SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 6 June 2019

doi: 10.2903/j.efsa.2019.5751

Re-evaluation of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as food additives

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Abstract

The Panel on Food Additives and Flavourings added to Food (FAF) provided a scientific opinion re-evaluating the safety of chlorides (E 507–509, E 511) as food additives. Chlorides are authorised food additives in the EU in accordance with Annex II and III to Regulation (EC) No 1333/2008. In the *non-brand-loyal scenario*, mean exposure to chlorides (E 507–509, E 511) as food additives ranged from 2 mg/kg body weight (bw) per day in the elderly to 42 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 5 mg/kg bw per day in the elderly to 71 mg/kg bw per day in toddlers. Chloride is an essential nutrient and after absorption is distributed to organs and tissues. The Panel considered chlorides to be of low acute oral toxicity and there is no concern with respect to genotoxicity and carcinogenicity. No effects were reported in developmental toxicity studies in rats following administration of magnesium chloride hexahydrate at 800 mg/kg bw per day. Some animal studies suggested a role of chloride in increasing blood pressure but based on the toxicological database available the Panel considered human data more appropriate to identify a level of chloride intake which does not raise a safety concern. The Panel identified a human dose of 40 mg chloride/kg bw per day as a reference value for the assessment. Mean levels of exposure in all age groups were below or at this reference value, which indicates no safety concern. In some age groups (toddlers, children and adolescents), the 95th percentile exposure estimates were slightly above this reference value. The Panel concluded that the exposure to chloride from hydrochloric acid and its potassium, calcium and magnesium salts (E 507, E 508, E 509 and E 511) does not raise a safety concern at the reported use and use levels.

Keywords: chloride, hydrochloric acid, food additive, safety, risk assessment, dietary exposure

Requestor: European Commission

Question numbers: EFSA-Q-2011-00657; EFSA-Q-2011-00658; EFSA-Q-2011-00659; EFSA-Q-2011-00660

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Acknowledgements: The Panel wishes to thank: Agnès De Sesmaisons-Lecarré of the NUTRI EFSA Unit for the support provided to this scientific output and Dimitrios Chrysafidis for the preparatory work on this scientific output. The FAF Panel wishes to acknowledge all European competent institutions, Member State bodies and other organisations that provided data for this scientific output.

Suggested citation: EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Fürst P, Gürtler R, Gundert-Remy U, Husøy T, Mennes W, Moldeus P, Oskarsson A, Shah R, Waalkens-Berendsen I, Wölfle D, Boon P, Crebelli R, Di Domenico A, Filipič M, Mortensen A, Van Loveren H, Woutersen R, Giarola A, Lodi F, Riolo F and Frutos Fernandez MJ, 2019. Scientific Opinion on the re-evaluation of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as food additives. EFSA Journal 2019;17 (7):5751, 51 pp. https://doi.org/10.2903/j.efsa.2019.5751

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

The present opinion document deals with the re-evaluation of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) when used as food additives.

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised food additives in the European Union (EU) in accordance with Annex II and III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) have been previously evaluated by the Scientific Committee for Food (SCF) in 1991 (SCF, 1991b) and several times by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the latest in 1965 (JECFA, 1966a) and both committees established an acceptable daily intake (ADI) 'not specified' for hydrochloric acid and its potassium, calcium and magnesium salts.

In 2002, hydrochloric acid and its potassium, calcium and magnesium sodium salts were evaluated by TemaNord which concluded that chlorides are safe food additives (TemaNord, 2002).

The EFSA's Panel on Dietetic Products, Nutrition and Allergies (NDA) has been asked to define a tolerable upper level (UL) of chloride (EFSA NDA Panel, 2005). The Panel concluded that 'The available data are not sufficient to establish an upper level for chloride from dietary sources' but reported a daily chloride intake of approximately 5–7 g which is in excess to the dietary need (2–2.5 g/chloride day in adults).

At the time when this opinion was adopted, the NDA Panel has issued for Public consultation a scientific opinion on the dietary reference value for chloride (EFSA NDA Panel, 2019).

Chlorides occurred in the normal diet. Chloride is an essential nutrient which together with certain cations (e.g. potassium calcium and magnesium) is involved in fluid and electrolyte balance and is required for normal cellular function (EFSA NDA Panel, 2005).

Hydrochloric acid is an essential component of human gastric fluid (EFSA NDA Panel, 2010). Hydrochloric acid and its potassium, calcium and magnesium salts are absorbed from the gastrointestinal tract. After absorption, chloride is distributed to organs and tissues. Chloride is excreted via sweat, urine or in faeces.

The Panel considered chlorides to be of low acute and short-term oral toxicity. *In vitro* genotoxic effects of hydrochloric acid and its salts were observed only at high concentrations that were associated with low pH or high osmolality of the experimental media, which cannot occur under the physiological conditions *in vivo*. The Panel concluded that the use of hydrochloric acid and its potassium, calcium and magnesium salts as food additives does not raise concern for genotoxicity.

No adverse effects were reported in mice exposed to magnesium chloride hexahydrate for 96 weeks and no treatment-related tumours were observed in male rats fed potassium chloride in the diet; therefore, the Panel concluded that there is no concern with respect to carcinogenicity.

No reproductive toxicity studies were available. In prenatal developmental toxicity studies, no maternal or developmental effects were reported in rats following administration of magnesium chloride hexahydrate at a dose level of 800 mg/kg body weight (bw) per day. The Panel noted that developmental studies did not cover for the period for very young animals.

Several studies to investigate the effects of various types of dietary chloride salts (sodium, potassium and magnesium chloride) on blood pressure have been conducted in normotensive and hypertensive rats. Those suggested a role of chloride in increasing blood pressure irrespectively to the associated counter ion (e.g. potassium, sodium, magnesium). The Panel however noted that in these studies only one dose of chloride salts was tested in comparison to controls.

The effect on chloride on blood pressure has been investigated also in humans. Two studies aiming to examine the effects of potassium chloride supplementation on blood pressure in normal women and in patients with mild to moderate hypertension, demonstrated either no effect or a slight lowering effect on blood pressure, respectively.

The effect of chloride anion on blood pressure and in particular on hypertensive subjects and on subjects falling under the medical definition of 'salt-sensitive population' is described in the literature in humans. This effect was mainly due to the combined activity of sodium and chloride.

Based on the toxicological database available the Panel considered human data more appropriate to identify a level of chloride intake which does not raise a safety concern. In humans, potassium chloride providing 40 mg chloride/kg bw per day for 4 weeks was without adverse effects (Barden et al.,

1986). Based on this study, a safe dose cannot be identified due to the lack of data describing the dose-response relationship between chloride intake and blood pressure.

Chlorides (E 507–509, E 511) are permitted as food additives in many food categories at *quantum satis* (*QS*).

Dietary exposure to chlorides derived from the use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as food additives was calculated according to different exposure scenarios based on the provided use levels. The Panel considered that the refined exposure assessment scenario resulted in more realistic long-term exposure estimates compared to the *maximum level exposure assessment scenario* which was considered very conservative.

The Panel, did not identify brand loyalty to any of the main contributing food categories, therefore selected the *non-brand loyal* scenario as the most relevant for risk characterisation. In the *non- brand-loyal scenario*, mean exposure ranged from 2 mg/kg bw per day in the elderly to 42 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 5 mg/kg bw per day in the elderly to 71 mg/kg bw per day in toddlers.

The Panel considered that the uncertainties in exposure assessment identified would, in general, result in an overestimation of the exposure to chloride derived from the combined use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) for all exposure scenarios.

The Panel identified a human dose of 40 mg chloride/kg bw per day as a reference value for the assessment. Mean levels of exposure in all age groups were below or at this reference value, which indicates no safety concern. In some age groups (toddlers, children and adolescents), the 95th percentile exposure estimates were slightly above this reference value.

Hydrochloric acid (E 507) is authorised in foods for infants below 16 weeks of age in FC 13.1.5.1 Dietary foods for infants for special medical purposes and special formulae for infants. Industry did not provide use levels for this food category and therefore it was not possible to perform exposure assessment for this age group. The average chloride content in human milk has been reported to be around 400 mg/L (EFSA NDA 2014). Based on the opinion of the SCF (2003), Directive 2006/141/EC provides for minimum and maximum chloride contents in infant formula and follow-on formula of 50 to 160 mg/100 kcal. The minimum and maximum levels for chloride in infant formula for special medical purposes are set at 60 and 160 mg/100 kcal (Commission Delegated Regulation (EU) 2016/128). In the absence of actual use levels of hydrochloric acid (E 507) in foods for infants for special medical purposes and special formulae for infants, the Panel considered that the use levels of E 507 should not lead to exceedance of the maximum limit for chloride set by the legislation.

In conclusion, chloride is a natural constituent of human, animals and plants and is present in all biological materials, including foodstuffs. Based on the toxicological database available the Panel concluded that the exposure to chloride from hydrochloric acid and its potassium, calcium and magnesium salts (E 507, E 508, E 509, E 511) does not raise a safety concern at the reported use and use levels.

The Panel noted that because of the lack of data on use levels of hydrochloric acid (E 507) in specific formulae used for infants under special medical conditions the safety of this use could not be assessed.

The Panel recommends that:

- the European Commission considers lowering the current limits for toxic elements (arsenic, lead and mercury) in the EU specifications for hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) in order to ensure that hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as a food additive will not be a significant source of exposure to those toxic elements in food.
- Information on the possible use and use levels of hydrochloric acid (E 507) as a food additive in specific formulae used for infants under special medical conditions should be provided in order to enable the Panel to estimate the exposure and evaluate the safety of use of this food additive in infants below 16 weeks of age.

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1. Introduction

The present opinion document deals with the re-evaluation of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) when used as food additives.

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised food additives in the European Union (EU) in accordance with Annex II and III to Regulation (EC) No 1333/2008 and have been previously evaluated by the EU Scientific Committee for Food (SCF) in 1978, 1988, 1989, 1991, 1993 and 2001 (SCF, 1978, 1989, 1991a,b, 1993, 2001a,b) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1963, 1965, 1973 and 1979 (JECFA, 1964, 1966a,b, 1974a, 1980).

1.1. Background and Terms of Reference as provided by the European Commission

1.1.1. Background

Regulation (EC) No 1333/2008[1] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[2]. This Regulation also foresees that food additives are re-evaluated whenever necessary in the light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU[3] of 2001. The report "Food additives in Europe 2000[4]" submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

1.1.2. Terms of Reference

The Commission asks the European Food Safety Authority to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.1.3. Interpretation of Terms of Reference

The Panel considered that potassium, calcium and magnesium salts of chlorides are expected to dissociate in the gastrointestinal tract into chloride and their corresponding cations. The safety of resulting potassium, calcium and magnesium cations is not the focus of this opinion.

[1] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16–33.
[2] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.
[3] COM(2001) 542 final.
[4] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002, 560.

1.2. Information on existing authorisations and evaluations

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised as food additives in the EU in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.[5]

In its first report on food additives of various technological functions adopted in 1990, the SCF evaluated chloride as ion: The Committee concluded '*These anions [chloride, sulphate and carbonate] are natural constituents of man, animals and plants, and therefore occur in foodstuffs. They, together with certain cations constitute the major electrolytes present in all biological materials. The Committee therefore established a group ADI not specified for these anions, although exhaustive systematic toxicological studies have not been carried out with these ions. No safety problems are likely to arise, provided the contributions from food do not disturb the homoeostatic mechanisms controlling the electrolyte balance of the body*' (SCF, 1991b). At the same occasion, the Committee accepted hydrochloric acid and its potassium, calcium and magnesium salts as food additives and allocated the acceptable daily intake (ADI) 'not specified' to the salts as well with the remark that large doses of magnesium ions cause diarrhoea and should be avoided.

The SCF has furthermore accepted the use of potassium chloride, calcium chloride and magnesium chloride as sources of potassium, calcium and magnesium, respectively, in infant formulae and in weaning foods (SCF, 1989, 1991a). For use as technological additives in weaning food, the SCF accepted hydrochloric acid, potassium chloride and calcium chloride when used as acid regulators according to good manufacturing practice (GMP) (SCF, 1991a).

Calcium chloride was found acceptable as an additive to fine bakers' wares up to 5 g/kg (SCF, 1978).

The nutritional property of chloride, potassium, calcium and magnesium was evaluated by the SCF in 1992 (SCF, 1993).

Hydrochloric acid and/or its salts have been evaluated by JECFA in several occasions. In 1963, calcium chloride was evaluated and an ADI 'not limited'[6] was allocated (JECFA, 1964).

Hydrochloric acid (E 507) has been evaluated by JECFA in 1965 who concluded that in concentrations approaching the physiological pH of gastric juice hydrochloric acid is probably of no toxicological significance. Thus, there appears to be no need to limit on toxicological grounds the use of hydrochloric acid in accordance with good manufacturing practice (JECFA, 1966a). JECFA concluded also that it is not regarded as a toxic substance in the concentrations that are used in food technology and therefore set an ADI 'not limited' for the substance used at GMP (JECFA, 1966a,b).

In 1973, calcium chloride was again on the agenda of JECFA, but no new data were submitted, so the Committee confirmed the ADI 'not limited' (JECFA, 1974a).

In 1979, JECFA included magnesium chloride and potassium chloride in the ADI 'not specified' for hydrochloric acid. This decision was based on the fact that these salts are freely ionisable and the ADI was based on the chloride anion as evaluated in 1965 (JECFA, 1980).

In 2002, hydrochloric acid and its potassium, calcium and magnesium sodium salts were evaluated by TemaNord which concluded that chlorides are safe food additives (TemaNord, 2002).

The EFSA's Panel on Dietetic Products, Nutrition and Allergies (NDA) performed aeesessment of available data for chloride with aim of setting a tolerable upper level (UL) of chloride (EFSA NDA Panel, 2005). The NDA Panel concluded that '*The available data are not sufficient to establish an upper level for chloride from dietary sources*'. In its opinion the NDA Panel furthermore reported a daily chloride intake of approximately 5–7 g and noted that it exceeded the dietary need (2–2.5 g/chloride day in adults).

At the time when this opinion was adopted, the NDA Panel has issued a scientific opinion on the dietary reference value for chloride for Public consultation (EFSA NDA Panel, 2019).

In addition to the authorised uses as food additives, to the potassium, calcium and magnesium chlorides are included in the list of mineral substances which may be used in the manufacture of food

[5] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) no 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p 1.

[6] This term was used by JECFA until 1973 for substances where the Committee found no reasons to allocate a numerical ADI considering the likely exposure when the substance was used according to Good Manufacturing Practice. From its 18th meeting in 1974 JECFA abandoned this term and substituted it with "not specified. JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1974b. Evaluation of certain food additives. Eighteenth Report of the Joint FAO/WHO Expert Committee on Food Additives. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_557.pdf.

supplements reported in the Annex II of Directive 2002/46/EC[7] and in the list of vitamin formulations and mineral substances which may be added to foods reported in the Annex II of Regulation (EC) No 1925/2006[8]

These are also included in the Union list set out in the Annex to Regulation (EU) No 609/2013[9] as permitted for use in: infant formula and follow-on formula, in processed cereal-based food and baby food, food for special medical purposes and total diet replacement for weight control.

In Canada, hydrochloric acid (E 507), potassium chloride (E 508) and calcium chloride (E 509) are authorised under the Marketing Authorization for Food Additives (Government of Canada) with food additive (MPL) rely on good manufacturing practice (GMP) (http://laws-lois.justice.gc.ca/PDF/C.R.C.,_c._870.pdf).

In Australia, hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised as food additives under the Standard 1.3.1 of the Australia New Zealand Food Standards Code (Food Standard Australia New Zealand http://www.foodstandards.gov.au/Pages/default.aspx; Federal Register of Legislation - Australian Government, https://www.legislation.gov.au/).

2. Data and methodologies

Data

The Panel on Food Additives and Flavourings (FAF) was not provided with a newly submitted dossier. EFSA launched public call for data[10] to collect information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data,[10] information from previous evaluations and additional available literature up to 12 March 2019. Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based however these were not always available to the Panel.

Additional information was requested from Specialised Nutrition Europe during the assessment process on 9 March 2018 regarding hydrochloric acid (E 507) as food additive in infant formula for uses in categories 13.1.5.1. No information was received.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database[11]) was used to estimate the dietary exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511).

The Mintel's Global New Products Database (GNPD) was used to identify the use of the additives in food and beverage products and food supplements within the EU's food market. This online database contains the compulsory ingredient information present on the label of products.

Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee.

The Panel assessed the safety of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the SCF (2001a,b,c) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

On 31 May 2017, EFSA published a guidance document on the risk assessment of substances present in food intended for infants below 16 weeks of age enabling EFSA to assess the safety of food

[7] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

[8] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.

[9] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35–56.

[10] Call for technical and toxicological data on miscellaneous food additives to be re-evaluated under the Regulation (EU) No 257/2010 Published: 11 August 2017. Available from: https://www.efsa.europa.eu/en/consultations/call/170811

[11] Available online: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

additives used in foods for infants below 16 weeks of age (EFSA Scientific Committee, 2017). Therefore, the current evaluation addresses all population groups, including the infants below 12 or 16 weeks of age following the principles outlined in that guidance.

When the test substance was administered in the feed or in the drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake was calculated by the Panel using the relevant default values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012) for studies in rodents or, in the case of other animal species, by JECFA (2000). In these cases, the daily intake is expressed as equivalent. When in human studies in adults (aged above 18 years), the dose of the test substance administered was reported in mg/person per day, the dose in mg/kg bw per day was calculated by the Panel using a body weight of 70 kg as default for the adult population as described in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012).

