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Re-evaluation of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) as food additives

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Abstract

The Panel on Food Additives and Nutrient Sources added to Food (ANS) provided a scientific opinion re-evaluating the safety of aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) as food additives. The Panel considered that adequate exposure and toxicity data were available. Aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) are permitted as food additives in only a few specific products and the exposure is probably near zero. Aluminium compounds have low bioavailability and low acute toxicity. There is no concern with respect to genotoxicity and carcinogenicity. The no observed adverse effect level (NOAEL) for aluminium compounds in subchronic studies was 52 mg Al/kg body weight (bw) per day in rats and 90 mg Al/kg bw per day in dogs and the lowest NOAEL for neurotoxicity in rats was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day in studies in mice and rats. The Panel concluded that aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) are of no safety concern in the current authorised uses and use levels.

Keywords: aluminium, E 520, E 521, E 522, E 523, E 541, sulphates

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Summary

The present opinion deals with the re-evaluation of the safety of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) as food additives.

Aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) are authorised as food additives in the European Union (EU) in accordance with Annex II to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Sodium aluminium phosphate (E 541) has been evaluated by the Scientific Committee for Food (SCF) in 1990 who agreed with the provisional tolerable weekly intake (PTWI) for Al of 7 mg/kg bw established by Joint FAO/WHO Expert Committee on Food Additives (JECFA).

The safety of aluminium from dietary intake was evaluated in 2008 by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (EFSA, 2008). Based on the range of available no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL), and applying a weight of evidence approach, the Panel established a tolerable weekly intake (TWI) of 1 mg Al/kg body weight (bw). This weekly health-based reference value took into account the potential accumulation of dietary aluminium in the body, and applied to all aluminium compounds in food, including additives.

Aluminium containing-food additives were also evaluated by JECFA several times, the latest in 2011. The Committee established a PTWI, which applied to all aluminium compounds in food. The PWTI was set at 2 mg Al/kg bw based on a NOAEL of 30 mg/kg bw per day from a neurodevelopmental study in rats (Poirier et al., 2011), with the application of a safety factor of 100. JECFA noted the complication of the identification of the LOAEL and NOAEL due to decreasing fluid consumption.

In 2017, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) published an opinion on tolerable intake of aluminium with regard to adapting the migration limits for aluminium in toys. The SCHEER used the same study of Poirier et al. (2011) and established a tolerable daily intake (TDI) of 0.3 mg/kg bw per day.

Aluminium compounds have low bioavailability and low acute toxicity. There is no concern with respect to genotoxicity and carcinogenicity.

The NOAEL for aluminium compounds in subchronic studies was 52 mg Al/kg bw per day in rats and 90 mg Al/kg bw per day in dogs.

Studies on reproductive, developmental and neurotoxicity were available; the lowest NOAEL for neurotoxicity in rats was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day in studies in rats and mice.

Aluminium sulphates (E 520–523) are permitted as food additives in two food categories with further restriction in use and sodium aluminium phosphate, acidic (E 541) is only permitted as a food additive in one food category with further restriction in use.

The Mintel's Global New Products Database (GNPD) indicated that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were used in a decreasing number of products over time, following the change in legislation coming into force in February 2014.

To assess the dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives, the exposure was only calculated based on the MPLs as set out in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*), because no use levels or analytical results were made available to EFSA.

The mean exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives at the regulatory maximum level exposure assessment scenario (MPL) ranged from 0.0 mg/kg bw per day in all population groups to 0.21 mg/kg bw per day in children. The 95th percentile of exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) ranged from 0.0 mg/kg bw per day in all population groups to 0.88 mg/kg bw per day in toddlers and children.

The exposure estimates in this highly conservative scenario exceeded the TWI of 1 mg Al/kg bw (equivalent to ~ 0.14 mg Al/kg bw per day) for all population groups at the 95th percentile, and for toddlers and children at the mean (Table 9). However, considering that these additives are only authorised in niche products of which the consumption is not captured in the dietary surveys of the EFSA Comprehensive Database, the Panel considered that these estimates are highly uncertain and the real exposure is most probably near the lower end of the calculated exposure (approximately 0). Due to these uncertainties a comparison of the calculated exposure with TWI is of little or no value.

Considering that:

- bioavailability of aluminium compounds is low (approximately 0.1% from food and beverages);
- inorganic aluminium salts are of low acute toxicity;
- the NOAEL identified for aluminium compounds in subchronic studies was 52 mg Al/kg bw per day in rats and 90 mg Al/kg bw per day in dogs;
- the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity and these compounds are unlikely to be human carcinogens;
- studies on reproductive, (neuro)developmental and neurotoxicity were available; the lowest NOAEL for neurotoxicity was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day;
- aluminium sulphates (E 520–523) are permitted as food additives in two food categories with further restriction in use;
- sodium aluminium phosphate (E 541) is only permitted as a food additive in one food category with further restriction in use;
- the Mintel's GNPD indicated that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were used in a decreasing number of products over time, following the change in legislation coming into force in February 2014, which is in line with the fact that EFSA did not receive any use levels of these additives from industry;
- these additives are only authorised in specific products which consumption is not captured in the dietary surveys of the EFSA Comprehensive Database the estimated exposure is most probably near the lower end of the calculated exposure (approximately 0).

The Panel concluded that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) are of no safety concern in the current authorised uses and use levels.

The Panel recommend that:

- the combined exposure to aluminium from all the aluminium-containing food additives should be assessed.

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1. Introduction

The present opinion document deals with the re-evaluation of aluminium sulphates (E 520–523) and sodium aluminium phosphate (SALP, E 541) when used as food additives.

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 aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522), aluminium ammonium sulphate (E 523) and sodium aluminium phosphate acidic (E 541) are expected to dissociate in the gastrointestinal tract into their respective ions. The resulting sodium, potassium, ammonium and phosphate will enter normal physiological processes. Therefore, these ions are not discussed further in this opinion which deals only with the aluminium moiety released from these food additives, because the Panel considered aluminium the critical component at the level of use of these food additives. This opinion does not aim at revising the health-based guidance value for aluminium set by EFSA in 2008 (EFSA, 2008) even though new toxicological evidence has been reviewed.

[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

Aluminium sulphates (E 520–523) and SALP (E 541) are authorised as food additives in the EU in accordance with Annex II 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 the EU, SALP (E 541) has been evaluated by the Scientific Committee for Food (SCF) in 1990 (SCF, 1991) who agreed with the provisional tolerable weekly intake (PTWI) for Al of 7 mg/kg bw established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

In 2008, the EFSA Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (EFSA AFC Panel, 2008) prepared a scientific opinion on safety of aluminium from dietary intake and in view of the cumulative nature of aluminium in the organism after dietary exposure, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) for aluminium rather than a tolerable daily intake (TDI). Based on the combined evidence from the above-mentioned studies, the Panel established a TWI of 1 mg aluminium/kg bw per week.

In 2011, a statement on the evaluation of a new study related to the bioavailability of aluminium in food was published by EFSA (2011a,b). EFSA concluded that the new study did not provide any additional information on the bioavailability of aluminium from aluminium-containing compounds that could modify the conclusions reached in 2008 by the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials. Therefore, EFSA concluded that this study did not give reason to reconsider the previous safety evaluation of aluminium-based food additives authorised in the EU performed by EFSA in 2008.

Aluminium salts (sodium and potassium sulphate) have been evaluated by JECFA in 1978 (JECFA, 1978) that concluded that the use of aluminium metal as a silvering decoration for certain items of confectionary was not considered to present a health hazard. SALP (E 541) was evaluated by JECFA in 1982, 1985, 1986, 1988, 2006 and 2011 (JECFA, 1982, 1986, 1987, 1989, 2007 and 2012). In its first evaluation in 1982, a temporary acceptable daily intake (ADI) of 0–6 mg/kg body weight (bw) was allocated due to insufficient data. This is equivalent to 0–0.6 mg/kg bw as aluminium. In 1985, in the light of new data, the Committee concluded that the previous temporary ADI should be applied to all aluminium salts added to food. In 1986, additional studies were reviewed and the temporary ADI of 0–0.6 mg/kg bw for aluminium was extended to be applied to all aluminium salts added to food. In 1989, the previous ADI for aluminium of 0.6 mg/kg bw was changed to a group PTWI 7 of mg/kg bw expressed as aluminium from all sources. The Committee concluded that there was no need to set a separate ADI for SALP, basic or acidic, since the PTWI included aluminium intake resulting from food additive sources. In 2006, the committee confirmed that the health-based guidance value should be expressed as a PTWI because of the potential of bioaccumulation. The Committee established a PTWI for Al of 1 mg/kg bw, which applies to all aluminium compounds in food, including additives. The previously established ADIs and PTWI for aluminium compounds were withdrawn. In 2011, JECFA established a PTWI of 2 mg/kg bw based on the no observed adverse effect level (NOAEL) of 30 mg/kg bw per day of a neurodevelopmental study (Poirier et al., 2011) and applying a safety factor of 100 (JECFA, 2012).

In 2017, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER, 2017) published an opinion on tolerable intake of aluminium with regards to adapting the migration limits for aluminium in toys. The SCHEER used the same study of Poirier et al. (2011) and established a TDI of 0.3 mg/kg bw per day.

SALP (E 541) has also been reviewed by the Nordic Council of Ministers (TemaNord, 2002), who concluded that 'The intake of food where this additive is used to the maximum level could lead to exceeding the PTWI. However, this salt is not soluble, so it should be investigated whether the aluminium is available to the same extend as from soluble aluminium salts'.

[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.

2. Data and methodologies

2.1. Data

The Panel on Food Additives and Nutrient Sources added to Food (ANS) was not provided with a newly submitted dossier. EFSA launched public calls for data[6] and, if relevant, contacted other risk assessment bodies to collect relevant information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to last Working Group meeting before the adoption of the opinion.[7] 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.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database[8]) was used to estimate the dietary exposure.

The Mintel's Global New Products Database (GNPD) is an online database which was used for checking the labelling of products containing aluminium sulphates (E 520–523) and SALP (E 541) within the EU's food products as the GNPD shows the compulsory ingredient information presented in the labelling of products.

2.2. 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 ANS Panel assessed the safety of aluminium sulphates (E 520–523) and SALP (E 541) 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 Scientific Committee on Food (SCF, 2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

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, 2012a,b,c) 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, 2012a).

Dietary exposure to aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives was estimated combining food consumption data available within the EFSA Comprehensive European Food Consumption Database with the maximum permissible levels (MPLs) according to Annex II to Regulation (EC) No 1333/2008[9] and/or reported use levels submitted to EFSA following a call for data. Different scenarios were used to calculate exposure (see Section 3.4.1). Uncertainties on the exposure assessment were identified and discussed.

An extensive literature search (ELS) on aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522), aluminium ammonium sulphate (E 523) and SALP, acidic, (E 541) has been performed, covering the period from January 1990 up to June 2018.

[6] Call for technical and toxicological data on miscellaneous food additives to be re-evaluated under the Regulation (EU) No 257/2010 - Extended deadline: 31 January 2018: https://www.efsa.europa.eu/en/data/call/170811

[7] 11–12/6/2018.

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

[9] Commission 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.

3. Assessment

3.1. Technical data

3.1.1. Identity of the substance(s)

Double salt compounds of the general formula $AlM(SO_4)_2$ – where M indicates a metal in its 1+ oxidation state – have traditionally been called alums (Darragh and Ertell, 2004); in particular, aluminium potassium sulphate ($AlK(SO_4)_2 \cdot nH_2O$) is the epitome of alums and is generally referred to as ordinary alum or potash alum.

Aluminium sulphate (E 520)

In Commission Regulation (EU) No 231/2012[5], (anhydrous) aluminium sulphate (E 520) is identified by the same chemical name, has chemical formula $Al_2(SO_4)_3$, and molecular weight 342.13 g/mol; no EINECS (EC) or CAS Registry numbers are reported. In JECFA (2011),[10] the chemical is defined as in the EU specifications and identified with CAS Registry No 10043-01-3.

In the EC inventory (online),[11] the EC number matching the aforesaid CAS is 233-135-0.

According to Commission Regulation No 231/2012 and JECFA (2011), aluminium sulphate is freely soluble in water and insoluble in ethanol; a 5% aqueous solution of the chemical shows an acidic reaction ($pH \geq 2.9$). Aluminium sulphate occurs as an odourless white powder, shining plates, or crystalline fragments.

Anhydrous aluminium sulphate melts at 700°C, with decomposition (WHO, 1997).

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, aluminium sulphate is also known by several synonyms, a selection of which follows: alum; INS No 520; dialuminum sulphate; dialuminum trisulphate.

Aluminium sodium sulphate (E 521)

In Commission Regulation (EU) No 231/2012[5], aluminium sodium sulphate (E 521) is identified by the same chemical name, has chemical formula $AlNa(SO_4)_2 \cdot nH_2O$ (n = 0 or 12), molecular weight 242.09 g/mol (anhydrous) and EINECS (EC) No 233-277-3 (anhydrous); no CAS Registry number is reported. According to WHO (2018),[12] the chemical – identified with CAS Registry No 10102-71-3 – was evaluated by JECFA in 1978 (WHO Technical Report Series 631, 1978); however, the evaluation was never consolidated into a subsequent final monograph and was later withdrawn (WHO, 2018).

According to Commission Regulation No 231/2012, aluminium sodium sulphate dodecahydrate is freely soluble in water; the anhydrous form is only slowly soluble in water. Both forms are insoluble in ethanol. The chemical occurs in the form of transparent crystals or white crystalline powder.

As reported by Darragh and Ertell (2004), aluminium sodium sulphate dodecahydrate (CAS Registry No. 7784-28-3) melts at 61°C and is the most water-soluble alum (75 g/100 mL of water at 20°C).

Based on Commission Regulation (EU) No 231/2012, WHO (2018) and PubChem, aluminium sodium sulphate is also known by several synonyms, a selection of which follows: soda alum; sodium alum; sodium aluminium sulphate; aluminium sodium disulphate.

Aluminium potassium sulphate (E 522)

In Commission Regulation (EU) No 231/2012[5], aluminium potassium sulphate (E 522) is identified by the chemical name aluminium potassium sulphate dodecahydrate, has chemical formula $AlK(SO_4)_2 \cdot 12H_2O$, molecular weight 474.38 g/mol and EINECS (EC) No 233-141-3 (anhydrous); no CAS Registry number is reported. In JECFA (2011),[13] two forms of the chemical are defined: aluminium potassium sulphate dodecahydrate and aluminium potassium sulphate anhydrous, respectively, identified with CAS Registry Nos 7784-24-9 and 10043-67-1,[14] the chemical formula $AlK(SO_4)_2 \cdot nH_2O$ (n = 12 or 0), and respective molecular weights 474.38 and 258.21 g/mol.

