STATEMENT OF EFSA

Health risk of ammonium released from water filters[1]

European Food Safety Authority[2, 3]

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ABSTRACT

The European Commission (EC) asked the European Food Safety Authority (EFSA) for scientific assistance regarding the possible impact on human health of exposure to ammonium released from water filter cartridges. EFSA was asked whether a level of ammonium between 0.5 mg/L and 5 mg/L in water poses a risk to human health when this water is consumed over a long period of time and in particular by certain vulnerable groups of the population. Ammonia is a naturally occurring compound and an important source of nitrogen for mammals. Large amounts (3-4 g per day, 43-57 mg/kg body weight (b.w.) per day for a 70 kg adult) of ammonium are produced in the gut and excess ammonium is metabolised in the liver and excreted in urine. For adults, the estimated exposure to ammonium in water within the specified concentration range (0.5-5 mg/L) would range from 0.014 mg/kg b.w. per day to 0.14 mg/kg b.w. per day and the estimated exposure would be slightly higher for infants and children. Considering the large amounts of endogenously produced ammonium compared to the exposure from water, it is concluded that additional exposure to ammonium from water at the specified range is negligible and does not pose a risk to human health, even for vulnerable groups.

KEY WORDS

Ammonium, drinking water, human health risk, water filter cartridges

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SUMMARY

Ammonia (NH_3) is colourless gas that is highly soluble in water. In aqueous solutions, most (> 90 % below pH 8) of the ammonia is in the protonated form ammonium (NH_4^+) under equilibrium.

In the environment ammonia originates from both natural and anthropogenic sources. Ammonia is an important source of nitrogen for mammals in the synthesis of amino acids, DNA, RNA and proteins. It is naturally present in different foods and is also produced endogenously in all mammalian species. For ammonium in drinking water, an indicator parameter of 0.50 mg/L has been laid down in the European Union legislation.

The European Food Safety Authority (EFSA) was asked by the European Commission (EC) for scientific assistance regarding the possible impact on human health due to exposure of ammonium released from water filters. Water filter cartridges are typically used by consumers in the home to filter their tap water prior to consumption. EFSA was asked whether a level of ammonium between 0.5 mg/L and 5 mg/L in water poses a risk to human health when this water is consumed over a long period of time and in particular by certain vulnerable groups of the population.

Based on the available information from one of the water filter manufacturers, ammonium is formed in the water filter cartridges during a steam sterilisation step at the end of their manufacturing process. This ammonium is released during the filtration of tap water.

The available information on ammonium concentrations released from water filters is very limited and therefore considered only indicative. However, the available data from one water filter company suggest that the average ammonium concentrations are expected to be well below 0.5 mg/L during the service life of the water filter cartridge.

Following oral exposure, exogenous ammonium is rapidly and extensively absorbed and transported to the liver together with endogenous ammonium produced in the gastrointestinal tract (estimated to be 3-4 g/person per day, (43-57 mg/kg body weight (b.w.) per day for a 70 kg adult)). In the liver, ammonium is metabolised to urea and glutamine. The metabolites are either excreted as urea or retained for the synthesis of amino acids or other biomolecules. However, genetic metabolic disorders or severe liver and kidney failure can lead to toxic ammonia levels in humans

Ammonia is considered to be of no concern for developmental or reproductive effects, or for carcinogenicity and it shows low acute oral toxicity.

For adults the estimated exposure to ammonium in water within the specified concentration range (0.5-5 mg/L) would range from 0.014 mg/kg b.w. per day to 0.14 mg/kg b.w. per day. For infants, the estimated exposure to ammonium in water would be at the range of 0.10-1.0 mg/kg b.w. per day and for children of 0.054-0.54 mg/kg b.w. per day.

Considering endogenously produced ammonium (about 40-60 mg/kg b.w. per day for a 70 kg adult), the additional exposure to ammonium from water at the concentration range of 0.5-5 mg/L is negligible and does not pose a risk to human health, even for vulnerable groups of the population (e.g. people suffering from enzyme deficiencies due to genetic disorders or severe kidney or liver failure).