Dietary exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) from their use as food additives was estimated combining food consumption data from the Comprehensive Database with reported use levels submitted to EFSA following a call for data. The exposure was estimated using different scenarios (see Section 3.4). Uncertainties in the exposure assessment were identified and discussed.

3. Assessment

3.1. Technical data

3.1.1. Identity of the substances

Hydrochloric acid (E 507)

According to Commission Regulation (EU) No 231/2012, hydrochloric acid (E 507) has molecular formula HCl, EINECS (EC) No 231-595-7 and molecular weight 36.46 g/mol. The corresponding CAS Registry number is 7647-01-0: this identifier is not present in the Regulation. Hydrochloric acid is soluble in water and in ethanol, and is a clear, colourless or slightly yellowish, corrosive liquid having a pungent odour.

In JECFA (2006), the chemical is identified as hydrochloric acid with INS No 507 and the CAS Registry number reported above.

Potassium chloride (E 508)

According to Commission Regulation (EU) No 231/2012), potassium chloride (E 508) has molecular formula KCl, EINECS (EC) No 231-211-8 and molecular weight 74.56 g/mol. The corresponding CAS Registry number is 7447-40-7: this identifier is not present in the Regulation. Potassium chloride is odourless and occurs as colourless, elongated, prismatic or cubital crystals or a white granular powder; it is freely soluble in water and insoluble in ethanol.

In JECFA (2006), the chemical is identified as potassium chloride with INS No 508 and the CAS Registry number reported above.

Calcium chloride (E 509)

According to Commission Regulation (EU) No 231/2012[12]), calcium chloride (E 509) has molecular formula $CaCl_2 \cdot nH_2O$ (n = 0, 2, or 6), EINECS (EC) No 233-140-8 and molecular weight (g/mol) 110.99 (anhydrous), 147.02 (dihydrate), or 219.08 (hexahydrate). The corresponding CAS Registry numbers for the three different chemical forms are 10043-52-4, 10035-04-8 and 7774-34-7, respectively: these identifiers are not present in the Regulation. In the Regulation, calcium chloride is described as a white, odourless, hygroscopic powder or deliquescent crystals, soluble in water and in ethanol.

In JECFA (2006), the chemical in its three different forms is identified as calcium chloride with INS No 509 and CAS Registry No 10043-52-4.

Magnesium chloride (E 511)

According to Commission Regulation (EU) No 231/2012[12]), magnesium chloride (E 511) has molecular formula $MgCl_2 \cdot 6H_2O$, EINECS (EC) No 232-094-6 and molecular weight 203.30 g/mol. The corresponding CAS Registry number is 7786-30-3: this identifier is not present in the Regulation.

[12] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1–295.

Magnesium chloride is described as colourless, odourless, very deliquescent flakes, granules, lumps, or crystals, very soluble in water and freely soluble in ethanol.

In JECFA (2006), the chemical is identified with the chemical name magnesium chloride hexahydrate, with INS No 511 and CAS Registry No 7786-30-3.

3.1.2. Specifications

The specifications for hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as defined in the Commission Regulation (EU) No 231/2012 and by JECFA (2006) are listed in Tables 1, 2, 3 and 4, respectively.

Table 1: Specifications for hydrochloric acid (E 507) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Definition	EINECS (EC) No: 231-595-7	CAS No: 7647-01-0
	Chemical name: hydrochloric acid	Chemical name: hydrochloric acid
	Chemical formula: HCl	Chemical formula: HCl
	Molecular weight (g/mol): 36.46	Formula weight: 36.46 g/mol
	Assay: hydrochloric acid is commercially available in varying concentrations. Concentrated hydrochloric acid contains not less than 35.0% HCl	Assay: not less than 97.0% and not more than 103.0% of the labelled amount
Description	Clear, colourless or slightly yellowish, corrosive liquid having a pungent odour	Clear colourless or slightly yellowish liquid with a pungent odour. Various concentrations are supplied as products of commerce
Synonyms	Hydrogen chloride; Muriatic acid	Muriatic acid
Functional uses	—	Acid
Identification	Test for acid: passes test	Test for acid: passes test[(a)]
	Test for chloride: passes test	Test for chloride: passes test
	Solubility: soluble in water and ethanol	Solubility: soluble in water and in ethanol
Purity	Total organic compounds (non-fluorine containing): not more than 5 mg/kg	Total organic compounds (non-fluorine): not more than 5 mg/kg
	Benzene: not more than 0.05 mg/kg	Benzene: not more than 0.05 mg/kg
	Fluorinated compounds (total): not more than 25 mg/kg	Fluorinated organic compounds (total): not more than 25 mg/kg
	Non-volatile matter: not more than 0.5%	Non-volatile residue: not more than 0.5%[(a)]
	Reducing substances: not more than 70 mg/kg (as SO_2)	Reducing substances: not more than 70 mg/kg as sulfur dioxide[(a)]
	Oxidising substances: not more than 30 mg/kg (as Cl_2)	Oxidising substances: not more than 30 mg/kg as chlorine[(a)]
	Sulfate: not more than 0.5%	Sulfate: not more than 0.5%[(a)]
	Iron: not more than 5 mg/kg	Iron: not more than 5 mg/kg[(a)]
	Arsenic: not more than 1 mg/kg	—
	Lead: not more than 1 mg/kg	Lead: not more than 1 mg/kg[(a)]
	Mercury: not more than 1 mg/kg	—

(a): In JECFA (2006), a specific test is directly available from the data sheet.

Table 2: Specifications for potassium chloride (E 508) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Definition	EINECS (EC) No: 231-211-8	CAS No: 7447-40-7
	Chemical name: potassium chloride	Chemical name: potassium chloride
	Chemical formula: KCl	Chemical formula: KCl
	Molecular weight (g/mol): 74.56	Formula weight: 74.56 g/mol
	Assay: content not less than 99% on the dried basis	Assay: not less than 99% on the dried basis
Description	Colourless, elongated, prismatic or cubital crystals or white granular powder. Odourless	Colourless, elongated, prismatic or cubital crystals or white granular powder; odourless
Synonyms	Sylvine; Sylvite	Sylvine; Sylvite
Functional uses	—	Seasoning agent, gelling agent, yeast food
Identification	Solubility: freely soluble in water. Insoluble in ethanol	Solubility: freely soluble in water; insoluble in ethanol
	Test for potassium: passes test	Test for potassium: passes test
	Test for chloride: passes test	Test for chloride: passes test
Purity	Loss on drying: not more than 1% (105 °C, 2 hours)	Loss on drying: not more than 1% (105 °C, 2 h)
	—	Acidity or alkalinity[(a)]
	—	Iodide or bromide[(a)]
	Test for sodium: negative	Test for sodium: negative test
	Arsenic: not more than 3 mg/kg	—
	Lead: not more than 2 mg/kg	Lead: not more than 2 mg/kg[(a)]
	Mercury: not more than 1 mg/kg	—
	Cadmium: not more than 1 mg/kg	—

(a): In JECFA (2006), a specific test is directly available from the data sheet.

Table 3: Specifications for calcium chloride (E 509) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Definition	EINECS (EC) No: 233-140-8	CAS No: 10043-52-4
	Chemical name: calcium chloride	Chemical name: calcium chloride
	Chemical formula: $CaCl_2 \cdot nH_2O$ (n = 0, 2, or 6)	Chemical formula: $CaCl_2$ (anhydrous) $CaCl_2 \cdot 2H_2O$ (dihydrate) $CaCl_2 \cdot 6H_2O$ (hexahydrate)
	Molecular weight (g/mol): 110.99 (anhydrous) 147.02 (dihydrate) 219.08 (hexahydrate)	Formula weight (g/mol): 110.99 (anhydrous) 147.02 (dihydrate) 219.08 (hexahydrate)
	Assay: content not less than 93% on the anhydrous basis	Assay: Anhydrous: not less than 93% Dihydrate: not less than 99.0% and not more than the equivalent of 107.0% of $CaCl_2 \cdot 2H_2O$ Hexahydrate: not less than 98.0% and not more than the equivalent of 110% of $CaCl_2 \cdot 6H_2O$

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Description	White, odourless, hygroscopic powder or deliquescent crystals	Anhydrous: white, deliquescent lumps or porous masses Dihydrate: white, hard, deliquescent fragments or granules Hexahydrate: colourless, very deliquescent crystals
Synonyms	—	—
Functional uses	—	Firming agent
Identification	Test for calcium: passes test	Test for calcium: passes test
	Test for chloride: passes test	Test for chloride: passes test
	Solubility: soluble in water and in ethanol	Solubility: anhydrous: freely soluble in water and ethanol dihydrate: freely soluble in water; soluble in ethanol hexahydrate: very soluble in water and ethanol
Purity	—	Free alkali: not more than 0.15% as Ca $(OH)_2$[(a)]
	Magnesium and alkali salts: not more than 5% on the dried basis (calculated as sulfates)	Magnesium and alkali salts: not more than 5%[(a)]
	Fluoride: not more than 40 mg/kg	Fluoride: not more than 40 mg/kg
	Arsenic: not more than 3 mg/kg	—
	Lead: not more than 2 mg/kg	Lead: not more than 2 mg/kg[(a)]
	Mercury: not more than 1 mg/kg	—

(a): In JECFA (2006), a specific test is directly available from the data sheet.

Table 4: Specifications for magnesium chloride (E 511) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Definition	EINECS No: 232-094-6	CAS No: 7786-30-3
	Chemical name: magnesium chloride	Chemical name: magnesium chloride hexahydrate
	Chemical formula: $MgCl_2 \cdot 6H_2O$	Chemical formula: $MgCl_2 \cdot 6H_2O$
	Molecular weight (g/mol): 203.30	Formula weight (g/mol): 203.30
	Assay: content not less than 99.0%	Assay: not less than 99.0% and not more than 105.0%
Description	Colourless, odourless, very deliquescent flakes or crystals	Colourless, odourless flakes, granules, lumps or crystals; very deliquescent
Synonyms	—	—
Functional uses	—	Firming agent, colour retention agent
Identification	Test for magnesium: passes test	Test for magnesium: passes test
	Test for chloride: passes test	Test for chloride: passes test
	Solubility: very soluble in water, freely soluble in ethanol	Solubility: very soluble in water; freely soluble in ethanol
Purity	Ammonium: not more than 50 mg/kg	Ammonium: not more than 50 mg/kg[(a)]
	Arsenic: not more than 3 mg/kg	—
	Lead: not more than 2 mg/kg	Lead: not more than 2 mg/kg[(a)]
	Mercury: not more than 1 mg/kg	—

(a): In JECFA (2006), a specific test is directly available from the data sheet.

The Panel noted that according to the EU specifications for E 507 the impurities of the toxic elements arsenic, lead and mercury are accepted up to a concentration of 1 mg/kg each; for E 508, E 509 and E 511, the corresponding limits are 3, 2 and 1 mg/kg, respectively; for E 508 there is also a limit for cadmium set at 1 mg/kg. Contamination at such levels could have a significant impact on the exposure to these metals, for which the exposure already is close to the health-based guidance values or benchmark doses established by EFSA (EFSA CONTAM Panel, 2009a,b, 2010, 2012a,b,c, 2014).

The Panel noted that, while the EU specifications have a limit for total organic compounds (non-fluorine containing), the identities of specific organic compounds are not indicated. The Panel assumed that residues of chlorinated compounds (including vinyl chloride) are included in this parameter but this should be better specified. Additionally, the identities of specific fluorinated compounds, for which also a limit is set in the EU specifications, are not indicated.

3.1.3. Manufacturing process

There are several ways to manufacture anhydrous hydrogen chloride – from which its aqueous solution, hydrochloric acid (E 507), is obtained – as per the following examples (IARC, 1992; Hisham and Bommaraju, 2000; OECD, 2002a): (a) by direct reaction of the elements hydrogen and chlorine; (b) decomposition of metal chlorides, particularly sodium chloride, by strong acids (namely, H_2SO_4); (c) as a by-product of chlorination processes, e.g. in the production of dichloromethane, trichloroethylene, tetrachloroethylene, or vinyl chloride; (d) from spent pickle liquor in metal treatment, by thermal decomposition of the hydrated heavy metal chlorides; (e) from incineration of chlorinated organic waste. By far, the most important process to obtain hydrogen chloride is as a by-product of chlorination. Anhydrous hydrogen chloride can be obtained with a purity greater than 99.7% (OECD, 2002a). The Panel noted that according to production process described in (c) some volatile organic chlorides could be present, among these vinyl chloride (a known carcinogenic compound. The Panel noted specifications for vinyl chloride are present in EU specification.

Potassium chloride (KCl) is extracted from natural sources of potassium salt deposits; minerals such as sylvinite, carnallite and kainite contain high levels (approximately 25–99%) of potassium chloride (OECD, 2001). Extraction is followed by milling, washing, screening, flotation, crystallisation, refining and drying. The marketed chemical is available with a purity greater than 99%; impurities (e.g. sodium and magnesium chlorides, alkaline earth sulfates) depend on the raw material and production process.

Commercial calcium chloride is produced using different processes: (a) in a closed system by refining of natural brines containing a sufficiently high proportion of calcium chloride: this is the primary route for making the chemical in the United States; (b) reaction of calcium hydroxide with ammonium chloride in soda production (Solvay process): this process involves the reaction of sodium chloride (ordinary salt) with calcium carbonate (limestone) using ammonia as a catalyst to form sodium carbonate and calcium chloride; (c) reaction of hydrochloric acid with calcium carbonate (limestone): typically, the hydrochloric acid employed is a by-product of another commercial process, and the conversion to calcium chloride is motivated by waste avoidance (Documentation provided to EFSA no.1; Vrana, 2000; OECD, 2002b). The first two processes account for over 90% of the total calcium chloride production. The marketed chemical is available with a purity greater than 94%; sodium, potassium and magnesium chlorides, some sulfates, calcium hydroxide, etc., can be present as impurities.

Magnesium chloride is produced in large quantities according to various procedures, among which: (a) using mother liquors from the recovery of potassium chloride from carnallite: the liquor, containing up to 28% magnesium chloride, is subject to evaporation to increase the concentration of the chemical, until potassium and sodium chlorides and sodium and magnesium sulfates crystallise out and are removed; iron(II) is also removed; following further evaporation, upon cooling the solution yields impure magnesium chloride as a glassy mass; magnesium chloride hexahydrate is purified by repeated crystallisations; (b) by chlorination of magnesium oxide from various sources in the presence of carbon or carbonaceous materials; (c) with a one-step process, based on the reaction of magnesite ($MgCO_3$) and chlorine gas in the presence of carbon monoxide at 900°C: anhydrous magnesium chloride and carbon dioxide are produced (Kramer, 2000). The latter is removed and liquid magnesium chloride is collected at the bottom of the reactor. Magnesium chloride hexahydrate is commercially available with a purity higher than 99%.

3.1.4. Methods of analysis in food

Volumetric methods based on argentometry have a long history behind, but they are still widely used for the determination of chlorides in various matrices. The most popular argentometric methods are named after their inventors K. Fajans (1887–1975), K.F. Mohr (1806–1879), and J. Volhard (1834–1910): as titrant, all use silver nitrate ($AgNO_3$) solutions to obtain a precipitate of a nearly insoluble silver chloride. Mohr's and Volhard's methods, variously adapted to analytical requirements over the years, have a specific interest for chloride determination in food.

According to Mohr's method, chlorides are determined in a neutral or slightly alkaline environment employing potassium chromate (K_2CrO_4) as an indicator; when all chloride ions have reacted with silver ions, excess silver reacts with chromate anions yielding a red-brown precipitate of silver chromate (Ag_2CrO_4). Volhard's method is a reverse titration that can be used to analyse chlorides as well as thiocyanates: excess silver nitrate is added to the analyte, which is then acidified with nitric acid (HNO_3); the silver chloride precipitate is filtered, and the remaining silver nitrate is titrated against potassium or ammonium thiocyanate (SCN^-) in the presence of ferric ammonium sulfate (FAS, $NH_4Fe^{III}(SO_4)_2 \cdot 12H_2O$); when all excess silver is precipitated as thiocyanate, the excess of the latter forms a red complex with iron(III) ions, $Fe(SCN)^{2+}$ (titration end-point).

Several titrimetric assays based on Mohr's and Volhard's methods are recommended by the Codex Alimentarius Commission (Codex Alimentarius, 2019) for the determination of chlorides in seafood products, fruit and vegetable juices and nectars, butter and mineral waters. Other standardised methods – employing silver nitrate as a titrant and potentiometric indication/detection – are also recommended for chloride determination in seafood products, special foods, infant formula, fruit and vegetable juices and nectars, dairy products and bouillons (soups, broths). A titrimetric method using mercury^{II} nitrate ($Hg(NO_3)_2$) as a titrant is also identified to measure chlorides in mineral waters.

In the aforementioned Codex Alimentarius Commission's document, a number of analytical methods are recommended for the determination of sodium, potassium, calcium and magnesium in a variety of foods, such as: special foods and infant formula, milk and dairy products, processed vegetables and fruit, fruit juices and nectars, table salt, and mineral waters. Methods are in general based on atomic absorption spectrometry (AAS), inductively coupled plasma (ICP) emission spectrometry, ICP-optical emission spectroscopy (OES) and complexometric titrimetry.

The recommended standardised methods referred to above were developed by the following international organisations: Association Internationale de l'Industrie des Bouillons et Potages (AIIBP), Association of Official Analytical Chemists (AOAC) International, European Committee for Standardization (CEN), European Salt Producers' Association (EuSalt), International Dairy Federation (IDF), International Fruit and Vegetable Juice Association (IFU), International Organization for Standardization (ISO) and Nordic Committee on Food Analysis (NMKL). A Codex Standard (CXS 167) and a method described by the World Health Organization (WHO), respectively, for chlorides and potassium determination, are also mentioned.

