114.334	220.568	425.922
IE4_N	0.000	All	0.840	m	38.858	75.644	145.793
H4_N	0.006	All	0.820	f	79.800	192.291	455.838
H4_N	0.006	All	0.820	m	34.709	63.989	117.739
LN4_N	0.001	All	0.831	f	98.071	214.901	477.092
LN4_N	0.001	All	0.831	m	33.815	64.030	121.421
G4_N	0.040	All	0.859	f	73.104	194.277	514.361
G4_N	0.040	All	0.859	m	28.605	54.388	103.661
QE4_N	0.000	All	0.863	f	139.511	242.896	422.468
QE4_N	0.000	All	0.863	m	104.977	137.547	180.202
P4_N	0.015	All	0.785	f	68.226	183.422	491.929
P4_N	0.015	All	0.785	m	31.358	57.649	107.045
L4_N	0.012	All	0.781	f	70.210	184.438	486.943
L4_N	0.012	All	0.781	m	32.835	60.059	109.900
E4_LN	0.189	All	0.902	f	53.699	148.929	410.612
E4_LN	0.189	All	0.902	m	44.762	82.791	152.215
IE4_LN	0.001	All	0.856	f	95.145	195.973	401.168
IE4_LN	0.001	All	0.856	m	79.350	127.733	206.973
H4_LN	0.104	All	0.898	f	58.161	153.182	399.425
H4_LN	0.104	All	0.898	m	51.460	92.521	164.823
LN4_LN	0.012	All	0.880	f	76.882	181.034	418.991
LN4_LN	0.012	All	0.880	m	63.420	108.818	185.212
G4_LN	0.337	All	0.918	f	50.638	150.416	445.988
G4_LN	0.337	All	0.918	m	38.231	74.755	145.509
QE4_LN	0.034	All	0.901	f	164.369	265.810	432.437
QE4_LN	0.034	All	0.901	m	108.547	145.208	193.965
P4_LN	0.230	All	0.924	f	49.996	145.902	421.299
P4_LN	0.230	All	0.924	m	40.508	76.739	146.069
L4_LN	0.000	BMD_d	1.000	f	1.350	4.818	17.272
L4_LN	0.000	BMD_d	1.000	m	136.967	233.362	397.428

**Model averaged BMD**

Group	BMDL	BMD	BMDU
F	53.649	156.906	434.320
M	39.189	78.665	154.622

**Visualisation**



**Study Report (2016b) – tT4 serum level in male and female Sprague Dawley rats exposed to NaBr for 4 weeks**

**Data description**

The endpoint to be analysed is: tT4 serum level in males and females after 4 weeks of treatment (sex as covariate).

**Data used for analysis**

Dose (mg Br <sup>-</sup> /kg bw per day)	tT4 (µg/dL)	Sex
0	5.07	m
0	5.06	m
0	5.7	m
0	4.42	m
0	4.86	m
0	5.08	m
0	4.77	m
0	4.32	m
0	6.2	m
0	4.79	m
46.6	4.36	m
46.6	3.81	m

(Continues)

(Continued)

Dose (mg Br <sup>-</sup> /kg bw per day)	tT4 (µg/dL)	Sex
46.6	2.93	m
46.6	4.45	m
46.6	3.34	m
46.6	3.85	m
46.6	6.09	m
46.6	4.91	m
46.6	4.45	m
46.6	5.21	m
135.9	4.09	m
135.9	2.67	m
135.9	4.13	m
135.9	3.38	m
135.9	3.66	m
135.9	3.75	m
135.9	3.72	m
135.9	3.4	m
135.9	2.58	m
135.9	4.91	m
388.3	2.67	m
388.3	2.49	m
388.3	2.89	m
388.3	3	m
388.3	2.21	m
388.3	2.18	m
388.3	2.12	m
388.3	2.06	m
388.3	2.2	m
388.3	2.12	m
0	4.03	f
0	5	f
0	2.69	f
0	2.79	f
0	3.2	f
0	3.62	f
0	2.91	f
0	3.99	f
0	3.25	f
0	5.36	f
46.6	3.26	f
46.6	2.18	f
46.6	2.72	f
46.6	2.97	f
46.6	2.45	f
46.6	3.33	f
46.6	3.12	f
46.6	2.21	f
46.6	2.37	f
135.9	2.04	f
135.9	2.95	f
135.9	1.69	f
135.9	1.78	f



(Continued)

Dose (mg Br <sup>-</sup> /kg bw per day)	tT4 (µg/dL)	Sex
135.9	2.77	f
135.9	2.4	f
135.9	2.95	f
135.9	1.31	f
135.9	2.3	f
135.9	4.19	f
388.3	1.31	f
388.3	3.08	f
388.3	1.74	f
388.3	1.48	f
388.3	1.52	f
388.3	1.33	f
388.3	2.19	f
388.3	3.33	f
388.3	1.5	f
388.3	2.2	f

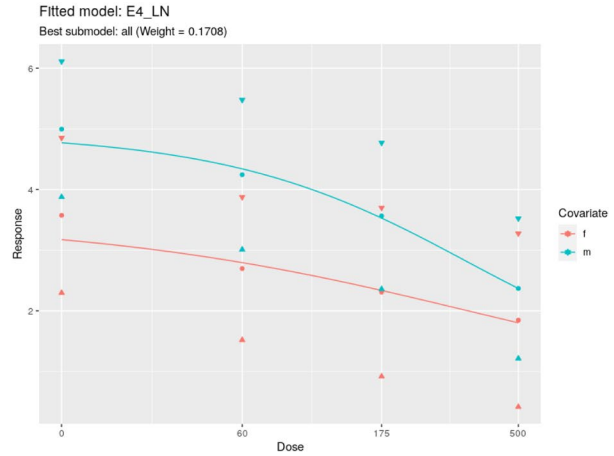
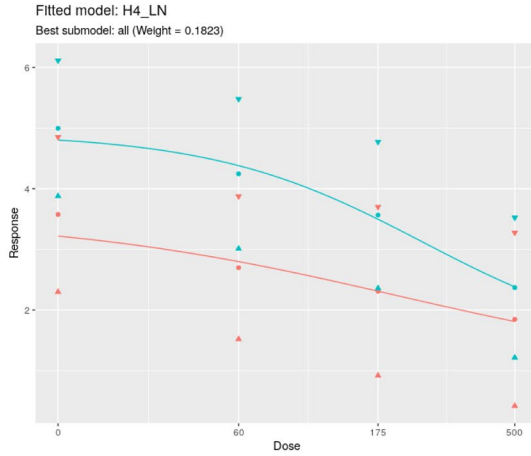
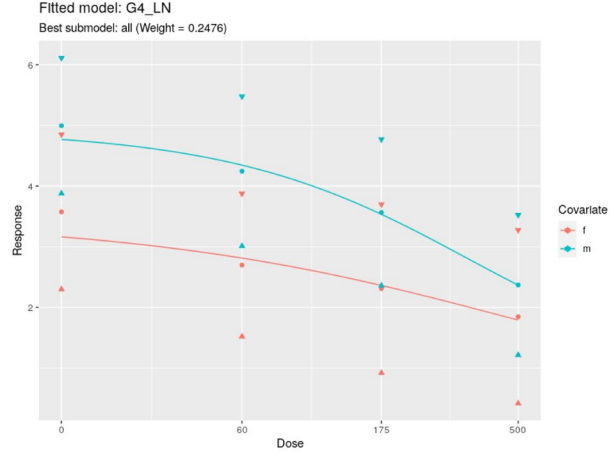
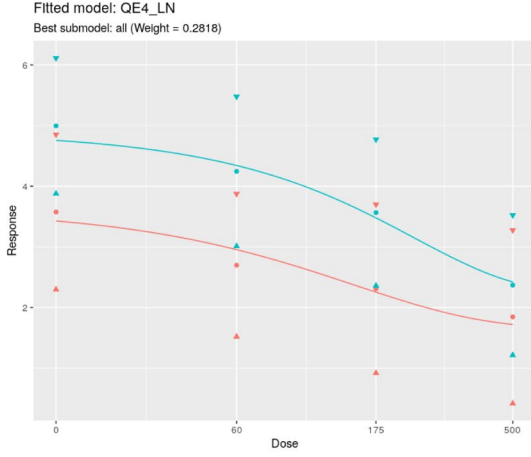
**Estimated BMDs per model**

Model	Weight	Submodel	Submodel weight	Covariate	BMDL	BMD	BMDU
E4_N	0.000	a_sigma2	0.933	f	43.318	71.512	117.835
E4_N	0.000	a_sigma2	0.933	m	43.318	71.512	117.835
IE4_N	0.000	All	0.756	f	15.503	40.734	107.990
IE4_N	0.000	All	0.756	m	51.794	81.949	129.603
H4_N	0.002	All	0.791	f	12.131	40.051	128.759
H4_N	0.002	All	0.791	m	54.502	87.765	140.313
LN4_N	0.001	All	0.758	f	14.206	42.282	128.186
LN4_N	0.001	All	0.758	m	54.865	86.786	138.546
G4_N	0.002	All	0.810	f	15.088	49.921	165.752
G4_N	0.002	All	0.810	m	56.338	90.316	144.134
QE4_N	0.001	All	0.751	f	23.177	52.481	118.546
QE4_N	0.001	All	0.751	m	60.131	89.052	132.192
P4_N	0.000	None	1.000	f	37.655	47.535	60.151
P4_N	0.000	None	1.000	m	37.655	47.535	60.151
L4_N	0.000	a_sigma2	0.912	f	43.936	73.150	120.791
L4_N	0.000	a_sigma2	0.912	m	43.936	73.150	120.791
E4_LN	0.182	All	0.761	f	11.274	43.586	168.860
E4_LN	0.182	All	0.761	m	49.665	85.804	148.549
IE4_LN	0.018	All	0.559	f	18.184	42.383	98.638
IE4_LN	0.018	All	0.559	m	101.055	127.622	160.676
H4_LN	0.190	All	0.767	f	11.809	42.291	150.222
H4_LN	0.190	All	0.767	m	51.771	87.884	148.201
LN4_LN	0.071	All	0.734	f	14.180	45.474	140.384
LN4_LN	0.071	All	0.734	m	53.775	90.534	150.780
G4_LN	0.275	All	0.790	f	12.728	49.854	194.379
G4_LN	0.275	All	0.790	m	50.263	86.846	149.698
QE4_LN	0.258	All	0.747	f	17.202	50.338	148.737
QE4_LN	0.258	All	0.747	m	55.632	86.674	134.828
P4_LN	0.000	BMD_d	1.000	f	19.607	33.968	58.479
P4_LN	0.000	BMD_d	1.000	m	105.977	146.574	202.540
L4_LN	0.000	BMD_d	1.000	f	19.579	33.895	58.501
L4_LN	0.000	BMD_d	1.000	m	102.356	168.140	276.354

Model averaged BMD

Group	BMDL	BMD	BMDU
F	13.318	46.893	164.133
M	51.870	87.753	146.482

Visualisation



## APPENDIX F

## Comparison of bromide occurrence data with the existing MRLs in the EU

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
110010	Grapefruits	30	357 (41)	11	11	95	1.7	5	No	–	3	
110020	Oranges	30	399 (49)	12	1.5	95	0.74	5	No	–	3	
110030	Lemons	30	310 (28)	9	2.4	95	0.9	5	No	–	3	
110040	Limes	30	186 (16)	6	0.71	95	0.45	5	No	–	3	
110050	Mandarins	30	400 (75)	16	3.6	95	0.97	5	No	–	3	
120000	Tree nuts	50	25 (16)	64	33	–	–	–	No	–		
120010	Almonds	50	112 (2)	2	20.7	95	2.5	5	No	–	3	
120020	Brazil nuts	50	93 (90)	97	120	95	100	100	Yes	35 (38%)	3	
120030	Cashew nuts	50	132 (5)	4	16	95	9.6	20	No	–	3	
120040	Chestnuts	50	46 (4)	8	71	90	33.17	33.17	Yes	1 (2%)	3	
120050	Coconuts	50	7 (1)	14	5.2	50	5.2	5.2	No	–	3	
120060	Hazelnuts/cobnuts	50	145 (1)	1	4.4	95	0	5	No	–	3	
120070	Macadamias	50	8 (4)	50	11.3	50	7.6	7.6	No	–	3	
120080	Pecans	50	22 (1)	5	26.1	50	0	5	No	–	3	
120090	Pine nut kernels	50	0	No data	No data	–	–	–	No data	–	3	
120100	Pistachios	50	40 (7)	18	180	90	180	180	Yes	2 (4%)	3	
120110	Walnuts	50	125 (13)	10	69	95	40.2	42	Yes	1 (<1%)	3	
120990	Others (2)	50	3 (0)	0	2		–		No	–		
130010	Apples	20	1105 (3)	<1	0.9	95	0	5	No	–	3	
130020	Pears	20	597 (1)	<1	0.7	95	0	5	No	–	3	
130030	Quinces	20	35 (0)	0	–	90	0	5	No	–	3	
130040	Medlars	20	13 (0)	0	–	50	0	5	No	–	3	
130050	Loquats/Japanese medlars	20	0	No data	No data		–		No data	–	3	
140010	Apricots	20	294 (5)	2	24.1	95	4.8	5	Yes	1 (<1%)	3	
140020	Cherries (sweet)	20	354 (0)	0	–	95	0	5	No	–	3	
140030	Peaches	20	581 (4)	<1	0.3	95	0	5	No	–	3	
140040	Plums	20	633 (9)	1	0.6	95	0	5	No	–	3	

(Continues)