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Water filter cartridges are used by the consumer to filter tap water in order to remove by chemical adsorption certain ions and off-flavours from the water before consumption. These water filters may release ammonium ions into the drinking water in concentrations above 0.5 mg/L, the indicator parametric value set out in the European Drinking Water Directive 98/83/EC.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 31 of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for its scientific assistance on the risk of release of ammonium from water filter cartridges.

The European Food Safety Authority is asked whether a level of ammonium between 0.5 mg/L and 5 mg/L in water poses a risk to human health when this water is consumed over a long time period in particular by certain vulnerable groups of the population.

ASSESSMENT

1. Introduction

Ammonia is an important source of nitrogen for mammals and plants due to its use in the synthesis of amino acids, DNA, RNA and proteins. It is produced endogenously in all mammalian species. In the environment ammonia originates from both natural and anthropogenic sources.

Ammonia (NH_3) is highly soluble in water where most of the ammonia forms ammonium ions. In this statement ammonia is considered to be fully ionised and being present as ammonium ions in drinking water (see Section 1.1).

In their recent assessment on ammonium in drinking water, the World Health Organization (WHO) reconfirmed that the exposure to ammonia[4] from environmental sources is insignificant in comparison with endogenous synthesis of ammonia. They reported that toxicological effects are observed only when exposure is above approximately 200 mg/kg body weight (b.w.) (WHO, 2011). It was further stated that since ammonia in drinking water is not of immediate relevance for human health, a health-based guidance value was not proposed. However, it was noted that ammonia can decrease the disinfection efficiency, result in nitrite formation in water distribution systems, cause failures of the manganese removal filters and create odour in water (WHO, 2011).

Water filter cartridges are typically used by consumers in the home to filter their tap water prior to consumption. The filters have been reported to remove certain ions and off-flavours from the filtered water (Serpieri et al., 2000). Materials such as activated carbon and a mixture of ion exchange resins and activated carbon are used in the water filter cartridges (Serpieri et al., 2000; BRITA GmbH, 2012, personal communication). As specified in the terms of reference from the European Commission, ammonium has been found in drinking water at levels above 0.5 mg/L after filtering the tap water with the water filter cartridges.

1.1. Chemistry of ammonium

Ammonia (NH_3) is a colourless gas with a sharp odour at room temperature and it can become liquid under pressure. Ammonia is easily dissolved in water in which most of the ammonia (ratio mostly depends upon the pH, but also temperature and dissolved/suspended matter) changes into ammonium cations (NH_4^+) by protonation. An equilibrium between the dissolved ammonia and ammonium is established in water.

At a pH of 7.25, 99 % of the ammonia is ionised and hence present as ammonium ions in aqueous solutions (ATSDR, 2004). The pH of drinking water is typically within the range of 6.5-9.5, and should preferably be below 8 to guarantee an effective disinfection process of the water. Extreme pH values can be due to various reasons such as accidental spills and failures in water treatment systems (WHO, 2007). Therefore, it can be considered that in tap water at a pH below 8, more than 90 % of the ammonia is ionised to ammonium.

The threshold concentration for ammonia at which it causes odour in water at alkaline pH is approximately 1.5 mg/L. For taste, the threshold concentration of the ammonium ions has been estimated to be 35 mg/L (WHO, 2011).

Ammonium commonly forms salts with other substances, such as ammonium chloride, ammonium sulphate and ammonium nitrate (ATSDR, 2004). Most of the ammonium salts are highly water soluble.

[4] The term ammonia included both non-ionized (NH_3) and ionized (NH_4^+) forms in the Guidelines for Drinking Water (WHO, 2011).

2. Legislation

General requirements on food contact materials are laid down in the Regulation (EC) No 1935/2004 of the European Parliament and the Council of 27 October 2004 on materials and articles intended to come into contact with food.[5] The filter materials such as ion-exchange resins and active carbon used in the water filter cartridges are pursuant to this regulation. Under the framework Regulation (EC) No 1935/2004, the specific Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food[6] stipulates the requirements for the plastic containers in which the water is filtered and the plastic cartridges in which the ion-exchange resin and other filter materials have been packed.