Additional methods to detect chloride, alkali metal and alkaline earth metal ions in food can be met in the scientific literature, as by the following examples specifically concerning chlorides. In Polish standard PN-EN ISO 10304, chlorides in water are analysed by ion chromatography (IC); Johnson and Olson (1985) compared the results of four methods – Mohr's, Volhard's, ion selective electrode (ISE) and chloride analyser – applied to chloride determination in a variety of cheeses; likewise, Rajković (2010) compared the results of Volhard's and ISE methods employed for chloride determination in several different cheeses.

3.1.5. Stability of the substance, and reaction and fate in food

Hydrochloric acid and its potassium, calcium and magnesium salts are readily soluble in water: these substances are expected to dissolve in aqueous media into their respective ions.

Concentrated hydrochloric acid is a strong and corrosive acid that reacts with most metals: as expected, the reaction rate depends on temperature, concentration of acid, inhibiting agents, nature of the surface oxide film, etc. (Hisham and Bommaraju, 2000; OECD, 2002a). However, when used in food processing, or as a food additive to adjust the pH, hydrochloric acid is neutralised or buffered by the food to which it is added. The small amounts of hydrochloric acid that may persist in foods or drinks, would, in turn, be neutralised and buffered during ingestion and digestion, or after absorption.

A group of process-induced food contaminants, including monochloropropanediols (MCPDs) and their esterified forms, has raised the interest of fats and oils producers in the past few years. Toxic MCPDs and their esters are contaminants of processed vegetable oils (EFSA CONTAM Panel, 2016):

they are formed in hydrolysed vegetable protein (HVP) – a flavour-enhancing food ingredient – during the hydrochloric acid-mediated hydrolysis step of the manufacturing process. In food production, MCPDs are formed from the reaction of endogenous or added chloride with glycerol or acylglycerols.

The Panel noted that the presence of 3-MCPD (and its esters) in processed foods could be mainly due to the ingredients in products containing refined oils or vegetable fats (Bakhiya et al., 2011) and in soy sauces because of the processing of HVP. Therefore, the use of potassium, calcium or magnesium chlorides as food additives, is not anticipated to contribute significantly to the exposure to chloropropanediols.

Potassium, as the other alkali metals, has a single *s* electron outside a noble gas core; as a result of the electronic structure and characteristics, its chemistry is principally that of the oxidation state K^{1+}; no other cation is known. The chemistry of the element is mainly that of its ionic salts in the solid state and solvated cation (Cotton et al., 1999).

According to Rammelberg et al. (2012), calcium chloride hydrates undergo some dehydration already at room temperature: under a heating rate of 1°C/min, the first dehydration phase ($CaCl_2{\cdot}6H_2O \rightarrow CaCl_2{\cdot}4H_2O$) appears to be completed at 63°C. As the temperature increases, the chemical undergoes a progressive dehydration until, at quite high temperatures, all water and chlorine are lost and only calcium oxide (CaO) remains. The dehydration kinetics depends on heating rate whereas the peak power of hydration strongly depends on vapour pressure and time.

Magnesium chloride hexahydrate is stable at standard temperature and pressure (STP). However, as temperature increases, the chemical undergoes a stepwise dehydration that starts at around 95–110°C (Kramer, 2000; Rammelberg et al., 2012). As for calcium chloride, the dehydration kinetics depends on heating rate.

3.2. Authorised uses and use levels

Maximum levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) have been defined in Annex II to Regulation (EC) No 1333/2008 on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, at least one of these four additives is authorised in the EU at *quantum satis* (*QS*) in the food categories listed in Table 5.

Table 5: MPLs of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) in foods according to Annex II to Regulation (EC) No 1333/2008

Food Category number	Food categories	E-number	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
01.3	Unflavoured fermented milk products, heat-treated after fermentation	Group I		*Quantum satis*
01.4	Flavoured fermented milk products including heat-treated products	Group I		*Quantum satis*
01.5	Dehydrated milk as defined by Directive 2001/114/EC	E 509		*Quantum satis*
01.6.3	Other creams	Group I		*Quantum satis*
01.7.1	Unripened cheese excluding products falling in category 16	Group I	Except mozzarella	*Quantum satis*
01.7.2	Ripened cheese	E 509		*Quantum satis*
01.7.5	Processed cheese	Group I		*Quantum satis*
01.7.6	Cheese products (excluding products falling in category 16)	Group I	E 509 only ripened products	*Quantum satis*
01.8	Dairy analogues, including beverage whiteners	Group I		*Quantum satis*
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Group I		*Quantum satis*
02.3	Vegetable oil pan spray	Group I		*Quantum satis*

Food Category number	Food categories	E-number	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
03	Edible ices	Group I		*Quantum satis*
04.2.1	Dried fruit and vegetables	Group I		*Quantum satis*
04.2.2	Fruit and vegetables in vinegar, oil, or brine	Group I		*Quantum satis*
04.2.3	Canned or bottled fruit and vegetables	E 509		*Quantum satis*
04.2.4.1	Fruit and vegetable preparations excluding compote	Group I		*Quantum satis*
04.2.4.2	Compote, excluding products covered by category 16	E 509	Only fruit compote other than apple	*Quantum satis*
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut purée as defined by Directive 2001/113/EC	E 509		*Quantum satis*
04.2.5.3	Other similar fruit or vegetable spreads	E 509		*Quantum satis*
04.2.5.4	Nut butters and nut spreads	Group I		*Quantum satis*
04.2.6	Processed potato products	Group I		*Quantum satis*
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	Group I	Only energy-reduced or with no added sugar	*Quantum satis*
05.2	Other confectionery including breath freshening microsweets	Group I		*Quantum satis*
05.3	Chewing gum	Group I		*Quantum satis*
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Group I		*Quantum satis*
06.2.2	Starches	Group I		*Quantum satis*
06.3	Breakfast cereals	Group I		*Quantum satis*
06.4.2	Dry pasta	Group I	Only gluten free and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	*Quantum satis*
06.4.4	Potato gnocchi	Group I	Except fresh refrigerated potato gnocchi	*Quantum satis*
06.4.5	Fillings of stuffed pasta (ravioli and similar)	Group I		*Quantum satis*
06.5	Noodles	Group I		*Quantum satis*
06.6	Batters	Group I		*Quantum satis*
06.7	Pre-cooked or processed cereals	Group I		*Quantum satis*
07.1	Bread and rolls	Group I	Except products in 7.1.1 and 7.1.2	*Quantum satis*
07.2	Fine bakery wares	Group I		*Quantum satis*
08.3.1	Non-heat-treated meat products	Group I		*Quantum satis*
08.3.2	Heat- treated meat products	Group I	Except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*	*Quantum satis*

Food Category number	Food categories	E-number	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
08.3.3	Casings and coatings and decorations for meat	Group I		*Quantum satis*
09.2	Processed fish and fishery products including molluscs and crustaceans	Group I		*Quantum satis*
09.3	Fish roe	Group I	Only processed fish roe	*Quantum satis*
10.2	Processed eggs and egg products	Group I		*Quantum satis*
11.2	Other sugars and syrups	Group I		*Quantum satis*
12.1.1	Salt	E 511	Only sea-salt	*Quantum satis*
12.1.2	Salt substitutes	Group I		*Quantum satis*
12.2.2	Seasonings and condiments	Group I		*Quantum satis*
12.3	Vinegars and diluted acetic acid (diluted with water to 4-30% by volume)	Group I		*Quantum satis*
12.4	Mustard	Group I		*Quantum satis*
12.5	Soups and broths	Group I		*Quantum satis*
12.6	Sauces	Group I		*Quantum satis*
12.7	Salads and savoury-based sandwich spreads	Group I		*Quantum satis*
12.8	Yeast and yeast products	Group I		*Quantum satis*
12.9	Protein products, excluding products covered in category 1.8	Group I		*Quantum satis*
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	E 507	Only processed cereal-based foods and baby foods, only for pH adjustment	*Quantum satis*
13.1.4	Other foods for young children	E 507	Only for pH adjustment	*Quantum satis*
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 507	Only as rising agent	*Quantum satis*
13.1.5.2[(a)]	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 507		*Quantum satis*
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	Group I		*Quantum satis*
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	Group I		*Quantum satis*
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Group I	Including dry pasta	*Quantum satis*
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Group I	Only vegetable juices	*Quantum satis*
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	Group I	Only vegetable nectars	*Quantum satis*
14.1.4	Flavoured drinks	Group I		*Quantum satis*

Food Category number	Food categories	E-number	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
14.1.5.2	Other	Group I	Excluding unflavoured leaf tea; including flavoured instant coffee	*Quantum satis*
14.2.3	Cider and perry	Group I		*Quantum satis*
14.2.4	Fruit wine and made wine	Group I		*Quantum satis*
14.2.5	Mead	Group I		*Quantum satis*
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Group I	Except whisky or whiskey	*Quantum satis*
14.2.7.1	Aromatised wines	Group I		*Quantum satis*
14.2.7.2	Aromatised wine-based drinks	Group I		*Quantum satis*
14.2.7.3	Aromatised wine-product cocktails	Group I		*Quantum satis*
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol	Group I		*Quantum satis*
15.1	Potato-, cereal-, flour- or starch-based snacks	Group I		*Quantum satis*
15.2	Processed nuts	Group I		*Quantum satis*
16	Desserts excluding products covered in category 1, 3 and 4	Group I		*Quantum satis*
17.1	Food supplements supplied in a solid form, excluding food supplements for infants and young children	Group I		*Quantum satis*
17.2	Food supplements supplied in a liquid form, excluding food supplements for infants and young children	Group I		*Quantum satis*
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	Group I		*Quantum satis*

(a): Based on note of the legislation: 'The additives of categories 13.1.2 and 13.1.3 are applicable'.
MPL: maximum permitted level.

Potassium, calcium and magnesium chlorides (E 508, E 509 and E 511) are also authorised according to Annex III, Part 1 (carriers in food additives) at *QS*.

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are also authorised according to Annex III to Regulation 1333/2008, Parts 2 (food additives other than carriers added to food additives), 3 (food additives including carriers in food enzymes), 4 (food additives added to food flavourings) and 5 section A (food additives in nutrients other than nutrients intended for food for infants and young children) at *QS*.

3.3. Exposure data

3.3.1. Reported use levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511)

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives with an MPL at *QS*.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued a

public call[13] for occurrence data (use level and/or concentration data) on hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511). In response to this call, use levels for these additives were submitted to EFSA by industry. No analytical data were made available by the Member States.

Summarised data on reported use levels in foods provided by industry

Industry provided use levels (n = 100) for the four chloride additives (E 507; E 508; E 509; E 511) in foods belonging to 18 out of the 78 food categories in which they are authorised according to Annex II to Regulation (EC) No 1333/2008 (Table 6). For E 509, one use level was provided for FC 'Entire fresh fruit and vegetables' for its authorised use according to Annex III to Regulation (EC) No 1333/2008.

Industry also provided use levels with functional type 'nutrients' (n = 327). These use levels were not considered in this opinion as only the use as additives was considered relevant. Also, four levels related to the use of E 508 as an ingredient of brine were not considered, as they refer to a non-authorised use.

Use levels were provided by the Association of the European Self-Medication Industry, EUROGUM A/S, European Snacks Association/SNACMA, Food Drink Europe, Food Supplement Europe, International Chewing Gum Association, Spanish Association of Postharvest Services and Processes, and Specialised Nutrition Europe (SNE).

The Panel noted that 30 use levels were reported on niche products. Additionally, 14 use levels reported for E 508 for food category (FC) 14.1.4 Flavoured drinks by SNE were attributed to niche products based on the provided description, although the type of product was not reported. Use levels for niche products are considered in the refined scenario only if no other use levels are available for the same food category.

Only data on niche products were available for E 507 in FC 13.1.4 Other foods for young children and 13.2 Dietary foods for special medical purposes defined in Directive 1999/21/EC, E 508 and E 509 in FC 14.1.4 Flavoured drinks, E 509 in FC 05.3 Chewing gum.

Two use levels were reported by the food additive producer EUROGUM for E 508 in FC 8.3.2 Heat-treated meat products. Use levels reported by food additive producers are not considered at the same level as those provided by food industry. Food additive producers may recommend use levels to the food industry, but the final levels used may, ultimately, be different. Therefore, these use levels are only considered in the *refined exposure scenario* when food additive producers confirm that the recommended levels are used by food industry. In the present assessment, these data were not used in the refined scenarios. However, data from food additive producers are used in the *maximum level exposure assessment* scenario in case of *QS* authorisation and when no data are available from food industry. In this way, the most complete exposure estimates are calculated.

According to the above exclusion principles, 11 use levels were excluded from further analysis in the *refined scenarios*, while no use level was excluded from the *maximum level exposure assessment* scenario.

Table 6: The number of use levels provided by industry, the number of food categories for which use levels were provided and the total number of authorised food categories according to Annex II to Regulation (EC) No 1333/2008 for hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511)

Number of	E 507	E 508	E 509	E 511
Use levels (n)	15	41	35	9
Food categories covered	4	11	10	2
Authorised food categories	71	67	73	68

Appendix A provides data on the use levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) in foods as reported by industry.

[13] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published: 24 May 2016. Available online: https://www.efsa.europa.eu/en/data/call/160524

3.3.2. Summarised data extracted from the Mintel's Global New Products Database

The Mintel's GNPD is an online database that monitors new introductions of packaged products in the market worldwide. It contains information of over 3 million food and beverage products of which more than 1,200,000 are or have been available on the European Union (plus Norway) food market. Mintel started covering EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel's GNPD.[14]

For the purpose of this Scientific Opinion, the Mintel's GNPD[15] was used for checking the labelling of food and beverages products and food supplements for hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) within the EU's food market as the database contains the compulsory ingredient information on the label.

Appendix B lists the number and percentage of the food products labelled with hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) out of the total number of food products per food subcategory of the Mintel's GNPD food classification.

According to the Mintel's GNPD, hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) were labelled on 8,449 products between January 2014 and May 2019. These products represented 1.9% of all the products within the food subcategories of Mintel's GNPD food classification in which at least one of the four food additives was labelled. However, this percentage included the labelling of these additives on baby foods, baby formulas and growing up milks (648 products) and cheeses (1,502 products). According to industry, these substances are used in these foods for another function than as a food additive: as nutrient in baby foods, baby formulas and growing up milks, and as processing aid in cheeses. When these substances are used with different functions than food additive should not be included in the exposure assessment. The Mintel database reports several cheese-related products (n = 1,407) in which E 509 was labelled as food additive.

When only those food subcategories were included for which the labelling referred to their function as food additive, the percentage of labelled products was 1.45%.

Potassium, calcium and magnesium chlorides (E 508, E 509 and E 511) were labelled on foods belonging to several food subcategories, while hydrochloric acid (E 507) was labelled on only 41 products belonging mainly to the food subcategories 'Meal replacements and Other Drinks' and 'Chilled Desserts' (Appendix B).

The subcategory with the highest percentage and the highest number of products labelled with these additives was Meat substitutes (17.7%; 688 products) belonging to the FC 12.9 Protein products, excluding products covered in category 1.8. No use levels were available for this subcategory.

For E 511 the subcategory 'Meat Substitutes' represented over 48% of the products on which it was labelled. Additionally, E 509 was labelled in 404 products of subcategory Pickled condiments belonging to category FC 4.2.2 Fruits and vegetables in vinegar, oil, or brine. Also, no use levels had been provided for this subcategory.

3.3.3. Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a). Consumption surveys added in the Comprehensive database in 2015 were also taken into account in this assessment.[16]

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

[14] Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.
[15] http://www.gnpd.com/sinatra/home/ accessed on 24th May 2019.
[16] Available online: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Food consumption data from infants, toddlers, children, adolescents, adults and the elderly were used in the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 7).

Table 7: Population groups considered for the exposure estimates of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511)

Population	Age range	Countries with food consumption surveys covering more than 1 day
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers[a]	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children[b]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly[b]	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Netherlands, Sweden, UK

(a): The term 'toddlers' in the Comprehensive Database (EFSA, 2011a) corresponds to 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013.
(b): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Comprehensive Database (EFSA, 2011a).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the food categorisation system (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, the FoodEx food codes were matched to the FCS food categories.

Food categories considered for the exposure assessment to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride

The food categories in which the use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) is authorised were selected from the nomenclature of the Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

The four additives are all allowed in FCs 13.2, 13.3 and 13.4. Food items belonging to these food categories, consumed by children, adolescents, adults and the elderly, may be very diverse and, in addition, the Comprehensive Database has only very limited information on their consumption. Therefore, eating occasions belonging to these food categories were reclassified under food categories in accordance to their main ingredient. For this reason, the eight reported use levels for E 507 in FC 13.2 were not considered for the exposure assessment.

The additives are also all allowed in FC 18 (Processed foods not covered by categories 1 to 17, excluding foods for infants and young children). As this food category is very unspecific, also the foods belonging to FC 18 (e.g. processed foods, prepared or composite dishes) were reclassified under food categories in accordance to their main ingredient and included as such in the exposure assessment.

In the Comprehensive Database, the form (liquid or solid) in which food supplements are ingested cannot be ascertained. Therefore, the use levels for the two categories FC 17.1 and FC 17.2 were assigned to the whole FC 17.

Overall, 16 food categories were included in the *maximum level exposure scenario* and 15 food categories in the refined exposure scenario (Appendix C).

