Review Article

Effect of Bromide on Livestock Development

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Thyroid hormones are critical for the growth, development and maintenance of the body. The review aims to elucidate the potential effects that bromide could have on the functioning of thyroid hormone and to present the risks of exposure and ingestion of bromide to livestock production.

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Introduction

This review refers to the term “bromide” (Br^-) as the negative univalent form of bromine according to the definition used by Winid (2015). Br^- bonds readily with univalent positive ions such as sodium (Na^+) and potassium (K^+) to form sodium bromide (NaBr) or potassium bromide (KBr), or with the methyl cation (CH_3^+) to form methyl bromide.

Br^- is ubiquitous in the environment and occurs naturally in water, soil, and air. Consequently, livestock and crops would be exposed to Br^- present in these sources. It is commonly accepted that Br^- has no defined biological role, hence it is not listed as an essential trace element and is consequently not mentioned in review articles on trace elements. However, McCall et al. (2014) demonstrated its essential role in the collagen IV structure of basal membranes (BM). Hence Br^- is an essential trace element that could become toxic when the ingested quantity surpasses the excretion capacity of healthy kidneys (McCall et al., 2014; Vlasova, 2018).

It is well documented that brominated chemicals such as flame retardants (Jugan, et al., 2009) and polybrominated diphenyl ethers (Crofton, 2005) that release Br^- are thyroid hormone (TH) disruptors. One natural occurring source of Br^- is NaBr, which dissociates into Na^+ and Br^- ions when present as water quality constituents (WQC) in groundwater. A WQC is any chemical element present in a water source that may be benign, beneficial or toxic based on the type of element, and its pharmacodynamics in the body.

Bromide source

Sea water contains 19345 mg/kg chloride (Cl^-) (Anthoni, 2006) and is also a reservoir for iodide (I^-) (Ito & Hirokawa, 2009). Inorganic Br^- commonly is highly water soluble (WHO, 2009). Br^- concentration is generally high in sea water at 65 mg/L (Magazinovic et al., 2004). Livestock produced in coastal regions may be exposed to Br^- naturally from the environment.

A large source of fresh water in agriculture is groundwater. The presence of inorganic WQC in groundwater is complex, and is due to the geology, volcanic activity, pH, oxygen, degree of dissociation, and water sources replenishing the aquifers. Dissociated inorganic WQC vary in their physical properties as they are categorised in the periodic table.

Drawing water from aquifers changes the composition of the water. Ayotte *et al*. (2011) reported that human-induced changes to flow-systems resulted in mobilisation of naturally occurring trace elements that could eventually exceed the no observed adverse effect level (NOAEL) of an element. Higher concentrations of Br^- may occur in groundwater found in hot and dry climates (Winid, 2015), which is consistent with subtropical climatic regions in which extensive livestock farming dominates. Intrusion of sea water into fresh water aquifers may result in an increase in Br^- and Cl^- contents in groundwater.

Water is a key element in livestock production as it affects feed intake and milk production, as well as all other essential metabolic functions in the animal body. Groundwater is used in many areas of low rainfall, such as across southern Africa, or where a constant supply of water is required for livestock. The risk of groundwater is the potential exposure to physiologically adverse WQC (Meyer & Casey, 2012).

The principal hormones essential for controlling developmental and metabolic processes are triiodothyronine (T_3) and thyroxine (T_4) (Velasco *et al*, 2018).

The thyroid gland forms during early embryogenesis and produces TH. TH is essential for normal growth and development of the foetus (Forhead & Fowden, 2014). During embryonic development, TH ensures that the correct sequence of tissue development is followed in each organ (Darras, 2019) therefore, disruption of TH during embryogenesis restricts organ development.

Lucht et al. (2018) showed a differential response in relative mass gain of the heart, liver and brain of chicken embryos after acute exposure to 1 mg/L Br- at the beginning of incubation, where the heart showed possible hypertrophic growth compared with the brain and liver. This has implications for broiler

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susceptibility to ascites in the post-hatch growth phase.