[10] Available online http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-017-m11.pdf
[11] Available online https://echa.europa.eu/information-on-chemicals/ec-inventory
[12] Available online http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=844
[13] Available online http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-014-m11.pdf
[14] Available online https://echa.europa.eu/it/information-on-chemicals/ec-inventory?p_p_id=disslists_WAR_disslistsportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=1&p_p_col_count=2&_disslists_WAR_disslistsportlet_javax.portlet.action=searchDissLists

According to Commission Regulation No 231/2012 and JECFA (2011), aluminium potassium sulphate dodecahydrate is freely soluble in water and insoluble in ethanol; a 10% aqueous solution of the chemical shows an acidic reaction (pH 3.0–4.0). The chemical is odourless and occurs in the form of large, transparent crystals or crystalline fragments, or white crystalline powder.

Aluminium potassium sulphate dodecahydrate is reported to have a melting point of 92.5°C; it dehydrates at about 200°C yielding desiccated potassium aluminium sulphate [$AlK(SO_4)_2$] (Darragh and Ertell, 2004).

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, aluminium potassium sulphate is also known by several synonyms, a selection of which follows: potassium alum; potash alum; Burnt alum (anhydrous); INS No 522; aluminium potassium disulphate.

Aluminium ammonium sulphate (E 523)

In Commission Regulation (EU) No 231/2012[5], aluminium ammonium sulphate (E 523) is identified by the same chemical name, has chemical formula $AlNH_4(SO_4)_2 \cdot 12H_2O$, molecular weight 453.32 g/mol and EINECS (EC) No 232-055-3(anhydrous); no CAS Registry number is reported. In JECFA (2011),[15] the chemical is defined as in the EU specifications and identified with CAS Registry No 7784-25-0 for the anhydrous form.

The CAS Registry for aluminium ammonium sulphate dodecahydrate is 7784-26-1.

According to Commission Regulation No 231/2012 and JECFA (2011), aluminium ammonium sulphate dodecahydrate is freely soluble in water and soluble in ethanol. The chemical, odourless, occurs in the form of large, colourless crystals, white granules or white powder.

Aluminium ammonium sulphate dodecahydrate has a melting point of 94.5°C; it dehydrates at about 250°C to turn into the dry aluminium ammonium sulphate, $AlNH_4(SO_4)_2$ (Darragh and Ertell, 2004); the anhydrous form starts to decompose at 280°C. γ-Alumina (γ-Al_2O_3) is formed between 1,000°C and 1,250°C.

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, aluminium ammonium sulphate dodecahydrate is also known by several synonyms, a selection of which follows: ammonium alum; INS No 523; ammonium aluminium sulphate hydrate; aluminium(III) ion ammonium dodecahydrate disulphate.

Sodium aluminium phosphate, acidic (E 541)

In Commission Regulation (EU) No 231/2012[5], the food additive known as sodium aluminium phosphate, acidic (SALP, E 541) comprises two chemicals: (A) sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate and (B) trisodium dialuminium pentadecahydrogen octaphosphate, and their respective chemical formulas and molecular weights are (A) $NaAl_3H_{14}(PO_4)_8 \cdot 4H_2O$, 949.88 g/mol, and (B) $Na_3Al_2H_{15}(PO_4)_8$, 897.82 g/mol. The EINECS (EC) No is 232-090-4 and no CAS Registry number is reported for either one. In JECFA (2011),[16] the food additive is defined as in the EU specifications; no CAS Registry No is reported.

With reference to EC Inventory, the aforesaid EINECS (EC) number pairs with CAS Registry No 7785-88-8. For $NaAl_3H_{14}(PO_4)_8 \cdot 4H_2O$, Gard (2006) reports CAS Registry No 10305-76-7.

According to Commission Regulation No 231/2012 and JECFA (2011), SALP, acidic is a white odourless powder insoluble in water but soluble in hydrochloric acid. Loss on ignition at 750–800°C for 2 h is 19.5–21.0% for (A) and 15–16% for (B).

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, SALP, acidic, is also known by several synonyms, a selection of which follows: SALP; INS No 541(i); phosphoric acid aluminium sodium salt; aluminium sodium salt; aluminium sodium phosphate; sodium aluminium phosphate.

3.1.2. Specifications

The specifications for aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522), aluminium ammonium sulphate (E 523) and SALP, acidic (E 541) as defined in Commission Regulation (EU) No 231/2012 and by JECFA (2011) (with the exception of E 521) are listed in Tables 1, 2, 3, 4, and 5, respectively.

[15] Available online http://www.fao.org/fyleadmin/user_upload/jecfa_additives/docs/monograph11/additive-012-m11.pdf
[16] Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-012-m11.pdf

Table 1: Specifications for aluminium sulphate E 520 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)[(b)]

	Commission Regulation (EU) No 231/2012	JECFA (2011)
Definition	EINECS (EC) No: –	CAS No: 10043-01-3
	Chemical name: aluminium sulphate	Chemical name: aluminium sulphate
	Chemical formula: $Al_2(SO_4)_3$	Chemical formula: $Al_2(SO_4)_3$
	Molecular weight (g/mol): 342.13	Formula weight (g/mol): 342.13
	Assay: content not less than 99.5% on the ignited basis	Assay: not less than 99.5% on the ignited base
Description	White powder, shining plates or crystalline fragments	White powder, shining plates or crystalline fragments; odourless
Identification	Test for aluminium: passes test	Test for aluminium: passes test
	Test for sulphate: passes test	Test for sulphate: passes test
	pH: 2.9 or above (5% solution)	pH: 2.9 or above (5% solution)
	Solubility: freely soluble in water, insoluble in ethanol	Solubility: freely soluble in water, insoluble in ethanol
Purity	Loss on ignition: not more than 5% (500°C, 3 h)	Loss on ignition: not more than 5% (about 500°C, 3 h)
	Alkalies and alkaline earths: not more than 0.4%	Alkalis and alkaline earths: not more than 4 mg (about 0.4%) of residue remains from treating a 2 g sample[(a)]
	Selenium: not more than 30 mg/kg	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg	Fluoride: not more than 30 mg/kg[(a)]
	Arsenic: not more than 3 mg/kg	–
	Lead: not more than 5 mg/kg	Lead: not more than 5 mg/kg
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011) a specific test is directly available from the data sheet.
(b): Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-017-m11.pdf

Table 2: Specifications for aluminium sodium sulphate E 521 according to Commission Regulation (EU) No 231/2012[(a)]

	Commission Regulation (EU) No 231/2012
Definition	EINECS (EC) No: 233-277-3
	Chemical name: aluminium sodium sulphate
	Chemical formula: $AlNa(SO_4)_2 \cdot nH_2O$ (n = 0 or 12)
	Molecular weight (g/mol): 242.09 (anhydrous)
	Assay: content on the anhydrous basis not less than 96.5% (anhydrous) and 99.5% (dodecahydrate)
Description	Transparent crystals or white crystalline powder
Identification	Test for aluminium: passes test
	Test for sodium: passes test
	Test for sulphate: passes test
	Solubility: dodecahydrate is freely soluble in water; the anhydrous form is slowly soluble in water; both forms are insoluble in ethanol
Purity	Loss on drying: anhydrous form: not more than 10.0% (220°C, 16 h) dodecahydrate: not more than 47.2% (50–55°C, 1 h, then 200°C, 16 h)
	Ammonium salts: no odour of ammonia detectable after heating
	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg
	Arsenic: not more than 3 mg/kg
	Lead: not more than 5 mg/kg
	Mercury: not more than 1 mg/kg

(a): The chemical was evaluated by JECFA in 1978 (WHO Technical Report Series 631, 1978); however, the evaluation was later withdrawn (WHO, 2018)[(b)].
(b): Available online http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=844

Table 3: Specifications for aluminium potassium sulphate E 522 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)[(b)]

	Commission Regulation (EU) No 231/2012	**JECFA (2011)**
Definition	EINECS (EC) No: 233-141-3	CAS No: 7784-24-9 (dodecahydrate) 10043-67-1 (anhydrous)
	Chemical name: aluminium potassium sulphate dodecahydrate	Chemical names: aluminium potassium sulphate dodecahydrate aluminium potassium sulphate anhydrous
	Chemical formula: $AlK(SO_4)_2 \cdot 12H_2O$	Chemical formula: $AlK(SO_4)_2 \cdot nH_2O$ (n = 0 or 12)
	Molecular weight (g/mol): 474.38	Formula weight: 474.38 (dodecahydrate) 258.21 (anhydrous)
	Assay: content not less than 99.5%	Assay: dodecahydrate: not less than 99.5% anhydrous form: not less than 96.5%
Description	Large, transparent crystals or white crystalline powder	Large, transparent crystals or crystalline fragments, or white crystalline powder; odourless
Identification	Test for aluminium: passes test	Test for aluminium: passes test
	Test for potassium: passes test	Test for potassium: passes test
	Test for sulphate: passes test	Test for sulphate: passes test
	pH: between 3.0 and 4.0 (10% solution)	pH: 3.0–4.0 (10% solution)
	Solubility: freely soluble in water, insoluble in ethanol	Solubility: freely soluble in water, insoluble in ethanol
Purity	Ammonium salts: no odour of ammonia detectable after heating	Ammonium salts: no odour of ammonia detectable after heating[(a)]
	Selenium: not more than 30 mg/kg	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg	Fluoride: not more than 30 mg/kg[(a)]
	Arsenic: not more than 3 mg/kg	–
	Lead: not more than 5 mg/kg	Lead: not more than 5 mg/kg
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011) a specific test is directly available from the data sheet.
(b): Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-014-m11.pdf

Table 4: Specifications for aluminium ammonium sulphate E 523 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)[(b)]

	Commission Regulation (EU) No 231/2012	**JECFA (2011)**
Definition	EINECS (EC) No: 232-055-3	CAS No: 7784-25-0
	Chemical name: Aluminium ammonium sulphate	Chemical name: aluminium ammonium sulphate
	Chemical formula: $AlNH_4(SO_4)_2 \cdot 12H_2O$	Chemical formula: $AlNH_4(SO_4)_2 \cdot 12H_2O$
	Molecular weight (g/mol): 453.32	Formula weight (g/mol): 453.32
	Assay: content not less than 99.5%	Assay: not less than 99.5% of $AlNH_4(SO_4)_2 \cdot 12H_2O$
Description	Large, colourless crystals or white powder	Large, colourless crystals, white granules or a powder; odourless
Identification	Test for aluminium: passes test	Test for aluminium: passes test
	Test for ammonium: passes test	Test for ammonium: passes test
	Test for sulphate: passes test	Test for sulphate: passes test
	Solubility: freely soluble in water, soluble in ethanol	Solubility: freely soluble in water, insoluble in ethanol

	Commission Regulation (EU) No 231/2012	JECFA (2011)
Purity	Alkali metals and alkaline earths: not more than 0.5%	Alkalis and alkaline earths: the weight of residue does not exceed 5 mg from treating a 1 g sample[(a)]
	Selenium: not more than 30 mg/kg	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg	Fluoride: not more than 30 mg/kg[(a)]
	Arsenic: not more than 3 mg/kg	–
	Lead: not more than 3 mg/kg	Lead: not more than 3 mg/kg
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011) a specific test is directly available from the data sheet.
(b): Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-014-m11.pdf

Table 5: Specifications for sodium aluminium phosphate, acidic E 541 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)[(b)]

	Commission Regulation (EU) No 231/2012	JECFA (2011)[(a)]
Definition	EINECS (EC) No: 232-090-4	–
	Chemical name: (A) sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate (B) trisodium dialuminium pentadecahydrogen octaphosphate	Chemical name: (A) sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate (B) trisodium dialuminium pentadecahydrogen octaphosphate
	Chemical formula: (A) $NaAl_3H_{14}(PO_4)_8 \cdot 4H_2O$ (B) $Na_3Al_2H_{15}(PO_4)_8$	Chemical formula: (A) $NaAl_3H_{14}(PO_4)_8 \cdot 4H_2O$ (B) $Na_3Al_2H_{15}(PO_4)_8$
	Molecular weight (g/mol): (A) 949.88 (B) 897.82	Formula weight (g/mol): (A) 949.88 (B) 897.82
	Assay: Content not less than 95.0% (both forms)	Assay: not less than 95% of (A) or not less than 95% of (B)
Description	White odourless powder	White, odourless powder
Functional uses	–	Raising agent
Identification	Test for sodium: passes test	Test for sodium: passes test
	Test for aluminium: passes test	Test for aluminium: passes test
	Test for phosphate: passes test	Test for phosphate: passes test
	pH: acid to litmus	pH: acid to litmus
	Solubility: insoluble in water; soluble in hydrochloric acid	Solubility: insoluble in water; soluble in hydrochloric acid
Purity	Loss on ignition: (A) 19.5–21.0% (750–800°C, 2 h) (B) 15–16% (750–800°C, 2 h)	Loss on ignition: (A) 19.5–21.0% (750–800°C, 2 h) (B) 15–16% (750–800°C, 2 h)
	Fluoride: not more than 25 mg/kg	Fluoride: not more than 25 mg/kg
	Arsenic: not more than 3 mg/kg	Arsenic: not more than 3 mg/kg
	Lead: not more than 4 mg/kg	Lead: not more than 2 mg/kg
	Cadmium: not more than 1 mg/kg	–
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011), sodium aluminium phosphate, acidic and sodium aluminium phosphate, basic are identified with INS No 541(i) and INS No 541(ii), respectively.
(b): Available online http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-389-m11.pdf (INS No 541(i)) http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-390-m11.pdf (INS No 541(ii))

The Panel noted that there was a difference in the claimed solubility in ethanol of aluminium ammonium sulphate dodecahydrate (E 523) (Table 4, Commission Regulation (EU) No 231/2012) between the EU and JECFA specifications.

The Panel further noted that in the case of aluminium sulphate (E 520), an upper limit of the pH was not given.