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
150000	Berries and small fruits		2 (0)	0	–	–	–	–	No	–		
151000	(a) grapes	20	12 (0)	0	–	–	–	–	No	–		
151010	Table grapes	20	984 (24)	2	3	95	0	5	No	–	4	
151020	Wine grapes	20	177 (4)	2	1.4	95	0.11	5	No	–	4	
152000	(b) strawberries	30	1069 (79)	7	2.7	95	0.35	5	No	–	3	
153010	Blackberries	20	128 (3)	2	3	95	0.24	5	No	–	4	
153020	Dewberries	20	0	No data	No data	–	–	–	No data	–	4	
153030	Raspberries (red and yellow)	20	462 (13)	< 1	6.9	95	0	5	No	–	4	
154010	Blueberries	5	412 (28)	7	2.1	95	0.38	5	No	–	4	
154020	Cranberries	5	10 (0)	0	–	50	0	5	No	–	4	
154030	Currants (black, red and white)	5	298 (10)	3	0.8	95	0.12	5	No	–	4	
154040	Gooseberries	5	59 (4)	7	5.7	95	5.7	5.7	Yes	1 (2%)	4	
154050	Rose hips	5	3 (0)	0	–	0	–	–	No	–	4	
154060	Mulberries (black and white)	5	0	No data	No data	–	–	–	No data	–	4	
154070	Azaroles/ Mediterranean medlars	5	0	No data	No data	–	–	–	No data	–	4	
154080	Elderberries	5	6 (6)	100	3.1	50	3.1	3.1	No	–	4	
161010	Dates	20	9 (1)	11	2.3	50	0	5	No	–	4	
161020	Figs	20	122 (26)	21	35.3	95	21.8	21.8	Yes	4 (3%)	4	
161030	Table olives	20	0	No data	No data	–	–	–	No data	–	4	
161040	Kumquats	20	33 (6)	18	3.2	90	3.2	5	No	–	4	
161050	Carambolas	20	21 (0)	0	–	50	0	5	No	–	4	
161060	Kaki/Japanese persimmons	20	249 (18)	7	3.8	95	0.54	5	No	–	4	
161070	Jambuls/jambolans	20	0	No data	No data	–	–	–	No data	–	4	
162010	Kiwi fruits (green, red, yellow)	50	277 (42)	15	3.6	95	1.1	5	No	–	4	
162020	Litchis/lychees	50	19 (0)	0	–	50	0	5	No	–	4	

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
162030	Passionfruits/maracujas	20	82 (8)	10	17.7	95	17.7	17.7	No	–	4	
162040	Prickly pears/cactus fruits	20	28 (6)	21	9.1	50	0	5	No	–	4	
162050	Star apples/cainitos	20	1 (0)	0	0	–	–	–	No	–	4	
162060	American persimmons/Virginia kaki	20	0	No data	No data	–	–	–	No data	–	4	
163010	Avocados	50	180 (0)	0	–	95	0	5	No	–	4	
163020	Bananas	50	472 (84)	18	3.3	95	1.3	5	No	–	4	
163030	Mangoes	50	355 (0)	0	–	95	0	10	No	–	4	
163040	Papayas	50	91 (24)	26	10.7	95	10.7	10.7	No	–	4	
163050	Granate apples/pomegranates	50	336 (70)	21	11.4	95	3.7	10	No	–	4	
163060	Cherimoyas	50	20 (8)	40	0.2	50	0.17	0.77	No	–	4	
163070	Guavas	20	3 (3)	100	9.3	0	–	–	No	–	4	
163080	Pineapples	50	292 (101)	35	5	95	1.3	5	No	–	4	
163090	Breadfruits	20	0	No data	No data	–	–	–	No data	–	4	
163100	Durians	20	0	No data	No data	–	–	–	No data	–	4	
163110	Soursops/guanabanas	20	0	No data	No data	–	–	–	No data	–	4	
211000	Potatoes	50	743 (158)	21	7	95	2	5	No	–	3	
212010	Cassava roots/manioc	50	7 (2)	29	1	50	1	5	No	–	4	
212020	Sweet potatoes	50	100 (40)	40	5.8	95	5.3	5.3	No	–	4	
212030	Yams	50	0	No data	No data	–	–	–	No data	–	4	
212040	Arrowroots	50	0	No data	No data	–	–	–	No data	–	4	
212990	Others	50	2 (2)	100	0.6	0	–	–	No	–		
213010	Beetroots	50	95 (13)	14	3.5	95	1.8	5	No	–	4	
213020	Carrots	50	503 (132)	26	7.2	95	2.8	6.3	No	–	4	
213030	Celeriacs/turnip rooted celeries	50	156 (36)	23	9.4	95	9.4	10	No	–	4	
213040	Horseradishes	50	111 (22)	20	16	95	10.8	10.8	No	–	4	

(Continues)

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
213050	Jerusalem artichokes	50	2 (0)	0	–	0	–	–	No	–	4	
213060	Parsnips	50	73 (6)	8	8.2	95	8.2	10	No	–	4	
213070	Parsley roots/ Hamburg roots parsley	50	29 (0)	0	–	50	0	10	No	–	4	
213080	Radishes	50	304 (71)	23	10.8	95	6.1	6.9	No	–	4	
213090	Salsifis	50	13 (3)	23	7.6	50	0	5	No	–	4	
213100	Swedes/rutabagas	50	11 (1)	9	3.6	50	0	5	No	–	4	
213110	Turnips	50	21 (6)	29	0.3	50	0	0.06	No	–	4	
220010	Garlic	30	110 (8)	7	4.4	95	2.6	5	No	–	3	
220020	Onions	30	330 (79)	24	4.1	95	2.4	5	No	–	3	
220030	Shallots	30	8 (3)	38	2.5	50	2.5	10	No	–	3	
220040	Spring onions/green onions and Welsh onions	30	110 (11)	10	7	95	4.4	10	No	–	3	
230000	Fruiting vegetables		7 (1)	14.3	3.1	–	–	–	No	–	4	
231010	Tomatoes	50	3525 (1006)	29	154	95	2.9	20	Yes	1 (<1%)	4	
231020	Sweet peppers/bell peppers	30	2733 (373)	14	47	95	1.5	20	Yes	1 (<1%)	4	
231030	Aubergines/eggplants	30	410 (109)	27	24.3	95	8.7	10	No	–	4	
231040	Okra/lady's fingers	30	28 (4)	14	7.1	50	0	5	No	–	4	
232010	Cucumbers	50	672 (111)	16	13.9	95	3	5	No	–	4	
232020	Gherkins	30	3 (2)	67	0.46				No	–	4	
232030	Courgettes	30	503 (64)	13	15.9	95	3.8	5	No	–	4	
233010	Melons	30	261 (55)	21	15.1	95	6.2	6.9	No	–	4	
233020	Pumpkins	30	188 (19)	10	8	95	1.6	10	No	–	4	
233030	Watermelons	30	77 (11)	14	2.6	95	2.6	20	No	–	4	
234000	Sweet corn	30	59 (5)	8	1.7	95	1.7	5	No	–	3	
239000	Other fruiting vegetables	30	0	No data	No data	–	–	–	No data	–		
241010	Broccoli	30	328 (38)	12	7.7	95	2.5	5	No	–	4	
241020	Cauliflowers	30	208 (28)	14	3.3	95	1	5	No	–	4	
242010	Brussels sprouts	30	247 (46)	19	4.6	95	2.4	5	No	–	4	



(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
242020	Head cabbages	30	483 (68)	14	4.9	95	2.7	10	No	–	4	
243010	Chinese cabbages/pe-tsai	30	143 (2)	1	10.7	95	0	10	No	–	4	
243020	Kales	30	192 (78)	41	25.8	95	17.3	17.3	No	–	4	
244000	Kohlrabies	30	275 (53)	20	29.8	95	6.8	7.7	No	–	3	
251010	Lamb's lettuces/corn salads	50	608 (143)	24	74	95	17.8	20	Yes	3 (<1%)	4	
251020	Lettuces	50	4459 (793)	18	49.4	95	3.2	20	No	–	4	
251030	Escaroles/broad-leaved endives	50	332 (55)	17	59	95	14	14	Yes	1 (<1%)	4	
251040	Cresses and other sprouts and shoots	50	9 (0)	0	–	50	0	5	No	–	4	
251050	Land cresses	50	20 (7)	35	0.51	50	0.09	0.51	No	–	4	
251060	Roman rocket/rucola	50	723 (472)	56	177	95	33	33	Yes	6 (1%)	4	
251070	Red mustards	50	0						No data	–	4	
251080	Baby leaf crops (including brassica species)	50	29 (6)	21	37.9	90	37.9	37.9	No	–	4	
252000	Spinaches and similar leaves	50	770 (165)	21	82	95	15.1	15.1	Yes	2 (<1%)	3	
252010	Spinaches	50	707 (145)	21	54.3	95	14.8	14.8	Yes	1 (<1%)	4	
252020	Purslanes	50	2 (0)	0	–	0	–	–	No	–	4	
252030	Chards/beet leaves	50	59 (18)	31	32	95	32	32	No	–	4	
253000	Grape leaves and similar species	50	5 (2)	40	17.8	50	17.8	17.8	No	–	3	
254000	Watercress	50	1 (0)	0	–	0	–	–	No	–		
255000	Witloofs/Belgian endives	50	60 (8)	13	6.2	95	6.2	10	No	–	3	
256000	Herbs and edible flowers	50	718 (174)	24	53	95	21.8	21.8	Yes	2 (<1%)	3	
256010	Chervil	50	4 (0)	0		0			No	–	4	
256020	Chives	50	109 (8)	7	8.2	95	1.7	5	No	–	4	
256030	Celery leaves	50	178 (58)	33	53.4	95	42.6	42.6	Yes	1 (<1%)	4	

(Continues)

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
256040	Parsley	50	200 (20)	10	18	95	12.7	12.7	No	–	4	
256050	Sage	50	6 (2)	33	11.9	50	11.9	11.9	No	–	4	
256060	Rosemary	50	20 (12)	60	9.3	50	5.3	5.3	No	–	4	
256070	Thyme	50	28 (12)	43	11	50	0.29	5	No	–	4	
256080	Basil and edible flowers	50	143 (47)	33	52.1	95	43.8	43.8	Yes	1 (< 1%)	4	
256090	Laurel/bay leaves	50	0	No data	No data	–	–	–	No data	–	4	
256100	Tarragon	50	30 (15)	50	46	50	46	46	No	–	4	
260010	Beans (with pods)	30	516 (37)	7	5.4	95	1.1	5	No	–	3	
260020	Beans (without pods)	30	8 (8)	100	3.1	50	2.6	2.6	No	–	3	
260030	Peas (with pods)	30	135 (5)	4	13.6	95	6.5	6.5	No	–	3	
260040	Peas (without pods)	30	69 (14)	20	7.3	95	7.3	7.3	No	–	3	
260050	Lentils	30	2 (1)	50	8.5	0	–	–	No	–	3	
270010	Asparagus	30	440 (82)	19	6.4	95	2.7	10	No	–	3	
270020	Cardoons	30	0	No data	No data	–	–	–	No data	–	3	
270030	Celeries	30	658 (228)	35	31	95	14.3	14.3	Yes	1 (< 1%)	3	
270040	Florence fennels	30	72 (8)	12	8.8	95	8.8	10	No	–	3	
270050	Globe artichokes	30	18 (4)	22	13.8	50	0	5	No	–	3	
270060	Leeks	30	370 (143)	39	6	95	3.6	10	No	–	3	
270070	Rhubarbs	30	72 (8)	11	2.7	95	2.7	5	No	–	3	
270080	Bamboo shoots	30	0	No data	No data	–	–	–	No data	–	3	
270090	Palm hearts	30	0	No data	No data	–	–	–	No data	–	3	
280010	Cultivated fungi	30	400 (7)	2	1.1	95	0	5	No	–	3	
280020	Wild fungi	30	1234 (7)	5	34.4	95	17.6	17.6	Yes	1 (< 1%)	3	
280990	Mosses and lichens	30	0	No data	No data	–	–	–	No data	–	3	
290000	Algae and prokaryotes organisms	5	3 (3)	100	83	0	–	–	Yes	2 (67%)	3	
300010	Beans	50	322 (53)	16	24.5	95	1.8	20	No	–	2	
300020	Lentils	50	360 (95)	26	23.2	95	8.8	50	No	–	2	
300030	Peas	50	61 (45)	77	47.7	95	47.7	47.7	No	–	2	
300040	Lupins/lupini beans	50	0	No data	No data	–	–	–	No data	–	2	
401010	Linseeds	20	53 (12)	23	2.8	90	2.8	5	No	–	3	

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
401020	Peanuts/groundnuts	50	172 (21)	12	27	95	13	20	No	–	3	
401030	Poppy seeds	20	16 (1)	6	27.9	50	0	5	Yes	1 (6%)	3	
401040	Sesame seeds	20	102 (41)	40	64	95	31.8	31.8	Yes	3 (3%)	3	
401050	Sunflower seeds	20	77 (44)	57	6.5	90	6.5	6.5	No	–	3	
401060	Rapeseeds/canola seeds	20	67 (14)	21	2.4	90	2.4	5	No	–	3	
401070	Soya beans	20	100 (20)	20	5.7	95	5.7	5.7	No	–	3	
401080	Mustard seeds	20	19 (0)	0		50	0	1	No	–	3	
401090	Cotton seeds	20	0	No data	No data	–	–	–	No data	–	3	
401100	Pumpkin seeds	20	16 (3)	19	6.6	50	0	5	No	–	3	
401110	Safflower seeds	20	0	No data	No data	–	–	–	No data	–	3	
401120	Borage seeds	20	0	No data	No data	–	–	–	No data	–	3	
401130	Gold of pleasure seeds	20	0	No data	No data	–	–	–	No data	–	3	
401140	Hemp seeds	20	2 (0)	0		0	–	–	No	–	3	
401150	Castor beans	20	0	No data	No data	–	–	–	No data	–	3	
402010	Olives for oil production	20	0	No data	No data	–	–	–	No data	–	3	
402020	Oil palms kernels	20	6 (6)	100	3	50	3	3	No	–	3	
402030	Oil palms fruits	20	0	No data	No data	–	–	–	No data	–	3	
402040	Kapok	20	0	No data	No data	–	–	–	No data	–	3	
500000	Cereals	50	8 (1)	13	2.3	0	–	–	No	–		
500010	Barley	50	179 (44)	25	19	95	13	15	No	–	2	
500020	Buckwheat and other pseudocereals	50	266 (31)	12	9.1	95	1.4	15	No	–	2	
500030	Maize/corn	50	50 (3)	6	6.6	90	4.9	5	No	–	2	
500040	Common millet/proso millet	50	73 (26)	36	6.2	95	6.2	15	No	–	2	
500050	Oat	50	428 (33)	8	10	95	1.4	20	No	–	2	
500060	Rice	50	2459 (351)	14	378	95	20	20	Yes	23 (< 1%)	2	
500070	Rye	50	610 (161)	26	7.3	95	2.3	15	No	–	2	
500080	Sorghum	50	0	No data	No data	–	–	–	No data	–	2	