The Council Directive 98/83/EC of November 1998[7] lays down the quality of water intended for human consumption. For ammonium in drinking water, an indicator parameter of 0.50 mg/L is stipulated in this Directive. The Directive stipulates that the values of the indicator parameters set out in the Annex I, Part C of the Directive, need to be fixed only for monitoring purposes and for fulfilment of the obligations imposed in the Article 8 of the Directive. It should be noted that the indicator parameter has not been set based on health-based guidance values but due to technological reasons and does not imply a health concern at concentrations higher than 0.50 mg/L

Several ammonium salts have been authorised for use as food additives at 'quantum satis' level specified in the Commission Regulation (EU) No 1129/2011 of November 2011 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council by establishing a Union list of food additives.[8] These ammonium salts include e.g. triammonium citrate (E 380), ammonium alginate (E 403), ammonium carbonates (E 503), and ammonium hydroxide (E 527). The same Regulation stipulates a specific maximum level of 10 g/kg food individually or in combination expressed as glutamate for monoammonium glutamate (E 624) and for ammonium phosphatides (E 442) as food additives.

Further to the EU legislation on drinking water, food and feed additives, the Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food[6] stipulates that ammonium salts of authorised acids, phenols or alcohols may be used in the manufacture of plastic layers in plastic materials, subject to the general requirements, restrictions and specifications rules detailed in the same Regulation. These substances are limited to the overall migration limit of 10 mg of total constituents released per dm^2 of food contact surface or 60 mg of total constituents per kg of food in the case that the food contact material is intended to be used for infants and young children.

3. Sources and occurrence of ammonium

Ammonia is an important source of nitrogen for mammals and plants due to its use in the synthesis of amino acids, DNA, RNA and proteins. It is produced endogenously in all mammalian species. Bacterial degradation of nucleic acids and amino acids in the gut produces ammonia in amounts of 3-4 g/day (ATSDR, 2004, EFSA, 2011). Most of this ammonia is transported to the liver for detoxification where it is used in the synthesis of urea and glutamine. This process is an important part of the regulation of systemic pH due to the neutralisation of excess bicarbonate, created from the breakdown of amino acids, by hydrogen ions released from ammonium during the synthesis of urea (Häussinger, 2007).

[5] Regulation (EC) No 1935/2004 of the European Parliament and the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC. OJ L 338, 13.11.2004, 4-16.

[6] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, 1-89.

[7] Council Directive 98/83/EC of November 1998 on the quality of water intended for human consumption. OJ L 330, 5.12.1998, 32-54.

[8] Commission Regulation (EU) No 1129/2011 of November 2011 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council by establishing a Union list of food additives. OJ L 295, 12.11.2011, 1-177.

In the environment ammonia originates from both natural and anthropogenic sources (ATSDR, 2004). Decomposition of organic matter from animal excrements, dead plants and animals is an important source of naturally occurring ammonia. It is a widely used industrial chemical, mostly in fertilizers, but also in various other applications such as plastics, cleaning products, explosives, animal feed and food additives (WHO/IPCS, 1986; ATSDR, 2004). In addition, sewage or waste water effluents and runoff from areas with intensive animal husbandry are other major sources for ammonia in the environment. For the use of ammonium as food additives see Section 2.

Ammonia and ammonium occur naturally in different foods at various concentrations. Some example concentrations are presented in Table 1. In vegetables, concentrations can range from 4 000 mg/kg to 15 000 mg/kg but higher concentrations can also be found (EFSA, 2011). Ammonium is present in dairy products due to processing of milk (sterilisation, acidification, ripening of cheese products). The enzymatic degradation of the proteins, peptides and amino acids, especially in ripened cheeses, can result in high concentrations of ammonium in cheese.

Table 1: Natural occurrence of ammonia and ammonium in different foods (TNO, 2010 as cited by EFSA, 2011).