3.1.3. Manufacturing process

Aluminium sulphate ($Al_2(SO_4)_3 \cdot nH_2O$; n = 0–27) is usually produced by allowing bauxite – a mineral with a relatively high content of aluminium (oxy)hydroxides – or clay to react with sulfuric acid (Darragh and Ertell, 2004). Clay (e.g. kaolin) is roasted to remove organic substances, break down the crystal structure, and make it more reactive. The purity of the starting bauxite or clay, especially the iron and potassium contents, has a bearing on the purity of the final product; the conditions for roasting the clay and the strength of the sulfuric acid to be used depend on the particular raw material. Ground bauxite or roasted clay is digested with sulfuric acid near the boiling point of the solution: the relative concentrations of bauxite/clay and acid are adjusted to produce either acidic or basic alum; solids are removed by sedimentation. The iron-free grade (< 0.005% Fe_2O_3) of aluminium sulphate hydrate is manufactured from pure alumina trihydrate ($Al_2O_3 \cdot 3H_2O$) rather than from bauxite or clay. According to Park et al. (2004), high purity aluminium sulphate (> 99.9%) was produced by the reaction of aluminium ammonium sulphate ($AlNH_4(SO_4)_2$) leach liquor derived from coal fly ash and 28% ammonia in water at a controlled pH, followed by successive crystallisation.

Aluminium sodium sulphate ($AlNa(SO_4)_2 \cdot 12H_2O$) occurs in nature as a rare mineral. However, the commercial product is obtained by adding a solution of sodium sulphate to a solution of aluminium sulphate. After adjusting the ratio of aluminium sulphate and sodium sulphate, water is evaporated to give a hard cake; this is further heated in roasters and ground to a powder of the desired particle size (Darragh and Ertell, 2004).

Aluminium potassium sulphate ($AlK(SO_4)_2 \cdot 12H_2O$) occurs naturally as a mineral. Commercial aluminium potassium sulphate is manufactured by treating bauxite with sulfuric acid followed by potassium sulphate (Darragh and Ertell, 2004). Alternatively, potassium sulphate is added to a concentrated solution of aluminium sulphate, or the mineral alunite ($K_2Al_6(SO_4)_4(OH)_{12}$) is calcined and leached with sulfuric acid.

Aluminium ammonium sulphate ($AlNH_4(SO_4)_2 \cdot 12H_2O$) is obtained by crystallisation from an aqueous mixture of ammonium and aluminium sulphates, or by treatment of aluminium sulphate and sulfuric acid with ammonia gas (Darragh and Ertell, 2004).

The general scheme to manufacture phosphate salts can be summarised as follows (Gard, 2006): orthophosphoric acid (H_3PO_4) is allow to react with the appropriate bases (e.g. sodium hydroxide, aluminium hydroxide, ammonia) until neutralisation is reached, to yield a solution or slurry with an acid/base ratio according to the orthophosphate product desired. The orthophosphate salt(s) may be recovered by crystallisation from solution; alternatively, the entire solution or slurry may be evaporated to dryness. Dewatering is also a method that may be used if allowed by the solubility properties of the product and by some desired physical properties (e.g. crystal size and shape, bulk density, surface area). Acid orthophosphate salts may be converted to condensed phosphates by calcination. Phosphate salts containing sodium and aluminium – such as acidic $NaAl_3H_{14}(PO_4)_8 \cdot 4H_2O$ and $Na_3Al_2H_{15}(PO_4)_8$ – are manufactured by crystallisation from a concentrated solution containing the appropriate $Na_2O/Al_2O_3/P_2O_5$ ratio.

3.1.4. Methods of analysis in food

The review by Wood et al. (2004) provides a compilation of published analytical methods suitable for the determination of aluminium in foods. The specific method to be used is function of the matrix to be analysed, the detection limit required, and the instrumentation available in the laboratory; methods may need to be adapted. In general, methods require a preliminary digestion stage to decompose the food sample; aluminium measurement is subsequently carried out by different techniques, as per the following examples (LOD, limit of detection for aluminium):

- *duplicate diets, milk powders*: inductively coupled plasma (ICP) and atomic absorption spectrometry (AAS); LOD, 0.02–10 mg/kg;
- *infant formula, evaporated milk*: graphite furnace atomic absorption spectrometry (GF-AAS); LOD (rounded off), 0.01 μg/g;

- *wine*: graphite furnace atomic absorption spectrometry (GF-AAS); linear calibration, 0–100 μg/L;
- *fish*: graphite furnace atomic absorption spectrometry (GF-AAS); LOD, 1–30 ng/g on a dry weight basis;
- *coffee, tea, Port wine*: electrothermal atomic absorption spectrometry (ET-AAS); LOD (rounded off), 1–2 μg/L;
- *baby foods*: electrothermal atomic absorption spectrometry (ET-AAS); LOD, 50 pg (25 ng/g for a 10% (w/v) suspension);
- *foods*: spectrophotometric oxine (8-hydroxyquinoline) method (SO) and flame atomic absorption spectroscopy (F-AAS); LOD (SO), 0.5 μg/mL; LOD (F-AAS), 6 μg/mL;
- *seafood, meat*: inductively coupled plasma atomic emission spectrometry (ICP-AES); LOD, as required.

Some specific examples of determinations of aluminium in a variety of foods are described below.

Müller et al. (1998) investigated the aluminium content of a comprehensive food assortment typical of German nutritional habits (market basket studies); sampling was carried out in 1988 and 1991. All foodstuffs were prepared ready for cooking, but raw; in general, fruit and vegetables were peeled and/or washed, the inedible parts being removed from the samples; canned products were analysed without liquid. Samples were then dried at 105°C, dry-ashed in a muffle furnace at 450°C, and dissolved in diluted hydrochloric acid. Aluminium determination was carried out by GF-AAS, having adequate sensitivity for all assessments. Aluminium content of the food samples analysed was low and comparable with literature data: most foodstuffs contained less than 5 μg/g fresh matter. Highest concentrations were determined in cocoa/cocoa products (33 μg/g), spices (145 μg/g), and black tea leaves (899 μg/g). In general, aluminium content increased in the following order: beverages, food of animal origin, food of plant origin.

According to WHO (1998), referring to International Organization for Standardization (ISO) guidelines, aluminium can be reacted with pyrocatechol violet, thereby obtaining a coloured complex that is measured by an absorption spectrophotometric method: the method – applicable to the analysis of potable waters, ground waters, and lightly polluted surface and sea waters – is restricted to the determination of the aquated cations and other forms of aluminium readily converted to that cationic form by acidification (LOD, 2 μg/L). The LOD for the determination of aluminium to assess water quality by ICP-AES ranges from 40 to 100 μg/L. F-AAS and GF-AAS methods are applicable for the determination of aluminium in water at concentrations of 5–100 mg/L and 0.01–0.1 mg/L, respectively.

In order to investigate the changes in aluminium concentration along with those of aroma constituents in beer during storage at different temperatures, GF-AAS and gas chromatography with static headspace sampler (GC-HSS) were used by Ivušić et al. (2006). Analyses were conducted periodically throughout 7 months of storage on three different brands of beer. Samples were taken before and after filling in aluminium cans. One part of samples was stored in a refrigerator (4°C) and the other in a thermostatic chamber (22°C). The effects of beer brand and storage conditions on aluminium concentration and level of aroma constituents were measured. To prove the effect of aluminium concentration on the changes of aroma compounds, aluminium sulphate was added to bottled beer samples stored at 28°C. Samples that were stored in the refrigerator were protected from aluminium migration from the can to the beer and showed increased aroma stability. The level of aroma constituents in the beer brands was significantly different. Elevated aluminium concentration did not have any noticeable effect on the level of aroma compounds in beer samples stored at 28°C.

Hua et al. (2016) investigated the applicability of wavelength dispersive X-ray fluorescence spectrometry (WDXRF) for analysis of aluminium levels in youtiao, a typical Chinese fried food. Youtiao samples with known amounts of aluminium were used for calibration; linearity, accuracy, precision and detection and quantification limits (approximately, 10 and 30 mg/kg, respectively). Test youtiao samples were analysed by both WDXRF and inductively coupled plasma optical emission spectrometry (ICP-OES). Comparison of the two methods showed that measurement performance was not significantly different. The authors concluded that WDXRF can allow a suitable methodology for measuring the aluminium content of youtiao, and that it is a good candidate for replacing ICP-OES.

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

In aqueous media, water molecules form relatively strong bonds with the aluminium(III) ion. The coordinated water molecules exhibit an octahedral geometry: the species $[Al(H2O)6]^{3+}$ behaves as a weak acid due to ion dipole forces between Al^{3+} and the oxygen atoms of the coordinated water

molecules. However, because of its amphoteric character, Al^{3+} reacts with mineral acids and strong alkalis (EFSA, 2008, EFSA 2011a,b; WHO, 1997).

The solubility of Al^{3+} in equilibrium with solid phase $Al(OH)_3$ is strongly pH-dependent. The ion $Al(H_2O)_6^{3+}$ predominates at low pH values (pH < 4), but as the pH of the solution increases (e.g., pH 4–6) and/or the temperature rises, the positive charge of Al^{3+} forces hydrolysis of a water ligand producing the $Al(OH)(H_2O)_5^{2+}$ ion. The degree of hydrolysis increases as pH increases, resulting in a series of aluminium(III) hydroxide complexes – such as $Al(OH)^{2+}$, $Al(OH)^{2+}$, $Al(OH)_3$, and $Al(OH)_4^-$ – accompanied by a corresponding decrease in the number of coordinating water molecules. Neutral solutions give an $Al(OH)_3$ precipitate that redissolves owing to the formation of the aluminate anion $Al(OH)_4^-$, with a tetrahedral geometry; a mixture of these species occurs at pH 5–7, but at pH > 6.2 $Al(OH)_4^-$ is the predominant soluble aqueous species (Martin, 1986, 1992).

Aluminium begins to polymerise when the pH of an acidic solution increases distinctly above pH 4.5. Polymerisation implies that in the first step, two hydroxyls are shared by two aluminium atoms, e.g.:

$$2Al(OH)(H_2O)_5^{2+} \rightarrow Al_2(OH)_2(H_2O)_8^{4+} + 2H_2O$$

Polymerisation gradually proceeds to larger structures, eventually leading to the formation of the 'Al_{13}' polycation (Hem and Roberson, 1967; Parker and Bertsch, 1992a,b). As polymers coalesce, their molecular mass increases, eventually becoming large enough for aluminium hydroxide to precipitate from solution. Tipping et al. (1988) found that, if precipitation occurs at pH 4–6, it involves the formation of aluminium (oxy)hydroxide, a compound whose solubility is highly temperature dependent.

When present, fluoride ions (F^-) can readily replace the hydroxyl ions in aluminium(III) hydroxide complexes. At pH > 7, the latter predominate in waters that are low in dissolved organic matter and silicate. Under acidic conditions, sulphate ions (SO_4^{2-}) also form complexes with Al^{3+}. Even though sulphate concentrations are typically higher than those of fluoride in surface waters, aluminium(III) sulphate complexes are significant only at high sulphate concentrations and low pH values (WHO, 1997; EFSA, 2008, 2011a,b).

3.2. Authorised uses and use levels

Maximum levels of aluminium sulphates (E 520–523) and SALP (E 541) have been defined in Annex II to Regulation (EC) No 1333/2008[17] on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, aluminium sulphates (E 520–523) are authorised food additives in the EU with MPLs in two food categories, whereas SALP (E 541) is authorised in one food category with MPL.

Tables 6 and 7 summarise the food categories (FCs) that are permitted to contain aluminium sulphates (E 520–523) and SALP (E 541), respectively, with the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.

Table 6: MPLs of aluminium sulphates (E 520–523) 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)
05.2	Other confectionery including breath freshening microsweets	E 520–523[(b)]	Only candied cherries[(a)]	200[(c)]
10.2	Processed eggs and egg products	E 520	Liquid egg white for egg foams only[(d)]	25[(c)]

MPL: maximum permitted level.
(a): Period of application: from 1 February 2014. Until 31 January 2014: only candied, crystallised or glacé fruit and vegetables MPL: 200 mg/kg.
(b): The additives may be added individually or in combination.
(c): Expressed as aluminium.
(d): Period of application: from 1 February 2014. Until 31 January 2014: E 520–E 523, only egg white, MPL: 30 mg/kg.

[17] 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.

Table 7: MPL of sodium aluminium phosphate (E 541) 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)
07.2	Fine bakery wares	E 541	Only sponge cakes produced from contrasting coloured segments held together by jam or spreading jelly and encased by a flavoured sugar paste (the maximum limit applies only to the sponge part of the cake)(a)	400(b)

MPL: maximum permitted level.
(a): Period of application: from 1 February 2014.
Until 31 January 2014: only scones and sponge wares, MPL: 1,000 mg/kg.
(b): Expressed as aluminium.

Aluminium sulphates (E 520–523) and SALP (E 541) are not authorised according to Annex III of Regulation (EC) No 1333/2008.

3.3. Exposure data

3.3.1. Reported use levels or data on analytical levels of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

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.

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 public calls[18,19] for occurrence data (usage level and/or concentration data) on aluminium sulphates (E 520–523) and SALP (E 541).

In response to these calls, no use level or concentration data on aluminium sulphates (E 520–523) and SALP (E 541) were submitted to EFSA by industry or Member States.

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

The Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 2.5 million food and beverage products of which more than 900,000 are or have been available on the European 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 GNPD.

For the purpose of this Scientific Opinion, the Mintel's GNPD was used for checking the labelling of food and beverages products and food supplements for aluminium sulphates (E 520–523) and SALP (E 541) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to the Mintel's GNPD, aluminium sulphates (E 520–523) were labelled on only 19 food products between January 2013 and February 2018 of which six belonged to food subcategory 'Cakes, Pastries & Sweet Goods' of the Mintel's GNPD food classification. Overall percentage of labelled products per subcategories was less than 0.1%. Note that the food products listed to contain aluminium sulphates (E 520–523) in the Mintel's GNPD were not in line with present authorisation (Tables 6 and 7).

SALP (E 541) was labelled in 117 products belonging to 14 food subcategories. Subcategories with the highest number of food products were 'Cakes, Pastries & Sweet Goods' (n = 53), 'Baking Ingredients & Mixes' (n = 37) and 'Bread & Bread Products' (n = 6). The percentages of labelled foods belonging to these subcategories were, again, less than 0.1%.

The Panel noted that a decrease of products labelled with aluminium sulphates (E 520–523) and SALP (E 541) observed during last 5 years period is in line with the fact that no use levels were reported by

[18] http://www.efsa.europa.eu/en/consultations/call/100608
[19] https://www.efsa.europa.eu/en/data/call/170223

industry during the call in 2017 (Table 8). The observed decrease in the uses in the first year (2013–2014) was most likely due to this change in the legislation which was coming into force in February 2014.

Table 8: Number of products labelled with aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) during last 5 years period[(a)]

Ingredient	2013	2014	2015	2016	2017	Total products
Sodium aluminium phosphates	53	26	16	16	5	116
Sodium aluminium sulphate	1	4	2	1	1	9
Aluminium sulphate	1	0	2	3	0	6
Ammonium aluminium sulphate	0	0	2	0	0	2
Aluminium potassium sulphate	0	0	2	0	0	2

(a): The number of products for 2018 is not included in the table as the data reported were not for the whole year.