The following food categories were considered, with some assumptions:

- FC 04.2.3 Canned or bottled fruit and vegetables. As this food category is not clearly distinguished in some cases in the Comprehensive Database from category FC 4.2.4.1 Fruit and vegetable preparations excluding compote, the reported use levels were combined and attributed to specific FoodEx categories referring to fruit and vegetables products.
- FC 4.2.4.1 Fruit and vegetable preparations excluding compote (reclassified from FC 18 Processed foods not covered by categories 1–17, excluding foods for infants and young children): use levels for this food category were assigned to the FoodEx category for Vegetable-based meals and Beans-based meals, as suggested by the data providers. No use levels were reported for foods that were directly classified in FC 4.2.4.1 (Appendix A).
- FC 04.2.6 Processed potato products. As this food category is not referenced as such in the Comprehensive Database, the following FoodEx category was used for the exposure assessment: Potatoes and potatoes products. As this FoodEx category includes unspecified potatoes, this may have contributed to an overestimation of the exposure.
- FC 12.2.2 Seasonings and condiments. As this food category is not referenced to this detail in the Comprehensive Database, use levels for this food category were assigned to the FoodEx category 'Condiment', and the FoodEx category 'Seasoning and extracts', except for the subcategories referring to salt.

FC 14.1.4 Flavoured drinks. The use level data referring to sport drinks were assigned to foods categorised in FoodEx category 'Food for sports people (labelled as such)' The use level of FC 08.3.2 Heat-treated meat products was only included in the *maximum level exposure scenario* as data for this food category were provided by a food additive producer (Section 3.3.1). As this category is not referenced to this detail in the Comprehensive Database, the use level used in the *maximum level exposure scenario* was attributed to the parent category (FC 08.3 Meat products). This may have contributed to an overestimation of the exposure in this scenario.

Additionally, the FCs 17.1/17.2 Food supplements, in solid and liquid form respectively were considered in the *Food Supplements scenario*. These food categories were considered as FC 17 as information about the form of the supplement consumed is not consistently included in the Comprehensive Database

3.4. Exposure estimate

3.4.1. Exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) from their use as food additives

Based on information from the Mintel's GNPD, the Panel considered that hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are not likely to be used in combination in the same food product and, therefore, exposure assessment was performed considering the highest reported use level for either E 507, E 508, E 509 and E 511 per food category. The Panel estimated the chronic dietary exposure to chloride derived from the exposure to the anion component of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. For this, the reported use levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) per food category (Appendix C) were multiplied with the following conversion factors to obtain the use level related to the anion part of each additive: 1, 0.48, 0.63 and 0.35, respectively. The resulting highest use level among the additives per food category was then selected to estimate the exposure.

Dietary exposure was calculated by multiplying these use levels per food category with their respective consumed amount per kilogram body weight for each individual in the Comprehensive Database according to the scenarios described below. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only 1 day per subject were excluded as they are not considered adequate to assess repeated exposure.

The exposure was calculated for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 7). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure could only be calculated for population groups with a

sufficiently large sample size (EFSA, 2011a). Therefore, the 95th percentile of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain was not estimated in the present assessment.

The exposure assessment to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride was carried out by the FAF Panel based on two different sets of concentration data: (1) maximum reported use levels and (2) typical reported use levels (defined as the *refined exposure assessment scenario*). These two scenarios are discussed in detail below.

These scenarios do not consider the intake through the consumption of food supplements. This exposure source was covered in an additional scenario detailed below (*food supplements consumers only scenario*).

A possible additional exposure from the use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) in accordance with Annex III to Regulation (EC) No 1333/2008 (Parts 1, 2, 3, 4 and 5 Section A) was only partly considered as only one use level for E 509 was available according to this authorisation. Furthermore, hydrochloric acid (E 507) is authorised in foods for special medical purposes (FSMP) via FCs 13.1.5.1 and 13.1.5.2. As the food additive is authorised at *QS* in these foods and no use level data were provided, no exposure assessment due to the consumption of FSMP, as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014), could be performed.

Maximum level exposure assessment scenario

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised according to *QS* in all food categories (Table 5). Therefore, a *maximum level exposure assessment scenario* was performed based on the maximum of the reported maximum use levels provided by industry (food industry and food additive producers) as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014). The use levels expressed as chloride as used in this scenario are listed in Appendix C.

The Panel considers the exposure estimates based on this scenario as the most conservative, because it is assumed that the food additive is always present in food at the maximum of the reported maximum use level.

Refined exposure assessment scenario

The refined exposure assessment scenario was based on all use levels reported by food industry.

Appendix C summarises the use levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride and used in this scenario. Based on the available dataset, the Panel calculated two refined exposure estimates based on two model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride present at the maximum of the reported maximum use levels for one food category. This exposure estimate is calculated as follows:
  - Combining consumption levels of the main contributing food category at the individual level with the maximum of the reported maximum use level.
  - Combining consumption levels of the remaining food categories with the mean of the reported typical use levels.
- The non-brand-loyal consumer scenario: it was assumed that a consumer is exposed long-term to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) present at the mean of the reported typical use levels in food.

Food supplement consumers only scenario

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised in FC 17 (Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children) at *QS*. As exposure via food supplements may deviate largely from the exposure via food, and the number of food supplement consumers may be low depending on populations and surveys, an additional scenario was calculated to reflect additional exposure to food additives from food supplements. This additional exposure was estimated

assuming that consumers of food supplements were exposed to the food additives present at the maximum reported use levels in food supplements on a daily basis. For the remaining food categories, the mean of the typical reported use levels was used.

Use levels for FC 17 were only available for hydrochloric acid (E 507) and potassium chloride (E 508) (Appendix C).

As FC 17 does not consider food supplements for infants and toddlers as defined in the legislation, exposure from food supplements was not estimated for these two population groups.

Dietary exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride

Table 8 summarises the estimated exposure to the four additives from their use as food additives expressed as chloride in six population groups according to the different exposure scenarios. Detailed results per population group and survey are presented in Appendix D.

Table 8: Summary of dietary exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) from their use as food additives expressed as chloride in the maximum level, refined and food supplement exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg chloride/kg bw per day)

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Maximum level exposure assessment scenario						
• Mean	7.7–18.5	22.1–93.9	23.4–83.4	15.7–52.3	9.5–35.5	7.9–25.0
• 95th perc.	32.3–60.2	55.5–143.0	55.1–181.0	37.4–116.6	23.1–81.9	20.7–60.1
Refined estimated exposure assessment scenario						
Brand-loyal scenario						
• Mean	5.3–12.9	8.4–46.6	11.8–49.3	5.4–29.8	4.5–16.2	4.1–9.9
• 95th perc.	21.0–26.3	31.5–105.2	32.0–134.2	14.0–85.4	14.0–57.1	11.1–36.7
Non-brand-loyal scenario						
• Mean	4.5–7.5	6.5–41.9	7.9–29.6	4.2–19.2	2.1–8.7	2.0–6.0
• 95th perc.	17.4–19.7	23.8–71.6	22.7–64.7	9.7–47.8	5.8–24.0	5.0–14.0

bw: body weight; perc.: percentile.

In the *maximum level exposure assessment scenario*, the mean exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride ranged from 8 mg/kg bw per day in the infants to 94 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 21 mg/kg bw per day in the elderly to 181 mg/kg bw per day in children.

In the *refined estimated exposure scenario*, in the *brand-loyal scenario*, the mean exposure ranged from 4 mg/kg bw per day in the elderly to 49 mg/kg bw per day in children. The 95th percentile of exposure ranged from 11 mg/kg bw per day in the elderly to 134 mg/kg bw per day in toddlers. In the *non-brand-loyal scenario*, mean exposure ranged from 2 mg/kg bw per day in the elderly to 42 mg/kg bw per day in toddlers. The 95th percentile of exposure to chlorides ranged from 5 mg/kg bw per day in the elderly to 72 mg/kg bw per day in toddlers.

In the *food supplements* consumers only scenario, the mean exposure ranged from 7 mg/kg bw per day in adults to 134 mg/kg bw per day in children. The 95th percentile of exposure ranged from 26 mg/kg bw per day in the elderly to 130 mg/kg bw per day in children.

Main food categories contributing to exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chloride

The main contributing food categories to the exposure to the four additives in all population groups from their use as food additives expressed as chlorides in the *maximum level exposure scenario* were FC 08.3 Meat products, FC 04.2 Processed fruit and vegetables and FC 12.6 Sauces. FC 14.1.4 Flavoured drinks was also a main contributor for adolescents and children. FC 05.2.1 Other confectionery with added sugar was also a main contributor for adolescents, adults, children and

toddlers. FC 15.1 Potato-, cereal-, flour- or starch-based snacks was also a main contributor for adolescents and children.

The main contributing food categories to the exposure in the *brand-loyal scenario, were* FC 04.2 Processed fruit and vegetables and FC 12.6 Sauces for all population groups. FC 05.2.1 Other confectionery with added sugar was also a main contributor for all age groups except infants and elderly.

In *non-brand-loyal scenario,* FC 04.2 Processed fruit and vegetables and FC 05.2.1 Other confectionery with added sugar were main contributors in all population groups except infants. FC 14.1.4 Flavoured drinks was also a main contributor for adolescents, adults and children. FC 12.6 Sauces were also a main contributor for all population groups except infants.

For details on the contribution of each category in the three scenarios, see Appendix E.

On consideration of these main contributing food categories, it was noted that they are rather broad descriptions for which the food consumption data taken from the EFSA comprehensive database are not likely to be dominated by a single product (see Appendix C). For this reason, the non-brand loyal scenario was considered to be the most relevant for estimating exposure to chloride from these four additives and it was therefore carried forward into the risk characterisation.

Uncertainty analysis

Uncertainties in the exposure assessment to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) expressed as chlorides have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 9.

Table 9: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies/representativeness/underreporting/misreporting/ no portion size standard	+/–
Methodology used to estimate high percentiles (95th) of long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Correspondence of reported use levels to the food items in the Comprehensive Database: uncertainties to which types of food the levels refer	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Inclusion of food categories without considering the restriction/exception (n = 2 for the maximum level exposure scenario and n = 1 for refined exposure scenario)	+
Use level data availability:	
– use levels were available for 18 out of 78 (23%) authorised categories and the food categories included corresponded to 0.6%–58.6% of the amount (grams of foods by body weight) of food consumption documented in the Comprehensive Database (where no use level was available the food additive was considered not to be used)	-
– use of E 509 and E 511 in Meat Substitutes and of E 509 in Pickled condiments in the Mintel database but no use level available	-
– use levels considered applicable to all foods within the entire food category	+
– only one use level reported on the use of these additives according to Annex III to Regulation (EC) No 1333/2008	-
– Inclusion of use levels of niche products	+
Maximum level exposure assessment scenario:	
– exposure calculations based on the maximum reported use levels (reported use from industries and food additive producers)	+
Refined exposure assessment scenarios:	
– exposure calculations based on the maximum or mean levels (reported use from industries)	+/– +
All scenarios for assessment: the co-occurrence of additives was dealt with by taking the highest use level per food category among those available for all additives.	+

(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised as Group I food additive in 67 food categories and have a specific authorised use in some other food categories (Table 5). Industry provided use levels for only a few food categories (Table 6).

Since, the majority of food categories corresponds to the general Group I food additives authorisation, the food additives may not necessarily be used in these food categories. This may explain why reported use levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) were available for only very few of the food categories in which they are authorised. This observation was supported by the information from the Mintel's GNPD (Appendix B) with the exception of the food subcategory Meat Substitutes and Pickled condiments (Table 8).

The Panel assumed that 100% of the foods belonging to a food category included in the assessment contained these additives, whereas the average percentage was 1.5% according to Mintel's GNPD. Therefore, the exposure estimates in all exposure scenarios resulted in overestimates of the exposure to of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) from their use as food additives according to Annex II to Regulation (EC) No 1333/2008 (Section 3.4.1).

The Panel considered exposure to hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) from their use as food additives and expressed in chloride, in European countries present in the Comprehensive Database for the maximum and refined level exposure scenarios is an overestimation. This was due to the overall uncertainties, in particular that:

- all foods within a food category considered in the exposure assessment contained one of the additives.
- the additive was always present at the highest reported use level among those available for all food additives.

3.5. Total exposure to chloride from the diet

Chloride is present in plant and animal foods. The NDA Panel has issued a scientific opinion on the dietary reference value for chloride for Public consultation (EFSA NDA Panel, 2019). Estimations of daily chloride intake from food consumption data are commonly not considered as a good source of information due to the limited knowledge about chloride content in foods and difficulties to capture all sources of chloride intake, including sodium chloride added at the table or while cooking. To address this, 24-h urinary excretion analysis of chloride is considered a valid biomarker for chloride intake. Publications report mean 24-h urinary excretion of chloride in Western populations as 124 mmol (4.4 g) in women and 191 mmol (6.8 g) in men (Sanchez-Castillo et al., 1987; Kübler, 1995; Wang et al.,2013; Curcio et al., 2016). In these publications, the urinary excretion values for chloride and sodium are similar on a molar basis. Therefore, the NDA Panel concluded that the vast majority of chloride intake comes from sodium chloride intake. However, the NDA Panel also noted that other sources of chloride intake including 'inherently food-borne sources and chloride-containing food additives, in which chloride may be associated with cations other than sodium' contribute to the intake of chloride.

The mean daily exposure to chlorides as food additives in the non-brand-loyal scenario in adults was approximately 0.4 g based on a 70-kg body weight, which corresponds to about 6– 9% of the total chloride excreted in urine of 6.8 g in men or 4.4 g in women.

3.6. Biological and Toxicological data

When relevant, the dose of the test substance as a salt of hydrochloric acid was calculated in mg of chloride on the basis of the molecular weight of the corresponding salt of hydrochloric acid in the anhydrous form.

3.6.1. Absorption, distribution, metabolism and excretion

The text below summarises common knowledge on the subject and it was extracted from SCF and EFSA NDA Panel evaluations of chloride. (SCF, 1993; EFSA NDA Panel, 2005).

Chloride is normal constituent of human body. Levels of this constituent is under homeostatic control in the body and therefore this will control their absorption and excretion.

Hydrochloric acid together with phosphoric and sulfuric acid is the principal acids in the body.

Hydrochloric acid, potassium chloride, magnesium chloride and calcium chloride are soluble and are expected to dissociate readily in the stomach to respective cations and anions.

Chloride

Chloride is the most abundant anion in all animal species and in adult humans.

Chloride is an essential nutrient involved in fluid and electrolyte balance. It is required for normal cellular function. The total body chloride averages about 33 mmol/kg bw (1.2 g/kg bw) in a normal adult male. Less than 15% of the body' chloride is located within the cells and the remaining chloride is located extracellularly.

The content of chloride in blood and the extracellular space is not related to dietary intake but is influenced by intake/plasma concentrations of other electrolytes like bicarbonate. The exchange of chloride for bicarbonate between erythrocytes and plasma (the chloride shift), in the gastrointestinal tract and renal collecting tubule is crucial to the control of blood pH.

Chloride from the diet is practically completely absorbed along the length of the intestine. Absorption of chloride takes place both passively and actively. The efficiency of passive absorption is decreasing along the length of the intestine. Chloride is actively reabsorbed in a one-to-one exchange for bicarbonate in the ileum and colon, with the net effect of making the intestinal contents more basic.

Chloride concentration in plasma is in the range of 3.55–3.90 mg/mL and the intracellular concentration of chloride is approximately in the range of 100–140 μg/mL (OECD, 2002a).

Urine is the main route of chloride excretion. Some chloride excretion happens by passive diffusion, but chloride also leaves the tubular lumen by active transport (EFSA NDA Panel, 2005).

Overall, the Panel noted that chloride is natural constituent of man, animals and plant and constitutes electrolytes present in all biological materials.

3.6.2. Acute toxicity

The LD_{50} value for hydrochloric acid reported to be in the range of 238–277 mg/kg bw for the rat (unpublished report from Hoechst (1966) cited in (OECD, 2002a). For potassium chloride, the reported LD_{50} value was 3,000 mg/kg bw in rats (Boyd and Shanas, 1961). The reported LD_{50} values in New Zealand rabbits for calcium chloride were 755 mg/kg bw (dehydrate), 507 mg/kg bw (hexahydrate) and 1,000 mg/kg bw (30% solution) (unpublished reports from Koopman (1986) cited in OECD (2002b)).

The Panel considered chlorides to be of low acute oral toxicity.

3.6.3. Short-term and subchronic toxicity

3.6.3.1. Mice

Potassium chloride

To investigate the effects of potassium chloride supplementation on growth rate, water intake and renal function, 54 adult male ICR mice (10–11 weeks old, initial weight 34–40 g) were assigned to a control diet group or a diet supplemented with 5% potassium chloride (equivalent to 10,000 mg/kg bw per day as potassium chloride or 4,800 mg chloride/kg) for 1–4 weeks (Murai et al., 2008). Body weights in the group receiving a potassium chloride supplemented diet were statistically significantly lower than in the control group. Feed intake was not affected by potassium chloride supplementation, but water intake of potassium chloride supplemented mice was statistically significantly higher than in the control group. Bone weights of treated mice tended to be lower than those of control mice after 2 weeks, but no effects were seen after 1 and 4 weeks of exposure. Serum K and Cl concentrations at 2 weeks and serum urea nitrogen concentration after 4 weeks were statistically significantly lower in treated mice compared with control. Serum concentrations of Ca, inorganic phosphorus and creatinine were unaffected by potassium chloride supplementation and no histological changes were found in the kidneys.