(Continues)

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
500090	Wheat	50	897 (223)	25	8.1	95	2.3	15	No	–	2	
500990	Cereals Others	50	3 (1)	33	1.1	0	–	–	No	–		
610000	Teas	70	91 (41)	45	6	95	6	6	No	–	3	
620000	Coffee beans	70	70 (30)	43	55	95	55	55	No	–	3	
631010	Herbal infusions from Chamomile flowers	250	69 (46)	67	49.7	95	49.7	49.7	No	–	4	
631020	Herbal infusions from Hibiscus/roselle flowers	100	803 (799)	100	216	95	58.6	58.6	Yes	4 (<1%)	4	
631030	Herbal infusions from rose flowers	50	17 (10)	59	6	50	2.9	2.9	No	–	4	
631040	Herbal infusions from Jasmine flowers	50	2 (0)	0	–	0	–	–	No	–	4	
631050	Herbal infusions from Lime/linden flowers	50	5 (4)	80	44.2	50	44.2	44.2	No	–	4	
632000	Herbal infusions from leaves and herbs	100	452 (262)	89	88	95	34.3	34.3	No	16 (5%)	3	
632010	Herbal infusions from Strawberry leaves and herbs	100	180 (169)	94	213	95	130	130	Yes	14 (8%)	4	
632020	Herbal infusions Rooibos, (leaves and herbs)	100	32 (32)	100	36.9	90	36.9	36.9	No	–	4	
632030	Herbal infusions Mate/maté leaves and herbs	100	26 (14)	54	19.5	50	11.6	11.6	No	–	4	
632990	Herbal infusions from leaves and herbs not explicitly mentioned under rest of the group codes	100	4 (4)	100	32	0	–	–	No	–		
633010	Herbal infusions from Valerian roots	70	17 (11)	65	12.5	50	4.4	4.4	No	–	4	

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
633020	Herbal infusion from Ginseng roots	70	2 (0)	0		0	–		No	–		
639000	Herbal infusion, any other parts of the plant	50	34 (26)	76	41	90	41	41	No	–	3	
640000	Cocoa beans	70	1 (0)	0	–	0	–	–	No	–	3	
650000	Carobs/Saint John's breads	70	2 (0)	0	–	0	–	–	No	–		
700000	HOPS	20	22 (7)	41	32	50	1.7	5	Yes	1 (5%)	2	
810000	Seed spices	400	1 (0)	0		0	–	–	No	–	3	
810010	Anise/aniseed	400	3 (2)	67	17	0	–	–	No	–	3	
810020	Black caraway/black cumin	400	9 (2)	22	32.8	50	1.2	5	No	–	3	
810030	Celery	400	1 (1)	100	4	0	–	–	No	–	3	
810040	Coriander	400	2 (1)	50	11	0			No	–	3	
810050	Cumin	400	8 (7)	88	17	50	15.9	15.9	No	–	3	
810060	Dill	400	0	No data	No data	–	–	–	No data	–	3	
810070	Fennel	400	19 (17)	89	17	50	6.2	6.2	No	–	3	
810080	Fenugreek	400	6 (5)	83	6.5	50	6.5	6.5	No	–	3	
810090	Nutmeg	400	2 (1)	50	2.8	0	–	–	No	–	3	
820010	Allspice/pimento spices	400	2 (2)	100	7.1	0	–	–	No	–	3	
820020	Sichuan pepper spices	400	0	No data	No data	–	–	–	No data	–	3	
820030	Caraway spices	400	14 (3)	21	49	50	0	5	No	–	3	
820040	Cardamom	400	2 (0)	0		0	–	–	No	–	3	
820050	Juniper berry	400	5 (0)	0		0	0	1	No	–	3	
820060	Peppercorn (black, green and white)	400	18 (16)	89	36	50	14	14	No	–	3	
820070	Vanilla	400	0	No data	No data		–	–	No data	–	3	
820080	Tamarind	400	0	No data	No data		–	–	No data	–	3	
830010	Cinnamon	400	16 (3)	19	15	50	0	5	No	–	3	
840010	Liquorice, spices	400	4 (3)	75	6.9	0	–	–	No	–	3	

(Continues)

(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
840020	Ginger, spices		0	No data	No data		–		No data	–	3	
840030	Turmeric/curcuma, spices	400	60 (49)	82	92	95	92	92	No	–	3	
840040	Horseradish, spices		0	No data	No data		–		No data	–	3	
850010	Cloves	400	1 (0)	–	–	0	–	–	No	–	3	
850020	Capers	400	0	No data	No data		–		No data	–	3	
860000	Flower pistil spices	400	0	No data	No data		–		No data	–	3	
870000	Aril spices	400	0	No data	No data		–		No data	–	3	
900010	Sugar beet roots	20	5 (0)	0		50	0	0.01	No	–	3	
900020	Sugar canes	20	0	No data	No data		–		No data	–	3	
900030	Chicory roots	5	0	No data	No data		–		No data	–	3	
1011010	Muscle, pig	0.05*	31 (0)	0	1	90	0	1	Yes	31 (100%)	4	All exceedances are from high LOQ
1011020	Fat, pig	0.05*	43 (5)	12	0.82	90	0.82	0.82	Yes	5 (12%)	4	
1012010	Muscle, bovine	0.05*	0	No data	No data		–		No data	–	4	
1012020	Fat, bovine	0.05*	44 (20)	45	0.62	90	0.62	0.62	Yes	19 (43%)	4	
1012030	Liver, bovine	0.05*	42 (19)	45	5.78	90	5.783	5.78	Yes	27 (64%)	4	LC it is 19 samples exceeding the MRL (45% of all samples)
1012040	Kidney, bovine	0.05*	0	No data	No data		–		No data	–		
1012050	Edible offals (other than liver and kidney), bovine	0.05*	0	No data	No data		–		No data	–		
1013000	Commodities from sheep	0.05*	0	No data	No data		–		No data	–		
1014000	Commodities from goat	0.05*	0	No data	No data		–		No data	–		
1015000	Commodities from equine	0.05*	0	No data	No data		–		No data	–		
1016000	Commodities from poultry, other than fat and eggs	0.05*	0	No data	No data		–		No data	–		



(Continued)

Code <sup>a</sup>	Groups and examples of individual products to which the MRLs apply	MRL (mg/kg)	N of analytical results all (LC)	% of LC data	Max level of quantified residue (mg/kg)	Percentile <sup>b</sup>	HRP LB <sup>c</sup> (mg/kg)	HRP UB <sup>d</sup> (mg/kg)	MRL exceeded yes/no	N of exceedance <sup>e</sup> (% exceedance)	Level	Comment
1016020	Fat, poultry	0.05*	22 (3)	14	0.85	50	0	0.01	Yes	3 (14%)	4	
1020010	Milk, Cattle	0.05*	47 (23)	49	7.5	90	6.4	6.4	Yes	30 (64%)	2	For LC it is 23 (49%) the number of samples with results above the MRL
1030010	Bird eggs (chicken)	0.05*	75 (61)	81	4.7	95	4.7	4.7	Yes	69 (95%)	2	For LB, it is 61 (84%)
1040000	Honey and other apiculture products	0.05*	55 (15)	27	1.1	90	1.1	2	Yes	39 (71%)	2	LB is 15 (27%)
1050000	Amphibians and Reptiles	0.05*	0	No data	No data	–	–	–	No data	–		
1060000	Terrestrial invertebrate animals	0.05*	0	No data	No data	–	–	–	No data	–		
1070000	Wild terrestrial vertebrate animals	0.05*	0	No data	No data	–	–	–	No data	–		

Abbreviations: HRP, highest reliable percentile; LB, lower bound; LC, left censored non-quantified results (< LOQ) considered zero; MRL, Maximum residue level; N, number of analytical data; UB, upper bound.

\*MRL set at the limit of quantification for enforcement of pesticide residues.

<sup>a</sup>Commodity code number, as listed in Annex I of Regulation (EC) No 396/2005.

<sup>b</sup>Percentile used for the derivation of the lower bound and upper bound levels.

<sup>c</sup>Used also as input value for PRIMo 3.1 for screening the LB exposure based on monitoring data.

<sup>d</sup>Used also as input value for PRIMo 3.1 for screening the UB exposure based on monitoring data.

<sup>e</sup>Number of exceedances based on upper bound data.

APPENDIX G

Pesticide Residue Intake Model (PRIMO)

Screening of safety – TMDI calculation based on MRLs

Long term



Bromide	
LOOs (mg/kg) range from:	0.05 to: 0.05
Toxicological reference values	
TDI (mg/kg bw/day):	0.4 ARID (mg/kg bw): 0.4
Source of TDI:	EFSA Scientific Committee Source of ARID: EFSA Scientific Committee
Year of evaluation:	2024 Year of evaluation: 2024

Input values

- Details - chronic risk assessment
- Supplementary results - chronic risk assessment
- Details - acute risk assessment/children
- Details - acute risk assessment/adults

Comments: ADI replaced by TDI ARID was derived to protect against elevated short term bromide exposures that could result in decreases in T4 in pregnant women.

**Normal mode**

Chronic risk assessment: JMPR methodology (IED/TMDI)

No of diets exceeding the TDI : 29

	Calculated exposure (% of TDI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of TDI)	Commodity / group of commodities	2nd contributor to MS diet (in % of TDI)	Commodity / group of commodities	3rd contributor to MS diet (in % of TDI)	Commodity / group of commodities	MRLs set at the LOQ (in % of TDI)	Exposure resulting from commodities not under assessment (in % of TDI)
TMDI(NED)/IEDI calculation (based on average food consumption)	528%	NL toddler	2110.98	88%	Maize/corn	67%	Bananas	54%	Apples	0.8%	
	335%	DE child	1338.37	62%	Apples	53%	Wheat	33%	Potatoes	0.3%	
	325%	GEMS/Food G06	1300.55	90%	Wheat	45%	Potatoes	25%	Potatoes	0.1%	
	298%	NL child	1192.04	51%	Wheat	43%	Potatoes	42%	Sugar beet roots	0.3%	
	286%	GEMS/Food G11	1065.02	49%	Potatoes	45%	Wheat	19%	Soybeans	0.1%	
	258%	GEMS/Food G08	1031.56	51%	Wheat	49%	Potatoes	14%	Potatoes	0.1%	
	255%	DK child	1020.82	69%	Rye	55%	Wheat	30%	Potatoes	0.2%	
	254%	GEMS/Food G10	1015.39	49%	Wheat	37%	Potatoes	17%	Potatoes	0.1%	
	252%	IE adult	1007.13	44%	Sweet potatoes	29%	Wheat	29%	Potatoes	0.1%	
	249%	GEMS/Food G15	996.01	57%	Wheat	44%	Potatoes	15%	Potatoes	0.1%	
	248%	GEMS/Food G07	992.32	53%	Wheat	47%	Potatoes	13%	Potatoes	0.1%	
	226%	FR child 3 15 yr	902.47	57%	Wheat	26%	Oranges	19%	Potatoes	0.4%	
	224%	RO general	897.33	63%	Wheat	47%	Potatoes	24%	Potatoes	0.2%	
	208%	SE general	833.42	52%	Potatoes	40%	Wheat	23%	Bananas	0.2%	
	207%	PT general	829.99	67%	Potatoes	49%	Wheat	12%	Wine grapes		
	201%	UK toddler	805.90	49%	Wheat	44%	Potatoes	16%	Sugar beet roots	0.3%	
	190%	UK infant	761.25	41%	Potatoes	33%	Wheat	18%	Bananas	0.5%	
	187%	FR toddler 2 3 yr	747.45	38%	Wheat	23%	Potatoes	16%	Apples	0.4%	
	183%	FI 3 yr	733.46	59%	Potatoes	17%	Bananas	15%	Wheat	0.0%	
	183%	ES child	732.85	55%	Wheat	23%	Potatoes	16%	Oranges	0.2%	
	179%	IT toddler	717.74	83%	Wheat	19%	Other cereals	18%	Potatoes		
	170%	FI adult	678.62	97%	Coffee beans	15%	Potatoes	9%	Rye		
	165%	DE women 14-50 yr	658.82	27%	Wheat	23%	Sugar beet roots	14%	Oranges	0.2%	
	158%	DE general	633.46	24%	Wheat	21%	Sugar beet roots	15%	Potatoes	0.2%	
	153%	NL general	611.79	30%	Potatoes	24%	Wheat	14%	Sugar beet roots	0.1%	
	145%	FI 6 yr	580.44	49%	Potatoes	12%	Wheat	10%	Bananas	0.0%	
	127%	IT adult	508.07	52%	Wheat	15%	Potatoes	9%	Other cereals		
	119%	ES adult	476.70	29%	Wheat	12%	Potatoes	10%	Potatoes	0.1%	
	112%	FR adult	449.71	28%	Wheat	12%	Wine grapes	9%	Potatoes	0.1%	
	108%	LT adult	431.14	40%	Potatoes	13%	Rye	13%	Wheat	0.1%	
106%	UK vegetarian	425.78	26%	Wheat	17%	Potatoes	8%	Potatoes	0.0%		
	100%	FR infant	398.47	24%	Potatoes	14%	Carrots	10%	Wheat	0.2%	
	92%	PL general	367.13	43%	Potatoes	11%	Potatoes	10%	Apples		
	88%	UK adult	350.31	21%	Wheat	17%	Potatoes	5%	Potatoes	0.1%	
	84%	DK adult	335.69	16%	Potatoes	14%	Wheat	7%	Rye	0.1%	
	39%	IE child	155.83	15%	Wheat	8%	Potatoes	4%	Rice	0.1%	

**Conclusion:**  
The estimated TMDI/NED/IEDI was in the range of 0 % to 527.7 % of the TDI.  
For 29 diet(s) the TDI is exceeded.  
DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union.

