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Re-evaluation of L(+)-tartaric acid (E 334), sodium tartrates (E 335), potassium tartrates (E 336), potassium sodium tartrate (E 337) and calcium tartrate (E 354) as food additives

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Abstract

The EFSA Panel on Food Additives and Flavourings (FAF) provides a scientific opinion on tartaric acid-tartrates (E 334-337, 354) when used as food additives. The Scientific Committee for Food (SCF) in 1990 established an acceptable daily intake (ADI) of 30 mg/kg body weight (bw) per day, for L(+)-tartaric acid and its potassium and sodium salts. The metabolism of L(+)-tartaric acid and its potassium sodium salt was shown to be species dependent, with a greater absorption in rats than in humans. No toxic effects, including nephrotoxicity, were observed in toxicological studies in which the L(+)-form was tested. There was no indication for a genotoxic potential of tartaric acid and its sodium and potassium salts. In a chronic study in rats, no indication for carcinogenicity of monosodium L(+)-tartrate was reported at the highest dose tested (3,100 mg/kg bw per day). The available studies for maternal or developmental toxicity did not report any relevant effects; no studies for reproductive toxicity were available; however, no effects on reproductive organs were observed in the chronic toxicity study. The Panel concluded that the data on systemic availability were robust enough to derive a chemical-specific uncertainty factor instead of the usual default uncertainty factor of 100. A total uncertainty factor of 10 was derived by applying a total interspecies uncertainty factor of 1 instead of 10, based on data showing lower internal exposure in humans compared to rats. The Panel established a group ADI for L(+)-tartaric acid-tartrates (E 334-337 and E 354) of 240 mg/kg bw per day, expressed as tartaric acid, by applying the total uncertainty factor of 10 to the reference point of 3,100 mg sodium tartrate/kg bw per day, approximately to 2,440 mg tartaric acid/kg bw per day. The exposure estimates for the different population groups for the refined non-brand-loyal exposure scenario did not exceed the group ADI of 240 mg/kg bw per day, expressed as tartaric acid. Some recommendations were made by the Panel.

Keywords: tartaric acid, sodium tartrate, potassium tartrate, calcium tartrate, E 334, E 335, E 336, E 337, E 354

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Summary

L(+)-Tartaric acid (E 334), sodium tartrate (E 335 (i)), disodium tartrate (E 335 (ii)), potassium tartrate (E 336 (i)), dipotassium tartrate (E 336 (ii)), potassium sodium tartrate (E 337) were evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)several times (JECFA, 1962, 1964, 1965, 1974a,b, 1975, 1977, 1978, 1983) and by the Scientific Committee for Food (SCF) in 1990 (SCF, 1991b). Both committees established a group acceptable daily intake (ADI) of 30 mg/kg body weight (bw) per day for L(+)-tartaric acid and its potassium and sodium salts.

Information on the manufacturing process of L(+)-tartaric acid using immobilised cells of the bacteria *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012 was submitted. *Rhodococcus ruber* has not been reported to be pathogenic to humans. Since no viable cells from *Rhodococcus sp* USA-AN012 remained in the final product, and the manufacturing conditions were shown able to fully degrade DNA, the use of immobilised cells of the bacteria *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012 was not considered to pose a safety concern.

The metabolism of L(+)-tartaric acid and its potassium sodium salt was shown to be species dependent. In rats, after oral administration, up to 81% of labelled tartrate was absorbed. In rats, L(+) and D(-)-tartrate were excreted differently in urine after gavage, the L(+)-form being more efficiently excreted than the D(-)-form. Up to 10% of labelled parenteral tartrate was expired as CO_2 within 6 h and 63% was found in the urine over 24 h, which indicated significant metabolism by tissues. High rate of renal excretion (up to 60% within 12 h) was reported in dogs receiving tartaric acid. After parenteral injection of tartrate, recovery ranged from 70% in rabbits, dogs and rats to almost 100% in guinea pigs. Therefore, tissue metabolism could not be excluded in these species; however, it played a minor role in disposal of tartrate.

In humans, only 12% of tartrate administered orally appeared in the urine; as this was unrelated to dose, the Panel considered this as passive absorption. The difference in urinary excretion after an oral dose (12%) or an intravenous dose (66%) suggested that only a fraction of the oral dose was systemically available. A 91% of an intramuscular dose of unlabelled tartrate was recovered in urine, which according to the authors, indicated that the human body cannot metabolise tartrate. After an intravenous injection of ^{14}C-L-tartrate, it has been reported that 66% of radioactivity was excreted in the urine in 22 h, and that 18% was excreted as $^{14}CO_2$ over 8 h. The concentration of $^{14}CO_2$ in expired air peaked after 1 h and contained 7% of the dose, suggesting rapid metabolism by tissue enzymes. The Panel considered that the different recoveries of 91 and 66% may be due to the different stereospecific forms used. However, these recoveries are not directly comparable because radioactivity was measured in one study while unlabelled tartrate was analysed in the other study. Tartrate was fermented by colonic bacteria, with L(+)-tartrate being metabolised faster than D(-)-tartrate. Tartaric acid/tartrate were fermented by colonic bacteria to Short Chain Fatty Acids (SCFA), which then can be absorbed in the colon.