In a follow-up study to clarify the effect of a high potassium chloride diet on feed intake, water intake, urine volume and nitrogen (N) balance in mice, 16 ICR male mice (10-week-old, initial weight, 36–40 g) were assigned to a control diet group or a 5% potassium chloride supplemented dietary group for 4 or 8 weeks (equivalent to 10,000 mg/kg bw per day as potassium chloride or 4,800 mg chloride/kg) (Murai et al., 2010). Body weights of treated mice were statistically significantly higher

than those of control mice at 24–28 days when compared with controls. Feed intake and urine volume of potassium chloride supplemented mice were statistically significantly higher in the group exposed to potassium chloride when compared with controls. Nitrogen absorption and urinary excretion of nitrogen, potassium and chloride were statistically significantly higher in potassium chloride-treated mice as compared with controls. Serum creatinine concentration at 8 weeks after treatment was statistically significantly lower in mice supplemented with potassium chloride as compared with controls. No histological changes were observed in the kidney of the mice at 4 and 8 weeks after treatment. No other statistically significant effects were reported. According to the authors, the results suggest that high potassium chloride supplementation increases water intake, urine volume and urinary N excretion in mice.

Magnesium chloride

Groups of 6-week-old B6C3F1 mice (10/sex per group) were administered magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at dietary levels of 0 (control), 0.3%, 0.6%, 1.25%, 2.5% or 5% for 13 weeks (Tanaka et al., 1994). Throughout the experiment, the mean body weights were statistically significantly decreased in both sexes at the 5% level as compared with controls. Feed and water intake in all treated groups were similar to the controls. The average intake of magnesium chloride hexahydrate was 610, 1,220, 2,690, 5,410 and 11,400 mg/kg bw per day (corresponding to 213, 427, 941, 1,893 and 3,990 mg chloride/kg) for males and 770, 1,580, 3,260, 6,810 and 13,830 mg/kg bw per day (corresponding to 269, 553, 1,141, 2,383 and 4,840 mg chloride/kg) for females at 0.3%, 0.6%, 1.25%, 2.5% and 5%, respectively. Fasted body weights before sacrifice were statistically significantly decreased for males at 0.3% (corresponding to 213 mg chloride/kg) and from 1.25% (corresponding to 1,893 mg chloride/kg) and above, and for females at 5% (corresponding to 4,840 mg chloride/kg). Haematology and blood biochemistry parameters were not affected by treatment. Some statistically significant increases in relative weights of the brain, kidneys, testes, heart or spleen were recorded, but these were, according to the authors, related to retardation of body weight increases as they were not accompanied by macroscopic or microscopic changes. In the kidneys, a statistically significantly increased incidence of vacuolar lesions was observed in the proximal tubules of males in the 5% (corresponding to 3,990 mg chloride/kg) group. In some treated mice of both sexes, squamous cell hyperplasia of the forestomach was now and then observed; however, this finding was not dose-dependent and as such was not considered of toxicological significance by the authors.

3.6.3.2. Rats

Hydrochloric acid

Wistar rats (10–60/group, sex not stated, around 4 months of age) were kept for 12–21 days on basal diets and drinking water without or with 0.3% hydrochloric acid (Matzner and Windwer, 1937). No lesions were seen in the controls and in the non-fasting group administered 0.3% hydrochloric acid in the drinking water, whereas ulcer-like lesions were observed in the group subjected to fasting and receiving 0.3% hydrochloric acid in their drinking water. The lesions were characterised by focal gastric submucosal oedema which detach the muscularis mucosae from its underlying coat.

In a series of experiments, the effects of supplementing hydrochloric acid in the diet of rats (strain not specified) were investigated (Upton and Lestrange, 1977). In experiment 1, weanling rats (4 males/4 females per group, initial weight about 60 g) were given a commercial rat diet alone (control group) or supplemented with hydrochloric acid at levels of 280 mmol/kg, 420 mmol/kg or 560 mmol/kg dry matter for 7 weeks (equivalent to 1,225, 1,838 or 2,450 mg/kg bw per day as hydrochloric acid). The supplement with hydrochloric acid in the diet statistically significant increased water intake at all doses compared with control but did not significantly affect feed intake, body weight gain, blood haemoglobin and haematocrit values, acid-base balance, femur length, fat-free solids, or the % ash in the bone of calcium, magnesium, sodium or potassium in the fat-free solids.

In experiment 2, approximately 1-year-old rats (strain not specified) (4 males/4 females per group, initial weight about 350 g) were given a commercial diet alone (control) or a diet supplemented with hydrochloric acid at concentrations of 312 mmol/kg, 625 mmol/kg, 937 mmol/kg or 1 250 mmol/kg dry matter for 9 weeks (equivalent to 569, 1,139, 1,708 or 2,279 mg/kg bw per day as hydrochloric acid) (Upton and Lestrange, 1977). The two highest concentrations (937 and 1,250 mmol/kg dry matter) resulted in 100% mortality of the rats, with an average survival time of 51.3 and 19.1 days, respectively. Feed intake and body weight gain of the rats were statistically significantly reduced in these two groups. The water intake was statistically significantly increased in the group given

625 mmol/kg hydrochloric acid and higher doses, but at the two higher dose levels, the animals only survived for a short period. Blood and bone analysis was carried out on rats which survived the experiment (i.e. no data from the two highest dose levels). Blood pH was statistically significantly reduced by dietary supplementation with hydrochloric acid. Plasma CO_2 concentration also tended to be reduced by the hydrochloric acid supplementation but the effect was not statistically significant.

In experiment 3, weanling rats (strain not specified) (6 males/4 female per group, initial weight of approximately 60 g) were given a commercial rat diet alone (control) or supplemented with hydrochloric acid at 300 mmol/kg, 600 mmol/kg and 900 mmol/kg dry matter for 12 weeks (equivalent to 984, 1,969 and 2,953 mg/kg bw per day as hydrochloric acid) (Upton and Lestrange, 1977). At 900 mmol hydrochloric acid/kg dry matter statistically significant decreased feed intake, a mild degree of metabolic acidosis and 30% mortality (3 animals died) were reported. The pH was not statistically significantly affected up to and including the highest dose level. Plasma CO_2 and plasma base excess values were both statistically significantly reduced at 900 mmol/kg dry matter and a statistically significant reduction in plasma CO_2 was also observed at 600 mmol/kg dry matter. Femur length, percentage of fat-free solids in the femur and percentage of ash in the fat-free solids were all statistically significantly reduced at 900 mmol/kg dry matter.

Groups of 3-week-old male Ico/Shoe:WIST rats (n = 8–10) received either drinking (tap) water (N = 8) or drinking water acidified with hydrochloric acid to a pH of either 2 (N = 8) or 3 (N = 10) for up to 21 weeks (Clausing and Gottschalk, 1989). No differences to controls were reported in body weight, feed or water intake. The haematology parameters in week 2, 13 and 21 and weights of adrenals, heart, kidneys, liver, spleen, testes and thymus at termination in the treated groups were not different compared to controls. The only reported differences to controls were a statistically significant decreased urine volume, excretion of phenol red and protein in the group receiving water with pH of 2, and a statistically significantly decreased urine volume and protein excretion in the group receiving water with pH of 3 in week 21.

Female Wistar rats (initial weight about 200 g) received for 14 weeks either a diet prepared with water (control, N = 21) or a diet where 0.5 mol/l hydrochloric acid was added instead of water (n = 32) (approximate dose was 1,496 mg HCl/kg bw per day calculated based on the reported intake of 10.3 mmol hydrochloric acid/day and the end body weight) (Throssell et al., 1995). In the treated group, body weight was statistically significantly reduced, urine volume after 14 weeks was statistically significantly increased and blood pH was statistically significantly decreased. The urinary excretion of total protein, lysozyme and albumin showed a statistically significant increase, peaking at week 8 but returning to baseline by week 14. Absolute heart weight was statistically significantly decreased in the treated group. Absolute kidney weight, glomerular filtration rates and serum creatinine were the same in both groups. Kidney/body weight and kidney/heart weight ratios were statistically significantly greater in the treated group but the kidneys were reported to appear normal by light microscopy.

Potassium chloride

Female Wistar rats (age not stated) received ad libitum either laboratory chow and water (control, N = 6) or this diet and a 2.5% aqueous solution of potassium chloride as the source of fluid (equivalent to 2,250 mg potassium chloride/kg bw per day or 1,080 mg chloride/kg bw per day; N = 14) for 15 weeks (Bacchus and Toompas, 1951). Thereafter, 10 of the potassium chloride-treated animals were killed; the remaining 4 animals were supplied with tap water in place of the potassium chloride solution for 1 month after the potassium chloride treatment was ended. At termination, the heart and the paired kidneys were weighed, adrenals and the kidneys were subjected to histological examination, and the heart and left gastrocnemius muscle of some animals of each group were analysed for water content. The relative heart weight was statistically significantly reduced while the relative kidney weights were statistically significantly increased in potassium chloride-treated animals compared with controls. The group treated with potassium chloride had an increased fluid intake compared to controls. Microscopic examination of the adrenals indicated hypertrophy of zona glomerulosa in the potassium chloride-treated animals. The adrenal of the animals reversed from potassium chloride to tap water appeared normal.

Calcium chloride

The effects of oral doses of calcium salts on urinary pH, volume and electrolytes excretion were investigated in groups (n = 7) of female albino Sprague–Dawley rats (weight 169-172 g) (Classen et al., 1995). The rats received by gavage for 3 days either bi-distilled water (vehicle control) or 3.5, 7.0 or 14.0 mmol Ca/kg bw (equivalent to 0, 388, 777 and 1,554 mg calcium chloride/kg bw per day

or 0, 244, 489 and 979 mg chloride/kg bw per day). Calcium chloride exposure statistically significantly decreased urine pH and statistically significantly increased urinary calcium, magnesium and chloride excretion at the two highest doses. Six hours following the treatment with the highest calcium dose statistically significant metabolic acidosis together with hypercalcaemia were observed in the calcium chloride-treated rats. Treatment with the highest dose of calcium chloride also induced statistically significant hypomagnesaemia and hyperchloraemia.

Three-month-old male Wistar rats (N = 8/group; weighing 140 ± 10 g) received either a normal diet or this diet supplemented to provide 0.5, 1.0 or 1.5 g $CaCl_2$/100 g diet (equivalent to 600, 1,200 or 1,800 mg/kg bw per day or 378, 756 and 1,134 mg chloride/kg bw per day for 60 days) (Chandra et al., 2012). The parameters studied were thyroid gland weight, histopathology, histomorphometry; thyroid peroxidase, 5′-deiodinase I, sodium–potassium adenosine triphosphatase (Na^+–K_+-ATPase) activities; serum total and free thyroxine (tT4, fT4), total and free triiodothyronine (tT3, fT3), thyroid stimulating hormone (TSH) levels. Statistically significantly increased absolute and relative thyroid weights were observed in the groups fed the two highest doses (1% and 1.5%). Microscopic examination of the thyroid gland revealed marked hypertrophy and/or hyperplasia of thyroid follicular epithelial cells without inflammatory changes in the groups treated with 1 and 1.5% calcium chloride. Both the follicular cell and colloid areas were statistically significantly increased in the treated groups as compared to the control group which indicated, according to the authors, hypertrophic and hyperplastic changes in the calcium exposed groups of animals. A statistically significant and dose-dependent lower activity of thyroid peroxidase was recorded in all calcium chloride treated groups compared to controls. The activity of thyroidal 5′-deiodinase I was statistically significantly reduced in the calcium treated groups. Na^+-K^+-ATPase activities were statistically significantly increased. Statistically significant increases in serum total T4 in the group fed the highest calcium chloride dose and in free T4 in the two highest dose group were seen. TSH was also statistically significantly increased in the groups fed the 1% and 1.5% calcium chloride, whereas a statistically significant decrease was observed in total and free T3 levels in these groups compared with control. The T3/T4 ratio was statistically significantly decreased in the treated groups receiving 1 and 1.5% calcium chloride (corresponding to 756 and 1,134 mg chloride/kg bw per day). According to the authors, all the findings indicated development of goitrogenesis upon exposure to excessive dietary calcium. The Panel noted that these findings relate to calcium rather than chloride.

Magnesium chloride

Four groups of 10 male and 10 female F344 rats (age not stated) received diet supplemented with magnesium chloride hexahydrate at concentration of 0, 0.1, 0.5 or 2.5% for 90 days (corresponding to 31, 157 and 787 mg chloride/kg bw per day) (Takizawa et al., 2000). No treatment-related death was observed during the study. At the high dose in males a slight reduction in body weight gain was noted. A temporary soft stool and a sustained increase in water consumption were observed in both males and females of the 2.5% (787 mg chloride/kg bw per day) group compared with control. According to the authors, there were no treatment-related changes in feed intake, organ weights, haematology and biochemistry parameters, and in the tissues examined by microscopy in any groups.

Overall, hydrochloric acid (1,496 mg/kg bw per day) given via the diet to female rats for 14 days was associated with a decrease in body weight, an increase in urine volume and relative kidney weight, but without histopathological changes in this organ. Similar changes were observed in mice after administration via the diet of 10,000 mg potassium chloride/kg bw per day (corresponding to 4,800 mg chloride/kg bw per day) for 4 weeks and in rats given 2,250 mg potassium chloride/kg bw per day (corresponding to 1,080 mg chloride/kg bw per day) for 15 weeks. Male, but not female, mice given 10,000 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 4,800 mg chloride/kg bw per day) via the diet for 13 weeks showed an increased incidence of vacuolar lesions in the proximal tubuli of the kidneys. Calcium chloride given by gavage to female rats at 777 or 1,554 mg/kg bw per day (corresponding to 489 and 979 mg chloride/kg bw per day) for 3 days statistically significantly decreased urine pH and statistically significantly increased urinary calcium, magnesium and chloride excretion.

3.6.4. Genotoxicity

In vitro

Hydrochloric acid

Hydrochloric acid was tested in microbial assays including the *Salmonella* reverse mutation assays using *Salmonella* Typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, mitotic gene conversion in *Saccharomyces cerevisiae* D4 and DNA repair in *Escherichia coli pol* $A^{+/-}$ (Isquith et al., 1988). The assays were conducted with and without a metabolic activation. In mouse lymphoma L5178Y tissue culture cells, the following endpoints were evaluated: forward gene mutation, sister chromatid exchange, DNA alkaline elution and chromosome aberration potential. The assays were performed with and without metabolic activation. No evidence of a gene mutation potential was observed up to a concentration of 5 μL/plate in the microbial tests and 1.6 μg/ml in the mouse lymphoma cells, and no clastogenic effects were observed in the mouse lymphoma cells up to 0.8 μg/mL.

Clastogenic effects of hydrochloric acid were observed in Chinese hamster ovary (CHO) K1 cells *in vitro*, in a study that aimed to evaluate the effect of acidic conditions on chromosomal aberration in the *in vitro* test system. Chromosomal aberrations were detected at concentrations of hydrochloric acid (8–14 mM) at which the pH value was < 6 while higher concentrations were toxic (Morita et al., 1989). The induced aberrations were almost all chromatid breaks. Clastogenic effects were also observed at a constant acidic pH using organic buffers, such as 2-(N-Morpholino)ethanesulfonic acid, 4-Morpholineethanesulfonic acid (MES) and Bis-Tris with pH-dependent increase in the chromosomal aberration frequency. The Panel considered that the clastogenic effect is due to the acidic conditions in the treatment medium that are not relevant for the physiological conditions *in vivo*.

Potassium, magnesium and calcium chloride

In the *S.* Typhimurium reverse mutation assay using TA 100, TA 97, TA 1535, TA 1537 and TA 98 strains, potassium chloride tested up to 10 000 μg/plate with and without metabolic activation was not mutagenic (Mortelmans et al., 1986). Magnesium chloride and calcium chloride tested at concentrations up to 1M were negative in *S.* Typhimurium TA 102 (Bronzetti et al., 1996). Calcium chloride (CAS no. 10043-52-4) and magnesium chloride (CAS no. 7786-30-3) were negative in the *Salmonella*/microsome test using *S.* Typhimurium strains TA 92, TA 94, TA 98, TA 100, TA 1535 and TA 1537 (Ishidate et al., 1984).

In the SOS Chromotest with *E. coli* strains PQ37 and PQ35, potassium chloride tested in the concentration range 1–100.000 nM/mL, magnesium chloride hexahydrate in the range 1–30,000 nM/mL for $MgCl_2 \cdot x6H_2O$ and calcium chloride in the range 1–1000 nM/mL did not induce SOS response (Olivier and Marzin, 1987).

The DNA damaging potential of calcium chloride, magnesium chloride and potassium chloride was tested in the Rec assay with *Bacillus subtilis*, H17 (Rec+, arg- try-) and M45 (Rec-, arg- try-). At concentrations up to 0.5 M all three compounds were negative (Kanematsu et al., 1980).

Magnesium chloride tested in the concentration range 8.2×10^{-6}–4.1×10^{-2} mol/l in the SOS/Umu assay with *S.* Typhimurium TA 1535/pSK1002 with and without metabolic activation gave positive SOS response in the absence of the metabolic activation (Yamamoto et al., 2002). The maximal response was detected at 4.12×10^{-3} mol/L.

In the yeast *S. cerevisiae* XV185-14C, potassium chloride administered at a concentration of 2 M (149 mg/ml) for 1, 2.5 or 3 h induced reverse mutations in *his*, *arg* and *hom* genes indicating that base substitutions, of both the transition and the transversion type, as well as frameshift mutations were induced (Parker and Vonborstel, 1987). The cell survival was time dependently reduced from 67% after 1 h exposure to 16% after 3 h exposure. The effects were observed when cells were treated in the exponential growth phase, while if treated in the stationary phase no effects were observed. The authors proposed that the observed effects were due to the high osmolality of the tested salt solution.