## Short term

Acute risk assessment /children	Acute risk assessment / adults / general population
Details - acute risk assessment /children	Details - acute risk assessment/adults

The acute risk assessment is based on the ARID. DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union. The calculation is based on the large portion of the most critical consumer group.

## Show results for all crops

Results for children		Results for adults	
No. of commodities for which ARID/ADI is exceeded (IESTI): 70		No. of commodities for which ARID/ADI is exceeded (IESTI): 54	
IESTI		IESTI	
Highest % of ARID/ADI	Commodities	Highest % of ARID/ADI	Commodities
MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
1922%	Potatoes	427%	Swedes/rutabagas
1265%	Pineapples	373%	Potatoes
1213%	Bananas	370%	Pineapples
1138%	Melons	354%	Yams
995%	Oranges	347%	Cucumbers
983%	Mangoes	324%	Mangoes
917%	Watermelons	315%	Head cabbages
819%	Cucumbers	305%	Watermelons
793%	Carrots	294%	Melons
778%	Kiwi fruits (green, red, yellow)	288%	Beetroots
727%	Tomatoes	264%	Bananas
713%	Beetroots	260%	Sweet potatoes
692%	Pears	252%	Escaroles/broad-leaved
691%	Celeriacs/turnip rooted celeries	246%	Carrots
688%	Grenate apples/pomegranates	236%	Charls/beet leaves
647%	Swedes/rutabagas	230%	Witloofs/Belgian endives
630%	Avocados	230%	Oranges
589%	Grapefruits	222%	Grenate apples/pomegranates
539%	Apples	203%	Aubergines/egg plants
530%	Papayas	198%	Tomatoes
502%	Escaroles/broad-leaved endives	190%	Chinese cabbages/pe-tsai
496%	Witloofs/Belgian endives	188%	Avocados
476%	Lettuces	179%	Broccoli
475%	Peaches	176%	Parsnips
452%	Parsnips	175%	Courgettes
449%	Turnips	174%	Papayas
446%	Sweet peppers/bell peppers	174%	Kiwi fruits (green, red, yellow)
445%	Mandarins	174%	Cauliflowers
442%	Leeks	170%	Table grapes
434%	Cauliflowers	153%	Pears
390%	Kohlrabies	152%	Lettuces
389%	Yams	148%	Celeriacs/turnip rooted celeries
388%	Salsifies	144%	Kales
365%	Table grapes	140%	Apples
349%	Courgettes	140%	Florence fennels
332%	Head cabbages	139%	Turnips
330%	Kales	135%	Mandarins
326%	Sweet corn	134%	Cherimoyas
312%	Broccoli	134%	Grapefruits
306%	Radishes	134%	Salsifies
283%	Spinaches	130%	Radishes
281%	Celeries	128%	Parsley roots/Hamburg roots parsley
279%	Rhubarbs	122%	Sweet peppers/bell peppers
257%	Lemons	120%	Celeries
241%	Chinese cabbages/pe-tsai	119%	Sweet corn
233%	Kaki/Japanese persimmons	119%	Wine grapes
228%	Beans	117%	Jerusalem artichokes
211%	Plums	111%	Onions
200%	Pumpkins	110%	Pumpkins
196%	Carambolas	110%	Kaki/Japanese persimmons
195%	Charls/beet leaves	108%	Coconuts
188%	Cherimoyas	106%	Rice
188%	Aubergines/egg plants	106%	Kohlrabies
181%	Wheat	105%	Wheat
180%	Coconuts	98%	Leeks
175%	Apricots	97%	Globe artichokes
170%	Onions	94%	Peaches
158%	Rice	91%	Horseradishes
151%	Limes	89%	Guavas
147%	Lichis/lychees	89%	Plums
144%	Asparagus	82%	Carambolas
138%	Carobs/Staint John's bread	82%	Beans
132%	Globe artichokes	78%	Cardoons
127%	Cultivated fungi	77%	Leentils
123%	Quinces	76%	Quinces
123%	Strawberries	70%	Strawberries
122%	Florence fennels	70%	Rhubarbs
118%	Spring onions/green onions and Welsh onions	67%	Lemons
112%	Prickly pears/cactus fruits	66%	Red mustards
110%	Guavas	61%	Rye
100%	Cassava roots/manioc	60%	Barley
86%	Beans (with pods)	58%	Beans (with pods)
84%	Maize/corn	58%	Asparagus

Results for children		Results for adults	
No. of processed commodities for which ARID/ADI is exceeded (IESTI): 39		No. of processed commodities for which ARID/ADI is exceeded (IESTI): 31	
IESTI		IESTI	
Highest % of ARID/ADI	Processed commodities	Highest % of ARID/ADI	Processed commodities
MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
1168%	Potatoes / fried	486%	Beetroots / boiled
1109%	Witloofs / boiled	414%	Pumpkins / boiled
828%	Escaroles/broad-leaved endives / boi	312%	Cauliflowers / boiled
742%	Potatoes / dried (flakes)	286%	Parsnips / boiled
665%	Pumpkins / boiled	255%	Escaroles/broad-leaved endives / boiled
634%	Turnips / boiled	253%	Celeries / boiled
634%	Parsnips / boiled	239%	Turnips / boiled
630%	Sweet potatoes / boiled	237%	Cassava roots / boiled
591%	Broccoli / boiled	231%	Witloofs / boiled
554%	Beetroots / boiled	227%	Celeriacs / boiled
551%	Sugar beets (root) / sugar	219%	Sugar beets (root) / sugar
522%	Cauliflowers / boiled	192%	Sweet potatoes / boiled
512%	Pineapples / canned	181%	Broccoli / boiled
449%	Carrots / juice	172%	Courgettes / boiled
429%	Leeks / boiled	167%	Apples / juice
396%	Oranges / juice	1582	Pineapples / canned
389%	Charls/beet leaves / boiled	1556	Kohlrabies / boiled
340%	Florence fennels / boiled	1360	Maize / oil
323%	Salsifies / boiled	1292	Charls/beet leaves / boiled
319%	Jerusalem artichokes / boiled	1275	Florence fennels / boiled
291%	Maize / oil	1164	Leeks / boiled
280%	Rhubarbs / sauce/puree	1119	Oranges / juice
271%	Apples / juice	1083	Pineapples / juice
266%	Courgettes / boiled	1063	Rhubarbs / sauce/puree
238%	Tomatoes / juice	952	Potatoes / chips
224%	Kiwi fruits / juice	896	Wine grapes / juice
216%	Wine grapes / juice	873	Spinaches / frozen/boiled
207%	Kales / boiled	827	Salsifies / boiled
181%	Pineapples / juice	723	Tomatoes / sauce/puree
180%	Celeriacs / juice	721	Carrots / canned
174%	Spinaches / frozen/boiled	696	Jerusalem artichokes / boiled
172%	Gherkins / pickled	690	Cardoons / boiled
163%	Pears / juice	652	Barley / beer
151%	Wheat / milling (flour)	605	Beans / canned
130%	Peaches / canned	520	Coffee beans / extraction
122%	Shallots / boiled	487	Grapefruits / juice
119%	Tomatoes / sauce/puree	477	Potatoes / dried (flakes)
107%	Coconuts / drink	430	Onions / boiled
101%	Leentils / boiled	403	Head cabbages / canned
94%	Beans (with pods) / boiled	376	Wheat / bread/pizza
89%	Peas / canned	357	Purslanes / boiled
83%	Peaches / juice	322	Rice / milling (polishing)
76%	Rice / milling (polishing)	306	Wheat / pasta
76%	Brussels sprouts / boiled	305	Wine grapes / wine

Screening of the safety based on monitoring data – lower bound long term



EFSA PRIMo revision 3.1; 2021/01/06

Bromide			
LOQs (mg/kg) range from:		to:	
<b>Toxicological reference values</b>			
TDI (mg/kg bw/day):	0.4	ARID (mg/kg bw):	0.4
Source of TDI:	EFSA Scientific Committee 2024	Source of ARID:	EFSA Scientific Committee 2024
Year of evaluation:		Year of evaluation	

Input values

Details - chronic risk assessment

Supplementary results - chronic risk assessment

Details - acute risk assessment/children

Details - acute risk assessment/adults

Normal mode											
No of diets exceeding the TDI : 1											
	Calculated exposure (% of TDI)	MS Diet	Expsoure (µg/kg bw per day)	Highest contributor to MS diet (in % of TDI)	Commodity / group of commodities	2nd contributor to MS diet (in % of TDI)	Commodity / group of commodities	3rd contributor to MS diet (in % of TDI)	Commodity / group of commodities	Exposure resulting from	
										MRLs set at the LOQ (in % of TDI)	commodities not under assessment (in % of TDI)
TMDI/NEDI/IEDI calculation (based on average food consumption)	127%	NL toddler	508.57	96%	Milk: Cattle	9%	Maize/corn	3%	Rice		
	81%	FI adult	323.07	77%	Coffee beans	0.6%	Rice	0.6%	Potatoes		
	76%	UK infant	302.31	62%	Milk: Cattle	3%	Rice	2%	Potatoes		
	59%	FR toddler 2 3 yr	234.25	47%	Milk: Cattle	3%	Rice	2%	Wheat		
	54%	NL child	214.29	39%	Milk: Cattle	2%	Wheat	2%	Potatoes		
	51%	FR child 3 15 yr	204.34	37%	Milk: Cattle	3%	Wheat	2%	Rice		
	49%	DE child	194.33	32%	Milk: Cattle	2%	Wheat	1%	Rice		
	45%	UK toddler	180.71	33%	Milk: Cattle	3%	Rice	2%	Wheat		
	38%	GEMS/Food G11	153.14	12%	Milk: Cattle	5%	Coffee beans	3%	Soyabeans		
	35%	GEMS/Food G10	138.87	9%	Milk: Cattle	6%	Rice	3%	Soyabeans		
	34%	IE adult	136.91	7%	Milk: Cattle	5%	Sweet potatoes	3%	Peas		
	34%	DK child	136.71	20%	Milk: Cattle	3%	Rye	3%	Wheat		
	34%	DE general	136.32	20%	Milk: Cattle	6%	Coffee beans	2%	Barley		
	34%	ES child	134.04	20%	Milk: Cattle	3%	Wheat	2%	Rice		
	33%	DE women 14-50 yr	133.40	20%	Milk: Cattle	6%	Coffee beans	1%	Wheat		
	33%	GEMS/Food G06	132.87	8%	Rice	4%	Wheat	4%	Milk: Cattle		
	33%	FR infant	131.92	27%	Milk: Cattle	1%	Potatoes	1.0%	Spinaches		
	33%	SE general	131.73	20%	Milk: Cattle	2%	Potatoes	2%	Rice		
	33%	RO general	130.54	19%	Milk: Cattle	3%	Wheat	2%	Potatoes		
	33%	GEMS/Food G15	130.50	11%	Milk: Cattle	3%	Coffee beans	3%	Wheat		
	31%	GEMS/Food G07	124.72	10%	Milk: Cattle	2%	Coffee beans	2%	Wheat		
	31%	GEMS/Food G08	122.96	9%	Milk: Cattle	3%	Barley	3%	Coffee beans		
	27%	NL general	109.27	14%	Milk: Cattle	4%	Coffee beans	1%	Potatoes		
	19%	FR adult	76.47	7%	Milk: Cattle	6%	Coffee beans	1%	Wheat		
	18%	ES adult	73.66	8%	Milk: Cattle	2%	Barley	1%	Wheat		
	15%	PT general	60.02	4%	Rice	3%	Potatoes	2%	Wheat		
	13%	DK adult	52.77	8%	Milk: Cattle	0.7%	Potatoes	0.6%	Wheat		
	13%	UK vegetarian	52.29	5%	Milk: Cattle	2%	Rice	1%	Wheat		
	12%	LT adult	49.96	6%	Milk: Cattle	2%	Potatoes	1%	Rice		
	12%	FI 3 yr	47.87	3%	Rice	2%	Potatoes	0.8%	Coffee beans		
	11%	UK adult	44.28	5%	Milk: Cattle	2%	Rice	1.0%	Wheat		
	10%	FI 6 yr	40.62	2%	Rice	2%	Potatoes	1.0%	Coffee beans		
	10%	IT toddler	39.07	4%	Wheat	1%	Tomatoes	1.0%	Rice		
	9%	IE child	36.50	6%	Milk: Cattle	1%	Rice	0.7%	Wheat		
	8%	IT adult	32.16	2%	Wheat	0.9%	Rice	0.8%	Tomatoes		
	4%	PL general	17.51	2%	Potatoes	0.6%	Tomatoes	0.3%	Walnuts		

**Conclusion:**  
 The estimated TMDI/NEDI/IEDI was in the range of 0 % to 127.1 % of the TDI.  
 For 1 diet(s) the ADI is exceeded.  
 DISCLAIMER: Dietary data from the UK were included in PRIMo when the UK was a member of the European Union.

## Screening of the safety based on monitoring data – lower bound short term

Acute risk assessment /children	Acute risk assessment / adults / general population
Details - acute risk assessment /children	Details - acute risk assessment/adults

The acute risk assessment is based on the ARfD. DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the EU. The calculation is based on the large portion of the most critical consumer group.