Food item	Concentration (mg/kg)
Apples (fresh)	235
Barley	8130
Beetroot	8800
Cooked Cabbage	11060 (up to)
Carrot	3970
Cauliflower	6376
Celery leaves, and/or stalks	19600
Tilsit cheese	164400
Fried Chicken	0.2
Coffee	820 (up to)
Sweet corn	10030
Egg	9 (up to)
Fish (fatty, salted)	2928 (up to)
Hop oil	10660
Kale	15260
Lettuce	10260
Malt	1192
Radish (raw)	8450
Rhubarb	6340
Black tea	400
Red wine	40 (up to)
White wine	69 (up to)

Ammonium in water comes normally from natural, industrial, agricultural sources and from disinfection with chloramine (guideline concentration of 3 mg chloramine/L water (WHO, 2011)). In ground and surface waters natural ammonium levels are usually below 0.2 mg/L (WHO, 2011). Similar levels have recently been reported for tap water in Italy (Dinelli et al., 2012). Elevated ammonium levels in water often indicate bacterial, sewage and waste pollution (Kuramaa et al., 2002; WHO, 2011).

Due to the lack of available information in the literature on the actual source of ammonium in the filtered water, the related concentrations and their variation, BRITA GmbH,[9] one of the water filter companies, was contacted. Based on the information provided, ammonium is known to be formed in the water filter cartridges during a steam sterilisation step at the end of the manufacturing process of the cartridges. The sterilisation step is needed to prevent bacterial growth in the water filter and the consequently elevated ammonium levels in the filtered water due to microbial contamination. During

[9] http://www.brita.co.uk/

the sterilisation at high temperatures, nitrogen compounds in the filter packing material react to form ammonium, which is then bound to the ion exchange resin. This ammonium is released when the ion exchange process with the anions present in the influent water takes place during the filtration of tap water (BRITA GmbH, 2012, personal communication).

According to the information provided by BRITA GmbH, the ammonium concentrations in the first litre of filtered water are below 10 mg/L and in the fifth litre below 5 mg/L. In the 15th litre of the filtered water the ammonium concentration declines further to 0.5 mg/L. For the total volume of 100 L of water filtered during the service life of a single filter cartridge, the average ammonium concentration in the filtered water is well below 0.5 mg/L (BRITA GmbH, 2012, personal communication). In addition, it is instructed to discard the first two litres of filtered water prior to consumption of the filtered water when using the filter cartridges manufactured by BRITA GmbH.[10] Thus this would suggest that the ammonium concentrations in the third litre, which is the first to be consumed when the user instructions are followed, are within the range of 5-10 mg/L. The water filters are only meant to be used for filtering tap water which fulfils the drinking water requirements (BRITA GmbH, 2012, personal communication).

The available information on ammonium concentrations in filtered water are obtained for the water filters produced by a single manufacturer only, and it cannot be assumed that the concentrations and the decrease rate of ammonium release also apply to filters from other filter manufacturers. Therefore, these concentrations are considered as indicative values only. In addition, it is not known how many cartridges have been tested. However, the available limited information suggests that the highest ammonium concentrations in filtered water are observed at the beginning of the use of the filter and that the levels decrease over time when the same filter cartridge is used repeatedly. The average ammonium concentrations are expected to be well below 0.5 mg/L during the time of the service life of a single water filter cartridge.

It should be noted that no original analytical results on the ammonium concentrations released from water filters available on the market, or the variations of these concentrations over a long period of time, have been provided to EFSA.

4. Toxicological considerations of ammonium

4.1. Toxicokinetics

Ammonium is rapidly absorbed via the gastrointestinal (GI) tract (Conn, 1972; ATSDR, 2004). Several studies in human volunteers orally administered ^{15}N-labelled ammonium indicated an almost complete absorption with subsequent excretion in the urine or retention in the organism, where the nitrogen is used for the synthesis of biomolecules or enters in the urea cycle (Richards et al., 1975; Patterson et al., 1995; Metges et al., 1999). In the GI tract, the bacterial degradation of nitrogenous compounds present in food or of secreted urea is estimated to produce about 3 to 4 g/day of endogenous ammonium (ATSDR, 2004; EFSA, 2011). The majority of the endogenously produced ammonium in the GI tract is then absorbed and transported to the liver.