The disruption of TH could be caused by absorbed chemicals that become thyrotoxic, referred to as thyroid disrupting chemicals (TDC). The TDC could be organic compounds such as methyl bromide or seemingly benign inorganic compounds like NaBr. It was established that acute exposure to 1 mg/L Br^- at the beginning of incubation was toxic to chicken embryos (Lucht et al., 2018).

The aim of this review was to present evidence of the occurrence of Br^- in nature, the mechanism of interaction with I^-, and to explore the essentiality of Br^- in the animal body.

Methods

The data incorporated in this review were of our own published research on water quality for livestock, interactions between Br^- and I^-, and the effect Br^- on the development of chicken embryos. We assimilated data from an extensive review of literature using ScienceDirect, PubMed and Google Scholar. Key words used included “bromide”, “toxicity”, “metabolism”, “thyroid hormone”, “hypothyroidism” and “iodine interaction”. Historical and recent literature were included.

Discussion

Billman (2020) defined homeostasis as “a self-regulating process by which biological systems maintain stability while adjusting to changing external conditions.” This definition allows us to understand the delicate physiological balance within the body, which may be disturbed so severely to result in pathology. When the NOAEL of a drug or substance is exceeded it may result in pathological conditions (adverse effects). An example of this is when a normally benign substance is present at concentrations that overwhelm the body’s capacity to excrete sufficient quantities to maintain homeostasis.

A key component of optimal physiological functioning is the control of principle electrolytes and fluid balance within the body. This is because extra- and intracellular fluid composition determines the effectiveness of cellular metabolism. These key electrolytes include Na^+ and K^+, and halides such as I^- and Cl^-.

I^- and Cl^- have clearly defined biological roles, however the role of Br^- was previously unclear as it was not described as an essential element. McCall et al. (2014) identified the essentiality of Br^- as a cofactor for peroxidasin-mediated crosslink formation in collagen IV scaffolds of BM using the *Drosophila* model. BM serve as mechanical support for epithelial cells, and BM integrity therefore influences the integrity of the tissue. When Br^- was fed to Br^- -deficient *Drosophila*, peroxidasin was once again able to form hypobromous acid (HOBr), which mediates cross-link formation (McCall et al., 2014). This indicated that Br^- is an essential element. Hypochlorous acid (HOCl) also mediates cross-link formation, but peroxidasin was shown to use Br^- to catalyse formation of sulfilimine bonds in the collagen IV scaffolds with 50,000-fold greater efficiency compared to Cl^- (McCall et al., 2014). Another positive role of Br^- is in inflammation reactions. The production of HOBr is important in innate immunity and physiologically important processes like apoptosis and cell signalling (Vlasova, 2018).

Concentrations of Cl^- and Br^- are present in a steady state in body fluids depending on intake, and are readily excreted (WHO, 2009) to maintain fluid homeostasis. The kidney must reabsorb the vast majority of the filtered load of Cl^- to maintain the steady state of Cl^- in the blood (Edwards, 2012). Cl^- plays a role in the control of the osmotic gradient between intra- and extracellular fluids allowing absorption or excretion of elements, including hormones, from cells.

It was demonstrated that Br^- is primarily excreted by the kidney 4 h after intraperitoneal injection in rats (Cole & Patrick, 1958). Cl^- is preferentially excreted over Br^- in the kidneys (Pavelka *et al*, 2000; Pavelka, 2004), although Langley Czerwinski (1958) reported that the biological half-life of Br^- could be shortened by administering a surplus of NaCl. This points to an interaction between Cl^- and Br^- in the body water spaces. At physiologically normal NaCl concentrations it would appear that Br^- toxicity may be diagnosable by the occurrence of clinical hypochloraemia.