The effects of potassium chloride and calcium chloride on recombination and on the production of disomic and/or diploid spores during meiosis of *S. cerevisiae* were investigated (Sora et al., 1986). Potassium chloride acted inhibitory on sporulation at a concentration of 300 mM and higher while at low concentrations it increased sporulation. Calcium chloride increased the frequency of diploid spores above 100–200 mM and also inhibited sporulation. The authors proposed that calcium and potassium are essential elements and that unbalanced internal pool for these specific ions is leading to cellular malfunctioning or to a chain of effects on other ion equilibria, affecting meiotic division.

In the yeast *S. cerevisiae* D7, calcium and magnesium chloride were tested at concentrations ranged from 0.1 mM to 1 M and showed no toxic and genotoxic effects in yeast both on stationary and logarithmic growth phase cells (Bronzetti et al., 1996).

The mutagenicity of potassium chloride was evaluated in the mouse lymphoma L5178Y TK+/− forward mutation assay with and without metabolic activation (Myhr and Caspary, 1988). In the absence of metabolic activation, potassium chloride induced small increase in mutant frequency at standard limit concentration 5,000 μg/mL. At these concentrations potassium chloride was not toxic and did not reduce relative total growth (RTG) below 50–65%. At higher concentrations (7,000 and 8,000 μg/mL) it was toxic (RTG below 30 and 12% respectively) and induced increase in the mutant frequency. In the presence of metabolic activation, increase in the mutation frequency was detected at concentrations higher 4,000 μg/ml that were also toxic (RTG below 30%).

In cultured Chinese hamster V79 cells, potassium chloride at concentration 12,000 μg/ml induced significant increase in chromosomal aberration but not sister chromatid exchange (Hasegawa et al., 1984). The effect was due to high osmotic pressure of the medium (530 mOsmol/kg) at this concentration.

Magnesium chloride was reported to be clastogenic in an *in vitro* Chinese hamster lung (CHL) fibroblasts assay in the absence of metabolic activation, but only at elevated dose level (12 mg/ml) (Ashby and Ishidate, 1986).

Ishidate et al. (1984) reported calcium chloride (CAS no. 10043-52-4) and magnesium chloride (CAS no. 7786-30-3) to be negative in the chromosomal aberration assay with Chinese hamster fibroblast cell line at the highest tested concentrations 4 mg/mL and 2 mg/L, respectively.

Potassium chloride was used as a model compound to investigate the effects of high dose levels and osmolarity-mediated artefacts in mutagenicity assays when using cultured mammalian cells (Seeberg et al., 1988). To test different genetic endpoints, three assays were used: mutation to 6-thioguanine resistance in Chinese hamster V79 cells, induction of chromosome aberrations in CHO cells and induction of unscheduled DNA synthesis in HeLa S3 cells. In the absence of metabolic activation, potassium chloride was toxic to V79 cells at concentrations higher than 10 mM and increase in the mutation frequency was observed only at 75 mM. In the presence of metabolic activation, potassium chloride was more toxic the cells viability was significantly reduced at 35.7 mM and the mutation frequency was increased, but was not reproducible between the experiments. Chromosome aberrations were induced at $\geq$ 75 mM in absence of metabolic activation and at concentrations $\geq$ 150 mM in the presence of metabolic activation. The osmotic pressure at 75 mM was in the absence of metabolic activation 425 mOsm/kg and at 150 mM in presence of metabolic activation 536 mOsm/kg. Unscheduled DNA synthesis was unaffected. An Ames test was also performed and gave negative results.

The effects of potassium chloride hyperosmolality on chromosomal aberration, sister chromatid exchange and DNA strand breaks were studied in CHO cells (Galloway et al., 1987). Significant increase in chromosomal aberrations was detected at 140 mM potassium chloride at which the osmotic pressure was 527 mOsm/kg H_2O. The increase was associated with cytotoxicity as well as cell cycle delay. At 180 mM, potassium chloride (626 mOsm/kg H_2O) induced slight elevations in sister chromatid exchange frequencies which was associated with severe cell cycle delay. Potassium chloride, at the tested conditions, did not induce significant increase in DNA single-strand breaks.

More recently, the extreme culture conditions of either pH or osmolality or exposure to high ionic strength were tested in two cell lines: CTLL-2 that is a stable subclone of cytotoxic T lymphocytes and CTLL-2 *BCL2* produced by stable transfection with the anti apoptotic gene *BCL2* (Meintieres and Marzin, 2004). Evaluating micronuclei induction in both CTLL-2 and CTLL-2 *BCL2* cells allowed to distinguish the genotoxic from the apoptotic effects of extreme culture conditions. For the CTLL-2 cell line, the number of micronucleated cells and the percentage of apoptosis increased with increasing osmolarity obtained by adding potassium chloride. The increase in number of apoptotic cells was statistically significant compared with the control at 380 mOsm/kg with 11% of apoptotic cells, and the number of micronucleated cells was statistically significantly different from the control at 360 mOsm/kg. In CTLL-2 *BCL2*cells, neither apoptosis nor induction of micronuclei was observed. According to the authors, the results suggested that apoptosis caused by extreme culture condition caused formation of micronucleated cells, which leads to false-positive results in the *in vitro* micronucleus test.

In summary, hydrochloric acid and potassium, magnesium and calcium chloride are not mutagenic in Salmonella/microsomal reverse mutation assay (Ishidate et al., 1984; Isquith et al., 1988; Bronzetti et al., 1996). In the *in vitro* mouse lymphoma gene mutation assay, hydrochloric acid was negative (Isquith et al., 1988), while potassium chloride was positive at high concentrations (Myhr and Caspary, 1988). At high concentrations, hydrochloric acid, potassium chloride and magnesium chloride induced

chromosomal aberrations *in vitro* in mammalian cells (Hasegawa et al., 1984; Ashby and Ishidate, 1986; Seeberg et al., 1988; Morita et al., 1989). The Panel noted that the *in vitro* genotoxic effects of hydrochloric acid and its salts were observed only at high concentrations that were associated with low pH or high osmolality of the experimental media, which cannot occur under the physiological conditions *in vivo*. The Panel concluded that the use of hydrochloric acid and its potassium, calcium and magnesium salts as food additives does not raise concern for genotoxicity.

3.6.5. Chronic toxicity and carcinogenicity

Mice

Magnesium chloride

Groups of 6-week-old male and female B6C3F$_1$ mice (n = 50/sex) received 0 (control), 0.5 and 2% of magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) in the diet for 96 weeks (equivalent to 750 and 3,000 mg magnesium chloride hexahydrate/kg bw per day and corresponding to 262 and 1,050 mg chloride/kg bw per day) (Kurata et al., 1989). Thereafter, all animals received the control diet for 8 weeks and then they were necropsied. A statistically significant decrease in body weight was observed in high-dose females. Survival was not different between the treated and control groups for males or females. In high-dose females, a statistically significant increase was observed in the level of serum albumin, but no effects were noted in any other clinical chemistry parameters. Clinical signs and urinary and haematological parameters showed no treatment-related effects. Tumours were mainly found in the skin/subcutis, liver and lymphatic system but there was no difference in the tumour incidences between the treated and control groups with one exception: the incidence of liver tumours of males of the high-dose group was statistically significantly lower than in controls.

Rats

Potassium chloride

Groups of 50 male rats were fed potassium chloride in the diet at 0, 0.25, 1 or 4% (equivalent to 0, 125, 500 or 2,000 mg potassium chloride/kg bw per day and corresponding to 0, 60 240 and 960 mg/chloride kg bw per day) for 2 years (Imai et al., 1986). Regarding non-neoplastic changes, nephritis was predominant in all treatment groups as well as in the control group. The incidence of chronic gastritis (6/24, 18/32, 18/29, 30/42) in the treated groups was higher than in the control group. No treatment-related tumours were observed.

Short- and long-term toxicity studies and a carcinogenicity study were performed in rats fed diets supplemented with sodium bicarbonate as the alkalising, ammonium chloride as the acidifying and potassium chloride as the neutral component (Lina and Kuijpers, 2004). Four studies were conducted; a 4-week (n = 10 rats/sex), 13-week toxicity study (n = 10 rats/sex), an 18-month toxicity study (n = 15 rats/sex) and a 30-month carcinogenicity study (n = 50 rats/sex). Groups were fed either a control diet or a diet supplemented with 3% potassium chloride (equivalent to 1,500 mg potassium chloride/kg bw per day and corresponding to 720 mg chloride/kg bw per day). The animals were observed daily for clinical signs and survival. Body weights were determined weekly and from 3 months, once every 4 weeks. Feed intake was determined weekly or (from 3 months) once every 4 week over 1-week periods. Water intake was recorded daily in weeks 1, 4, 6, 8, 12, 35, 55 and 75. Haematology and blood gas characteristics were examined at several stages of the studies. Potassium chloride did not affect the acid–base balance nor were clinical condition or death rate affected. Average body weights were decreased in the 30-month study in both sexes and in males in the 18-month study. The water intake was increased in the various studies. A statistically significant increase in urinary volume were noted in males in week 6, 16 and 78, urinary potassium excretion was increased in both sexes, and urine density was decreased in males week 6. No consistent or treatment-related effects on red blood cell variables, clotting potential or total and differential white blood cell counts were reported. Potassium levels in plasma were generally increased, although the differences with the controls were not always statistically significant. The relative kidney weight tended to be increased in the various studies, but the increase reached a statistical significance only in males in the 18-month study. The incidence of hypertrophy of the adrenal zona glomerulosa was statistically significantly increased compared to the incidence in control animals in both males and females at the end of the 30-month study. The authors suggested that this effect was due to chronic stimulation of the adrenal cortex by potassium-induced acidosis. The Panel agreed with this suggestion and noted that this was not considered the effect of chloride anion.

Overall, no adverse effects were reported in mice exposed to magnesium chloride hexahydrate up to a dietary dose level of 3,000 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 1,050 mg chloride/kg bw per day) for 96 weeks except for a decrease in the body weight of females at the highest dose level (3,000 mg magnesium chloride hexahydrate/kg bw per day corresponding to 1,050 mg chloride/kg bw per day) (Kurata et al., 1989). No treatment-related tumours were observed in male rats fed potassium chloride in the diet (up to approximately 2,000 mg potassium chloride/kg bw per day corresponding to 960 mg chloride/kg bw per day) for 2 years (Imai et al., 1986). After feeding 1,500 mg/kg bw per day potassium chloride (corresponding to 720 mg chloride/kg bw per day) for 18 months, no tumours were reported (Lina and Kuijpers, 2004).

3.6.6. Reproductive and developmental toxicity

Reproductive toxicity

No studies available.

Developmental toxicity

In all studies performed by the Food and Drug Res. Lab. (FDRL 1974, 1975) described below, body weights were recorded at regular intervals during gestation and all animals were observed daily for appearance and behaviour. To test the methodology and the sensitivity of the laboratory animal, positive controls were tested. All dams were subjected to caesarean section, and the numbers of implantation sites, resorption sites, live and dead fetuses, and body weights of live fetuses were recorded. All fetuses were examined grossly for sex distribution and for external abnormalities (one-third detailed visceral examination and two-third stained and examined for skeletal defects). For the rabbits, all live pups were placed in an incubator for 24 hours to evaluate the postnatal survival prior to sacrifice. All pups were examined for external, visceral and skeletal abnormalities.

Mice

Potassium chloride

Groups of 5–10 pregnant ICR mice were assigned to a control group or a group fed on a diet supplemented with potassium chloride to elucidate the effects of high potassium chloride supplementation on water intake, body weight gains and serum components in pregnant and lactating mice (Murai et al., 2013). Control mice were given a standard diet, which contained 25.4% CP (abbreviation not explained by the authors), 1.18% Ca, 1.03% P, 1.06% K and 0.26% Na. The potassium chloride groups' diet was supplemented with 5% potassium chloride (equivalent to 10,000 mg/kg bw corresponding to 4,800 mg chloride/kg bw per day). The dose was designed in a way to provide 13 times the normal potassium requirement and 48 times the normal chloride requirement (0.2% and 0.05%, respectively) in mice. Two studies were performed and 5% potassium chloride was supplemented in potassium chloride diets from gestation day (GD) 6.5 to either 1 or 14 days after parturition in studies 1 and 2, respectively. In study 1, body weight gains and feed intake in mice were not affected by treatment, but water intake and urine volume of treated mice were significantly higher than control. In study 2, feed intake was unaffected by treatment, but supplemental potassium chloride decreased body weight gains of dams during gestation and lactation, and also decreased body weight gains of offspring. An increase in water intake of mice during pregnancy and lactation in the treated group compared with control was also observed in study 2. In study 1, serum urea N concentration was lower in treated mice, while serum concentrations of Ca, inorganic phosphate, K, Na, Cl and creatinine were unaffected by treatment. Urinary excretion of K and Cl was higher in treated mice, however, no effects of potassium chloride supplementation was observed in N intake, urinary N excretion, faecal N excretion, N retention and urinary Ca excretion. No histological alterations in the kidneys of any of the animals were observed. In study 2, absolute kidney weights of lactating mice were similar between the control group and treated group 14 days after parturition; however, the relative kidney weight was statistically significantly increased ($p < 0.01$). Serum K concentration was statistically significantly higher ($p < 0.05$) in treated mice, whereas serum concentrations of Ca, inorganic phosphate, Na, Cl, urea N and creatinine were not altered. No histological changes were reported for the kidneys. According to the authors, these results indicated that high potassium chloride supplementation accelerates water intake in lactating mice and prevents body weight gains of maternal and neonatal mice during lactation. The only developmental effect described was a decreased was decreased body weight gain in study 2 (exposure from GD 6.5 to

14 days post parturition). However, no data were reported on this or other developmental effects. This study cannot be used for risk assessment.

In a prenatal developmental toxicity study, groups of 25 virgin adult female albino CD-1 outbred mice were dosed with potassium chloride at a daily dose of 0, 2.35, 10.9, 50, or 235.0 mg potassium chloride/kg bw (corresponding to 0, 1.1, 5.2, 24 or 112 mg chloride/kg bw per day) by gavage (vehicle: water) from GD 6 to 15 (FDRL, 1975). Body weights were recorded on GD 0, 6, 11, 15 and 17. Caesarean section was performed on GD 17. No significant effects of potassium chloride exposure up to 235 mg potassium chloride/kg bw per day (corresponding to 112 mg chloride/kg bw per day) were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, live offspring, sex ratio, fetal weight, external abnormalities, soft tissue defects or skeletal defects.

Calcium chloride

In a prenatal developmental toxicity study, groups of 25 virgin adult female albino CD-1 outbred mice were dosed with calcium chloride at a daily dose of 0, 1.89, 8.78, 40.8 or 189 mg/kg bw (corresponding to 0, 1.1, 5.5, 25.7 or 119 mg chloride/kg bw) by gavage (vehicle: water) from GD 6 to 15 (FDRL, 1974). Body weights were recorded on GD 0, 6, 11, 15 and 17. Caesarean section was performed on GD 17. No significant effects of calcium chloride exposure up to 189 mg calcium chloride/kg bw per day (corresponding to 119 mg chloride/kg bw) were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, soft tissue observations, or live offspring. There were no effects reported in the offspring on survival, sex ratio, average offspring weight, external abnormalities, soft tissue defects or skeletal defects.

Rats

Potassium chloride

In a prenatal developmental toxicity study, groups of 21–28 virgin adult female albino Wistar rats were dosed with potassium chloride in a daily dose of 0, 3.1, 14.4, 66.8 or 310.0 mg potassium chloride/kg bw (corresponding to 0, 1.4, 6.9, 32 or 148.8 mg chloride/kg bw) by gavage (vehicle: water) from GD 6 to 15 (FDRL, 1975). Body weights were recorded on GD 0, 6, 11, 15 and 20 of gestation. Caesarean section was performed on GD 20. No significant effects of potassium chloride exposure up to 310 mg/kg bw per day were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, live offspring, sex ratio, fetal weight, external abnormalities, soft tissue defects or skeletal defects.

Calcium chloride

In a prenatal developmental toxicity study, groups of 25 virgin adult female albino Wistar rats were dosed with calcium chloride in a daily dose of 0, 1.76, 8.18, 38.0 or 176 mg calcium chloride/kg bw (corresponding to 0, 1.1, 5.1, 23.9 or 110.8 mg chloride/kg bw) by gavage (vehicle: water) from day 6 to day 15 of gestation (FDRL, 1974). Body weights were recorded on GD 0, 6, 11, 15 and 20. Caesarean section was performed on GD 20. No significant effects of potassium chloride exposure up to 176 mg/kg bw per day were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, live offspring, sex ratio, fetal weight, external abnormalities, soft tissue defects or skeletal defects.

Magnesium chloride

Groups of pregnant Wistar rats (n = 22/group) were dosed orally with magnesium chloride hexahydrate by gavage from GD 6 to 15 at doses of 0, 200, 400 and 800 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 0, 70, 140 and 280 mg chloride/kg bw per day) (Usami et al., 1996). On GD 20, the rats were sacrificed and their fetuses were examined for malformations. No increased incidences of fetal malformations, and no toxic signs in the pregnant rats and the fetuses were reported. The authors concluded that magnesium chloride hexahydrate was not teratogenic in rats when administered by gavage. The Panel identified a no-observable-adverse-effect level (NOAEL) of 800 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 280 mg chloride/kg bw per day) for developmental toxicity, the highest dose tested.

Rabbits

Calcium chloride

In a prenatal developmental toxicity study, groups of 16–22 female Dutch rabbits (11-14 pregnant per group) were dosed daily with calcium chloride by gavage (vehicle: water) at dose levels of 0, 1.69, 7.85, 35.6 or 169 mg calcium chloride/kg bw per day (corresponding to 0, 1.03, 4.9, 22.4 or 106.4 mg chloride/kg bw per day) from GD 6 to 18 (FDRL, 1974). All animals were observed daily for appearance and body weight. On GD 29, a caesarean section was performed. No significant effects of calcium chloride exposure up to 169 mg calcium chloride/kg bw per day (corresponding to 106.4 mg chloride/kg bw per day) were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, live offspring, sex ratio, fetal weight, external abnormalities, soft tissue defects or skeletal defects.