Show results for all crops								
<b>Unprocessed commodities</b>	<b>Results for children</b>				<b>Results for adults</b>			
	9				2			
	<b>IESTI</b>				<b>IESTI</b>			
	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
	261%	Pistachios	0 / 180	1043	151%	Chards/beet leaves	0 / 32	605
	235%	Melons	0 / 6.2	940	120%	Pistachios	0 / 180	481
	199%	Milk: Cattle	0 / 6.4	795	83%	Kales	0 / 17.3	333
	190%	Kales	0 / 17.3	761	71%	Escaroles/broad-leaved endives	0 / 14	282
	141%	Escaroles/broad-leaved endives	0 / 14	562	62%	Milk: Cattle	0 / 6.4	247
	134%	Celeries	0 / 14.3	535	61%	Figs	0 / 21.8	243
	130%	Celeriacs/turnip rooted celeries	0 / 9.4	520	61%	Melons	0 / 6.2	243
	125%	Chards/beet leaves	0 / 32	499	59%	Aubergines/egg plants	0 / 8.7	236
	113%	Papayas	0 / 10.7	454	57%	Celeries	0 / 14.3	229
	88%	Kohlrabies	0 / 6.8	354	43%	Rice	0 / 20	170
	84%	Spinaches	0 / 14.8	334	41%	Florence fennels	0 / 8.8	164
	81%	Potatoes	0 / 2.1	323	40%	Peas	0 / 47.7	158
	79%	Watermelons	0 / 2.6	318	37%	Chestnuts	0 / 33.17	149
78%	Peas	0 / 47.7	313	37%	Papayas	0 / 10.7	149	
74%	Parsnips	0 / 8.2	296	29%	Parsnips	0 / 8.2	115	
64%	Figs	0 / 21.8	256	29%	Witloofs/Belgian endives	0 / 6.2	114	
63%	Rice	0 / 20	252	28%	Celeriacs/turnip rooted celeries	0 / 9.4	111	
<b>Processed commodities</b>	<b>Results for children</b>				<b>Results for adults</b>			
	5				2			
	<b>IESTI</b>				<b>IESTI</b>			
	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
	249%	Chards/beet leaves / boiled	0 / 32	996	121%	Celeries / boiled	0 / 14.3	483
	232%	Escaroles/broad-leaved endives / boiled	0 / 14	928	100%	Chards/beet leaves / boiled	0 / 32	400
	137%	Witloofs / boiled	0 / 6.2	550	72%	Escaroles/broad-leaved endives / boiled	0 / 14	286
	119%	Kales / boiled	0 / 17.3	477	66%	Coffee beans / extraction	0 / 11	262
	104%	Parsnips / boiled	0 / 8.2	416	44%	Parsnips / boiled	0 / 8.2	174
	100%	Florence fennels / boiled	0 / 8.8	399	43%	Celeriacs / boiled	0 / 9.4	171
	85%	Peas / canned	0 / 19.08	341	43%	Florence fennels / boiled	0 / 8.8	171
	67%	Sweet potatoes / boiled	0 / 5.3	267	36%	Kohlrabies / boiled	0 / 6.8	145
	51%	Spinaches / frozen; boiled	0 / 14.8	206	32%	Peas / canned	0 / 19.08	126
51%	Leeks / boiled	0 / 3.56	204	31%	Spinaches / frozen;	0 / 14.8	122	
<b>Conclusion:</b>								
The estimated short term intake (IESTI) exceeded the toxicological reference value for 9 commodities.								
For processed commodities, the toxicological reference value was exceeded in one or several cases.								

Screening of the safety based on monitoring data – upper bound long term



Bromide			
LOQs (mg/kg) range from: to:			
Toxicological reference values			
TDI (mg/kg bw/day):	0.4	ARfD (mg/kg bw)	0.4
Source of TDI:	EFSA Scientific Committee	Source of ARfD:	EFSA Scientific Committee
Year of evaluation:	2024	Year of evaluation:	2024

Input values

Details - chronic risk      Supplementary results -

Details - acute risk assessment/children      Details - acute risk assessment/adults

Comments: ADI replaced by TDI      Upper bound calculations. ARfD relevant only for adults.

**Normal mode**

**Chronic risk assessment: JMPR methodology (IED/TMDI)**

		No of diets exceeding the TDI : 2						Exposure resulting from																																																																																																																																																																																																																																																																																																																																																																																																														
Calculated exposure (% of TDI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of TDI)	Commodity / group of commodities	2nd contributor to MS diet (in % of TDI)	Commodity / group of commodities	3rd contributor to MS diet (in % of TDI)	Commodity / group of commodities	MRLs set at the LOQ (in % of TDI)	commodities not under assessment (in % of TDI)																																																																																																																																																																																																																																																																																																																																																																																																												
											<p><b>TMDI/NEDI calculation (based on average food consumption)</b></p> <table border="1"> <tr><td>188%</td><td>NL toddler</td><td>753.62</td><td>96%</td><td>Milk: Cattle</td><td>15%</td><td>Wheat</td><td>13%</td><td>Apples</td><td></td><td></td></tr> <tr><td>104%</td><td>DE child</td><td>417.68</td><td>32%</td><td>Milk: Cattle</td><td>16%</td><td>Wheat</td><td>16%</td><td>Apples</td><td></td><td></td></tr> <tr><td>99%</td><td>UK infant</td><td>397.79</td><td>62%</td><td>Milk: Cattle</td><td>10%</td><td>Wheat</td><td>4%</td><td>Potatoes</td><td></td><td></td></tr> <tr><td>92%</td><td>FI adult</td><td>369.81</td><td>77%</td><td>Coffee beans</td><td>3%</td><td>Tomatoes</td><td>3%</td><td>Rye</td><td></td><td></td></tr> <tr><td>92%</td><td>NL child</td><td>369.72</td><td>39%</td><td>Milk: Cattle</td><td>15%</td><td>Wheat</td><td>7%</td><td>Apples</td><td></td><td></td></tr> <tr><td>92%</td><td>GEMS/Food G06</td><td>367.30</td><td>27%</td><td>Wheat</td><td>18%</td><td>Tomatoes</td><td>8%</td><td>Rice</td><td></td><td></td></tr> <tr><td>85%</td><td>FR child 3 15 yr</td><td>341.08</td><td>37%</td><td>Milk: Cattle</td><td>17%</td><td>Wheat</td><td>4%</td><td>Oranges</td><td></td><td></td></tr> <tr><td>85%</td><td>FR toddler 2 3 yr</td><td>339.44</td><td>47%</td><td>Milk: Cattle</td><td>12%</td><td>Wheat</td><td>4%</td><td>Apples</td><td></td><td></td></tr> <tr><td>83%</td><td>DK child</td><td>330.52</td><td>21%</td><td>Rye</td><td>20%</td><td>Milk: Cattle</td><td>17%</td><td>Wheat</td><td></td><td></td></tr> <tr><td>75%</td><td>UK toddler</td><td>300.88</td><td>33%</td><td>Milk: Cattle</td><td>15%</td><td>Wheat</td><td>4%</td><td>Potatoes</td><td></td><td></td></tr> <tr><td>74%</td><td>RO general</td><td>297.67</td><td>19%</td><td>Wheat</td><td>19%</td><td>Milk: Cattle</td><td>10%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>72%</td><td>GEMS/Food G15</td><td>289.83</td><td>17%</td><td>Wheat</td><td>11%</td><td>Milk: Cattle</td><td>6%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>71%</td><td>GEMS/Food G11</td><td>285.54</td><td>14%</td><td>Wheat</td><td>12%</td><td>Milk: Cattle</td><td>5%</td><td>Soybeans</td><td></td><td></td></tr> <tr><td>71%</td><td>GEMS/Food G10</td><td>282.84</td><td>15%</td><td>Wheat</td><td>9%</td><td>Milk: Cattle</td><td>7%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>68%</td><td>GEMS/Food G08</td><td>272.65</td><td>15%</td><td>Wheat</td><td>9%</td><td>Milk: Cattle</td><td>6%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>67%</td><td>GEMS/Food G07</td><td>266.66</td><td>16%</td><td>Wheat</td><td>10%</td><td>Milk: Cattle</td><td>5%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>67%</td><td>ES child</td><td>266.05</td><td>20%</td><td>Milk: Cattle</td><td>17%</td><td>Wheat</td><td>5%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>64%</td><td>IE adult</td><td>254.33</td><td>9%</td><td>Wheat</td><td>7%</td><td>Milk: Cattle</td><td>5%</td><td>Sweet potatoes</td><td></td><td></td></tr> <tr><td>63%</td><td>SE general</td><td>252.74</td><td>20%</td><td>Milk: Cattle</td><td>12%</td><td>Wheat</td><td>5%</td><td>Potatoes</td><td></td><td></td></tr> <tr><td>58%</td><td>DE women 14-50 yr</td><td>232.19</td><td>20%</td><td>Milk: Cattle</td><td>8%</td><td>Wheat</td><td>6%</td><td>Coffee beans</td><td></td><td></td></tr> <tr><td>57%</td><td>DE general</td><td>228.82</td><td>20%</td><td>Milk: Cattle</td><td>7%</td><td>Wheat</td><td>6%</td><td>Coffee beans</td><td></td><td></td></tr> <tr><td>46%</td><td>NL general</td><td>184.96</td><td>14%</td><td>Milk: Cattle</td><td>7%</td><td>Wheat</td><td>4%</td><td>Coffee beans</td><td></td><td></td></tr> <tr><td>46%</td><td>PT general</td><td>183.13</td><td>15%</td><td>Wheat</td><td>7%</td><td>Potatoes</td><td>4%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>45%</td><td>IT toddler</td><td>178.88</td><td>25%</td><td>Wheat</td><td>7%</td><td>Tomatoes</td><td>1%</td><td>Lettuces</td><td></td><td></td></tr> <tr><td>44%</td><td>FR infant</td><td>176.57</td><td>27%</td><td>Milk: Cattle</td><td>3%</td><td>Wheat</td><td>2%</td><td>Potatoes</td><td></td><td></td></tr> <tr><td>40%</td><td>ES adult</td><td>161.32</td><td>9%</td><td>Wheat</td><td>8%</td><td>Milk: Cattle</td><td>4%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>37%</td><td>FR adult</td><td>149.63</td><td>8%</td><td>Wheat</td><td>7%</td><td>Milk: Cattle</td><td>6%</td><td>Coffee beans</td><td></td><td></td></tr> <tr><td>35%</td><td>FI 3 yr</td><td>141.09</td><td>6%</td><td>Potatoes</td><td>4%</td><td>Wheat</td><td>3%</td><td>Oat</td><td></td><td></td></tr> <tr><td>33%</td><td>IT adult</td><td>133.78</td><td>16%</td><td>Wheat</td><td>6%</td><td>Tomatoes</td><td>2%</td><td>Lettuces</td><td></td><td></td></tr> <tr><td>32%</td><td>UK vegetarian</td><td>126.44</td><td>8%</td><td>Wheat</td><td>5%</td><td>Milk: Cattle</td><td>3%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>30%</td><td>LT adult</td><td>120.94</td><td>6%</td><td>Milk: Cattle</td><td>4%</td><td>Rye</td><td>4%</td><td>Potatoes</td><td></td><td></td></tr> <tr><td>29%</td><td>FI 6 yr</td><td>115.16</td><td>5%</td><td>Potatoes</td><td>4%</td><td>Wheat</td><td>2%</td><td>Rye</td><td></td><td></td></tr> <tr><td>28%</td><td>DK adult</td><td>111.87</td><td>8%</td><td>Milk: Cattle</td><td>4%</td><td>Wheat</td><td>3%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>25%</td><td>UK adult</td><td>101.38</td><td>6%</td><td>Wheat</td><td>5%</td><td>Milk: Cattle</td><td>2%</td><td>Tomatoes</td><td></td><td></td></tr> <tr><td>17%</td><td>PL general</td><td>69.40</td><td>4%</td><td>Tomatoes</td><td>4%</td><td>Potatoes</td><td>3%</td><td>Apples</td><td></td><td></td></tr> <tr><td>15%</td><td>IE child</td><td>60.08</td><td>6%</td><td>Milk: Cattle</td><td>4%</td><td>Wheat</td><td>1%</td><td>Rice</td><td></td><td></td></tr> </table>											188%	NL toddler	753.62	96%	Milk: Cattle	15%	Wheat	13%	Apples			104%	DE child	417.68	32%	Milk: Cattle	16%	Wheat	16%	Apples			99%	UK infant	397.79	62%	Milk: Cattle	10%	Wheat	4%	Potatoes			92%	FI adult	369.81	77%	Coffee beans	3%	Tomatoes	3%	Rye			92%	NL child	369.72	39%	Milk: Cattle	15%	Wheat	7%	Apples			92%	GEMS/Food G06	367.30	27%	Wheat	18%	Tomatoes	8%	Rice			85%	FR child 3 15 yr	341.08	37%	Milk: Cattle	17%	Wheat	4%	Oranges			85%	FR toddler 2 3 yr	339.44	47%	Milk: Cattle	12%	Wheat	4%	Apples			83%	DK child	330.52	21%	Rye	20%	Milk: Cattle	17%	Wheat			75%	UK toddler	300.88	33%	Milk: Cattle	15%	Wheat	4%	Potatoes			74%	RO general	297.67	19%	Wheat	19%	Milk: Cattle	10%	Tomatoes			72%	GEMS/Food G15	289.83	17%	Wheat	11%	Milk: Cattle	6%	Tomatoes			71%	GEMS/Food G11	285.54	14%	Wheat	12%	Milk: Cattle	5%	Soybeans			71%	GEMS/Food G10	282.84	15%	Wheat	9%	Milk: Cattle	7%	Tomatoes			68%	GEMS/Food G08	272.65	15%	Wheat	9%	Milk: Cattle	6%	Tomatoes			67%	GEMS/Food G07	266.66	16%	Wheat	10%	Milk: Cattle	5%	Tomatoes			67%	ES child	266.05	20%	Milk: Cattle	17%	Wheat	5%	Tomatoes			64%	IE adult	254.33	9%	Wheat	7%	Milk: Cattle	5%	Sweet potatoes			63%	SE general	252.74	20%	Milk: Cattle	12%	Wheat	5%	Potatoes			58%	DE women 14-50 yr	232.19	20%	Milk: Cattle	8%	Wheat	6%	Coffee beans			57%	DE general	228.82	20%	Milk: Cattle	7%	Wheat	6%	Coffee beans			46%	NL general	184.96	14%	Milk: Cattle	7%	Wheat	4%	Coffee beans			46%	PT general	183.13	15%	Wheat	7%	Potatoes	4%	Tomatoes			45%	IT toddler	178.88	25%	Wheat	7%	Tomatoes	1%	Lettuces			44%	FR infant	176.57	27%	Milk: Cattle	3%	Wheat	2%	Potatoes			40%	ES adult	161.32	9%	Wheat	8%	Milk: Cattle	4%	Tomatoes			37%	FR adult	149.63	8%	Wheat	7%	Milk: Cattle	6%	Coffee beans			35%	FI 3 yr	141.09	6%	Potatoes	4%	Wheat	3%	Oat			33%	IT adult	133.78	16%	Wheat	6%	Tomatoes	2%	Lettuces			32%	UK vegetarian	126.44	8%	Wheat	5%	Milk: Cattle	3%	Tomatoes			30%	LT adult	120.94	6%	Milk: Cattle	4%	Rye	4%	Potatoes			29%	FI 6 yr	115.16	5%	Potatoes	4%	Wheat	2%	Rye			28%	DK adult	111.87	8%	Milk: Cattle	4%	Wheat	3%	Tomatoes			25%	UK adult	101.38	6%	Wheat	5%	Milk: Cattle	2%	Tomatoes			17%	PL general	69.40	4%	Tomatoes	4%	Potatoes	3%	Apples		
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**Conclusion:**  
 The estimated TMDI/NEDI/IEDI was in the range of 0 % to 188.4 % of the ADI.  
 For 2 diet(s) the ADI is exceeded.  
 DISCLAIMER: Dietary data from the UK were included in PRIMo when the UK was a member of the European Union.