Kidney anatomy and physiology is known to differ between species, and animals within species adapted to different regions. Br^- may cause kidney damage, and also has the capacity to exacerbate kidney dysfunction. The U.S. Centres for Disease Control and Prevention (CDC) reported that people surviving serious Br^- poisoning can develop kidney damage. Yokota et al. (2017) confirmed that 250 mg/kg NaBr administered to mice with a hereditary, progressive kidney disease, Alport syndrome (AS), exacerbated the existing renal dysfunction.

Serum Br^- concentration is difficult to quantify due to interference with I^- and Cl^- (Rayamajhi et al., 2023). Inorganic Br^- dissolved in solution, originating either from water or feed, is absorbed by the gastrointestinal tract into the circulation (Braam et al., 2006). I^- was shown to interact with Br^- by having an ameliorative effect on high concentrations of Br^- ingested by broilers (Du Toit & Casey, 2012).

Bromide dynamics in biological systems

After intraperitoneal injection of ^{82}Br into Br^- -deficient rats it was found that blood concentration values indicated equal distribution between cells and plasma, although the concentration was initially higher in the plasma (Cole & Patrick, 1958). The bioavailability of ingested Br^- as NaBr in Merino sheep was 92% and the terminal half-life was 14 ± 3 days (Quast *et al.*, 2015) This long half-life shows the possibility of Br^- accumulation in the body water spaces.

Ingested Br^- moves easily through the body water spaces by means of passive and active transport using Cl^- channels. Intracellular movement of Br^- via Cl^- channels is the mechanism by which Br^- functions as an anticonvulsant (Moeser *et al.*, 2015). Br^- partitions in the body similarly to Cl^- (Ullberg *et al.*, 1964).

Regulation of the hypothalamus-pituitary-thyroid (HPT) axis can be the target of TDC, affecting TH clearance in the liver and kidneys (Jugan et al., 2009). Van Logten *et al.* (1973) administered NaBr to Wistar rats at 0, 300, 1200, 4800 or 19 200 mg/kg diet for 4 weeks and reported a dose-related replacement of Cl^- by Br^- in plasma and organs, where the highest dose level affected electrolyte balance. Similarly, when renal excretion of I^- is accelerated by excessive Br^- it may influence the pool of exchangeable I^- in the thyroid gland (Pavelka, 2004).

It is an indisputable fact that Br^- has an effect on biological systems as inorganic Br^- is widely used in pharmaceuticals, especially epilepsy drugs in dogs and a sedative in horses (e.g., KBr) (Environment Agency, 2005) The discontinuation of the routine use of KBr as a sedative in humans has reduced the incidence of chronic Br^- intoxication (Environment Agency, 2005). The distribution and dynamics of Br^- in the bodies of different animals, using chemical analytical methods and isotopic techniques utilising ^{82}Br, indicated that Br^- has thyrotoxic characteristics that cause hypothyroidism (Mason, 1936; Cole & Patrick, 1958; Hellerstein *et al.*, 1960; Ullberg *et al*, 1964). Br^- toxicity that causes hypothyroidism will disrupt normal physiological functioning in the animal body, due to the interaction of the HPT axis with other hormone axes in the body.

Homeostasis, growth and tissue differentiation of an animal depends on TH (van der Spek *et al.*, 2017). The thyroid gland is a target organ of Br^- (Suwanlaong & Phanthumchinda, 2008). The most likely underlying cause of thyroid dysfunction and, subsequently, the observed HPT axis changes, is the interaction of Br^- with I^- uptake by the thyroid gland (Loeber *et al.*, 1983; Van Leeuwen *et al.*, 1983, 1988; Pavelka *et al.*, 2001). Severe disruption of TH synthesis by Br^- will result in hypothyroidism (Buchberger *et al.*, 1990).

It is noted that high doses of NaBr in rats inhibited thyroid function, lowered TH levels, and increased thyroid stimulating hormone (TSH) levels (Van Leeuwen *et al.*, 1983; Loeber *et al.*, 1983). Increased TSH levels indicate the drive of the body to restore thyroid gland function, as controlled by feedback mechanisms in the HPT axis.