Non-authorised use of the additives aluminium sulphates (E 520–523) and SALP (E 541) from February 2014 onwards was investigated in the Mintel's GNPD as the change in their authorisation was coming into force that time (see Section 3.2).

The Panel noted that none of the 17 products (belonging to subcategories 'Baking Ingredients & Mixes', 'Cakes, Pastries & Sweet Goods', 'Hors d'oeuvres/Canapes', 'Seasonal Chocolate', 'Sweet Biscuits/Cookies', 'Poultry Products', 'Meat Products', 'Cooking Sauces', 'Corn-Based Snacks', 'Fish Products') in which aluminium sulphates (E 520–523) were listed as ingredient was in line with the current authorisation.

In addition, SALP (E 541) was also listed as ingredient in 17 food products belonging to the following Mintel's GNPD sub-categories, where its use is not authorised: 'Bread & Bread Products', 'Hors d'oeuvres/Canapes', 'Chilled Desserts', 'Sweet Biscuits/Cookies', 'Meal Kits', 'Poultry Products', 'Potato Products', 'Wheat & Other Grain-Based Snacks', 'Salads' and 'Pizzas'.

Appendix A lists the percentage of the food products labelled with aluminium sulphates (E 520–523) and SALP (E 541) out of the total number of food products per food subcategories according to the Mintel's GNPD food classification.

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.

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.

Food consumption data from the following population groups were used for the exposure assessment: infants, toddlers, children, adolescents, adults and the elderly. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 9).

Table 9: Population groups considered for the exposure estimates of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

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 EFSA Comprehensive Database 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 Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (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 of aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

The food categories in which the use of aluminium sulphates (E 520–523) and SALP (E 541) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

Some food categories or their restrictions/exceptions are not referenced in the EFSA Comprehensive Database and could therefore not be taken into account in the present estimate resulting potentially in an underestimation of the exposure. FC 10.2 'Processed eggs and egg products', (E 520), 'liquid egg for egg foams only' was considered very specific which cannot be specified in the FoodEx system, and represented only a very small part of the food category. Considering the whole food category would thus have resulted in an unduly large overestimation of the exposure.

A refinement of the exposure was elaborated for FC 07.2 'Fine bakery wares'. Taking into account the restriction 'only sponge cakes produced from contrasting coloured segments held together by jam or spreading jelly and encased by a flavoured sugar paste', all sponge cakes in the EFSA Comprehensive Database were considered instead of the full category. More specific FoodEx code was not available for specifying this type of sponge cake.

For FC 05.2 'Other confectionery including breath freshening microsweets' 'only candied cherries', the refinement was applied by selecting entries with the FoodEx code of 'candied cherry' from the Comprehensive Database (Appendix B).

3.4. Exposure estimate

3.4.1. Exposure to aluminium sulphates (E 520–523) and sodium aluminium phosphate acidic (E 541) from their use as food additives

The Panel estimated a combined chronic dietary exposure to aluminium from aluminium sulphates (E 520–523) and SALP, acidic (E 541) for the following population groups: infants; toddlers, children, adolescents, adults and the elderly. Dietary exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) was calculated by multiplying MPLs of aluminium sulphates (E 520–523)

and SALP (E 541) per food category (Appendix B) with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. 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 considered not adequate to assess repeated exposure.

This was carried out for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 9). On the basis of these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011a). Therefore, in the present assessment, the 95th percentile of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not estimated.

Exposure assessment to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) was carried out by the ANS Panel based on MPLs (expressed as aluminium) as set down in the EU legislation, defined as the *regulatory maximum level exposure assessment scenario*.

As no use levels or concentration data were available for aluminium sulphates (E 520–523) and SALp (E 541), refined exposure scenarios could not be carried out.

Regulatory maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008. For aluminium sulphates (E 520–523) and SALP (E 541), the MPLs (expressed as aluminium) used in the assessment are listed in Table 1.

The Panel considers the exposure estimates derived following this scenario as the most conservative since it is assumed that the population will be exposed to the food additive present in food at the MPL over a longer period of time.

Dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

Table 10 summarises the estimated exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives in six population groups (Table 9). Detailed results per population group and survey are presented in Appendix C.

Table 10: Summary of dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives in the maximum level exposure assessment scenario in six population groups (minimum–maximum across the dietary surveys in mg Al/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)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Mean	0	0.03	0	0.15	0	0.21	0	0.08	0	0.05	0	0.04
95th percentile	0	0	0	0.88	0	0.88	0	0.48	0	0.38	0	0.43

The mean exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives at the MPL ranged from 0.0 mg/kg bw per day in all population groups to 0.21 mg/kg bw per day in children. The 95th percentile of exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) ranged from 0.0 mg/kg bw per day in all population groups to 0.88 mg/kg bw per day in toddlers and children.

The vast majority (99–100%) of the exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) in all population groups comes from sodium aluminium phosphate (E 541). The intake of SALP (E 541) comes from the assumptions that all sponge cakes contain SALP (E 541), and that all sponge cakes are produced from contrasting coloured segments held together by jam or spreading jelly and encased by a flavoured sugar paste.

Uncertainty analysis

Uncertainties in the exposure assessment of aluminium from aluminium sulphates (E 520–523) and SALP (E 541) 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 11.

Table 11: 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	+/–
Use of data from food consumption surveys covering only a few days to estimate high percentiles (95th) long-term (chronic) exposure	+
Consumption of sponge cakes taken into account to represent consumption of specific cakes that can be assumed to be consumed rarely by a small percent of the population (occasional eating)	+
Assumption that all sponge cakes contain the additives while regulation indicates that only very specific cakes should contain the additive and the Mintel GNPD indicates that only a few sponge cakes were labelled with the additives	+
Food categories selected for the exposure assessment: exclusion of FC 10.2 processed eggs and egg products due to missing FoodEx linkage	–
Regulatory maximum level exposure assessment scenario: • exposure calculations based on the MPL according to Annex II to Regulation (EC) No 1333/2008	+

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

The Panel noted that information from the Mintel's GNPD (Appendix A) indicated that aluminium sulphates (E 520–523) were only used in a limited number of products (n = 19). This is in line with the fact that EFSA did not receive any use levels of these additives from industry. The Panel also noted that the food products labelled with aluminium sulphates (E 520–523) in the Mintel's GNPD were not in line with the present authorisation, which only allows the use of these additives in candied cherry in confectionary and liquid egg white for egg foam only.

For SALP (E 541), the foods labelled according to the Mintel's GNPD belonged mainly to the food subcategories 'Cakes, Pastries & Sweet Goods' and 'Baking Ingredients & Mixes'. This was in line with the authorised use of this additive. However, also for this additive the percentage of foods labelled to contain the additive was very low. The assumption in the exposure assessment that all foods belonging to the two included food categories contained the additives was very likely conservative.

In addition, the restriction in legislation for the use of SALP (E 541) in FC 07.2 Fine bakery wares (Table 7) was very specific. This restriction could only be approximated and has very likely contributed to an overestimation of the exposure.

Given these observations, as well as those listed in Table 11, the Panel considered overall that the uncertainties identified result in an overestimation of the exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives according to Annex II in the assessment.

3.4.2. Exposure via the regular diet

Aluminium is the most abundant metallic element in the earth's crust and diet is the most important source of exposure, both due to the natural occurrence in, e.g. fruit, vegetables, cereals, seeds and meat, and due to the use of aluminium and aluminium compounds as food additives, in food processing, packaging and storage (EFSA, 2008). In addition to the aluminium compounds evaluated in the present opinion other forms of aluminium are authorised as food additives: elemental aluminium (E 173), aluminium silicates (E 554 and E 555) and in the form of aluminium lakes of food colours. EFSA (2008) compiled data on dietary exposure to aluminium and reported that the mean exposure 'ranged from 1.6 to 13 mg aluminium per day, corresponding to an exposure of approximately 0.2–1.5 mg/kg bw/week from water and food in a 60 kg adult. Children generally have a higher food intake than adults when expressed on a body weight basis, and therefore represent the group with the highest potential exposure

to aluminium per kg body weight. In children and young people the estimated exposure at the 97.5th percentile in the UK and France ranged from 0.7 to 2.3 mg aluminium/kg bw/week'. It was not possible to distinguish between the specific sources of aluminium, such as the contribution of aluminium-containing food additives to the total dietary exposure of aluminium. Aluminium in drinking water was reported to represent a minor source of exposure.

More recent studies of dietary exposure to aluminium from EU countries have reported daily intake in adults at the lower end of the range reported by EFSA in 2008: 1.6 mg per day in Sweden (NFA, 2010); 0.04 mg/kg bw per day (equivalent to 2.8 mg per day at 70-kg bw) in France (ANSES, 2011); 3.7–6.4 mg per day in Greece (Bratakos et al., 2012); 0.03 mg/kg bw per day (equivalent to 2.1 mg per day at 70-kg bw) in Belgium (Fekete et al., 2013) and 0.04 mg/kg bw per day (equivalent to 2.8 mg per day at 70-kg bw) in Norway (VKM, 2013).

3.4.3. Exposure via other sources

The Panel is aware that exposure to aluminium can come from other sources for example from use in cosmetic and vaccines. The exposure assessment of aluminium by VKM (2013) showed that cosmetic products and in particular antiperspirants, contribute considerably more than diet to the total systemic aluminium exposure in persons using such products.

3.5. Biological and Toxicological data

The safety of dietary intake of aluminium from any sources (food, food additives, food contact materials and drinking water) was previously evaluated by the EFSA AFC Panel (2008). In addition, a new study related to the bioavailability of aluminium in food was evaluated in a Statement by EFSA (2011a,b).

The present section summarises the major findings from the previous EFSA evaluations (2008; 2011), and any additional data retrieved from the subsequent literature search.

3.5.1. Absorption, distribution, metabolism and excretion

The oral bioavailability of aluminium compounds depends on the chemical form, the pH in the gastrointestinal tract and the presence of complexing ligands. In the acidic stomach environment, most of ingested aluminium compounds exist mainly as $Al(H_2O)_6)^{3+}$. As a result of the increase in pH from the stomach to the intestines insoluble aluminium hydroxide is formed at the neutral pH in the intestines with subsequent faecal excretion, leaving only a minor fraction available for absorption.

Oral bioavailability in rats of aluminium from 12 radioactively labelled aluminium (^{26}Al) compounds was investigated in a study provided by the industry and evaluated by EFSA (2011a,b). The compounds included four soluble aluminium salts: citrate, chloride, nitrate and sulphate; and eight aluminium compounds administered in suspension: hydroxide, oxide, metallic, powdered pot electrolyte, FD&C red 40 aluminium lake, SALP acidic, SALP basic, and sodium aluminium silicate. The ratio was determined between the radioactivity left in the carcass seven days after oral administration of the aluminium compounds and the radioactivity left in carcass seven days after intravenous administration of radioactively labelled citrate. The oral bioavailability varied between 0.03% (aluminium hydroxide) and 0.21% (aluminium sulphate). Three compounds had carcass levels below detection limit: aluminium metal, and the two SALPs. The Panel noted that less than 10% of the bioavailable dose remained in the carcass after 7 days. In another rat study, the bioavailability of aluminium from SALP, acidic, when incorporated in a biscuit, was about 0.1% (as cited in EFSA, 2011a,b).

Blood and tissue levels of aluminium were analysed in rats (n = 5) gavaged with water (controls) or six different salts of aluminium: citrate, sulphate, nitrate, chloride and hydroxide with a daily dose of 30 mg Al/kg bw per day for 7 or 14 days (Poirier et al., 2011). There were no statistically significant differences in blood or brain concentrations between the groups, while kidney and bone levels of aluminium were statistically significantly increased in the group administered aluminium citrate compared to controls or the other aluminium salts.

Human data on toxicokinetics of aluminium compounds are very limited (Weisser et al., 2017). No data are available in children and adolescents (< 18 years of age) and data on kinetics in persons with renal dysfunction are available only from two patients (Steinhausen et al., 2004). Available studies indicate that the oral bioavailability of aluminium in humans and experimental animals from drinking water is in the range of 0.3%, whereas the bioavailability of aluminium from food and beverages generally is considered to be lower, about 0.1%. Bioavailability of sodium aluminium phosphate acidic

was demonstrated in a crossover study in 18 subjects consuming four pancakes per day for one week, containing 860 mg Al/kg (allowed concentration before 2014) (Glynn et al. unpublished; Document provided to EFSA n.3)). Creatinine-adjusted urinary excretion of Al (median 67 μmol Al/mol creatinine, range 23–230; corresponds to 16 μg Al/g creatinine) was increased approximately twofold (paired T-test, $p \leq 0.05$), compared to excretion after consumption of four pancakes per day without aluminium phosphate (< 0.5 mg Al/kg) (32 μmol Al/mol creatinine, 4.5–103; corresponds to 7.6 μg Al/g creatinine).

Toxicokinetic data from subjects receiving an oral dose of $AlCl_3$ were used to predict plasma levels after exposure to the EFSA TWI of 1 mg/kg bw. The predicted steady state plasma levels were 1–4 μg/L (Weisser et al., 2017). This is in accordance with reported normal levels of aluminium in serum of approximately 1–3 μg/L. Normal median (upper range) levels of aluminium in plasma are 3.2 (6) μg/L. After absorption, aluminium binds to transferrin and distributes to tissues, accumulating in the bone where it can persist for a very long time. Total body burden in healthy human subjects has been reported to be approximately 30–50 mg/kg bw, half of which or more is in the skeleton. Higher body burden and tissue levels of aluminium have been reported in dialysis encephalopathy patients. In persons with renal failure the ability to excrete aluminium is reduced and aluminium exposure may increase, due to aluminium-containing dialysis water or consumption of aluminium-containing phosphate binders. Mean concentrations of aluminium in the brain were higher in 7 patients dying in dialysis encephalopathy, 15.9 μg Al/g dry weight, than in 11 dialysed controls, 4.4 μg Al/g dry weight and in two non-dialysed uraemic patients, 2.7 μg Al/g dry weight (McDermott et al., 1978).

Following ingestion in humans, absorbed aluminium from the blood is eliminated primarily by the kidneys, presumably as the citrate, and excreted in the urine. Two patients with chronic renal dysfunction, administered a single oral dose of $AlCl_3$ (100 μg Al), had similar levels of aluminium in the plasma but lower levels in urine, compared to healthy persons, indicating that more aluminium is stored in the body (Steinhausen et al., 2004). Unabsorbed aluminium is excreted in the faeces. Excretion via the bile constitutes a secondary, but minor route.