Screening of the safety based on monitoring data – upper bound short term

Acute risk assessment /children				Acute risk assessment / adults / general population				
Details - acute risk assessment /children				Details - acute risk assessment/adults				
The acute risk assessment is based on the ARID. DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union. The calculation is based on the large portion of the most critical consumer group.								
<b>Show results for all crops</b>								
<b>Unprocessed commodities</b>	<b>Results for children</b>				<b>Results for adults</b>			
	25				4			
	<b>IESTI</b>				<b>IESTI</b>			
	Highest % of ARID/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARID/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
	611%	Watermelons	0 / 20	2445	203%	Watermelons	0 / 20	812
	298%	Sweet peppers/bell peppers	0 / 20	1190	151%	Chards/beet leaves	0 / 32	605
	291%	Tomatoes	0 / 20	1163	120%	Pistachios	0 / 180	481
	262%	Melons	0 / 6.9	1047	105%	Head cabbages	0 / 10	421
	261%	Pistachios	0 / 180	1043	83%	Kales	0 / 17.3	333
	199%	Milk: Cattle	0 / 6.4	795	82%	Sweet peppers/bell peppers	0 / 20	326
	197%	Mangoes	0 / 10	786	79%	Tomatoes	0 / 20	317
	192%	Potatoes	0 / 5	769	77%	Lentils	0 / 50	308
	190%	Lettuces	0 / 20	761	71%	Escaroles/broad-leaved endives	0 / 14	282
	190%	Kales	0 / 17.3	761	68%	Aubergines/egg plants	0 / 10	271
	173%	Pears	0 / 5	692	68%	Melons	0 / 6.9	270
	166%	Oranges	0 / 5	663	65%	Mangoes	0 / 10	259
	147%	Leeks	0 / 10	589	63%	Chinese cabbages/pe-tsai	0 / 10	253
	141%	Escaroles/broad-leaved endives	0 / 14	562	62%	Milk: Cattle	0 / 6.4	247
	138%	Celeriacs/turnip rooted celeries	0 / 10	553	61%	Figs	0 / 21.8	243
	138%	Granate apples/pomegranates	0 / 10	550	61%	Lettuces	0 / 20	243
	135%	Apples	0 / 5	539	57%	Celeries	0 / 14.3	229
	134%	Celeries	0 / 14.3	535	47%	Florence fennels	0 / 10	186
	126%	Pineapples	0 / 5	506	46%	Witloofs/Belgian endives	0 / 10	184
	125%	Chards/beet leaves	0 / 32	499	44%	Granate apples/pomegranates	0 / 10	177
	121%	Bananas	0 / 5	485	43%	Swedes/rutabagas	0 / 5	171
	119%	Peaches	0 / 5	475	43%	Rice	0 / 20	170
	113%	Papayas	0 / 10.7	454	42%	Table grapes	0 / 5	170
	111%	Head cabbages	0 / 10	442	40%	Peas	0 / 47.7	158
	100%	Kohlrabies	0 / 7.7	400	38%	Oranges	0 / 5	153
	100%	Carrots	0 / 6.3	399	38%	Pears	0 / 5	153
	99%	Witloofs/Belgian endives	0 / 10	397	37%	Chestnuts	0 / 33.17	149
	98%	Grapefruits	0 / 5	393	37%	Potatoes	0 / 5	149
	<b>Total number of commodities exceeding the ARID/ADI in children and adult diets (IESTI calculation)</b>							
	25							
<b>Processed commodities</b>	<b>Results for children</b>				<b>Results for adults</b>			
	10				3			
	<b>IESTI</b>				<b>IESTI</b>			
	Highest % of ARID/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARID/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
	249%	Chards/beet leaves / boiled	0 / 32	996	138%	Pumpkins / boiled	0 / 10	552
	232%	Escaroles/broad-leaved endi	0 / 14	928	121%	Celeries / boiled	0 / 14.3	483
	222%	Pumpkins / boiled	0 / 10	887	100%	Chards/beet leaves / boiled	0 / 32	400
	222%	Witloofs / boiled	0 / 10	887	72%	Escaroles/broad-leaved endives / boiled	0 / 14	286
	143%	Leeks / boiled	0 / 10	573	66%	Coffee beans / extraction	0 / 11	262
	127%	Parsnips / boiled	0 / 10	507	53%	Parsnips / boiled	0 / 10	213
	119%	Kales / boiled	0 / 17.3	477	52%	Cauliflowers / boiled	0 / 5	208
	117%	Potatoes / fried	0 / 5	467	49%	Beetroots / boiled	0 / 5	194
	113%	Florence fennels / boiled	0 / 10	453	48%	Florence fennels / boiled	0 / 10	194
	101%	Lentils / boiled	0 / 50	403	46%	Witloofs / boiled	0 / 10	185
	98%	Broccoli / boiled	0 / 5	394	45%	Celeriacs / boiled	0 / 10	182
	<b>Conclusion:</b>							
	The estimated short term intake (IESTI) exceeded the toxicological reference value for 25 commodities. For processed commodities, the toxicological reference value was exceeded in one or several cases.							

## APPENDIX H

### Uncertainty analysis

This Opinion includes 'case-specific' assessment methods with elements of standardised uncertainties, according to the categorisation detailed in the EFSA Guidance on Uncertainty (EFSA Scientific Committee, 2018a). The sources of uncertainty were identified and prioritised for the four areas of the assessment: Hazard assessment for human and animal health (Table H.1); screening scenarios of bromide in food and dietary exposure assessment in food producing and non-food producing animals feed (Table H.2).

The procedures described in Sections 7, 8 and 9 of the EFSA 2018 Guidance on Uncertainty analysis were followed to (i) identify uncertainties in each of the two main parts, (ii) further group uncertainties, when possible, according to their source and (iii) prioritise uncertainties according to their impact on the respective assessment (hazard or exposure). Prioritisation was based on the potential impact on the overall conclusion of the related section.

### Uncertainty characterisation for bromide hazard assessment

Uncertainties that were assigned higher priority in the prioritisation stage were individually examined for their impact on the reference value and the direction of the likely true value. Uncertainties assigned lower priority would not substantially impact the reference value and were not individually examined but taken into consideration in the overall uncertainty.

Impact of the prioritised sources of uncertainty on the reference value:

- a) Low method accuracy increases variability of the BMD modelling and overestimates risk (lower BMDL). Low sensitivity of analytical methods results in higher reference points and underestimates risk (higher BMDL), due to inability to detect low hormone levels, and/or small changes, and/or analysis of small samples. Since fetuses or pups were not subject to analysis, the lower analytical sensitivity does not directly impact the reference point. Measurements in young adult animals were used and methods such as RIA and ELISA are established and acceptable. These analytical methods have a poor dynamic range (steep standard curve), which leads to high variability in analytical results even from small differences in plasma T4 concentrations. A higher variability results in a wider confidence interval of the dose response data and therefore in a lower BMDL. Overall, this element was not expected to have a big effect on the calculation of the TDI.
- b) The relationship between plasma T4 and brain fT3 concentrations is not characterised. Thyroid hormones (T4, TSH) are surrogates of potential HPT disruption by bromide, while fT3 is the marker most functionally meaningful for interpretation of risk to brain development. While plasma T4 is an established and appropriate indicator of effects on the thyroid in adult animals, there are no data of the fT3 concentrations in the brain (developing or adult). If fetal brain T3 is affected more than maternal plasma T4, then risk to fetal brain is underestimated; if fetal brain T3 is less affected than maternal plasma T4, e.g. due to adaptive responses, then risk to fetal brain is overestimated. There is uncertainty about the effectiveness of adaptive response to decreased maternal plasma T4 in maintaining fetal brain fT3. If their adaptive response is effective, changes in plasma T4 may overestimate the changes in brain fT3. This uncertainty may lead to a reference point that is either higher or lower than the true (equal uncertainty in both directions). It is noted that the available plasma T4 data were obtained during a relevant life stage.
- c) The method for assessing histopathological changes in the thyroid (determining hypertrophy by differences in follicular height compared to control) is not optimal. The scoring of observed alterations is qualitative and subjective and underestimates relevant alterations. A more sensitive method would likely result in lower reference point. The method is well established and does not overrepresent alterations (does not overestimate risk) and it is not likely that it would result in higher reference point, as this method. This uncertainty leads to a reference point value that is higher than the true (true reference point is more likely lower).
- d) Data on plasma T4 in young adult animals may not be representative of the most sensitive population, the fetus. There are no data on the impact of bromide on fetal plasma T4 concentrations. There is altered maternal homeostasis during pregnancy and increased need for iodine. The fetus may be just as sensitive or more sensitive than the tested organisms (and not able to compensate for changes in thyroid hormone concentrations) and the reference point may be lower. It is less likely that the fetus is less sensitive, considering the key role of the thyroid in development; hence, the reference point will not be higher. A comparative thyroid assessment would reduce this uncertainty if available: where thyroid hormones are measured in the dam and the fetus with sensitive methods (such as LC-MS-MS), including total and free T3, T4 and TSH in blood and fT3 in the fetal brain and after birth, under conditions of I-sufficient and I-deficient diets and iodine measurements in the thyroid gland. Assessment of DNT endpoints in the same animals would further reduce the uncertainty. Currently, there is no experience with effects of chemicals on fT3 levels in brain and this constitutes a large uncertainty.

The expert group also identified aspects for which there is considerable certainty, such as:

- a) The use of plasma T4 is an established and reliable marker of thyroid changes and a surrogate of perturbation of HPT axis, based on the established AOP (as a MIE). Parallel data on TSH concentrations would improve the interpretation of plasma T4 changes. These data are not available in all studies but there is evidence of moderate increase in TSH in some studies (even if not statistically significant) that corroborate the evidence of thyroid depression by bromide.
- b) Studies in young adult animals are reliable models to detect thyroid effects that are relevant to humans. Adult animals are considered to be at least as sensitive as adult humans.
- c) The methodologies for measurement of thyroid hormones in plasma (in adults) are well established, and in this case, the LOD is not a limitation to detecting hormone concentrations.

For these reasons, the endpoint selected is considered sensitive enough and relevant for extrapolating effects to humans. Based on similar sensitivity for the endpoint selected, an interspecies uncertainty factor for toxicodynamics is not needed.