Endogenous ammonium is ubiquitously present in humans and animals. In healthy adults, the physiological ammonium levels in blood are normally below 35 μmol/L (corresponding approximately to 0.67 mg/L) (Häussinger, 2007). In humans, most of the ammonium absorbed in the GI tract is metabolised in the liver and it has only limited influence upon the systemic levels of ammonium. For instance, only small, transient increases in blood levels were observed 15 minutes after the oral administration of 44.4 mg/kg b.w. of ammonium chloride (corresponding to 15 mg ammonium/kg b.w.) to male and female healthy volunteers (Conn, 1972). Due to its positive charge, ammonium entering the systemic circulation has a limited mobility in the organism. However, under physiological pH of 7.4 ammonium is in equilibrium with its neutral form ammonia, which can diffuse through cell membranes including the blood-brain barrier and distribute into tissues (ATSDR, 2004). The fraction

[10] http://www.brita.co.uk/brita/en-GB/cms/faq.grid

of ammonia in equilibrium with ammonium is less than 5 % under physiological pH.[11] However, toxic ammonia concentrations in the body can be reached in subjects with reduced ammonia metabolism or urea excretion (e.g. enzyme deficiencies due to genetic disorders, or severely impaired hepatic or renal functions) (Van de Poll et al., 2008; Ryan and Shawcross, 2011).

In the liver, ammonium is metabolised either via the formation of urea (which is considered the main metabolic pathway) or via the formation of glutamine (ATSDR, 2004; Häussinger, 2007) While the metabolism to urea mainly occurs in the liver, formation of glutamine from ammonium is observed also in other tissues, notably in the brain (ATSDR, 2004). Evidence shows that the hepatic metabolism can efficiently control the physiological ammonium levels even under partial hepatic functionality or high exogenous uptake (Häussinger, 1990; ATSDR. 2004; Van de Poll et al., 2008).

In humans, urinary excretion of urea is the main elimination pathway of both exogenous and endogenous ammonium. Oral administration of ^{15}N-labelled ammonium salts to human volunteers led to a urinary excretion up to approximately 70 % of the administered ammonium dose as urea (Richards et al., 1975; ATSDR, 2004).

4.2. Toxicity in experimental animals

Toxicity data are available for different ammonium salts, notably for ammonium chloride and ammonium sulphate. Beside ammonium, the anions characterise the toxicity of the salts. In particular, the toxicity of ammonium chloride is mainly driven by the release of hydrochloric acid during the metabolism of ammonium into urea, leading to hyperchloremic metabolic acidosis (WHO/IPCS, 1986; ATSDR, 2004).[12] In view of this specific mode of action, ammonium chloride is more toxic than other ammonium salts.

The available data, mainly on ammonium chloride and ammonium sulphate, have been evaluated previously by WHO/IPCS (1986), OECD (2003, 2004), ATSDR (2004) and EFSA (2011), and are briefly summarised below.

Acute toxicity

Ammonium chloride has been tested for acute toxicity in several species. A single gavage dose of 303 mg ammonium/kg b.w. induced mortality in guinea pigs, with pulmonary oedema being established as the cause of death (ATSDR, 2004). According to WHO/IPCS (1986) this effect was not secondary to metabolic acidosis and was observed with other ammonium salts and in other species at similar concentrations by the same research group. However, pulmonary oedema following gavage exposure to ammonium salts was not reproduced in other species at comparable ammonium chloride doses and pulmonary effects were considered secondary to metabolic acidosis by ATSDR (2004).

In more recent studies, rats and mice did not show pulmonary effects following acute exposure to ammonium chloride by gavage. Following a single exposure to aqueous solutions of ammonium chloride by gavage, LD_{50} values of 1630 mg/kg b.w. (equivalent to 548 mg ammonium/kg b.w.) and 1 220 mg/kg b.w. (equivalent to 410 mg ammonium/kg b.w.) were observed in male and female rats, respectively (OECD, 2003). An LD_{50} of 1300 mg/kg b.w. (equivalent to 437 mg ammonium/kg b.w.) was established in male mice after a single gavage dose of ammonium chloride in water (OECD, 2003). Oral LD_{50} values for ammonium sulphate range from 2000 mg/kg b.w. to 4250 mg/kg b.w. (544-1156 mg ammonium/kg b.w.) (OECD, 2004).