Overall, oral bioavailability of aluminium from aluminium compounds is low as a result of formation of insoluble aluminium hydroxide at the neutral pH in the intestines. Data from humans and experimental animals indicate that the bioavailability is approximately 0.3% of aluminium compounds in drinking water and 0.1% in food and beverages. Predicted plasma levels at the EFSA TWI of 1 mg Al/kg bw were within the reported normal levels of aluminium in serum, 1–3 μg/L. Absorbed aluminium accumulates in the bone. Kidney is the main route of excretion. Increased brain levels of aluminium have been reported in dialysis encephalopathy patients.

3.5.2. Acute oral toxicity

The acute oral toxicity of a number of inorganic aluminium salts has been evaluated in rats and mice, and shows a wide range of LD_{50} values from 162 to 750 mg aluminium/kg bw in rats and from 164 to 980 mg aluminium/kg bw in the mouse for different compounds (EFSA, 2008).

3.5.3. Short-term and subchronic toxicity

In EFSA (2008), it was reported that aluminium nitrate in drinking water for 28 days caused mild histopathological changes in spleen and liver or decreased body weights in rats; the NOAEL for these effects was 52 mg Al/kg bw per day. In contrast, dietary exposure to SALP for 28 days had no adverse effects in the highest doses tested corresponding to 140–300 mg Al/kg bw per day. Similarly, no effects were reported in dogs exposed in the diet to acidic SALP providing daily doses of 90 mg Al/kg bw per day for 26 weeks.

The following oral toxicity study with aluminium compounds, published after the adoption of the previous opinion, was also considered in the current opinion.

In a short-term toxicity study of fluoride or aluminium, Swiss albino male mice (10/group, mean body weight of 30 ± 0.5 g, age 75–80 days) received by oral gavage either distilled water (vehicle control) or sodium fluoride (NaF, 190 mg/kg bw per day), aluminium sulphate ($Al_2(SO_4)_3 16H_2O$, 78.4 mg Al/kg bw per day) or aluminium fluoride (AlF_3, 103 mg/kg bw per day) in a volume of 0.5 mL/animal for seven days (Sharma et al., 2010). In both aluminium-treated groups, blackening of nails and the tails, increase in abdominal circumference, dullness and a tendency to dispone, statistically significantly decreased feed and water intake and body weight, 20% mortality during clinical phase and balloning of lungs and gastrointestinal tract due to presence of odorous gas at necropsy of surviving animals were reported. The changes to the vehicle control values in haematology parameters in both aluminium groups were a

statistically significant decrease in haemoglobin concentration and mean corpuscular haemoglobin concentration, and increased poikilocytosis. In the aluminium sulphate group, there were statistically significant increases of alanine aminotransferase, serum urea, globulin, cholesterol and total lipid, and statistically significant decreases in alkaline phosphatase activity, and bilirubin. The only statistically significant difference in organ weights as compared to the vehicle control group was a decreased absolute kidney weight. Histological examination was not performed on any of the tissues. The Panel considered that this study cannot be used for the risk assessment.

3.5.4. Genotoxicity

Published genotoxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions concerning genotoxicity were as follows: 'Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation *in vitro*. Clastogenic effects were also observed *in vivo* when aluminium sulphate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the variety of genotoxic effects elicited by aluminium salts in experimental systems. Cross-linking of DNA with chromosomal proteins, interaction with microtubule assembly and mitotic spindle functioning, induction of oxidative damage, damage of lysosomal membranes with liberation of DNAase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidised bases in experimental systems. The Panel noted that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet'. The Panel noted that the conclusions on genotoxicity of aluminium in the Scientific Committee on Consumer Safety (SCCS 2014) and the European Commission and its Scientific Committee on Health, Environmental and Emerging Risks opinion (SCHEER, 2017) are in agreement with the EFSA (2008) evaluation.

The following genotoxicity studies of aluminium compounds, published after the adoption of the previous opinion, were also considered in the current opinion.

In vitro

Turkez and Geyikoglu (2011) reported that $Al_2(SO_4)_3$ induced increase in the frequencies of sister chromatid exchange (SCE) and chromosomal aberrations (CA) in isolated human white blood cells at 20 μg/mL, together with the decrease in the activities of antioxidant enzymes reduced glutathione (GSH), superoxide dismutase (SOD), glucose-6-phosphate dehydrogenase (G-6-PDH) and catalase (CAT). At the lower tested concentration 10 μg/mL, neither induction of SCE and CA nor inhibition of the activities of antioxidant enzymes was observed.

In an *in vitro* toxicity and genotoxicity test with zebrafish embryonic cells ZF4 (Pereira et al., 2013), $AlCl_3$ tested at concentrations 5–100 μM induced dose dependent cytotoxicity. Significant increase in DNA single-stranded binding (ssb), determined by comet assay, was observed only at 50 μM, an increase in DNA double-strand break (dsb) determined as γH2AX foci was observed at concentrations up to 30 μM with a decline at higher concentrations, whereas induction of micronuclei formation was dose dependent at all tested concentrations.

In vivo

In an *in vivo* study, 8 weeks aged rats were orally administrated 34 mg $AlCl_3$/kg bw for 30 days. $AlCl_3$ caused a significant increase the serum levels of alkaline phosphatase (ALP), transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and lactate dehydrogenase (LDH). In liver, a significant increase in micronucleated hepatocytes was observed along with histopathological changes including sinusoidal dilatation, congestion of central vein, lipid accumulation and lymphocyte infiltration in liver. The toxic and genotoxic effects of aluminium administration were suppressed by the concurrent administration of propolis (50 mg/kg bw), suggesting the involvement of an oxidative stress mediated mechanism in Al genotoxicity, counteracted by the antioxidant properties of propolis (Turkez et al., 2010). The Panel noted that the test method used in this study, i.e. the analysis of micronuclei in rat liver after repeated administration, has not yet received sufficient validation. In particular, according to the IWGT (International Workshop on Genotoxicity Testing) recommendations, more data on non-genotoxic but toxic chemicals are considered necessary to

evaluate the test specificity and its suitability for risk assessment (Martus et al., 2015). The Panel also note the high level of toxicity elicited by $AlCl_3$ in this study, not consistent with findings from other studies. Overall, the Panel considered that this study should not be used for risk assessment.

CA in bone marrow and spermatocyte and sperm abnormalities were determined in an *in vivo* study with male white Swiss mice that were treated intraperitoneal (i.p.) with $Al_2(SO_4)_3$ (98%) daily for 3 weeks at doses of 47, 94 and 188 mg/kg bw representing 1/16, 1/8 and 1/4 of $Al_2(SO_4)_3$ LD_{50}. The results demonstrated significant increase in the percentage of bone marrow CA and spermatocyte and sperm abnormalities that were dose and time of exposure dependent. The genotoxic effects of Al administration were largely reduced (up to 83%) by the co-administration of a soybean supplemented diet or soybean extracts rich in antioxidants and antimutagens (isoflavons, saponins) (Al-Ashaal et al., 2012).

Swiss albino mice received single doses of 50, 100 and 150 mg aluminium acetate (basic) ($C_6H_9AlO_6$)/kg bw, or daily doses of 50 mg/kg bw for seven consecutive days, via i.p. administration. Evaluated genotoxicity endpoints were CA and micronuclei (MN) in bone marrow, MN in fetal liver and sperm abnormalities. CA and MN in bone marrow were analysed after 24, 48 and 72 h post-single treatment, and 24 h after repeated administration; MN in fetal liver were examined following treatment of pregnant females on day 14 of gestation and 24 h transplacental exposure of fetus; abnormalities in sperm were examined 5 weeks of treatment. In bone marrow time- and dose-dependent induction of CA was observed after single and repeated administration of aluminium acetate whereas MN induction was observed only after the repeated administration. The induction of CA and MN was associated with significant reduction of the mitotic index and of the polychromatic/normochromatic erythrocytes ratio, indicating a mitodepressive effect on bone marrow. The increase in MN frequency in fetal liver erythrocytes after single dose exposure indicated transplacental exposure to aluminium acetate. At all doses after the single exposure, a dose-dependent increase in different types of sperm abnormalities as well as reduced sperm count were observed (D'Souza et al. 2014).

The subchronic exposure of 8-week-old Sprague–Dawley rats to $AlCl_3$ administered i.p. for 10 weeks at dose of 5 mg/kg bw demonstrated increase in serum enzyme activities of ALP, AST, ALT and LDH, and the levels of creatinine, urea (U) and uric acid (UA) levels as indicators of hepatotoxicity and nephrotoxicity (Geyikoglu et al. 2012). The indicators of haematotoxicity red blood cells (RBCs), haemoglobin (Hb) concentration, haematocrit (Ht), platelets (PLTs) and white blood cells (WBCs) were compared to the control groups significantly decreased. In hepatocytes of $AlCl_3$-treated animals, a significant increase in MN was observed. In addition in the samples of liver as well as in kidney of the exposed animals, severe pathological damages were observed.

Overall, the available studies indicate that aluminium compounds are genotoxic *in vitro*, inducing primary DNA damage and clastogenicity, and *in vivo* following i.p. administration, which however is not relevant for oral risk assessment. Only few of the available genotoxicity studies on aluminium compounds were performed with aluminium sulphates and phosphate. However, in view of the common activity profile of aluminium compounds, the Panel considered appropriate read-across among different aluminium salts, and all the available results relevant for genotoxicity assessment of E 521–523 and E 541. The Panel also noted that the genotoxic activity elicited by aluminium compounds is ascribed to indirect and thresholded mechanisms (EFSA, 2008), which are unlikely to be relevant at low dietary exposure levels, and considered that the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity.

3.5.5. Chronic toxicity and carcinogenicity

Cancer risk related to in aluminium production was evaluated by the International Agency for Research on Cancer (IARC, 1984). IARC concluded that the available epidemiological studies provided limited evidence that certain exposures in the aluminium production industry were carcinogenic to humans; however, IARC noted that aluminium exposure was confounded by exposure to other agents, and that there was no evidence of increased cancer risk in non-occupationally exposed persons. Overall, IARC did not implicate aluminium itself as a human carcinogen (IARC, 1984).

In its previous evaluation (EFSA, 2008), the AFC Panel noted that the database on carcinogenicity of aluminium compounds was limited, with the majority of available studies old, containing little experimental detail and with inadequate low dose levels. Overall, the AFC Panel concluded that it was not possible to reach a conclusion on the carcinogenicity of aluminium from these studies. The AFC Panel noted that in a poorly reported oral drinking water study in rats exposed to aluminium potassium sulphate, a significantly increased incidence of gross tumours was reported in males (Schroeder & Mitchner, 1975). The types of tumours were not further specified. The same authors reported that this

aluminium compound produced a significantly increased incidence of gross tumours and 'lymphoma leukaemia' in treated female mice. However, the more recent and robust study of Oneda and co-workers in the B6C3F1 mouse did not indicate any carcinogenic potential of aluminium potassium sulphate at levels of up to 850 mg Al/kg bw per day in the diet (Oneda et al., 1994). The AFC Panel also noted the absence of epidemiological evidence for carcinogenicity of aluminium compounds used therapeutically, the conclusion of IARC evaluation and concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake (EFSA, 2008). The Panel agreed with this overall conclusion.

3.5.6. Reproductive and developmental toxicity

Published reproductive and developmental toxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions were as follows:

'Several studies have been performed on the reproductive and developmental toxicity of aluminium compounds. Two studies in male mice using either intraperitoneal or subcutaneous administration of aluminium nitrate or chloride clearly demonstrated the ability of aluminium to produce testicular toxicity, decreased sperm quality and reduced fertility in male mice. However, no effects on male fertility were observed in one rat study where aluminium nitrate was administered by gavage. Unfortunately no data were reported on histological examination of testes, as it is well known that male rats maintain fertility even after severe testicular lesions. This also means that they may be less sensitive to this effect than humans. Reduced testicular weight and impaired semen quality have also been observed in male rabbits after daily administration by gavage of 34 mg/kg bw of aluminium chloride (corresponding to 6.4 mg aluminium/kg bw/day), the only dose applied, for 16 weeks. In male beagle dogs, dietary administration for 26 weeks of basic sodium aluminium phosphate (SALP), at a level corresponding to 75 mg aluminium/kg bw/day produced a decrease of testicular weight and degeneration of germinal epithelium. The NOAEL was 27 mg aluminium/kg bw/day. Only two studies are available on reproductive toxicity in females. No effects on female fertility was seen in rats after exposure for two weeks before mating and during gestation to aluminium nitrate by gavage or dissolved in drinking water. None of the aluminium compounds authorised as food additives in the EU have been tested for reproductive toxicity. However, the Panel noted that when SALP, acidic, was tested in dogs using a protocol similar to that used for SALP, basic, no testicular effects were reported after doses up to 88 mg aluminium/kg bw/day for 26 weeks. The potential of aluminium to produce embryotoxicity and teratogenicity has been demonstrated in rats given intraperitoneal injections of 0, 75, 100, or 200 mg aluminium chloride/kg bw/day on days 9 -13 or 14 -18 of pregnancy, corresponding to 15, 20, or 40 mg Al/kg bw/day. However, after oral administration, only one study has reported congenital malformations (cleft palate) in mice after gavage exposure to 627 mg aluminium lactate/kg bw/day. In this study 166 mg aluminium hydroxide/kg bw per day had no effect. In general, high doses of aluminium nitrate, chloride or lactate given by gavage were able to induce some signs of embryotoxicity in mice and rats, in particular, reduced fetal body weight or pup weight at birth and delayed ossification. The lowest LOAEL was reported for aluminium nitrate at a daily dose corresponding to 13 mg aluminium/kg bw/day in the rat. After dietary exposure of rats to aluminium chloride and lactate the lowest NOAEL was 100 mg aluminium/kg bw/day, respectively. Gavage administration of aluminium hydroxide at doses providing up to 264 mg aluminium/kg bw/day was without embryotoxic effects in rats'.

The following reproductive toxicity studies of aluminium compounds, published after the adoption of the previous opinion, were also considered in the current opinion.