## EKE results

## Overview of the results of the expert knowledge elicitation

Parameter	Uncertainty assessment of the TDI of bromides for humans														
Stratification	None														
Question	Assuming an ideal database of studies according to the scenario is available, how much would the result of this ideal database differ from the current reference point, expressed as ratio 'perfect/current'?														
Unit	[-]; < 1 higher risk; > 1 lower risk														
Results	P1%	P2.5%	<b>P5%</b>	P10%	P16.7%	P25%	P33.3%	<b>P50%</b>	P66.7%	P75%	P83.3%	P90%	<b>P95%</b>	P97.5%	P99%
Elicited values	0.50					0.75		1.00		1.25					2.00
EKE results	0.50	0.53	<b>0.56</b>	0.62	0.68	0.76	0.83	<b>0.98</b>	1.16	1.27	1.40	1.55	<b>1.72</b>	1.86	2.01
Uncertainty factor needed to compensate for the uncertainties	2.00	1.89	<b>1.78</b>	1.61	1.46	1.32	1.20	<b>1.02</b>	0.86	0.79	0.71	0.65	<b>0.58</b>	0.54	0.50
Fitted distribution	BetaGeneral (1.6617, 4.7334, 0.465, 2.68)														

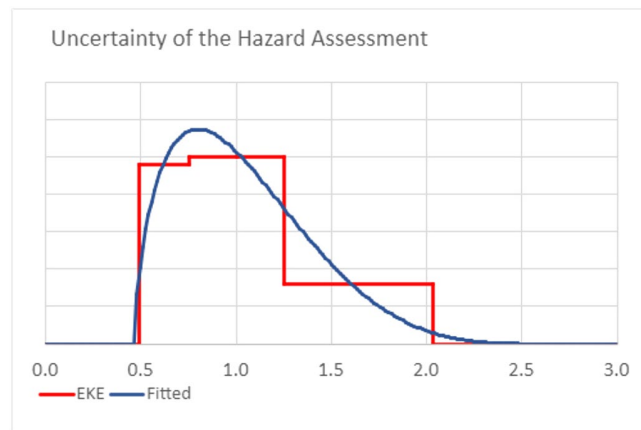


Figure (a): Comparison of elicited and fitted values/density function to describe the remaining uncertainties of the parameter

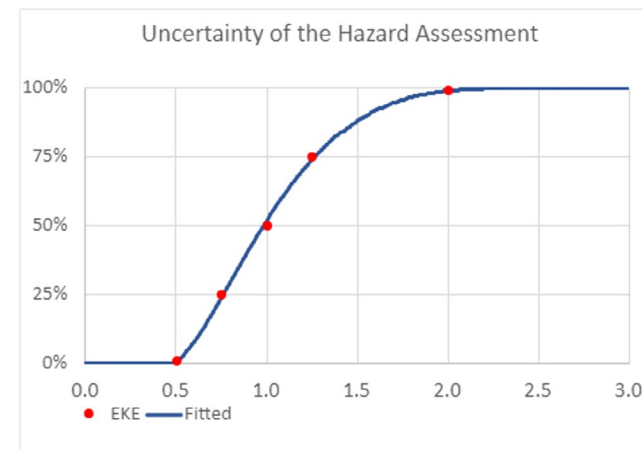


Figure (b): Cumulative distribution function (CDF) of the likelihood of the parameter

### Summary of the evidence used for the evaluation

In a weight of evidence approach, the Scientific Committee took into account the range of BMDL20 values (39.19–57.99 mg Br<sup>-</sup>/kg bw per day) from the studies of Loeber et al. (1983) and van Leeuwen et al. (1983), and the results of the OECD compliant study, identified a reference point (RP) of 40 mg Br<sup>-</sup>/kg bw per day based on the rat studies. Details can be found in the opinion.

#### Main uncertainties

- High variability of hormone measurements in the experiments
- Extrapolation of effects in the brain from measurements of T4 in blood
- Different methods of thyroid histopathology used in the studies
- Missing evidence for sensitive populations, e.g. fetus

Reasoning for a scenario which would lead to a reasonable high ratio (higher reference point, lower risk)

The judgement on the upper limit considers that

- Less variation in the measurements would lead to higher BMDL values
- Brain effects are downstream to decreased plasma T4, and possible adaptive responses may prevent them from happening
- Histopathology is well established and not overestimating tissue alterations
- Fetus is **not** more sensitive to the effect size of T4 decrease (uncertainty with high importance)

Reasoning for a scenario which would lead to a reasonable low ratio (lower reference point, higher risk)

The judgement on the lower limit considers that

- More exact measurements would lower the LOD and the possibly the reference point (esp. in pups)
- The fetal brain is more sensitive to decreased T4/T3
- Scoring in histopathology may underestimate alterations
- Fetus is more sensitive to the effect size of T4 decrease (uncertainty with high importance)

Fair estimate as judgement on the weighted evidence

The judgement on the median considers that

- Uncertainties may over- or under-estimate the reference point in similar magnitude
- The current assessment is unbiased

Precision of the judgement as description of remaining uncertainties

The judgement on the interquartile range considers that

- Highest uncertainty is about the sensitive population, which may lead to higher risk. Thus, high uncertainties for lower ratios.
- Scenarios for higher ratios (lower risk) are less likely. Thus low/medium uncertainties for higher ratios.

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Date and place of the EKE

1st March 2024, in a virtual meeting

**TABLE H.1** Uncertainties in hazard identification and characterisation for human and animal health.

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
<b>ADME</b>	<b>Is there uncertainty in any aspect of ADME?</b>	Uncertainty about steady state kinetics of bromide. Rat study has quality limitations: 5 animals, short study duration (17 days) insufficient to reach steady state. However, bromide salts are efficiently absorbed and distributed in humans when used therapeutically.	0
	<ul style="list-style-type: none"> <li>• For assessment of human health</li> <li>• For assessment of animal health</li> </ul>	Administration of bromide in water vs. food and feed may impact the bioavailability but might not be less than 75% after oral exposure from diet in humans.	1
	Insufficient information on the level of chloride in the diet in animal and human studies, which impacts half-life or clearance (at equal external doses, bromide internal levels are higher at low dietary chloride). High salt diets in the critical studies would result in higher TDI and low salt diets would result in lower TDI.	1	
	Insufficient information on tissue distribution for species other than rat, such as food producing and non-food producing animals This introduces uncertainty on distribution of bromide to the target tissues in animals. However, there are no reasons to expect that bromide distribution differs substantially among species and can be assumed with confidence that it reaches the brain and the thyroid.	0	
	Lack of information about distribution to fetal tissues. However, bromide readily crosses to the fetus where there are no further barriers and can be reasonably assumed to reach all fetal tissues.	1	
<b>Chemical composition</b>	<b>Is there uncertainty associated with the dose in the critical studies used in the risk assessment?</b>	Some studies do not make clear whether doses are expressed as the bromide salt or as bromide; and/or do not specify the bromide salt used; and/or purity information is lacking. Stability of dosing solutions is not checked.	0
		However, it is possible to deduce dose of bromide in the critical studies used for establishing the TDI. In addition, bromide degradation, agglomeration, adsorption or evaporation are unlikely and stability of the solutions can be assumed.	
<b>Critical endpoints and critical study design</b>	<b>Are there limitations in the study design of the studies that can result in uncertainties?</b>	<p>Most available studies are older, with study design limitations. However, taken together they provide consistent overall evidence for effects on thyroid and there are sufficient dose–response data.</p> <ul style="list-style-type: none"> <li>• Many studies are not compliant with OECD guidelines.</li> <li>• Lack of long-term studies</li> <li>• Some studies tested only one dose</li> <li>• In developmental studies, the litter size at birth is not specified and low sample size may reduce the power of the study to detect an adverse effect</li> <li>• No analytical certificates from supplier of batch of diet and bedding in the context of ED (e.g. presence of phytoestrogens in the diet).</li> <li>• Type of cages used not specified.</li> <li>• Lack of information for bromide content in the diet in most studies, and no information on content in drinking water in any study: Therefore, lack of data on total exposure to the animals. However available data indicates that basal diet and drinking water would make a minimal contribution in most studies</li> <li>• Sodium or potassium dose equivalent of equivalent osmolarity of high dose sodium or potassium bromide not always included</li> <li>• Unclear if standardised protocols were used for sample collection (blood collection, time...) (avoiding stress) and hormonal analysis</li> </ul>	1



TABLE H.1 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
	Are there sources of uncertainties associated with the selection of the critical endpoint?	Serum T4 measurements are an appropriate critical endpoint. The coefficients of variation in control for T4 levels are not specified (OECD guideline 407). The time of sample collection for T4 measurement is not explicit.	2
	Are there sources of uncertainty associating the critical endpoint with downstream adverse effects in the CNS?	Neurodevelopmental effects are a downstream adverse outcome of thyroid perturbation and the ultimate adverse endpoint. Studies on neurodevelopmental effects of bromide in the offspring are lacking and there is also lack of evidence to identify possible U-shaped dose–response relationship. However, thyroid hormone changes are an early event that can lead to developmental effects, a relationship supported by AOP. A reference value protecting against changes in thyroid in pregnant women should also protect against developmental effects mediated by thyroid hormones.	1
	Is there uncertainty about effects of bromide on CNS independent of the critical endpoint?	Neurotoxicity is not well characterised. Clinical signs are reported at doses used therapeutically and which are above those resulting in changes in thyroid hormones, but there is uncertainty as to whether more subtle effects would occur at lower doses and whether these may occur during development independently of thyroid-mediated developmental neurotoxicity. This uncertainty is unlikely to have a large impact on the selection of reference point, since the critical endpoint selected is sufficiently sensitive and protective of other effects.	1
<b>Animal model</b>	<b>Are there uncertainties in the use of the animal model?</b>	There are recognised species differences between rat and human: <ul style="list-style-type: none"> <li>• Quantitative difference in NIS activity,</li> <li>• Histological difference of the thyroid gland</li> <li>• Differences in TH transport (TBG) and TH metabolism</li> <li>• T4 and TSH levels are lower in human compared to rats.</li> <li>• Difference in available stock of hormones stored in the colloid.</li> <li>• Sexual dimorphism in histology of thyroid gland.</li> <li>• Higher functional activity in rodent thyroid gland</li> </ul> Despite these differences, according to the ECHA/EFSA Guidance the rat is a relevant model for assessment of thyroid active substances and sensitive to detect changes in hormone levels indicative of thyroid alterations. Chronic consequences of thyroid deregulation such as neoplasia in rodents is not relevant to humans.	1
<b>Other effects</b>		Reproductive effects and developmental effects are reported. Based on the available evidence, the reference point for reproductive effects is higher than for thyroid effects.	1
<b>Genotoxicity</b>	<b>Is there uncertainty on the genotoxicity of the substance?</b>	Data only available from secondary sources. Data are considered reliable	0

(Continues)

TABLE H.1 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
BMD modelling	<b>Is there uncertainty on the biological relevance of the selected BMR?</b>	<p>There is uncertainty about thyroid hormone changes related to adverse effects in thyroid function and thyroid-dependent functions. However, histological changes have been reported in at least one study together with hormone level changes to provide sufficient evidence of adverse effects on the thyroid in the tested dose range (Loeber 1983).</p> <p>A BMR of 60% is indicative of downstream adverse effects on the thyroid function in the adult.</p> <p>A lower BMR is relevant for the developing fetus (pregnant women). There is uncertainty about a threshold of serum T4 reduction associated with impaired neurodevelopment. A biologically based BMR of 20% T4 decrease in animals indicates changes that are adverse for neurodevelopment in the fetus and is above the range of variability in control animals.</p> <p>A BMR of 15% reduction in T4 is based on variability in control animals. This would result in a more conservative BMDL which is considered adverse for neurodevelopment when occurring in the same individual during pregnancy, but not when occurring as <i>mean</i> T4 decrease (within range of variability).</p>	2
	<b>Are there uncertainties in the selection of the RP that are not covered by the BMD confidence interval e.g. is model uncertainty covered?</b>	<p>The RP is derived from studies (Loeber 1983, van Leeuwen 1983, or ECHA 2016b report) in which parallel lines of evidence are reported, including changes of thyroid hormone levels and histopathology. This reduces the uncertainty about the selection of the reference point.</p> <p>Some studies of lower reliability have reported possible thyroid effects at lower doses than the studies used for establishing the RP (Velicky et al.). However, limitations in the study design and conduct introduce uncertainty about the reliability of the results. Furthermore, the effect size of T4 decrease reported remained below the BMR of 20% (see above).</p> <p>Due to large interindividual variability in levels of thyroid hormones, the range representing adverse effect is wide; however, the BMR is expressed as % change rather than hormone level and is less subject to individual variability.</p>	2
	<b>Sensitive populations Is there uncertainty about the relevance of the critical endpoint to sensitive populations?</b>	<p>There is lack of data for free T4, for T4 levels and for TSH levels in pregnant women or neonates, in response to bromide. Because of the higher need for iodine and for effective thyroid homeostasis during pregnancy, it is uncertain whether the same dose of bromide may have a larger effect size in the sensitive population (more readily perturbed thyroid hormone levels) compared to the general population.</p> <p>The BMR of 20% T4 reduction based on evidence of adverse DNT effects in humans. The application of UF 10 for individual variability to the BMDL20 covers the sensitive population.</p>	2
<b>Dose response analysis of critical endpoints</b>	<b>Is there uncertainty regarding the dose response analysis e.g. trend occurrence, large data variation, possible covariants?</b>	Lack of raw data; summary data only digitised from figures. This does not impact the accuracy significantly.	1
<b>Chemical composition</b>	<b>Is there uncertainty associated with the dose in the critical studies used in the risk assessment?</b>	Dose administered is clear.	0

TABLE H.1 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
<b>Critical endpoints and critical study design</b>	<b>Are there limitations in the study design of the studies that can result in uncertainties?</b>	Only two studies available reporting on thyroid hormones and EEG changes and they have design limitations that introduce uncertainty about the findings, such as: <ul style="list-style-type: none"> <li>• Limited number of participants</li> <li>• Lack of reproducibility and external validity</li> <li>• Relevance of studies with healthy young (<math>\leq 31</math> years) volunteers for other subgroups</li> <li>• Lack of long-term studies</li> <li>• tT4 increased in contrast to observations in rats</li> </ul>	2
<b>Exposure characterisation in the studies</b>	<b>Are there limitations leading to uncertainty in how exposure assessment was performed in the studies?</b>	Exposure was controlled in the available studies as known administered dose and internal levels of bromide were measured (urine, plasma). There is uncertainty about contribution of bromide from background intakes (diet and drinking water). These were not assessed, but assumed to be low relative to the administered doses.	1
<b>Outcome assessment</b>	<b>Are there limitations leading to uncertainty in outcome assessment in the studies?</b>	Thyroid hormone (T4) in humans is variable and is not a sensitive endpoint (TSH is a better marker). In addition, the method of measurement used in the study is less reliable than later methods. These introduce uncertainty that may explain the change of T4 in direction opposite than expected from MOA and rat studies. Considering the complexity of thyroid regulation and homeostasis in humans, it is uncertain if the observed change is a reliable indicator of altered thyroid status. Despite the statistical significance of the change, it is uncertain if it represents actual change or is subject to analytical artefact and individual variability or a chance observation due to the small sample size and power of the study. Since there was no change in other thyroid parameters, especially TSH, it is uncertain if the change observed in T4 is physiologically relevant. The replication study did not confirm the findings of the first on for thyroid hormone changes	2
	<b>Is there uncertainty about effects of bromide on CNS?</b>	EEG changes were observed. It is uncertain whether such changes are adverse and whether they are thyroid-mediated effects or direct effects of bromide in the CNS. However, the dose levels at which they are observed are within range of the reference point set on the critical endpoint and do not impact the resulting reference value.	1
<b>Confounding</b>	<b>Are there confounders introducing uncertainty?</b>	No information on confounders, e.g. iodine intake or status or salt intake. Therefore, it is uncertain whether the reported change in T4 is a result of confounding.	1
<b>MOA</b>	<b>Are there uncertainties on the MoA of the substance that could affect the conclusions of the risk assessment?</b>	Limited evidence in vitro indicate weak competition with iodine for NIS, if any. Competition with iodine for TPO is not supported. However, there is evidence of decreased T4 and increased TSH, although they are not always measured together. It is more likely that T4/T3 hormone synthesis is reduced and less likely that hormone degradation is increased as a result of bromide activity, because there is no evidence that bromide affects liver metabolism. Based on this evidence and on the fact that bromide is an ion similar to iodide, the MOA is assumed to be mediated through ion competition for uptake in the thyroid. No data on liver nuclear receptors (PXR, CAR...) activation, UGT induction activation, extra-thyroidal MOA	1