Repeat dose toxicity

Repeated exposure to ammonium chloride causes effects secondary to hyperchloremic metabolic acidosis in laboratory animals (decreased body weight, decreased pH in blood and urine, increased

[11] Considering a pKa of about 9 at 37 °C in plasma (Lang et al., 1998), ammonium/ammonia ratio is 97.5/2.5 %.
[12] Increased acidity of the body fluids.

serum calcium related to bone demineralisation, enlargement of kidney and adrenal gland hypertrophy). These secondary effects are also observed with other substances inducing metabolic acidosis and as such are not related specifically to ammonium.

Rats exposed for 70 days to ammonium chloride at 684 mg/kg b.w. per day (equivalent to 230 mg ammonium/kg b.w. per day) showed decreased urinary pH and increased calcium levels in urine, but no histopathological changes in the bladder (OECD, 2003). In another series of studies, ammonium chloride was administered to rats in the diet for period of 4 weeks, 13 weeks, 18 months or 30 months (Lina and Kuijpers, 2004; EFSA, 2011). No effects other than those related to metabolic acidosis were observed up to doses of approximately 3500-4000 mg/kg b.w. per day (1200-1400 mg ammonium/kg b.w. per day) in the 4 and 13-week studies, or up to approximately 1200-1300 mg/kg b.w. per day (400-440 mg ammonium/kg b.w. per day) in the 18 and 30-month studies (Lina and Kuijpers, 2004).

In contrast, ammonium sulphate did not induce metabolic acidosis in rats exposed via the diet to up to 1527 mg/kg b.w. per day (415 mg ammonium/kg b.w. per day) for 52 weeks or up to 1371 mg/kg b.w. per day (373 mg ammonium/kg b.w. per day) for 104 weeks (Ota et al., 2006). Increased absolute and relative liver and kidney weights were only observed at the highest dose tested in male and female rats in the 52-week study. These organ weight increases were without related histopathological changes and within 10 % in both sexes, and are likely indicative of an adaptive response to ammonium metabolism and urea excretion. In the 104-week study, an increased incidence of chronic nephropathy was observed only in male rats exposed at all the tested doses (564 and 1288 mg/kg b.w. per day, equivalent to 153 and 350 mg ammonium/kg b.w. per day, respectively) (Ota et al., 2006). Chronic nephropathy is a common finding in aging rats, particularly in males, and its incidence and severity are exacerbated by many chemicals, therefore this effect is thus considered of low relevance for humans (Hard and Khan, 2004).

Genotoxicity

Both ammonium chloride and ammonium sulphate gave negative results when tested in bacterial reverse mutation assays (OECD, 2003, 2004). Positive results were observed for ammonium chloride but not for ammonium sulphate when tested in *in vitro* chromosomal aberration assays (OECD, 2003, 2004). However, the results observed for ammonium chloride were attributed to the acidity of the substance rather than to a direct interaction with the DNA (OECD, 2003, EFSA, 2011). Negative results were observed for ammonium chloride in an *in vivo* micronucleus test in mouse bone marrow (OECD, 2003). Overall, based on this information ammonium shows no genotoxic potential.

Carcinogenicity

No increased incidence of neoplastic changes was observed in two chronic dietary studies on ammonium chloride (Lina and Kuijpers, 2004) and ammonium sulphate (Ota et al., 2006), with doses of ammonium up to approximately 370-400 mg/kg b.w. per day. In view of these study results and of the absence of genotoxicity, ammonium can be considered of no carcinogenic concern.

Reproductive and developmental toxicity

Diammonium phosphate was tested for fertility and developmental toxicity in a screening study in male and female rats exposed by gavage for 35 days throughout the mating and gestation period. No adverse effects on fertility and development were observed up to 1500 mg/kg b.w. per day (approximately 410 mg ammonium/kg b.w. per day) (OECD 2004). In another study reported by ATSDR (2004), pregnant rats were exposed to 4293 mg ammonium/kg b.w. per day from gestational day 1 through lactation day 21. Following this treatment, the offspring showed a significant decrease in body weight at 120 days of age. ATSDR (2004) concluded that the effects observed in the offspring were secondary to maternal toxicity.