Reproductive studies

A two-generation reproductive toxicity study was performed in Sprague–Dawley rats (24/dose per group) with aluminium sulphate ($Al_2(SO_4)_3$; purity 98.5%) which was administered in the drinking water at concentrations of 0, 120, 600 or 3,000 mg $Al_2(SO_4)_3$/L (equal 0, 8.6, 41 or 188 mg $Al_2(SO_4)_3$/kg bw per day for F_0-males or, total Al exposure, drinking water and food combined, of 1.62, 2,96, 8.06 or 31.2 mg Al/kg bw per day; the exposure of males of the F_1-generation and the females of both generations were higher) (Hirata-Koizumi et al., 2011a). The test concentrations were chosen based on a preliminary study in which toxicity was observed at 3,000 and 10,000 mg $Al_2(SO_4)_3$/L. The study included developmental landmarks and behavioural tests (spontaneous locomotor activity, and a T-maze test for spatial learning

ability). The latter results will be described in Section 3.5.7. Water consumption was decreased in all test substance-treated groups. The authors assumed this was related to palatability (acidity). In the mid- and high-dose groups, decreased water consumption was associated with decreased food consumption and with decreased body weight gain of both sexes in the high-dose group of the F_0-generation. At the end of both lactation periods, the food consumption of the females was also decreased in the mid- and high-dose groups. High-dose group pups of both generations showed a decreased weight on postnatal day (PND) 21 and slight delay in vaginal opening of the F_1-females. Pup organ weights were changed in the high-dose group (relative weight: brain increased, decreases in liver spleen, and thymus). No effects on fertility, reproductive (including oestrus cyclicity, sperm parameters and histopathology of the reproductive organs) or developmental parameters were observed. The authors concluded that 600 mg $Al_2(S0_4)_3$/L is the NOAEL for parental and reproductive and developmental toxicity and stated that the Al dose for this group was calculated to be 8.06 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet). The Panel agreed with this conclusion however, agreed with Willhite et al. (2012) that the NOAEL identified in this study 'may reflect more the acidic properties of the water than any intrinsic systemic hazard posed by ingested Al'.

A two-generation reproductive toxicity study was performed in Sprague–Dawley rats (24/dose per group) with aluminium ammonium sulphate ($AlNH_4(SO_4)_2$; AAS; purity 99.5%) which was administered in the drinking water at concentrations of 0, 50, 500 or 5,000 mg AAS/L (equal 0, 3.78, 33.5 or 305 mg AAS/kg bw per day for F_0-males or, total Al exposure, drinking water and food combined, of 1.56, 1.98, 5.35 or 36.3 mg Al/kg bw per day; the exposure of males of the F_1-generation and the females of both generations were higher) (Hirata-Koizumi et al., 2011b). The study was performed according to the OECD guideline 416 and in compliance to Good laboratory practice (GLP). The test concentrations were chosen based on a preliminary study in which toxicity was observed at 3,000 and 10,000 mg AAS/L. The study included developmental landmarks and behavioural tests (spontaneous locomotor activity, and a T-maze test for spatial learning ability). The latter results will be described in Section 3.5.7. No treatment-related clinical observations were observed. Water consumption was decreased in all test substance-treated groups. The authors assumed this was related to palatability due to the astringent taste. Food consumption was significantly lower during week 1 of dosing of the F_1-males of the high-dose group and in F_0-females of the mid-and high-dose groups. In the F_0-generation body weight was decreased compared to controls in the highest dose group in both sexes in the first 2–3 weeks of dosing and on day 21 of lactation of the F_1-generation. High-dose group pups of both generations (only statistically significant in the F_1) showed a decreased weight on postnatal day (PND) 21 and delay in vaginal opening in the F_1 animals approx. 2 days and no clear relation to body weight was observed). Pup organ weights were changed in the high-dose group (relative weight: increase in brain, kidney and adrenals, decrease in liver, spleen, and thymus). No effects on fertility, reproductive (including oestrus cyclicity, sperm parameters and histopathology of the reproductive organs) or developmental parameters were observed. The authors concluded that 500 mg AAS/L is the NOAEL for parental and reproductive and developmental toxicity and stated that the Al dose for this group was calculated to be 5.35 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet). The Panel agreed with this conclusion.

Male Wistar rats (N = 7 per group) were administered 0, 200, 400 or 1,000 ppb Al ($Al_2(S0_4)_3$) (equivalent to 0, 0.01, 0.02 or 0.05 mg Al/kg bw per day) in drinking water during 6 months (Muselin et al. 2016). Three F_0 males of each group were mated with unexposed females (one male to 2 females). Females were exposed during gestation and lactation to the same levels as males. The authors described that 'the F1 generation males were divided as described and exposed the same AS [aluminium sulphate] levels. The protocol to obtain F2 was similar to that described for F1'. The authors described effects on testosterone levels (dose-related decrease in all generation males), sperm counts (decrease mainly in the F_1 and F_2 males), sperm motility and abnormal sperm (dose-related decrease in all generation males) and on serum LH (increase in the F_0). Testis weight and histopathology were affected. The Panel noted that the study showed limitations such as low number of animals per group, not clear from which litters pups were selected. The amount of Al added to the drinking water was very low; it might have been a mistake in the publication. In addition the purity of the test substance was unknown and the Al level in the diet was not measured. Therefore, the Panel considered that the study cannot be used for risk assessment.

Developmental studies

No additional developmental studies were available, however neurodevelopmental studies were reported (see Section 3.5.5).

Other studies on reproductive organs

Male albino rats (*Rattus rattus*) (N = 7 per group) were given daily by gavage 0 or 50 mg aluminium sulphate/kg bw per day (8 mg Al/kg bw per day for 45 days (Rawi and Seif al Nassr, 2015). The purity of the test substance was not given. In this study also, the effects of zinc sulphate) and vitamin E and the combination of both in addition to aluminium sulphate were studied. Daily administration of 50 mg aluminium sulphate/kg bw per day induced decreased body weight, testis weight and histological changes. Treatment with zinc sulphate and/or vitamin A reduced the toxic effects.

Overall, as reported by the EFSA AFC Panel (EFSA, 2008), effects on male reproductive organs and/or semen were observed after oral administration in rabbits (LOAEL 6.4 mg Al/kg bw per day) and dogs (NOAEL 27 mg Al/kg bw per day). No effects on male and female fertility were observed in the rat after oral dietary administration. Furthermore, four additional reproductive studies or studies on reproductive organs were identified. The study of Rawi and Seif al Nassr (2015) and Muselin et al. (2016) could not be used for risk assessment. In the two-generation reproduction toxicity study in rats (Hirata-Koizumi et al., 2011a) exposed via the drinking water to aluminium sulphate a NOAEL of 8.06 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet) for parental, reproductive and developmental toxicity was identified. In another two-generation reproductive toxicity study in rats (Hirata-Koizumi et al., 2011b) also exposed via the drinking water to aluminium ammonium sulphate, a NOAEL of 5.35 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet) Al/kg bw was identified. Willhite et al. (2012) assumed that the NOAEL identified in the study with aluminium sulphate 'may reflect more the acidic properties of the water than any intrinsic systemic hazard posed by ingested Al'. The Panel agreed with these considerations as the effects observed were effects on body weight which may be due to decreased intake of water because of palatability at higher concentrations of aluminium in the drinking water for both two-generation reproductive toxicity studies.

As reported by EFSA AFC Panel (EFSA, 2008), oral administration of 57 mg aluminium/kg bw per day (as aluminium lactate) by gavage from GD 6 to GD 15 induced cleft palate in mice fetuses. The lowest dose which produced an effect on rat was 13 mg Al/kg bw per day (as aluminium nitrate) when administered by gavage from GD 1 to GD 14. Gavage administration of aluminium hydroxide up to 264 mg Al/kg bw per day from GD 6 to GD 15 did not induce developmental effects in rats. After dietary administration of aluminium chloride and lactate during gestation (GD 1 or 8 to parturition in the rat, the lowest NOAEL for developmental toxicity was 18 mg Al/kg bw per day. No additional developmental toxicity studies were identified.

3.5.7. Neurotoxicity and developmental neurotoxicity

Published neurotoxicity and developmental neurotoxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions concerning neurotoxicity were as follows: 'In humans neurotoxicity was observed in patients undergoing dialysis due to the use of unpurified water containing high concentrations of aluminium. Furthermore, aluminium was associated with Alzheimer's disease. However, the Panel and also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there is no scientific prove and that in addition the aluminium content of the diets was not taken into account. Aluminium is considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. Behavioural impairment (passive and conditioned avoidance responses) has been observed in the absence of overt encephalopathy or neurohistopathology in rats and mice exposed to soluble aluminium salts (e.g. lactate, chloride) in the diet or drinking water generally at doses of 200 mg aluminium/kg bw per day or higher. Effects recorded in more than one study in immature animals included impaired performance of reflexes and simple behaviours. Reduced grip strength and startle responsiveness were found to persist up to 150 days of age. There was no effect on reactions to the light avoidance task in rats after gestational or postnatal exposure. In these studies, LOAELs were identified that ranged from maternal doses of 50 to 500 mg aluminium/kg bw per day. From the study in mice where the lowest LOAEL of 50 mg aluminium/kg bw per day, given as lactate, was reported for neurodevelopmental effects in the offspring, NOAELs of 10 mg aluminium/kg bw per day in the mother during pregnancy and 42 mg/kg bw per day during lactation could also be identified. However, it should be noted that, in another study performed by the same group of researchers, with administration of aluminium lactate from conception throughout the whole lifespan at 100 mg/kg bw/day no clear signs of neurotoxicity were observed in the same strain of mice'.

The following neurodevelopmental toxicity studies of Al compounds, published after the adoption of the previous opinion, were also considered in the current opinion.

In a two-generation reproductive toxicity study with $Al_2(SO_4)_3$ in the drinking water, no changes in reflex ontogeny of the F_1 and F_2 pups and on spontaneous motor activity at 4 weeks of age were observed (Hirata-Koizumi et al., 2011a; study description see Section 3.5.6). In the T-maze water test a transient effect was only seen in the mid-dose groups at 600 mg $Al_2(SO_4)_3$/L, and therefore, this effect was not considered as a neurodevelopmental effect. The highest dose (3,000 mg $Al_2(SO_4)_3$/L, equal 188 mg $Al_2(SO_4)_3$/kg bw or total Al exposure of 31.2 mg Al/kg bw per day for F_0 males) was the NOAEL for neurodevelopmental effects.

In a two-generation reproductive toxicity study with aluminium ammonium sulphate (AAS) in the drinking water, no changes in reflex ontogeny of the F_1 and F_2 pups. In the spontaneous locomotor activity a transient effect was only seen in the 500 mg AAS/L group and therefore this effect was not considered as a neurodevelopmental effect no dose-related effect on spontaneous motor activity at 4 weeks of age were observed (Hirata-Koizumi et al., 2011b; study description see Section 3.5.6). In the T-maze water test for spatial learning, no treatment-related effects were observed. The highest dose (5,000 mg AAS/L, equal 305 mg AAS/kg bw or total Al exposure of 36.3 mg Al/kg bw per day for F_0 males) was the NOAEL for neurodevelopmental effects.

A neurodevelopmental study in which Sprague–Dawley rats were exposed *in utero* and up to 12 months of age was described by Poirier (Poirier et al., 2011). The supplementary data containing individual test results including for example pivotal information on Functional Observational Battery (FOB) tests and clinical chemistry data were not available. Therefore, the Panel was not able to assess these results. The study was performed in compliance with GLP and was sufficiently powered. The groups were blinded for the test facility staff. Pregnant female rats (n = 20/group) were administered aluminium citrate (intended doses of 0, 30, 100 or 300 mg Al/kg bw per day) in the drinking water during gestation and lactation and F1 animals were exposed to the same dose up to 364 days. Endpoints observed were general observations in dams and their litters and in F1 animals. Furthermore, developmental landmarks, T-maze, auditory startle, the FOB with domains targeting autonomic function, activity, neuromuscular function, sensimotor function, and physiological function), cognitive function (Morris swim maze), haematology, clinical chemistry, tissue/blood levels of aluminium, brain weight, and neuropathology. In the high-dose group, renal pathology and significant morbidity and mortality were observed mainly in the male pups. Male F_1-animals of this group were therefore euthanised on PND 89. In the FOB, an increased excitability was observed in female animals but not in males. No effect on autonomic and sensimotor dysfunctions was observed in the treated animals. A reduced auditory startle was observed on PND 64 in males of the high-dose group and on PND 120 in females of the high-dose group. The latter effects were not observed at PND 364. Furthermore, no evidence of significant effects on learning and memory were observed even not in the females of the high-dose group. In male and female animals of the mid- and high-dose groups, neuromuscular functions (hind-limb grip strength and to a lesser extent foot splay) were impaired according to the authors but data were not available. The authors reported that 'The effect was more pronounced in young animals; presumably because animals got larger and stronger over time, they better compensate for the original impairment'. However, the Panel noted that the dose (mg Al/kg bw per day) at a younger age is much higher than later in life. No treatment-related histopathological brain lesions were observed. The authors considered the mid-dose group as the LOAEL based on clinical observations and clinical biochemistry and FOB parameters (neuromuscular function). The target concentration of 100 mg Al/kg bw per day (mid-dose group) and the real concentration of this group indicated by the authors was 40 mg Al/kg bw per day differed significantly. The authors considered the low-dose group as the NOAEL (target concentration of 30 mg Al/kg bw per day; the real dose coming down to 5 and 10 mg/kg bw per day in males and females, respectively). However, the Panel noted the low intake of drinking water in all dose groups of F_1 animals and in F_1 controls, expected to be 120 ml/kg bw per day but was reported to be down to 20 mL/kg bw per day. The Panel agreed with JECFA (2012) describing the difficulties with the target versus the achieved dose as follows: JECFA noted the following: 'Identification of the LOAEL and NOAEL in this study is complicated by the decreasing fluid consumption and uncertainty regarding the critical exposure period. In the low-dose group, the achieved dose was about 40 mg/kg bw per day in the 1st week post-weaning, decreasing to 30 mg/kg bw per day (target dose) by week 5, and was about 15-45% of the target dose from post weaning week 13 onwards'.

Overall, in humans, neurotoxicity was observed in patients undergoing dialysis due to the use of unpurified water containing high concentrations of aluminium (EFSA, 2008). In 2008, the Panel and

also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there was no scientific proof aluminium was associated with Alzheimer's disease. Aluminium was considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. NOAELs of 10 mg Al/kg bw per day for neurodevelopmental effects were observed (EFSA, 2008). From two-generation reproductive toxicity studies in rats with $Al_2(S0_4)_3$ (Hirata-Koizumi et al., 2011a) or AAS (Hirata-Koizumi et al., 2011b) in drinking water, no neurodevelopmental effects were recorded up to 31.2 mg Al/kg bw per day or 36.3 mg Al/kg bw, respectively. From a neurodevelopmental study in rats (Poirier et al., 2011), a NOAEL for developmental toxicity was identified at 30 mg/kg bw per day (target low-dose level of the study). The Panel noted that in accordance with JECFA, there were uncertainties concerning the real dose level. Furthermore, the Panel was not able to assess the study due to non-availability of crucial data.