(Continues)

TABLE H.1 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
<b>Human relevance</b>	<b>Is there uncertainty on the human relevance of the MoA identified in experimental animals?</b>	Despite species differences for thyroid effects between rat and human, the suggested MOA of competition with iodide for uptake in the thyroid and decreased thyroid hormone synthesis is similarly relevant to rats and humans. Species differences pertain to the downstream events following reduced hormone synthesis and do not add uncertainty on the MOA.	1
<b>Chemical composition</b>	<b>Is there uncertainty associated with the dose in the critical studies used in the risk assessment?</b>	The salt of bromide and dose administered are reported in most studies, although purity information is generally lacking. Therefore, for most studies the dose of bromide is clear.	0
<b>Critical endpoints and critical study design</b>	<b>Are there limitations in the study design of the studies that can result in uncertainties?</b>	Most studies have several design limitations and no study of sufficient design could be identified that was appropriate for use as critical study for any species except the dog. Limitations included one or more of the following: <ul style="list-style-type: none"> <li>• Study was designed as a kinetic study rather than a toxicity study</li> <li>• Only one dose tested</li> <li>• No untreated control group</li> <li>• Too few animals were used</li> <li>• Short (insufficient) duration</li> <li>• Poor reporting</li> </ul>	3
	<b>Are there sources of uncertainties associated with the selection of the critical endpoint?</b>	Lack of studies that assessed bromide effects on the thyroid in these animal species, except dog. There is uncertainty about the effects of bromide on thyroid in these species and the literature cannot be used for assessment of critical endpoint not available. Due to the high uncertainty from this body of literature in these animal species, the evidence was not used for setting a reference value for the species. The high uncertainty was addressed by extrapolating reference values from the data in rat studies.	3
<b>Exposure characterisation in the studies</b>		There is uncertainty about the dose received during the course of the studies due to growth of animals during the treatment period, which is not captured in the dose calculations. In addition, there is uncertainty of dose received in studies where bromide concentrations were given in feed or water for drinking without measurement of feed or water consumption data. Total bromide intake, including contribution of bromide present in feed and water, was not determined.	2
<b>Outcome assessment</b>		Only overt signs of neurological observations and general health status and performance parameters were assessed in the available studies. Feed and water intake were not determined as part of the general health status of the animals. Statistical analysis was not reported. Thyroid endpoints (TH and TSH) were not assessed in any species except in dog (see below). Since these outcomes are not used for setting a reference value in these species, the uncertainties about outcome assessment are not relevant to the reference values set for these species.	3
		Only one study reporting effects on the thyroid is available for dogs. The lack of additional studies in dog assessing thyroid effects introduces uncertainty in the evidence and the reference point for this species. Additional studies are needed to reduce this uncertainty. However, since this is not a sensitive species for thyroid effects and the reference value is not applied to other species, this uncertainty does not have an impact on the reference value for other animal species.	2

TABLE H.1 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
<b>Confounding</b>	<b>Are there confounders introducing uncertainty?</b>	Simultaneous administration of bromide with other compounds, as e.g. anticonvulsant treatment presents uncertainty about the compound responsible for the general toxicity effects reported. Since the endpoints reported are not used as the basis for setting a reference value this uncertainty does not impact the conclusion of the opinion.	3
<b>Selection of reference point for relevant animal species and dose response analysis</b>	<b>What are the uncertainties in the use of NOAEL/LOAEL and the dose response analysis e.g. trend occurrence, large data variation, possible covariants?</b>	Uncertainties about the dose response data and the NOAEL in the dog	1
		Selection of a reference point was not feasible from data in these species due to inadequacies in the studies (as noted above). The reference point for all species other than dog is based on evidence from experimental animals (rats) and the reference values for each species are obtained with application of extrapolation factors. There is uncertainty about species variability not captured by such uncertainty factors. However, such variability is mostly based on chemical-specific differences in kinetics, particularly in metabolism. In the case of bromide, the standard uncertainty factors applied are expected to cover species differences as there are no significant differences in kinetics exceeding these values and metabolism is not a concern for a halogen.	1
	<b>Uncertainty in extrapolation between species</b>	The reference values for animal species other than dog are extrapolated from data obtained in experimental animals (rats), using default factors for interspecies and interindividual variability together with conversion factors based on feed intake and body weight. Because bromide is a simple elemental ion and the hazard profile is based on a MOA which is applicable to different species, neither toxicokinetic nor toxicodynamic interspecies differences larger than 10-fold are expected, with respect to thyroid effects.	2

**TABLE H.2** Elements of uncertainty for bromide occurrence and exposure.

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
<b>Analytical methods</b>	<b>General limitations of the methods, specificity, sensitivity, validation</b>	Most modern analytical methods using mass spectrometry can be considered reliable. There is a lack of CRMs and PTs for bromide.	0
	<b>Measurement of bromide ion vs. total bromide</b>	Specificity of analytical methods is not sufficient to distinguish bromide ion from other bromide forms or compounds	1
<b>FOOD - Analytical measurements for food and drinking water</b>	<b>Is there uncertainty due to the performance of the analytical method? This may include identification, sensitivity and recovery</b>	Method not sufficiently sensitive for some commodities that are considered of high relevance, such as foods of animal origin (e.g. meat, fish). However, only very limited data were submitted to EFSA for any such commodities. Limited data for drinking water were submitted to EFSA and the method is was not sufficiently sensitive for this matrix. (overall, low uncertainty regarding method sensitivity because we do not use any data where this would be an issue)	1
		Analytical data for drinking water were reported to EFSA as bromide ion, bromine, bromides and methyl bromide. Since all of these are monitored as bromide, they were all treated as bromide ion. This may overestimate the levels of bromide ion in drinking water depending on the number of other brominated compounds present and their concentrations	2
<b>FOOD - Data reporting</b>	<b>Is there uncertainty on whether there are errors in the reported occurrence data or linked to missing information?</b>	It is not possible to exclude that some unidentified errors in reporting of occurrence data in particular with regard to food classification and/or expression of the result might be included	1
		For almost 50% of data, no information on analytical methods was reported. However, data analysis showed that the reported bromide ion concentrations without reference to analytical methods were consistent with those measured by valid methods of analysis.	0
	<b>Is there uncertainty in the information on sampling strategy</b>	52% of data were obtained through 'selective sampling' which might be considered not fully random. However, the mean concentration of bromide levels were in line with the data obtained through 'objective sampling'.	0
	<b>Is there uncertainty in the form of the food reported (cooked/uncooked, powder/liquid/reconstituted, etc.)</b>	An error in reporting of physical form of the food might be considered.	0–1 depending on type of food
<b>FOOD - Representativeness and completeness of the data</b>	<b>Is there uncertainty in the occurrence data due to limited data availability</b>	A FoodEx2 classification of food categories mostly relevant for the assessment provided with very good level of detail. However, there might be mislinkage between the FoodEx2 and food categorisation as defined in the legislation setting the MRLs	1



TABLE H.2 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
		Low number of samples for several highly consumed food, e.g. fish, drinking water	1–3 depending on food category
		No optimal distribution of sampling countries (data coming mostly from one country)	1
		Outdated data that might not be representative of the current levels were excluded from the data set	0
		The Annex I of Regulation (EC) No 396/2005 clearly defines the part of the product to which the MRL applies (e.g. whole product after removal of stems), but from the data description it was not clear whether these requirements were respected when analysing the samples collected through the call for data for chemical food contaminants.	1
	<b>Is there uncertainty in the occurrence data due to lack of data for potentially relevant major food categories?</b>	Either no data or only limited number of occurrence data were available for relevant food categories expected to be important contributors of bromide intake, e.g. no data on fish, seafood, algae, drinking water. This introduces uncertainty about the bromide contribution from potentially major contributors (fish, seafood) and may underestimate an exposure estimate based on occurrence data if so requested.	2
		Since there are no MRLs for these foods, this source is not represented in the safety screening of the MRLs.	
<b>Left censorship</b>	<b>Is there uncertainty in the occurrence data due to extrapolation or use of models?</b>	For several food categories, the difference between LB and UB mean concentration is considerable. Systematic checks for possible LOQ cut-offs were not conducted. For milk, eggs, meat/muscle, liver and honey the LOQs were sometimes exceeding the MRL (0.05 mg/kg). However, as the quantifiable residues were anyhow exceeding the MRLs in these cases, this had no impact for the exercise of comparing against the MRLs.	2
	<b>Is there uncertainty in the occurrence data due to left censorship and the substitution method</b>	Several very relevant food categories had a very high percentage of left-censored data (e.g., drinking water, different types of fruits)	2
<b>FEED - Data reporting</b>	<b>Is there uncertainty on whether there are errors in the reported occurrence data or linked to missing information?</b>	Very limited data are available for the occurrence of bromide in animal feed. For those that are available, it is not possible to exclude that some unidentified errors in reporting of occurrence data in particular with regard to feed classification and/or expression of the result might be included	1
		Information on analytical method missing for old data (sampled in 2009). These data had very high LOQs and it was not possible to clarify what analytical method was used.	2
	<b>Is there uncertainty in the information on sampling strategy</b>	Almost all feed occurrence data were collected through objective sampling	0

(Continues)

TABLE H.2 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Priority ranking of the uncertainty 0 – negligible 1 – Low 2 – Medium 3 – High
	Is there uncertainty in the form of the feed material reported (compound feed/ complementary, etc.)	No data available to assess this uncertainty	0
FEED – Representativeness and completeness of the data	Is there uncertainty in the occurrence data due to limited data availability	A FoodEx2 classification of feed categories provided with very good level of detail.	0
		Extremely small number of samples for all feed categories and lack of (quantified) data	3
		Data reported only by three countries	3
	Is there uncertainty in the occurrence data due to lack of data for potentially relevant major feed categories?	Data obtained from 2009 to 2021 with majority of them sampled in 2009 and it is uncertain if they are representative of current feed levels	3
		Small number of feed categories and lack of (quantified) data for many relevant major feed categories.	3
Left censorship	Is there uncertainty in the occurrence data due to extrapolation or use of models?	Very high LODs/LOQs reported for the majority of data	3
	Is there uncertainty in the occurrence data due to left censorship and the substitution method	Due to very high LOQs the methods were not able to measure the bromide ion in feed samples and for majority feed categories the proportion of left-censored data was very high	3
FEED – Consumption Data reporting	Is there uncertainty in consumption data, e.g. due to methodology of the dietary survey, weekdays, national recipes?	The example diets might not be including all the relevant feed materials	2
FEED – Representativeness of the consumption data	Is there uncertainty in the representativeness of the consumption data (e.g. of the countries, special population groups, sample size and response rates.	Very few data on a small number of feed types	2

TABLE H.2 (Continued)

Area of assessment	Overarching questions	Sources of uncertainty in the opinion	Impact on exposure estimate	Priority ranking of the uncertainty 0 - negligible 1 – Low 2 – Medium 3 – High			
<b>Screening of safety scenarios</b>	<b>Humans</b>	<b>Is there uncertainty linked to the methodology used for calculating the exposure in humans based on MRLs?</b>	Use of MRLs instead of bromide occurrence levels in the edible portion of each commodity consumed results in overestimation of exposure. Methodology not representative of actual exposure in the population.	3	3		
		<b>Is there uncertainty linked to the methodology used for screening the exposure in humans based on occurrence data reported to EFSA?</b>	Commodities not having occurrence data from at least 5 samples were disregarded, noting that these commodities were generally not major components of the European diets.  Lack of occurrence data and consumption data in PRIMo 3.1 for potential major contributors to dietary intake, in particular drinking water and fish and seafood.  The screening calculation was based on highest reliable percentile concentration which is considered as conservative for long-term exposure  Possible transfer of bromide to milk or meat of food producing animals as source of human exposure is uncertain due to limited data. In these foods, bromide may originate either directly from the feed or via conversion in the animal of bromoform present in macroalgae. This uncertainty underestimates potential exposure through animal-based foods.	2	2	3	3
<b>Food producing and non-food producing animals</b>	<b>Is there uncertainty linked to the methodology used for calculating the exposure in food producing and non-food producing animals?</b>	Exposure assessment for animals was not possible due to lack of data – to be taken up in future assessments	3	3			

## ANNEXES

### ANNEX A

#### Technical Report of the Public Consultation

Annex A is available under the supporting information section of this output.

### ANNEX B

#### Protocol (amended)

Annex B is available under the supporting information section of this output.

### ANNEX C

#### Literature search

Annex C is available under the supporting information section of this output.

### ANNEX D

#### Bromide MRLs and Occurrence in Food and Feed

Annex D is available under the supporting information section of this output.