The tissue TH status depends on the TH secretion from the thyroid gland as well as normal TH metabolism (Malik & Hodgson, 2002). In birds, T_4 levels increase throughout the last week of embryonic development, reaching a peak at hatching, and the consistently low T_3 levels throughout incubation increase sharply when the hatched chick begins breathing independently (De Groef *et al.*, 2008).

Consequences of bromide ingestion

Inorganic Br^- was shown to influence broiler growth and feed efficiency negatively even after short-term exposure to a maximum concentration of 3 mg/L Br^- in drinking water (Du Toit & Casey, 2010). Despite this being a relatively low concentration in comparison to values reported to range from 0-132 mg/L in the groundwater used for livestock (Lucht & Casey, 2019), it was far above the recommended NOAEL of 0.01 mg/L that Lucht *et al.* (2018) had established using chicken embryos as a sentinel. This illustrated that Br^- is potentially toxic to actively growing poultry even at low concentrations.

Accumulation of Br^- in the liver (Mamabolo *et al.*, 2009) suggests the possibility of Br^- entering the human food chain in cases where the fifth quarter is a main source of protein for people. Another concern is that Br^- is readily transferred into milk (Vobecký, 2005) and this will affect the production performance of pre-weaned animals. Vobecký *et al.* (2005) reported decreased feed and water intake in lactating rats, which resulted in depressed milk production. Another concern is the direct exposure of humans to Br^- when milk from animals is consumed posing an inadvertent risk of hypothyroidism in people.

Influence of Br on livestock production

Normal TH production requires tyrosine from thyroglobulin (TG) to be iodinated in the thyroid gland. The formation of brominated TG is likely to occur when the Br^-/I^- ratio is high due to either I^-deficiency or high Br^- intake (Buchberger, 1988) in which case the Br^- becomes thyrotoxic.

The level of I^- supply within the organism affects the degree to which Br^- may become thyrotoxic. Excessive Br^- has the potential to affect the exchangeable I^- pool in the thyroid gland by increasing renal excretion of I^- (Pavelka, 2004). This is noteworthy since an excess of Br^- in the plasma may manifest as a secondary I^- deficiency even when a sufficient quantity of I^- is ingested. The threshold level at which Br^- causes hypothyroidism has not yet been established.

In vertebrates, the role of TH is to control growth and differentiation of nearly every organ (Darras, 2019; Jugan et al., 2009). Embryonic growth and development in chickens takes 21 days to complete (Darras *et al*, 2011). Thus, *in ovo* TDC exposure has a relatively short window-period in which lasting negative effects are ingrained. This can affect hatchability.

Hatchability is the proportion of eggs that survive to the end of incubation to produce chicks. Lucht *et al.* (2018) reported that concentrations of 0.05, 0.5 and 1 mg/L Br^- negatively affected chick hatchability when administered into the albumen by *in ovo* injection prior to incubation at standard conditions. Lucht et al. (2018) reported a high negative correlation (R^2= -0.92) between increasing concentrations of Br^- and the percentage of embryo survival, and a high positive correlation (R^2 = 0.82) between increasing concentrations of Br^- and the percentage of embryo mortality. The effect of Br^- exposure on hatchability can therefore present economic consequences for the livestock industry. In mammals the variation of gestation length between species will affect the time the foetus is exposed to Br^- ingested by the pregnant dam.

These concentrations were low compared to the 3 mg/L used by du Toit and Casey (2010; 2012). Further research is required to elucidate the effect of Br^- on the foetal development of livestock. This is essential as TH is required for skeletal muscle development, contractile function and muscle regeneration (Salvatore *et al.*, 2014), and foetal programming of muscle growth and development occurs at a critical stage of gestation. Br^- induced hypothyroidism will affect the attainment of production goals in animals raised for food.

Body mass accretion is the cornerstone of livestock production, and T_3 controls somatotropin (GH) and insulin-like growth factor I (IGF-I) activities, which influence body growth (Cabello & Wrutniak, 1989). Increased plasma T_3 concentration will increase metabolic rate (MR) (Mohammadalipour *et al.*, 2017) and stimulate increased mitochondrial oxygen consumption (Harvey & Williams, 2002).