Overall, no reproductive toxicity studies were available. In prenatal developmental toxicity studies, no maternal or developmental effects were reported in mice and rats following administration of potassium chloride at dose levels up to 235 and 310 mg potassium chloride/kg bw per day (corresponding to 112.8 and 148.8 mg chloride/kg bw per day), respectively (FDRL, 1975); in mice, rats and rabbits following administration of calcium chloride at dose levels up to 189, 176 and 169 mg calcium chloride/kg bw per day (corresponding to 119, 110 and 106 mg chloride/kg bw per day), respectively (FDRL, 1974); and in rats following administration of magnesium chloride hexahydrate at a dose level of 800 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 280 mg chloride/kg bw per day) (Usami et al., 1996).

3.6.7. Hypersensitivity, allergenicity and food intolerance

No data were available to the Panel.

3.6.8. Other studies

Effects on urinary bladder

Potassium chloride was administered at a dietary concentration of 3% to 5-week-old male and female Wistar rats (equivalent to 3,600 (4 weeks), 2,700 (13 weeks) and 1,500 mg potassium chloride/kg bw per day (78 and 130 weeks), corresponding to 1,728, 1,296 and 720 mg/chloride kg bw per day) and control groups received a normal diet (Lina et al., 1994). Group sizes were 10–50 rats/sex per group with 10 animals in studies of duration up to 13 weeks, 15 animals in the studies lasting for 78 weeks, and 50 animals in the studies with duration of 130 weeks. Body weights and feed and water intake were recorded at regular intervals. For urine examination, 24 h urine samples were collected individually from 10 rats/sex per group at various stages and examined for volume, density and content of potassium, sodium and calcium. Urinary pH was determined regularly. Mean body weights of treated animals were 5–7% lower than those of controls throughout the experiment, but food intake was not statistically significantly affected. Water intake was increased by 20-30% in treated animals. Urinary volume was statistically significantly increased in males in weeks 7, 12, 18 and 78, but not in week 38 and not in females. Potassium levels were statistically significantly increased in males and in females in weeks 7, 12, 18, 38 and 78. Exposure to potassium chloride did not affect urinary pH or urinary calcium excretion. Sodium excretion was not affected in females but was decreased in males in weeks 7 and 13. In the group supplemented with potassium chloride, simple epithelial hyperplasia was observed in one male rat at week 78. Epithelial proliferations in the bladder were observed at week 130 in four males and three females. Among these animals, there was one male with papillary epithelial hyperplasia and one female with nodular hyperplasia and a papilloma. In the majority of these rats, the epithelial proliferations were associated with submucosal inflammatory infiltrates or overt cystitis, which indicated, according to the authors, that in these animals cystitis might have contributed to urothelial proliferation. In control rats, the only urinary bladder lesions observed were simple epithelial hyperplasia in one female at week 78 and in one male and one female at week 130. Examination of the kidneys from potassium chloride group revealed no proliferative lesions in renal pelvic epithelium. The Panel noted that high level potassium chloride induced only a few hyperplastic epithelial lesions in urinary bladder after dietary exposure.

Initiation-promotion studies

Male Wistar rats (20/group) were given 0.05% *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) in their drinking water for 4 weeks and then treated for 32 weeks with either basal diet (controls) or this diet supplemented with equimolar amounts of 2.34% NaCl (equivalent to 2106 mg sodium chloride/kg bw and corresponding to 1,296 mg chloride/kg bw per day) or 2.98% KCl (equivalent to 2,682 mg potassium chloride and corresponding to 1,287 mg chloride/kg bw per day) (Lina and Woutersen, 1989). NaCl and KCl induced high urinary sodium or potassium ion concentrations without alteration of the urinary pH. This was accompanied by increased incidences of simple hyperplasia, papillary/nodular hyperplasia and/or papillomas but no carcinomas. The authors concluded that both sodium and potassium ions may exert weak promoting activity under conditions of neutral urinary pH. The Panel noted that the chloride ion was considered to have no effect on the urinary bladder epithelium.

The effects of alkalisers and acidifiers on bladder cell proliferation and two-stage carcinogenesis under conditions of high urinary sodium or potassium were investigated in male F344 rats (Shibata et al., 1992). For the first 4 weeks, animals were given drinking water containing 0.05% BBN as an initiator and then received powdered basal diet (control) or a basal diet containing 3% potassium chloride from weeks 5 to 8 and from weeks 12 to 20 (based on the average final body weights and the mean food intakes from week 5 to 36, a dose of 1 216 mg potassium chloride/kg bw per day was calculated corresponding to 583 mg chloride/kg bw per day). In order to accelerate transitional cell proliferation, the rats received 3% uracil in the diet during weeks 9–11 (3 weeks). General health and body weight were assessed daily, and food and water consumptions were measured weekly. At week 20, the animals were killed and bladders were excised. Urine analyses were performed on five rats each at weeks 14 and 20. No effects of potassium chloride on body weights or water intake was observed, nor on relative or absolute bladder weights. Excretion in the urine of magnesium ($p < 0.05$) or potassium ($p < 0.01$) was statistically significantly increased in the potassium chloride exposed group compared with control; no effects were observed on urine osmolality or pH. Numbers of preneoplastic or neoplastic lesions per rat were similar in control and potassium chloride treated rats. The incidence of bladder tumours was not statistically significantly different from controls.

Overall, in studies investigating the effect of 130 weeks of intake of a diet with 3% potassium chloride (equivalent to 1,500 mg potassium chloride/kg bw per day and corresponding to 720 mg chloride/kg bw per day) on urinary bladder of rats only epithelial proliferation was recorded in few animals but no urinary bladder tumours were found (Lina et al., 1994). Sodium and potassium ions may exert weak promoting activity on BBN induced-urinary bladder carcinogenicity under conditions of neutral urinary pH (Lina and Woutersen, 1989). In another initiation–promotion study in rats, 3% potassium chloride (1,216 mg potassium chloride/kg bw per day and corresponding to 583 mg chloride/kg bw per day) did not affect incidence of urinary bladder tumours (Shibata et al., 1992).

3.6.9. Effect of chlorides on blood pressure in normotensive and hypertensive rats

Potassium chloride

The effects of various levels and types of dietary chloride salts on blood pressure were examined in studies with normotensive rats by Kaup et al. (1991a,b) (the present description is given only for sodium and potassium chlorides). Weanling male Sprague–Dawley rats (6–8/treatment) were fed semipurified diets containing from 1.7 to 2.1 mg Cl/g diet (corresponding to 153 and 189 mg chloride/kg bw per day) or supplemental chloride from 15.3 to 17.4 mg Cl/g diet (corresponding to 1,377 and 1,566 mg chloride/kg bw per day) as sodium chloride or potassium chloride for 8 or 17 weeks. Systolic blood pressure measurements were made during week 7 and week 13. The systolic blood pressure of the rats fed high levels of sodium- or potassium chloride for 7 or 13 weeks were significantly higher than in the rats fed the basal level of chloride. Relative kidney weight of rats consuming high levels of sodium- or potassium chloride was statistically significant increased at 8 weeks and 17 weeks. Ingestion of high levels of sodium chloride caused an increase in water consumption during the first 7 weeks, which was not present anymore after 16 weeks. Ingestion of sodium- and potassium chloride significantly elevated the urine volumes during the first 7 weeks only.

The authors suggested that the increase in systolic blood pressure by the ingestion of supplemental chloride as sodium- or potassium salt by normotensive rats was not related to permanent changes in fluid compartments but seemed to be related to renal function. However, the Panel noted that this assumption is not substantiated in the papers.

Two rat studies investigated whether chloride salts (potassium or sodium) have a greater effect on blood pressure than other sodium salts (sodium acetate) and assessed changes in plasma hormones, kidney function, and mineral metabolism) when added to either a basal diet with cottage cheese or a lactalbumin-based diet in the diet (Greger and Tseng, 1993). Increased systolic blood pressure and relative kidney weight were observed in normotensive male rats following dietary administration of potassium chloride (3,364 mg potassium chloride/kg bw per day corresponding to 1,614 mg chloride/kg bw per day and 1750 mg potassium/kg bw per day) for 3 weeks. These rats had also, decreased body weight and increased urine volume. Furthermore, increased systolic blood pressure and relative kidney weight were seen following dietary administration of potassium chloride (3,318 mg/kg bw per day corresponding to 1,592 mg chloride/kg bw per day and 1,726 mg potassium/kg bw per day) for 8 weeks. According to the authors the results suggest that dietary chloride affected blood pressure more rapidly than dietary sodium and that changes in renal function were involved in the induced hypertension. The Panel noted that the special formulation of the diets makes it impossible to conclude on the effect of chloride alone on blood pressure.

The hypothesis that dietary chloride determines the phenotypic expression of the stroke-prone spontaneously hypertensive rat (SHRSP) was tested (Tanaka et al., 1997). Groups of 10-week-old male SHRSP rats (n = 15–20) were either fed a normal diet (control,) or a 2% potassium diet formulated either with (ii) potassium chloride (KCl,); or (iii) either potassium bicarbonate ($KHCO_3$) or potassium citrate (KB/C) (equivalent to 3,432 mg KCl/kg bw per day corresponding to 1647 mg chloride/kg bw/day). Over the 4-week period preceding the start of the supplementation of the diet, all rats were fed the last, (iii), diet. The average daily intake of food consumed in each of the three treatment groups was calculated weekly. The treatment group with the least daily intake of 1 week became the target group of the next week. Successive mean weekly values of systolic blood pressure and diastolic blood pressure were calculated from measurements of systolic and diastolic blood pressure from 9 to 24 weeks of age. Rats were examined for signs of stroke daily and decapitated at the end of week 25. Blood samples were collected at the end of the study and urine samples were obtained weeks 10, 14, 18, 22 and 25 for the measurement of electrolytes, arterial blood PCO_2 and pH. The diet supplemented with dietary potassium chloride statistically significantly increased hypertension from 16 weeks of age, whereas supplementing either $KHCO_3$ or potassium citrate (KB/C) reduced hypertension. Urinary excretion of chloride was only statistically significantly increased in the group receiving a potassium chloride supplemented diet ($p < 0.05$). After 4 weeks, the serum concentration of chloride in the potassium chloride group was statistically significantly higher than that in the KB/C and control groups, and the blood concentration of bicarbonate was statistically significantly lower. Serum concentration of sodium and potassium did not differ among groups. After blood pressure had reached a maximal level, stroke occurred in 1/20 (5%) in the control group, 6/17 (35.3%) in the potassium chloride group and in 0/15 (0%) in the KB/C group. The frequency of stroke was statistically significantly greater in the potassium chloride group than in the KB/C group. The median value of plasma renin activity was statistically significantly higher with treatment with potassium chloride than with KB/C supplementation and the values of systolic blood pressure and plasma renin activity from individual rats varied directly and statistically significantly with each other.

Schmidlin et al. (2005) tested the hypothesis that the pressor effect (salt-sensitivity) of dietary sodium chloride is dominantly determined by the chloride ion was conducted in 10-week-old male SHRSP rats assigned to five groups (N = 15–20/group): 1) control; 2) sodium chloride (NaCl) (44 mmol/100 grams chow, equivalent to 3 086 mg sodium chloride/kg bw per day, corresponding to 1,851 mg chloride/kg bw per day); 3) potassium chloride (KCl) (44 mmol/100 grams, equivalent to 3,936 mg potassium chloride/kg bw per day corresponding to 1,889 mg chloride/kg bw per day); 4) sodium chloride (44 mmol/100 grams, equivalent to 3,086 mg sodium chloride/kg bw per day corresponding to 1,851 mg chloride/kg bw per day) combined with potassium bicarbonate (77 mmol/100 grams, equivalent to 9,251 mg/kg bw per day) (NaCl/KBC);or 5) sodium chloride (44 mmol/100 grams, equivalent to 3,086 mg sodium chloride/kg bw per day corresponding to 1,851 mg chloride/kg bw per day) combined with potassium chloride (NaCl/KCl) (77 mmol/100 grams, equivalent to 6,889 mg potassium chloride/kg bw per day corresponding to 3,306 mg chloride/kg bw per day). From age 10 to 15 or 16 weeks, the systolic blood pressure increased linearly in all groups. The value of dp/dt (change in systolic blood pressure as a function of time) in potassium chloride treated rats matched the change observed in the sodium chloride treated rats. In the NaCl/KCl group, the value of dp/dt was statistically significantly greater than in any of the 4 other groups. In the NaCl-, KCl- and NaCl/KBC-treated groups (which were receiving the same amount of dietary chloride), the values of dp/dt were not different from each other. Compared with the potassium chloride treated group dt/dp was statistically significantly less in the control group. After 4 weeks of treatment, systolic

blood pressure had increased statistically significantly more in the group treated with NaCl/KCl than in any of the four other groups. The average value of dp/dt of each group was directly and linearly related to both the average urinary excretion rates of chloride and the dietary level of chloride but not to urinary excretion rate of sodium or the dietary level of sodium or urinary sodium/potassium ratio ($p = 0.8$), or the dietary sodium/potassium ratio. Strokes were reported to occur in eight NaCl/KCl-treated rats, in none NaCl treated rats, and in two NaCl/KBC-treated rats. The frequency of strokes was statistically significantly higher in the NaCl/KCl group than in either NaCl or NaCl/KBC groups. The frequency of stroke did not differ between NaCl and NaCl/KBC. The authors concluded that chloride ion dominantly determined the pressor effect induced with dietary sodium chloride, both with sodium chloride loaded alone and combined with either potassium chloride or potassium bicarbonate, and thereby likely determined the occurrence of stroke with sodium chloride loading. The authors further concluded that in the SHRSP rat, the chloride ion of dietary sodium chloride dominantly determines the salt sensitivity and thereby phenotypic expression and suggested that the chloride ion might do so by inducing renal vasoconstriction.

In a further study, 10-week-old male SHRSP rats were treated with hydrochlorothiazide, 25 mg/kg bw per day, alone (n = 11); hydrochlorothiazide combined with either KCl (2% K, equivalent to 2,360 mg/kg bw per day, n = 10) or KHCO3 (2% K, equivalent to 2,360 mg/kg bw per day, n = 11) and (n = 11) over 10 weeks (Schmidlin et al., 2010). The dose of hydrochlorothiazide was selected to increase the sodium excretion and to attenuate the spontaneous increase in blood pressure in this specific rat model. The group with hydrochlorothiazde and the group with hydrochlorothiazed combined with KHCO3 had a no increase in systolic blood pressure over the baseline measurement. Their blood pressure was statistically significant lower than the control group receiving no hydrochlorothiazide and no potassium salt, the difference being 38 mmHg (30/46; 25–75 percentile) and the blood pressure in these groups was statistically differed also from the blood pressure in the group treated by KCl which increased to 17 mmHg (13/21; 25–75 percentile) over baseline. The results indicate that in this special rat model, hydrochlorothiazide-induced natriuresis does not prevent a pressor effect by dietary KCl loading. The results hint on a blood pressure increase by chloride and a sodium-independent mechanism.

Magnesium chloride

Groups of weanling, male Sprague–Dawley rats (n = 6–8) were fed a semipurified diet that contained 'moderate chloride' (1.9 mg Cl/g diet, control) or 'high chloride' (15.6 mg Cl/g diet) as magnesium chloride (corresponding to 171 and 1,404 mg chloride/kg bw per day) for 8 weeks (Kaup et al., 1991a). A statistically significant increase in systolic blood pressure was found in the 'high chloride' group.

A 2% magnesium chloride solution was administered to eight 2-month-old female SHRSP rats for 17 months (equivalent to 1,160 mg magnesium chloride/kg bw per day corresponding to 406 mg chloride/kg bw per day) (Saito et al., 1990). As control groups, there were three groups receiving tap water for the same period. One control group consisted of nine female age-matched SHRSP rats, another control group of six stroke-resistant spontaneously hypertensive rat (SHRSR) and a third control group consisted of seven WKY (Wistar Kyoto rats). Systolic blood pressure and serum magnesium was measured. Rat organs were removed and prepared for microscopic examination. Serum magnesium statistically significantly increased in the SHRSP treated with the magnesium chloride solution as compared to the SHRSP given tap water. In the mesenteric artery, macroscopically bead-like nodular lesions were found in 89% of nine SHRSP given tap water, while in 25% of eight SHRSP given magnesium chloride solution and in 0% of six SHRSR or seven WKY given tap water. Furthermore, microscopically periarteritis nodosa of the mesenteric artery was observed in 80% of five SHRSP rats given tap water, in 0% of five SHRSP rats given magnesium chloride solution and five SHRSR rats or five WKY rats given tap water. The effects of the magnesium chloride solution on arteriolar lesions were also found in renal and cerebral tissues of the SHRSP rats. Serum cholesterol, fructosamine, creatinine and systolic blood pressure did not differ between SHRSP groups.

Overall, all animal studies in normotensive and hypertensive rats suggested a role of chloride in increasing blood pressure. The Panel however noted that in these studies only one dose of chloride salts was tested in comparison to controls. In addition, the Panel noted that there was no difference in blood pressure increase between sodium and potassium salt.