3.5.8. Immunotoxicity

Aluminium is applied in many vaccines as adjuvant, boosting the efficacy of the vaccines. Inadvertent enhanced immune responses may be regarded as adverse; hence, effects of aluminium on the immune system may pose a hazard. Whereas the activity of aluminium as an adjuvant may be local, i.e. at the site of vaccination, and whereas the action as an adjuvant is thought to be primarily based on the slow release of the antigen from the vaccination site, optimising the immune response, it cannot be excluded that some aluminium may get systemic into the body and has effects elsewhere than at the vaccination site. Zhu et al. (2014) reviewed the literature and concluded that the results of several studies in the literature demonstrated that Al could adversely affect the immune system. The Panel noted that most immune parameters reported to be influenced were intermediate parameters and cannot easily be interpreted in terms of adversity. Zhu et al. (2011) showed that reductions of total immunoglobulin M (IgM) levels and increases of IgA and IgG levels occurred in male Wistar rats orally exposed to 0, 64.18, 128.36 and 256.72 mg $AlCl_3$/kg bw per day for 120 days, equivalent to 0, 13, 26 and 52 mg Al/kg bw per day.

3.6. Discussion

The present opinion deals with the re-evaluation of the safety of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) when used as food additives.

Aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) are authorised as food additives in the EU according to Annex II of Regulation (EC) No 1333/2008. Specifications for aluminium sulphates and sodium aluminium phosphate have been defined in the EU in Commission Regulation (EU) No 231/2012 and also by JECFA in 2011. The Panel is aware that, in addition to the aluminium compounds evaluated in the present opinion, other forms of aluminium are authorised as food additives: elemental aluminium (E 173), starch aluminium octenyl succinate (E 1452), aluminium silicates (E 554 and E 555) and in the form of aluminium lakes of food colours. These food additives are not considered in the present opinion.

The safety of aluminium from dietary intake was evaluated in 2008 by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (EFSA, 2008). Based on the range of available NOAEL and LOAEL, and applying a weight of evidence approach, the Panel established a TWI of 1 mg aluminium/kg bw per week. This weekly health-based reference value took into account the potential accumulation of dietary aluminium in the body, and applied to all aluminium compounds in food, including additives.

Aluminium-containing food additives were also evaluated by JECFA several times, the latest in 2011. The Committee established a PTWI, which applied to all aluminium compounds in food. The PWTI was set at 2 mg Al/kg bw per week based on a NOAEL of 30 mg/kg bw per day from a neurodevelopmental study in rats (Poirier et al., 2011), with the application of a safety factor of 100. JECFA noted the complication of the identification of the LOAEL and NOAEL due to decreasing fluid consumption.

The present opinion considered major findings from the previous EFSA evaluation (EFSA, 2008), and additional relevant data published since then and retrieved in an ELS covering the period from 1990 up to June 2018 (Documentation provided to EFSA n.2).

Available studies indicate that oral bioavailability of aluminium compounds is low as a result of formation of insoluble aluminium hydroxide at the neutral pH in the intestines. Data from humans and experimental animals indicate that the bioavailability is approximately 0.3% of aluminium compounds in drinking water and 0.1% in food and beverages. Predicted plasma levels at the EFSA TWI of 1 mg Al/kg bw were within the reported normal levels of aluminium in serum, 1–3 μg/L. Absorbed aluminium

is accumulating in the bone. Kidney is the main route of excretion. Increased brain levels of aluminium have been reported in dialysis encephalopathy patients.

The acute oral toxicity of inorganic aluminium salts in rats and mice shows a wide range of LD_{50} values (from 162 to 750 mg Al/kg bw in rats and from 164 to 980 mg Al/kg bw in the mouse). In EFSA (2008), it was reported that aluminium nitrate in drinking water for 28 days caused mild histopathological changes in spleen and liver or decreased body weights in rats; the NOAEL for these effects was 52 mg Al/kg bw per day. In contrast dietary exposure to SALP for 28 days had no adverse effects in the highest doses tested corresponding to 140–300 mg Al/kg bw per day. Similarly, no effects were reported in dogs exposed in the diet to acidic SALP providing a dose of 90 mg Al/kg bw per day for 26 weeks.

The available genotoxicity studies indicate that aluminium compounds are genotoxic *in vitro*, inducing primary DNA damage and clastogenicity, and *in vivo* following i.p. administration, which however is not relevant for oral risk assessment. Only few of the available genotoxicity studies on aluminium compounds were performed with aluminium sulphates and phosphate. However, in view of the common activity profile of aluminium compounds, the Panel considered appropriate read-across among different aluminium salts, and all the available results relevant for genotoxicity assessment of E 520–523 and E 541. The Panel also noted that the genotoxic activity elicited by aluminium compounds is ascribed to indirect and thresholded mechanisms (EFSA, 2008), which are unlikely to be relevant at low dietary exposure levels, and considered that the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity.

The database on carcinogenicity of aluminium compounds is limited. In its previous evaluation (EFSA, 2008), the AFC Panel noted that dose levels of aluminium were generally low and that it was not possible to reach a conclusion on the carcinogenicity of aluminium from these studies. However, a more robust study in the B6C3F1 mouse (Oneda et al., 1994) did not indicate any carcinogenic potential of aluminium potassium sulphate at levels of up to 850 mg Al/kg bw per day in the diet. The Panel also noted the absence of epidemiological evidence for carcinogenicity of aluminium compounds used therapeutically, and the conclusion of IARC that aluminium itself is unlikely to be a human carcinogen. Overall, the Panel considered that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake.

The EFSA AFC Panel (EFSA, 2008) reported effects on male reproductive organs and/or semen after oral administration in rabbits (LOAEL 6.4 mg Al/kg bw per day) and dogs (NOAEL 27 mg Al/kg bw per day). No effects on male and female fertility were observed in the rat after oral dietary administration. In a two-generation reproduction toxicity study in rats (Hirata-Koizumi et al., 2011a) exposed via the drinking water to aluminium sulphate, a NOAEL of 8.06 mg Al/kg bw per day for parental, reproductive and developmental toxicity was identified. In another two-generation reproductive toxicity study in rats (Hirata-Koizumi et al., 2011b) also exposed via the drinking water to aluminium ammonium sulphate, a NOAEL of 5.35 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet) Al/kg bw was identified. Willhite et al. (2012) assumed that the NOAEL identified in the study with aluminium sulphate 'may reflect more the acidic properties of the water than any intrinsic systemic hazard posed by ingested Al'. The Panel agreed with these considerations as the effects observed were effects on body weight which may be due to decreased intake water because of palatability at higher concentrations of aluminium in the drinking water for both two-generation reproductive toxicity studies.

The EFSA AFC Panel (EFSA, 2008) reported that oral administration of 57 mg Al/kg bw per day (as aluminium lactate) by gavage from GD 6 to GD 15 induced cleft palate in mice fetuses. The lowest dose which produced an effect on rat was 13 mg Al/kg bw per day (as aluminium nitrate) when administered by gavage from GD 1 to GD 14. Gavage administration of aluminium hydroxide up to 264 mg Al/kg bw per day from GD 6 to GD 15 did not induce developmental effects in rats. After dietary administration of aluminium chloride and lactate during gestation (GD 1 or 8 to parturition in the rat), the lowest NOAEL for developmental toxicity was 18 mg Al/kg bw per day. No additional developmental toxicity studies were identified.

In humans, neurotoxicity was observed in patients undergoing dialysis due to the use of water containing high concentrations of aluminium (EFSA, 2008). In 2008, the Panel and also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there was no scientific proof aluminium was associated with Alzheimer's disease. Aluminium was considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. NOAELs of 10 mg Al/kg bw per day for neurodevelopmental effects were observed (EFSA, 2008). From two-generation reproductive toxicity studies in rats with $Al_2(S0_4)_3$ (Hirata-

Koizumi et al., 2011a) or AAS (Hirata-Koizumi et al., 2011b) in drinking water, no neurodevelopmental effects were recorded up to 31.2 mg Al/kg bw per day or 36.3 mg Al/kg bw, respectively. From a neurodevelopmental study in rats (Poirier et al., 2011), a NOAEL for developmental toxicity was identified by the authors at 30 mg Al/kg bw per day (target low-dose level of the study). The Panel noted that in accordance with JECFA, there were uncertainties, such as declining fluid consumption in all groups of pups and the real dose levels. Furthermore, despite several requests, the supplementary information containing crucial data linked to the main publication was not provided to the Panel, and thus the Panel was not able to assess the study.

To assess the dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives, the exposure was only calculated based on the MPLs as set out in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*), because no use levels or analytical results were made available to EFSA. The Panel noted that the vast majority (99–100%) of the estimated exposure to aluminium was coming from sodium aluminium phosphate (E 541) only from the consumption of fine bakery wares linked with sponge cake products. The Panel also noted that the estimated long-term exposures based on this scenario are very conservative, due to among others, the use of the MPL. Furthermore, as listed in Table 10, also other assumptions have resulted in an extreme overestimation of the exposure. Considering that these additives are only used in niche products which consumption is not captured in the dietary surveys of the EFSA Comprehensive Database, the Panel considered that these estimates are highly uncertain and are most probably near the lower end of the calculated exposure (approximately 0).

The Panel noted that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were listed as ingredient in the Mintel GNPD subcategories where the uses are not authorised (see Section 3.3.2). However, the overall percentage of labelled products per subcategories was less than 0.1%.

The exposure estimates in this highly conservative scenario exceeded the TWI of 1 mg Al/kg bw (equivalent to ~ 0.14 mg Al/kg bw per day) for all population groups at the 95th percentile, and for toddlers and children at the mean (Table 9). Due to these high uncertainties in this exposure assessment, a comparison of the calculated exposure with TWI is of little or no value.

The Panel also noted that the estimated dietary exposure to aluminium in the general population, assessed in several European countries, varied from 0.2 to 1.5 mg/kg bw per week at the mean and was up to 2.3 mg/kg bw per week in highly exposed consumers (EFSA, 2008). Thus, the TWI of 1 mg/kg bw per week is likely to be exceeded in a significant part of the European population. The Panel noted that a holistic exposure assessment to aluminium from all sources would be desirable but it is out of the remit of the Panel.

Cereals and cereal products, vegetables, beverages and certain infant formulae appear to be the main contributors to aluminium intake. Even though the design of the studies performed did not allow to distinguish the specific contribution of aluminium-based food additives, the Panel noted that the limited authorised uses of E 520–523 and E541 would only provide a minor contribution to aluminium intake compared to other food categories identified as main sources of dietary aluminium (Stahl et al., 2011; Hardisson et al., 2017).

4. Conclusions

Considering that:

- bioavailability of aluminium compounds is low (~ 0.1% from food and beverages);
- inorganic aluminium salts are of low acute toxicity;
- the NOAEL identified for aluminium compounds in subchronic studies was 52 mg Al/kg bw per day in rats and 90 mg Al/kg bw per day in dogs;
- the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity and these compounds are unlikely to be human carcinogens;
- studies on reproductive, developmental and neurotoxicity were available; the lowest NOAEL for neurotoxicity in rats was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day in studies in rats and mice;
- aluminium sulphates (E 520–523) are permitted as food additives in two food categories with further restriction in use;
- sodium aluminium phosphate (E 541) is only permitted as a food additive in one food category with further restriction in use;

- the Mintel's GNPD indicated that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were used in a decreasing number of products over time, following the change in legislation coming into force in February 2014, which is in line with the fact that EFSA did not receive any use levels of these additives from industry;
- these additives are only authorised in specific products which consumption is not captured in the dietary surveys of the EFSA Comprehensive Database and the estimated exposure is most probably near the lower end of the calculated exposure (approximately 0).

The Panel concluded that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) are of no safety concern in the current authorised uses and use levels.

5. Recommendations

The Panel recommend that:

- the combined exposure to aluminium from all the aluminium-containing food additives should be assessed.

Documentation provided to EFSA

1) CEFIC-PAPA, 2017. Reply to EFSA call for data – EFSA-Q-2013-00697 – Sodium Aluminium Phosphate Acidic – E541 on biochemistry and toxicology, preparation and use in studies of oral aluminum bioavailability from foods utilizing ^{26}Al as an aluminum tracer and Aluminium in the food chain with special respect to the safety of acid sodium aluminium phosphate (SALP) E 541 as additive in bakery products. Submitted on 1 December 2017.
2) Extensive Literature search covering from January 1990 up to June 2018. Analytica LASER submitted in June 2018.
3) Glynn A, 2018. Personal communication, unpublished study.

References

AFSSA (French Agency for Food Safety), 2003. Health risk assessment related to the exposure of the French population to aluminum, Water, Food and Health Products.

Al-Ashaal HA, Fahmy MA, Melek FR, Aly NH and Hasan ZM, 2012. Effect of supplemented soybean (Glycine max L) diet and extracts on aluminum sulphate-induced genotoxicity. Toxicological & Environmental Chemistry, 94, 965–986. https://doi.org/10.1080/02772248.2012.684688

ANSES (The French Agency for Food, Environmental and Occupational Health & Safety), 2011. ANSES, Etude de lálimentation totale francaise 2 (EAT 2).

BfR (Federal Institute for Risk Assessment), 2007. No risk of Alzheimer's disease from aluminium in consumer product. Updated BfR Health Assessment No. 033/2007, 13 Decembre 2005, updated 2007. http://www.bfr.bund.de/cm/230/no_risk_of_alzheimers_disease_fr

Bratakos Sotirios M., Lazou Andriana E., Bratakos Michael S and Lazos Evangelos S, 2012. Aluminium in food and daily dietary intake estimate in Greece. Food Additives and Contaminants: Part B, 5, 33–44

Darragh KV and Ertell CA, 2004. Aluminum sulphate and alums. In: Kirk-Othmer Encyclopedia of Chemical Technology, 5th Edition, Volume 2, pp. 434–441. Wiley-Interscience, John Wiley & Sons, Inc., Hoboken.

D'Souza P, Vijayalaxmi KK and Naik P, 2014. Assessment of genotoxicity of aluminium acetate in bone marrow, male germ cells and fetal liver cells of Swiss albino miceSr. Mutation Research, 766, 16–22.