T_3 is involved in cell proliferation (Harvey & Williams, 2002). In avian embryogenesis, the sequence of cell proliferation, differentiation and maturation of each tissue and organ is controlled by TH (Darras, 2019). The sequence of embryological tissue development is nervous tissue > bone > muscle > fat.

A higher growth rate typical of broiler chickens, results in higher MR and thus greater turnover of T_4 to T_3 in tissues, which predisposes fast-growing birds to lower thermal stress tolerance when plasma TH concentration is insufficient to support a higher MR (Al-Rukibat *et al.*, 2017). A similar challenge may be seen in beef and lamb production, where high growth rate is a production goal. Hypothyroidism resulting from exposure to a TDC such as Br^- will slow the growth rate of the animals.

Increased thyroid gland activity in late embryogenesis increases the plasma T_4 concentration necessary to support fast growth in the latter stages of incubation in birds (Al-Rukibat *et al.*, 2017). The process by which T_4 is formed in the thyroid gland can be disrupted by competition between I^- and Br^- resulting in hypothyroidism.

Hypothyroidism can affect the structure and function of the liver directly. Decreased concentration of T_3 in the hepatocytes led to decreased liver metabolism (Malik & Hodgson, 2002). In the case of Br^- toxicity, a decreased production of TH in the liver when Br^- replaces I^- during cellular TH production, would impair liver function. This is crucial given the role that the liver plays in filtration and distribution of nutrients from digestion, and the importance of such nutrients for development and maintenance.

Thus, exposure to Br- at concentrations exceeding the NOAEL may affect TH production, which limits animal production efficiency byinducing a hypothyroid state in the body.

Conclusion

The evidence presented in this review suggests that Br^- is an essential element for tissue development. It further suggests that Br^- ingested from the environment, such as groundwater, can satisfy the requirements for Br^- in BM formation and immune response. Conversely it was shown that Br^- has the capacity to act as a TDC by interfering directly with TH production when the ingested quantity exceeds the NOAEL.

The NOAEL of 0.01 mg/L was proposed in the South African Water Quality Guidelines for Livestock Watering, and validated using the chicken embryo model. Further research is required to establish the NOAEL of Br^- in ruminant livestock, as well as the effect of Br^- ingestion on foetal development in mammalian livestock.

Annex

Effect of bromide	Reference
Sedative (KBr), horses and dogs	Environment Agency, 2005
Thyrotoxic characteristics, hypothyroidism	Mason, 1936 Cole & Patrick, 1958 Hellerstein *et al.*, 1960 Ullberg *et al.*, 1964
Apoptosis and cell signalling	Vlasova, 2018
Interaction of Br^- with I^- uptake by the thyroid	Loeber *et al.*, 1983 Van Leeuwen *et al.*, 1983, 1988 Pavelka *et al.*, 2001
Target organ is thyroid gland	Suwanlaong & Phanthumchinda, 2008
Intracellular movement of Br^- via Cl^- channels, Br as anticonvulsant	Moeser *et al.*, 2015
Br^- partitions in the body similarly to Cl^-	Ullberg *et al.*, 1964
92% bioavailablity when administered as NaBr or KBr	Quast *et al.*, 2015
High negative correlation (R^2= -0.92) between increasing concentrations of Br^- and the percentage of chicken embryo survival	Lucht et al., 2018
High positive correlation (R^2 = 0.82) between increasing concentrations of Br^- and the percentage of embryo mortality in chickens	Lucht et al., 2018
I^- has an ameliorative effect on high concentrations of Br^-	Du Toit & Casey, 2012
High concentrations (3 mg/L) Br- caused depressed feed and water intake in broilers	Du Toit & Casey, 2010

Table 1. The effects of bromide in the body

Statements and Declarations

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Conflict of interest disclosure

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