5. Exposure estimates and their relevance for human health

The terms of reference request EFSA to assess the human health risk following exposure from ammonium in water at the concentration range of 0.5-5 mg/L. The exposure estimates were calculated for adults and children at this range only. The EFSA Scientific Committee (SC) has recommended the use of a default value of 2 L/day for chronic liquid consumption (i.e. water, milk and other beverages) for adults ($\geq$ 14 years old) (EFSA, 2012). This value was used for calculating exposure to ammonium in drinking water for adults. For the body weight of adults, a default weight of 70 kg recommended by the SC was used (EFSA, 2012). For infants and children the total water consumption was obtained from EFSA (2010). EFSA (2010) reported that a total daily water consumption of 0.68 L per day can be considered for 0-6 months old infants (infants who are not breast fed), 0.8-1 L for 6-12 months old infants, 1.1-1.2 L for one year old children and 1.3 L for 2-3 years old children. These total water consumptions were also considered appropriate by the SC (EFSA, 2012). A total water consumption of 1 L/day for infants and 1.3 L/day for toddlers were chosen to be used for the chronic exposure estimations. The recommended default body weights of 5 kg for infants (0-12 months of age) and of 12 kg for toddlers (1-3 years of age) by the SC were applied (EFSA, 2012).

Using the above figures, the estimated exposure to ammonium in water within the specified concentration range for adults would range from 0.014 mg/kg b.w. per day to 0.14 mg/kg b.w. per day. For infants and children the exposures to ammonium from water within the same concentration range are higher. For infants, the estimated exposure to ammonium in water would be in the range of 0.10-1.0 mg/kg b.w. per day and for children of 0.054-0.54 mg/kg b.w. per day. These estimated exposures are approximately three orders of magnitude lower than the no-effect levels reported in experimental animals, and do not indicate a health concern. If the information on decreasing concentrations associated with repeated filter use, as provided by BRITA GmbH, similarly applies to other filters, then exposure at the higher end of this range would be infrequent.

Previously WHO (2003) estimated that the daily dietary exposure to ammonium from food and drinking water is 18 mg per person (0.26 mg/kg b.w. per day for a 70 kg adult). In addition, WHO (2003) estimated that the exposure to ammonia from inhalation and smoking cigarettes is less than 2 mg/person per day (equivalent to 0.029 mg/kg b.w. per day for a 70 kg adult). WHO (2011) reconfirmed that the daily exposure to ammonia from environmental sources is insignificant in comparison to endogenous synthesis of ammonia (3000-4000 mg/person (equivalent to 43-57 mg/kg b.w. per day for a 70 kg adult)).

Considering the large contribution of endogenously produced ammonium to the overall exposure, and the efficient detoxification of ammonium in humans, the additional exposure to ammonium from water at the concentration range of 0.5-5 mg/L is negligible and does not pose a risk to human health. Subjects with reduced ammonia metabolism or urea excretion (caused by e.g. enzyme deficiencies due to genetic disorders, or severely impaired hepatic or renal functions) are exposed to higher concentrations of ammonia in the body and represent thus the vulnerable groups of the population to ammonium exposure. However, even for these vulnerable groups of the population the contribution of ammonium in water is marginal, the endogenous ammonium production being by far the most relevant sources.

6. Considerations on uncertainties

The objectives of the assessment were defined in the terms of reference. The concentration range of 0.5-5 mg ammonium/L in water was specified in the terms of reference and the exposure assessment was carried out for the specified range only, as requested in the terms of reference. The uncertainty in the assessment objectives is considered to be negligible.

Due to the lack of original analytical data on ammonium concentrations and their variations, and the fact that the information on the release of ammonium from the water filters was only available from one water filter supplier, the available occurrence data were only considered being indicative. This contributes to the overall uncertainty of the assessment.

The default drinking water consumption figures, which take into consideration the total daily water consumption including water from drinking water, beverages of all kind and from food moisture, were used to calculate exposures for the appropriate population groups. These are likely to be overestimations of the daily drinking water consumptions and thus overestimate the exposures to ammonium from the drinking water.

In addition, since information on the measured levels of ammonium in water released from filters over time was not available, it is unclear whether the specified range of concentrations (0.5-5 mg/L) is representative of water that consumers drink. Based on information provided by one manufacturer, use of this range, particularly at the higher end of the range, is likely to result in overestimation of the exposures.