EC inventory, online. Available online: https://echa.europa.eu/information-on-chemicals/ec-inventory

EFSA (European Food Safety Authority), 2007. Scientific opinion of the Scientific Committee related to uncertainties in dietary exposure assessment. EFSA Journal 2007;5(1):438, 54 pp. https://doi.org/10.2903/j.efsa.2007.438

EFSA (European Food Safety Authority), 2008. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials on a request from European Commission on Safety of aluminium from dietary intake. EFSA Journal 2008;754, 1–34. https://doi.org/10.2903/j.efsa.2008.754

EFSA (European Food Safety Authority), 2011a. Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. EFSA Journal 2011;9(3):2097, 34 pp. https://doi.org/10.2903/j.efsa.2011.2097

EFSA (European Food Safety Authority), 2011b. Evaluation of the FoodEx, the food classification system applied to the development of the EFSA Comprehensive European Food Consumption Database. EFSA Journal 2011;9(3):1970, 27 pp. https://doi.org/10.2903/j.efsa.2011.1970

EFSA AFC Panel, 2008. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) on the Safety of aluminium from dietary intake. EFSA Journal 2008;6(7):754, 34 pp. https://doi.org/10.2903/j.efsa.2008.754

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2012. Guidance for submission for food additive evaluations. EFSA Journal 2012;10(7):2760, 60 pp. https://doi.org/10.2903/j.efsa.2012.2760

EFSA Scientific Committee, 2009. Guidance of the Scientific Committee on Transparency in the Scientific Aspects of Risk Assessments carried out by EFSA. Part 2: general principles. EFSA Journal 2009;7(7):1051, 22 pp. https://doi.org/10.2903/j.efsa.2009.1051

EFSA Scientific Committee, 2012a. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579, 32 pp. https://doi.org/10.2903/j.efsa.2012.2579

EFSA Scientific Committee, 2012b. Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). EFSA Journal 2012;10(7):2750, 103 pp. https://doi.org/10.2903/j.efsa.2012.2750

EFSA Scientific Committee, 2012c. Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578, 5 pp. https://doi.org/10.2903/j.efsa.2012.2578

Fekete V, Vandevijvere S, Bolle F and Van Loco J, 2013. Estimation of dietary aluminum exposure of the Belgian adult population: evaluation of contribution of food and kitchenware. Food and Chemical Toxicology, 55, 602–608.

Gard DR, 2006. Phosphoric acids and phosphates. In: Kirk-Othmer Encyclopedia of Chemical Technology, 5th Edition, Volume 18, Wiley-Interscience, John Wiley & Sons, Inc., Hoboken. pp. 814–863.

Geyikoglu F, Turkez H, Bakir TO and Cicek M, 2012. The genotoxic, hepatotoxic, nephrotoxic, haematotoxic and histopathological effects in rats after aluminium chronic intoxication. Toxicology and Industrial Health, 29, 780–791.

Hardisson A, Revert C, Gonzales-Weler D and Rubio C, 2017. Aluminium exposure through the diet. Journal of Food Science Nutrition, 3, 019. https://doi.org/10.24966/FSN-0176/100019

Hem JD and Roberson CE, 1967. Form and stability of aluminum hydroxide complexes in dilute solution. In: Chemistry of Aluminum in Natural Water. Geological Survey-Water Supply Paper 1827-A, US Department of the Interior, Geological Survey, US Government Printing Office (Washington, DC). Available online: https://pubs.usgs.gov/wsp/1827a/report.pdf

Hirata-Koizumi M, Fujii S, Ono A, Hirose A, Imai T, Ogawaa K, Ema M and Nishikawa A, 2011a. Two-generation reproductive toxicity study of aluminium sulfate in rats. Reproductive Toxicology, 31, 219–230.

Hirata-Koizumi M, Fujii S, Ono A, Hirose A, Imai T, Ogawa K, Ema M and Nishikawa A, 2011b. Evaluation of the reproductive and developmental toxicity of aluminium ammonium sulfate in a two-generation study in rats. Food and Chemical Toxicology, 49, 1948–1959.

Hongying Hua, Xiaofei Jiang and Shimin Wu, 2016. Validation and comparable analysis of aluminum in the popular Chinese fried bread youtiao by wavelength dispersive XRF. Food Chemistry 207, 1–5.

IARC (International Agency for Research on Cancer), 1984. Polynuclear aromatic compounds, Part 3, industrial exposures in aluminium production, coal gasification, coke production, and iron and steel founding. Lyon, France: World Health Organization, International Agency for Research on Cancer.

Ivušić F, Soldo Gjeldum M, Nemet Z, Gracin L and Maric V, 2006. Aluminium and Aroma Compound Concentration in Beer During Storage at Different Temperatures. Food Technology and Biotechnology, 44, 499–505.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1978. Evaluation of certain food additives. Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives. No. 617. World Health Organization, Geneva, Switzerland.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1982. 26th Report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants, World Health Organization Technical report series 683.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1986. 29th Report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants. World Health Organization Technical report series 783.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1987. 30th Report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants. World Health Organization Technical report series 751.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1989. 33rd Report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants. World Health Organization Technical report series 776.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2000. Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2007. 67th Report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants. World Health Organization Technical report series 940.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2011. Aluminium sulfate, anhydrous. Prepared at the 55th JECFA (2000) and published in the Combined Compendium of Food Additive Specifications, FAO JECFA Monographs 1 (2005).
JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2012. 74th Meeting of the Joint FAO/WHO Expert Committee on Food Additives. Safety evaluation of certain food additives and contaminants. World Health Organization Technical report series 65.
Martin RB, 1986. The chemistry of aluminum as related to biology and medicine. Clinical Chemistry, 32, 1797–1806.
Martin RB, 1992. Aluminum speciation in biology. Ciba Foundation Symposia 169, 5–25. [This reference comes from a CFS held in 1992. Proceedings were apparently re-published in 2007 by Novartis Foundation Symposia (Wiley Online Library). I presume the reference in draft should be updated]. Available online: https://onlinelibrary.wiley.com/doi/pdf/10.1002/9780470514306.ch2
Martus H-J, Hayashi M, Honma M, Kasper P, Gollapudi B, Mueller L, Schoeny R, Uno Y and Kirkland DJ, 2015. Summary of major conclusions from the 6th International Workshop on Genotoxicity Testing (IWGT), Foz do Iguaçu, Brazil, 2015. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 783, 1–5.
McDermott JR, Smith AI, Ward MK, Parkinson IS and Kerr DN, 1978. Brain-aluminium concentration in dialysis encephalopathy. Lancet, 1, 901–904.
Muselin F, Cristina RT, Igna V, Dumitrescu E, Brezovan D and Trif A, 2016. The consequences of aluminium intake on reproductive function in male rats: a three-generation study. Turkish Journal of Medical Sciences, 46, 1240–1248. https://doi.org/10.3906/sag-1501-101
Müller M, Anke M and Illing-GuÈnther H, 1998. Aluminium in foodstu€s. Food Chemistry, 61, 419–428.
NFA (National Food Administration. Market Basket), 2010. Chemical analysis, exposure estimation and health-related assessment of nutrients and toxic compounds in Swedish food baskets. Report nr 7, 2012.
Oneda S, Takasaki T, Kuriwaki K, Ohi Y, Umekita Y, Hatanaka S, Fujiyoshi T, Yoshida A and Yoshida H, 1994. Chronic toxicity and tumorigenicity study of aluminum potassium sulfate in B6C3F1 mice. Vivo, 8, 271–278.
Park HC, Park YJ and Stevens R, 2004. Synthesis of alumina from high purity alum derived from coal fly ash. Materials Science and Engineering (2004); 367, 166–170.
Parker DR and Bertsch PM, 1992a. Identification and quantification of the "Al_{13}" tridecameric polycation using ferron. Environmental Science and Technology, 26, 908–914.
Parker DR and Bertsch PM, 1992b. Formation of the "Al_{13}" tridecameric polycation under diverse synthesis conditions. Environmental Science and Technology, 26, 914–921.
Pereira S, Cavalie I, Camilleri V, Gilbin R and Adam-Guillermin C, 2013. Comparative genotoxicity of aluminium and cadmium in embryonic zebrafish cells. Mutation Research, 750, 19–26.
Poirier J, Semple H, Davies J, Lapointe R, Dziwenka M, Hiltz M and Mujibi D, 2011. Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminium salts in the rat. Neuroscience, 193, 338–362.
Rawi SM and Seif Al Nassr FM, 2015. Zinc sulphate and vitamin E alleviate reproductive toxicity caused by aluminium sulphate in male albino rats. Toxicology and Industrial Health, 31, 221–234.
SCCS (Scientific Committee on Consumer Safety), 2014. Opinion on the safety of aluminium in cosmetic products. Available online: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_153.pdf
SCF (Scientific Committee for Food), 1991. Reports of the Scientific Committee for Food, 25th series. First series of food additives of various technological function. Opinion expressed on 18 May 1990.
SCF (Scientific Committee for Food), 2001. Guidance on submissions for food additive evaluations by the Scientific Committee on Food. Opinion expressed on 11 July 2001. Available online: http://ec.europa.eu/food/fs/sc/scf/out98_en.pdf
SCHEER (Scientific Committee on Health, Environmental and Emerging Risks opinion), 2017. SCHEER Final Opinion on Tolerable intake of aluminium with regards to adapting the migration limits for aluminium in toys. Available online: https://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scheer_consultation_04_en
Schroeder HA and Mitchener M, 1975. Life-term studies in rats: effects of aluminum, barium, beryllium, and tungsten. The Journal of Nutrition, 105, 421–427.
Sharma S, Sharma D, Sharma S, Rajawat A, Jain S, Upreti N, Yadav A, Pandey A and Sharma KP, 2010. Comparative study on acute toxicity of fluoride, aluminium and aluminium fluoride to swiss albino mice. Australasian Journal of Ecotoxicology Vol. 16, pp. 41–47.
Stahl T, Taschan H and Brunn H, 2011. Aluminium content of selected foods and food products. Environmental Sciences Europe, 23, 37. https://doi.org/10.1186/2190-4715-23-37
Steinhausen C, Kislinger G, Winklhofer C, Beck E, Hohl C, Nolte E, Ittel TH and Alvarez-Brückmann MH, 2004. Investigation of the aluminium biokinetics in humans: a 26Al tracer study. Food and Chemical Toxicology, 42, 363–371.
TemaNord, 2002. Food Additives in Europe 2000 - Status of safety assessments of food additives presently permitted in the EU, yyy-yyy.
Tipping E, Woof C, Walters PB and Ohnstad M, 1988. Conditions required for the precipitation of aluminium in acidic natural waters. Water Research, 22, 585–592.
Turkez H, Yousef MI and Geyikoglu F, 2010. Propolis prevents aluminium-induced genetic and hepatic damages in rat liver. Food and Chemical Toxicology, 48, 2741–2746.

Turkez H and Geyikoglu F, 2011. The efficiacy of bismuth subnitrate against genotoxicity and oxidative stress induced by aluminum sulphate. Toxicology and Industrial Health 27, 133–142.
VKM, 2013. Norwegian Scientific Committee for food safety. Risk assessment of the exposure to aluminium through food and the use of cosmetic products in the Norwegian population.
Weisser K, Stübler S, Matheis W and Huisinga W, 2017. Towards toxicokinetic modelling of aluminium exposure from adjuvants in medicinal products. Regulatory Toxicology and Pharmacology, 88, 310–321.
WHO (World Health Organization), 1997. International Programme on Chemical Safety. Enviromental Health Criteria 194. Aluminium.
WHO (World Health Organization), 1998. Aluminium in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization 2003. Originally published in Guidelines for drinking-water quality, 2nd ed. Addendum to Vol. 2. Health criteria and other supporting information. World Health Organization, Geneva, 1998.
Willhite CC, Ball GL and McLellan CJ, 2012. Total allowable concentrations of monomeric inorganic aluminum and hydrated aluminum silicates in drinking water. Critical Reviews in Toxicology, 42, 358–442.
Wood R, Foster L, Damant A and Key P, 2004. Analytical methods for food additives. Woodhead Publishing Ltd, CRC Press, Boca Raton Boston New York Washington, DC.
Zhu Y, Li Y, Miao L, Wang Y, Liu Y, Yan X, Cui X and Li H, 2014. Immunotoxicity of aluminum. Chemosphere, 104, 1–6.
Zhu YZ, Xu JF, Sun H, Hu CW, Zhao HS, Shao B, Bah AA and Li YF, 2011. Effects of aluminum exposure on the allergic responses and humoral immune function in rats. Biometals, 24, 973–977.

Abbreviations

ADI	acceptable daily intake
AES	atomic emission spectrometry
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANS	EFSA Scientific Panel on Food Additives and Nutrient Sources added to Food
AST	aspartate aminotransferase
Bfr	German Federal Institute for Risk Assessment
bw	body weight
CA	chromosomal aberrations
CAS	Chemical Abstracts Service
CAT	catalase
CONTAM	EFSA Panel on Contaminants in Food Chain
EINECS	European Inventory of Existing Chemical Substances
ELS	extensive literature search
ET-AAS	electrothermal atomic absorption spectrometry
F-AAS	flame atomic absorption spectroscopy
FAO	Food and Agriculture Organization of the United Nations
FCs	food categories
FCS	food categorisation system
FOB	Functional Observational Battery
G-6-PDH	glucose-6-phosphate dehydrogenase
GC-HSS	gas chromatography with static headspace sampler
GD	gestation day
GF-AAS	graphite furnace atomic absorption spectrometry
GLP	Good laboratory practice
GNPD	Global New Products Database
GSH	glutathione
Hb	haemoglobin
HPLC	high-performance liquid chromatography
Ht	haematocrit
i.p.	intraperitoneal
ICP	inductively coupled plasma
Ig	immunoglobulin
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LDH	lactate dehydrogenase
LOD	limit of detection

MCP	monocalcium phosphate
MN	micronuclei
MPL	maximum permitted level
MS	mass spectrometry
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OES	optical emission spectrometry
PLT	platelet
PND	postnatal day
PTWI	Provisional Maximum Tolerable Weekly Intake
RBC	red blood cell
SALP	sodium aluminium phosphate
SAS	sodium aluminium sulphate
SCE	sister chromatid exchange
SCF	Scientific Committee on Food
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SOD	superoxide dismutase
SO	spectrophotometric oxine
TDI	tolerable daily intake
TemaNord	is a publishing series for results of the often research-based work that working groups or projects under Nordic Council of Ministers have put in motion
TLC	thin-layer chromatography
UA	uric acid
U	urea
WBC	white blood cell
WDXRF	wavelength dispersive X-ray fluorescence spectrometry
WHO	World Health Organization

Appendix A – Number and percentage of food products labelled with aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) out of the total number of food products present in Mintel GNPD per food subcategory between January 2013 and February 2018

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

Appendix B – Summary Levels of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) used in the exposure scenario (mg/kg or mL/kg as appropriate)

Appendix B can be found in the online version of this output ('Supporting information' section).

Appendix C – Summary of total estimated exposure of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives for the maximum level exposure scenario per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix C can be found in the online version of this output ('Supporting information' section).