3.6.10. Effect of chlorides on blood pressure in human studies

In a cross-over trial aimed at examining the effect of dietary potassium supplementation on blood pressure in normotensive women with moderate potassium intake, two groups (n = 22) of women were randomly assigned to receive 80 mmol potassium chloride/day (corresponding to 85 mg potassium chloride/kg bw per day and 40.8 mg chloride/kg bw per day) in a wax matrix formulation for 4 weeks or matching placebo (Barden et al., 1986). The treatments were reversed during the second 4-week period. Blood pressure, heart rate, urinary volume, electrolytes and creatinine, were measured weekly during the initial screening period and the two 4-week treatment periods. Measurement of systolic and diastolic blood pressures at the end of each treatment period did not show a significant treatment-related effect. A statistically significant increase in plasma and urine potassium was observed. No changes were seen in creatinine excretion between the screening, placebo and potassium periods. Statistically significant decrease in plasma bicarbonate and increase in plasma urea following potassium supplements were observed. There were no significant changes in plasma renin activity, plasma sodium, creatinine, or calcium.

In a study investigating the effect of potassium supplementation in patients with mild to moderate essential hypertension, 32 women received 65 mmol potassium chloride/day (corresponding to 69 mg potassium chloride/kg bw per day and to 33 mg chloride/kg bw per day) (Matlou et al., 1986). The women were randomly assigned to one of two groups who were given either 65 mmol/day of potassium chloride, or matching placebo (glucose with 0.3% quinine) for a 6 weeks treatment period. The treatments were reversed after the 6-week period. During the treatment period, blood pressure, and urinary sodium and potassium and creatinine were measured weekly. Plasma sodium and potassium and serum albumin, calcium and magnesium were only measured at week 6. Intake of potassium chloride induced a statistically significant reduction in systolic and diastolic blood pressure, and a statistically significant increase in serum and urine potassium. Urine sodium was statistically significantly increased. Serum albumin, magnesium and calcium were unaffected by treatment. The changes observed in blood pressure did not correlate with changes in serum and urine electrolytes. According to the authors, the analysis of the 95% confidence intervals in this and five other studies suggests that potassium chloride supplementation seems to lower blood pressure in essential hypertensive women, but that the change is small and within the confidence levels of all six trials.

Overall, two studies in human aiming to examine the effects of potassium chloride supplementation on blood pressure in normotensive women and in patients with mild to moderate hypertension, demonstrated either no effect or a slight lowering effect on blood pressure, respectively.

4. Discussion

Hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised food additives in the EU under Annex II and III of Regulation (EC) No 1333/2008 and have been previously evaluated by the SCF in 1991 (SCF, 1991b) and several times by JECFA, the latest in 1965 (JECFA, 1966a) and Both committees established an ADI 'not specified' for hydrochloric acid and its potassium, calcium and magnesium salts.

Specifications for hydrochloric acid and its potassium, calcium and magnesium salts have been defined in the EU in Commission Regulation (EU) No 231/2012 and also by JECFA (2006). The purity for hydrochloric acid is specified to be not less than 97.0% and not more than 103.0% (JECFA), and not less than 99, 93 and 99% for potassium, calcium (anhydrous) and magnesium chloride, respectively.

Chlorides occurred in the normal diet. Chloride is an essential nutrient which together with certain cations, e.g. potassium calcium and magnesium is involved in fluid and electrolyte balance and is required for normal cellular function (EFSA NDA Panel, 2005).

Hydrochloric acid is an essential component of human gastric fluid (EFSA NDA Panel, 2010). Hydrochloric acid and its potassium, calcium and magnesium salts are absorbed from the gastrointestinal tract. After absorption, chloride is distributed to organs and tissues. Chloride is excreted via sweat, urine or in faeces.

The Panel considered chlorides to be of low acute oral toxicity.

Hydrochloric acid (1,496 mg/kg bw per day) given via the diet to female rats for 14 days was associated with a decrease in body weight, an increase in urine volume and relative kidney weight, but without histopathological changes in this organ. Similar changes were observed in mice after administration via the diet of 10,000 mg potassium chloride/kg bw per day (corresponding to

4,800 mg chloride/kg bw per day) for 4 weeks and in rats given 2,250 mg potassium chloride/kg bw per day (corresponding to 1,080 mg chloride/kg bw per day) for 15 weeks. Male, but not female, mice given 10,000 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 4,800 mg chloride/kg bw per day) via the diet for 13 weeks showed an increased incidence of vacuolar lesions in the proximal tubuli of the kidneys. Calcium chloride given by gavage to female rats at 777 or 1,554 mg/kg bw per day (corresponding to 489 and 979 mg chloride/kg bw per day) for 3 days statistically significantly decreased urine pH and statistically significantly increased urinary calcium, magnesium and chloride excretion. The Panel considered the short-term and subchronic studies of low oral toxicity.

In vitro genotoxic effects of hydrochloric acid and its salts were observed only at high concentrations that were associated with low pH or high osmolality of the experimental media, which cannot occur under the physiological conditions *in vivo*. The Panel concluded that the use of hydrochloric acid and its potassium, calcium and magnesium salts as food additives does not raise concern for genotoxicity.

In long-term studies, no adverse effects were reported in mice exposed to magnesium chloride hexahydrate up to a dietary dose level of 3,000 mg magnesium chloride hexahydrate/kg bw per day (corresponding to 1,050 mg chloride/kg bw per day) for 96 weeks except for a decrease in the body weight of females at the highest dose level (3,000 mg magnesium chloride hexahydrate/kg bw per day corresponding to 1,050 mg chloride/kg bw per day) (Kurata et al., 1989). No treatment-related tumours were observed in male rats fed potassium chloride in the diet (up to approximately 2,000 mg potassium chloride/kg bw per day corresponding to 960 mg chloride/kg bw per day) for 2 years (Imai et al., 1986). After feeding 1,500 mg/kg bw per day potassium chloride (corresponding to 720 mg chloride/kg bw per day) for 18 months, no tumours were reported (Lina and Kuijpers, 2004). The Panel concluded that there is no concern with respect to carcinogenicity

There were no reproductive toxicity studies available. In prenatal developmental toxicity studies, no maternal or developmental effects were reported in mice and rats following administration of potassium chloride at dose levels up to 235 and 310 mg/kg bw per day (corresponding to 112 and 148 mg chloride/kg bw per day), respectively (FDRL, 1975) from implantation until the end of organogenesis; in mice, rats and rabbits following administration of calcium chloride at dose levels up to 189, 176 and 169 mg/kg bw per day (corresponding to 119, 110 and 106 mg chloride/kg bw per day), respectively (FDRL, 1974); and in rats following administration of magnesium chloride hexahydrate at a dose level of 800 mg/kg bw per day (corresponding to 280 mg chloride/kg bw per day) (Usami et al., 1996). No effects were observed at the highest doses tested. The Panel noted that developmental studies did not cover for the period for very young animals, which is relevant for the assessment of chlorides in food for infants below 16 weeks of age, and reproductive studies were not available.

Several studies to investigate the effects of various types of dietary chloride salts (sodium, potassium and magnesium chloride) on blood pressure have been conducted in normotensive and hypertensive rats (Saito et al., 1990; Kaup et al., 1991a,b; Greger and Tseng, 1993; Tanaka et al., 1997; Schmidlin et al., 2005, 2010). All animal studies in normotensive and hypertensive rats suggested a role of chloride in increasing blood pressure irrespective of the associated counter ion (e.g. potassium, sodium, magnesium). The Panel noted that in these studies only one dose of chloride salts was tested in comparison to controls.

The effect on chloride on blood pressure has been investigated also in humans. Two studies aiming to examine the effects of potassium chloride supplementation on blood pressure in normotensive women and in patients with mild to moderate hypertension, demonstrated either no effect or a slight lowering effect on blood pressure, respectively.

The effect of chloride anion on blood pressure and in particular on hypertensive subjects and on subjects falling under the medical definition of 'salt-sensitive population' is described in the literature in humans. This effect was mainly due to the combined activity of sodium and chloride. McCallum et al. (2015) published a review summarising the evidences of the link between chloride anion and hypertension. However, this effect of chloride anion on hypertensive or salt-sensitive subjects has been demonstrated mainly when chloride is associated with sodium (Kurtz and Morris, 1983; Shore et al., 1988; Kotchen, 2005; Boegehold and Kotchen 1991, Boegehold and Kotchen, 1989; Schmidlin et al., 2007). Chloride anion associated with potassium (at the dose of 40 mg chloride/kg bw per day) showed either no effect on blood pressure (Barden et al., 1986) or an effect of decreasing blood pressure (Matlou et al., 1986).

The analysis of the data on blood pressure due to chloride exposure in animals, showed an increase in blood pressure in five single-dose animal studies. Among those studies the lowest dose tested was 1,377 mg chloride/kg bw per day. Rather than exploring to derive a substance-specific uncertainty factor for chloride, the Panel considered human data more appropriate to identify a level of chloride intake which does not raise a safety concern. In humans, potassium chloride providing 40 mg chloride/kg bw per day for four weeks was without adverse effects (Barden et al., 1986). This study used only a single dose and so an upper safe dose cannot be identified due to the lack of data describing the dose–response relationship between chloride intake and blood pressure increase.

Dietary exposure to chlorides derived from the use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as food additives was calculated according to different exposure scenarios based on the provided use levels, as described in Section 3.4.1. The Panel considered that the refined exposure assessment scenario resulted in more realistic long-term exposure estimates compared to the *maximum level exposure assessment scenario* which was considered very conservative.

The Panel, did not identify brand loyalty to any of the main contributing food categories, therefore selected the non-brand loyal scenario as the most relevant for risk characterisation.

The Panel estimated that in the *non- brand-loyal scenario*, mean exposure ranged from 2 mg/kg bw per day in the elderly to 42 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 5 mg/kg bw per day in the elderly to 71 mg/kg bw per day in toddlers.

The Panel assumed that 100% of the foods belonging to a food category included in the assessment contained these additives, whereas the average percentage was 1.5% according to the Mintel's GNPD. Therefore, taking into account the other uncertainties (Table 9), the Panel considered that the overall exposure assessment would result in an overestimation of the exposure to chloride derived from the use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as food additives.

The Panel noted that the exposure to chloride derived from the use of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) according to the Annex III (Parts 1, 2, 3, 4 and 5A) was only partly considered in the exposure assessment.

The Panel also noted that the refined exposure estimates are based on information provided on the reported use levels of hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511). If actual practice changes this refined estimate may no longer be representative and should be updated.

The Panel identified a human dose of 40 mg chloride/kg bw per day as a reference value for the assessment. Mean levels of exposure in all age groups were below or at this reference value, which indicates no safety concern. In some age groups (toddlers, children and adolescents), the 95-percentile exposure estimates were slightly above this reference value.

The FAF Panel noted that potassium chloride can be and is used to replace sodium chloride and acknowledged the potential risk of arrhythmia due to excessive use of potassium chloride as salt substitute especially in vulnerable populations (e.g. subject with chronic kidney disease) (EFSA NDA Panel, 2005; VKM, 2014; COT, 2017). However, this is not a food additive use, therefore not evaluated in this opinion.

Hydrochloric acid (E 507) is authorised in foods for infants below 16 weeks of age in FC 13.1.5.1 Dietary foods for infants for special medical purposes and special formulae for infants. Industry did not provide use levels for this food category and therefore it was not possible to perform exposure assessment for this age group. The average chloride content in human milk has been reported to be around 400 mg/L (EFSA NDA Panel, 2014). Based on the opinion of the SCF (2003), Directive 2006/141/EC provides for minimum and maximum chloride contents in infant formula and follow-on formula of 50 to 160 mg/100 kcal. The minimum and maximum levels for chloride in infant formula for special medical purposes are set at 60 and 160 mg/100 kcal (Commission Delegated Regulation (EU) 2016/128). In the absence of actual use levels of hydrochloric acid (E 507) in foods for infants for special medical purposes and special formulae for infants, the Panel considered that the use levels of E 507 should not lead to exceedance of the maximum limit for chloride set by the legislation.

5. Conclusions

Chloride is a natural constituent of human, animals and plants and is present in all biological materials, including foodstuffs. Based on the toxicological database available the Panel concluded that

the exposure to chloride from hydrochloric acid and its potassium, calcium and magnesium salts (E 507, E 508, E 509 and E 511) does not raise a safety concern at the reported use and use levels.

The Panel noted that because of the lack of data on use levels of hydrochloric acid (E 507) in specific formulae used for infants under special medical conditions the safety of this use could not be assessed.

6. Recommendations

The Panel recommends that:

- the European Commission considers lowering the current limits for toxic elements (arsenic, lead and mercury) in the EU specifications for hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) in order to ensure that hydrochloric acid (E 507), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) as a food additive will not be a significant source of exposure to those toxic elements in food.
- Information on the possible use and use levels of hydrochloric acid (E 507) as a food additive in specific formulae used for infants under special medical conditions should be provided in order to enable the Panel to estimate the exposure and evaluate the safety of use of this food additive in infants below 16 weeks of age.

Documentation provided to EFSA

1) CEFIC Calcium Chloride Working Group, 2018. Scientific data on food additive of Calcium chloride E 509. Submitted to EFSA, 2 February 2018.
2) ReachCentrum SA. Hydrochloric acid, E 507. Submitted to EFSA 30 November 2017.
3) BVfL. Aufruf der EFSA-052/2012 zur Neubewertung diverser in der EU zugelassener Lebensmittelzusatzstoffe unterschiedlicher Funktionsklassen im Kontext der Verordnung (EG) Nr. 1333/2008 des Europäischen Parlaments und des Rates vom 16. Dezember 2008 über Lebensmittelzusatzstoffe. 14 August 2012.
4) NOVACID. Answer to the call for scientific data on miscellaneous food additives-Hydrochloric acid and Calcium chloride. July 2012.
5) Polish EFSA Focal Point. Answer to the call for scientific data on miscellaneous food additives July 2012.
6) Pre-evaluation document Hydrochloric acid and its potassium, calcium and magnesium salts (E 507, 508, 509 and 511) prepared by DTU Food n 06/08/2014AESGP (Association of the European Self-Medication Industry), 2017. Data on usage levels of Potassium chloride (E 508) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 5). Submitted to EFSA on 31 January 2017.
7) AGRUPOST (Spanish Association of Postharvest Services and Processes), 2017. Data on usage levels of calcium chloride (E 509) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 5). Submitted to EFSA on 30 January 2017.
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12) ICGA (International Chewing Gum Association), 2017. Data on usage levels of calcium chloride (E 509) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 5). Submitted to EFSA on 19 May 2017.

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Abbreviations

AAS	atomic absorption spectrometry
ADI	acceptable daily intake
AI	adequate intake
AIIBP	Association Internationale de l'Industrie des Bouillons et Potages
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AOAC	Association of Official Analytical Chemists
AST	aspartate aminotransferase
BBN	*N*-butyl-*N*-(4-hydroxybutyl)nitrosamine
bw	body weight
Ca	calcium
CAS	Chemical Abstract Service
CE	capillary electrophoresis
CEFIC	European Chemical Industry Council
CEN	European Committee for Standardization
CHL	Chinese hamster lung
CHO	Chinese hamster ovary
Cl	chloride
EINECS	European Inventory of Existing Commercial chemical Substances
EuSalt	European Salt Producers' Association
FAF	EFSA Panel on Food Additives and Flavourings
FC	food category
FCS	food categorisation system
FDA	US Food and Drug Administration
FDRL	Food and Drink Research Laboratories
FSMP	Food for Special Medical Purposes
GD	gestation day
GNPD	Global New Products Database
HPLC	high-performance liquid chromatography
HVP	hydrolysed vegetable protein
IC	ion chromatography
ICP	inductively coupled plasma
IDF	International Dairy Federation
IFU	International Fruit and Vegetable Juice Association
ISE	ion selective electrode
ISO	International Organization for Standardization

JECFA	Joint FAO/WHO Expert Committee on Food Additives
IC	ion chromatography
IPCS	International Program on Chemical Safety
K	potassium
LD_{50}	lethal dose, 50% i.e. dose that causes death among 50% of treated animals
MCPD	monochloropropanediol
MES	2-(N-Morpholino)ethanesulfonic acid, 4-Morpholineethanesulfonic acid
Mg	magnesium
N	nitrogen
Na	sodium
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NMKL	Nordic Committee on Food Analysis
NOAEL	no-observable-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
OES	optical emission spectroscopy
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
RTE	relative total growth
SCF	Scientific Committee for Food
SDP	plasma spectrometry
SHRSP	stroke-prone spontaneously hypertensive rat
SHRSR	stroke-resistant spontaneously hypertensive rat
SNE	Specialised Nutrition Europe
STP	standard temperature and pressure
TemaNord	Nordic Council of Ministers
TSH	thyroid stimulating hormone
UL	Upper Level
WHO	World Health Organization

Appendix A – Summary of the reported use levels (mg/kg or mg/L as appropriate) of hydrochloric acid and potassium, calcium and magnesium chloride (E 507, E 508, E 509 and E 511) provided by Industry

Appendix B – Number and percentage of food products labelled with hydrochloric acid and potassium, calcium and magnesium chloride (E 507, E 508, E 509 and E 511) out of the total number of food products present in the Mintel GNPD per food subcategory between January 2014 and May 2019

Appendix C – Use levels of hydrochloric acid and potassium, calcium and magnesium chloride (E 507, E 508, E 509 and E 511) used in the exposure assessment scenarios (mg/kg or mL/kg as appropriate)

Appendix D – Summary of total estimated exposure of hydrochloric acid and potassium, calcium and magnesium chloride (E 507, E 508, E 509 and E 511) from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix E – Main food categories contributing to exposure to Hydrochloric acid and Potassium, Calcium and Magnesium chlorides (E 507, E 508, E 509 and E 511) using the maximum level exposure assessment scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendixes A–E can be found in the online version of this output ('Supporting information' section).