Since the information on the release of ammonium from the water filters was only available from one water filter manufacturer, it is uncertain whether similar release of ammonium could also occur from other brands or other filter types on the market. In addition, it is not known if ammonium is released only from a particular type of water filter or all types. Thereby these aspects contribute to the overall uncertainty.

There is uncertainty regarding the levels of endogenous ammonium production in infants and children. However, efficient metabolism of ammonia in humans including infants and children is reported in the literature. Thus this adds minimally to the overall uncertainty.

It should also be noted that typically elevated ammonium levels in water indicate microbiological contamination. It is uncertain whether filtered water that has been left standing prior to the consumption could contain elevated ammonium levels due to microbial growth.

Given the above uncertainties, the assessment of human exposure to ammonium in water is likely to be an over- rather than under-estimate of the risk.

CONCLUSIONS

General considerations

- Ammonia (NH_3) is highly soluble in water where it is mainly ionised to ammonium, and an equilibrium is established between ammonia and ammonium. Under normal pH conditions of drinking water (pH below 8) more than 90 % of ammonia is ionised to ammonium.

- For ammonium in drinking water, an indicator parameter of 0.50 mg/L has been laid down in the European Union legislation. The indicator parameter has been set based on technological reasons and does not imply a health concern at concentrations higher than 0.50 mg/L.

- Ammonia is an important source of nitrogen for mammals and plants due to its use in the synthesis of amino acids, DNA, RNA and proteins. It is produced endogenously in all mammalian species.

- In the environment ammonia originates from both natural and anthropogenic sources. It is naturally present at high levels in different foods.

- Water filter cartridges are typically used by consumers in the home to filter tap water prior to consumption.

- Based on the available information from one of the water filter manufacturers, ammonium is formed in the water filter cartridges during a steam sterilisation step at the end of their manufacturing process. This ammonium is released during the filtration of tap water.

- The available information on ammonium concentrations released from water filters is very limited and therefore considered only indicative. However, the average ammonium concentrations obtained from one water filter company are well below 0.5 mg/L during the service life of the water filter cartridge.

Toxicological considerations

- Following oral exposure, exogenous ammonium is rapidly and extensively absorbed and transported to the liver together with endogenous ammonium produced in the gastro intestinal tract (estimated to be 3-4 g/person per day). In the liver, ammonium is metabolised to urea and glutamine. The metabolites are either excreted as urea or retained for the synthesis of amino acids or other biomolecules.

- Genetic metabolic disorders or severe liver and kidney failure can lead to toxic ammonia levels in humans.

- Ammonium has low acute oral toxicity.

- Rats chronically exposed to ammonium sulphate showed a slight increase in liver and kidney weights at 415 mg/kg body weight (b.w.) per day, which is considered to be of low toxicological relevance.

- Two long-term studies with ammonium chloride and ammonium sulphate showed no neoplastic changes in rats exposed orally to up to approximately 370-400 mg ammonium/kg b.w. per day. This, together with the absence of evidence for genotoxicity, indicates that ammonium is of no carcinogenic concern.

- Available information on developmental and reproductive toxicity indicates no effects on fertility. Adverse effects on development were observed only secondarily to maternal toxicity.

Exposure estimates and their relevance for human health

- For adults the estimated exposure to ammonium in water within the specified concentration range (0.5-5 mg/L) would range from 0.014 mg/kg b.w. per day to 0.14 mg/kg b.w. per day. For infants, the exposure to ammonium in water would be at the range of 0.10-1.0 mg/kg b.w. per day and for children of 0.054-0.54 mg/kg b.w. per day. These estimated exposures are approximately three orders of magnitude lower than the no-effect levels reported in experimental animals, which does not indicate a health concern.

- Considering endogenously produced ammonium (about 40-60 mg/kg b.w. per day for a 70 kg adult), the additional exposure to ammonium from water at the concentration range of 0.5-5 mg/L is negligible and does not pose a risk to human health, even for vulnerable groups of the population (e.g. people suffering from enzyme deficiencies due to genetic disorders or severe kidney or liver failure).

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ABBREVIATIONS

b.w.	Body weight
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
GI	Gastrointestinal
SC	EFSA Scientific Committee
WHO	World Health Organization