It is necessary to consider whether the hazard could only be due to the parent compounds. In this respect, the metabolic products originating from the metabolism of the unabsorbed tartaric acid/tartrate by the microbiome in the lower part of the gastrointestinal tract have to be evaluated. It was confirmed that tartrate is not metabolised to oxalate, a potential metabolite with toxic properties for the kidney; most of the ^{14}C- label was recovered as $^{14}CO_2$. Hence, from the absorption, distribution, metabolism, excretion (ADME) data, it can be concluded that the metabolites would not cause potential side effects.

A LD_{10} value for disodium tartrate above 4,000 mg/kg bw in mice was indicative of a low oral toxicity of tartrate in this species. In outdated studies, acute renal toxicity was seen in rabbits and dogs after a single oral dose of tartaric acid or Rochelle salt (potassium sodium tartrate) from 26.6 and 600 mg/kg bw (expressed as tartaric acid), respectively. In these studies, the stereoisomeric composition of the studied material was not specified. The species differences between rats, rabbits and dogs in terms of renal toxicity reflected probably the species differences in the absorption of tartaric acid and tartrates.

No adverse effects were observed in rats given 2,730 monosodium L-tartrate/kg bw per day. In the same study, DL-tartaric acid was shown to cause kidney effects. Furthermore, in a 90-day study in rats, a no observed adverse effect level (NOAEL) of 60 mg/kg bw per day was identified for monopotassium DL-tartrate, based on kidney histological alterations (obstructive nephropathy) reported at higher doses. In rabbits given 550 mg monosodium tartrate/kg bw per day acid (stereoisomeric composition not specified), no adverse effects were observed. Advanced tubular degeneration of the kidneys and increased blood non-protein nitrogen (NPN), creatinine and albumin were observed in one out of the four dogs given 990 mg/kg bw per day tartaric acid (stereoisomeric composition not specified), the

only dose tested. The Panel considered that the renal effects reported with tartrates were most likely due to the presence of the D(-)-form of tartaric acid.

The Panel considered that there was no concern for genotoxicity for tartaric acid and its sodium and potassium salts.

A dosage-related reduction of body weight and higher relative weights for a number of organs were reported for rats fed monosodium tartrate at doses equal to or above 1,620 and 2,050 mg/kg bw per day for males and females, respectively, for 2 years. These increased relative organ weights were mainly due to decreased body weights. The Panel considered that the decrease in body weights was due to a nutritional imbalance likely due to palatability effect, and therefore, considered these increased relative organ weights not of toxicological significance. Histopathological examination did not reveal a difference between treated animals and controls. From the available chronic and carcinogenicity studies, the Panel considered that monosodium L(+)-tartrate was not carcinogenic and identified an NOAEL of 3,100 mg monosodium tartrate/kg bw per day, the highest dose tested.

No maternal or developmental effects were reported at the highest dose tested (mice: 274 mg/kg bw per day, rats: 181 mg/kg bw per day, hamsters: 225 mg/kg bw per day or rabbits: 215 mg/kg bw per day for 13 days). No studies for reproductive toxicity were available; however, from the available chronic studies, there was no indication of a possible effect on reproductive organs at the doses tested.

Some publications reported that excessive consumption of tartaric acid by humans induced some effects. Daily doses of 10 g sodium tartrate caused nausea, vomiting and abdominal cramps in a minority of patients (< 2.1%) with pre-existing health problems. Four cases of acute tubular necrosis in patients who had consumed 'large amounts of tartaric acid'; the form of tartaric acid absorbed was not specified. The Panel noted that adverse effects of tartrate or tartaric acid were observed only at high oral intakes and, the form of tartaric acid consumed was not indicated. Therefore, although being indicative of an acute toxicity in humans, and given the difference in toxicity between the D(-)- and L(+)-forms, these effects were considered not relevant for the purpose of evaluating L(+)-tartaric acid and tartrates as food additives.

A group ADI of 30 mg/kg bw per day was established by JECFA in 1974 and later endorsed by the SCF in 1991. This ADI was derived from an NOAEL of 3,000 mg monosodium tartrate/kg bw per day, the highest dose tested in a chronic toxicity study in rats and applying an uncertainty factor of 100.

The Panel considered whether this uncertainty factor would be appropriate given the fact that the absorption of tartaric acid/tartrate is greater in rats than humans. Whereas in the rat the systemic availability was 81%, the systemic availability in humans amounted to 18%.

The Panel decided that the available data on systemic availability were robust enough to derive a chemical-specific adjustment factor instead of the usual default uncertainty factor of 100.

The default uncertainty factor of 100 is composed of a factor of 10 accounting for the difference between animal and human and a second factor of 10 accounting for the variability in the human population. In 2004, the IPCS/WHO proposed a framework indicating how chemical-specific toxicokinetic and/or toxicodynamic data can be used to replace the default factors or its subfactors.

When considering the systemic toxicity of the parent compounds tartaric acid/tartrates, toxicity is related to the amount, which is given as the internal dose. Accordingly, the external (administrated) dose can be adjusted to the internal dose by taking into account how much is absorbed and systemically available after oral administration. In humans, 18% of the dose is systemically available whereas in rats, the figure is 81%. Furthermore, it is to be noted that the rate of metabolism is similar between rats and humans as measured by the rate of expired CO_2. The usual default value for the toxicokinetic differences between rats and humans is 4 assuming that in general the internal human exposure is four times higher than in the rat with the same external dose. In case of tartrate, the situation is reverse; in humans the internal exposure is 22% of that in rats. Hence, when considering the different absorption in rats and humans, together with the similar rate of metabolism, the interspecies toxicokinetic factor may be reduced to 0.22 instead of 4.

Multiplying this interspecies toxicokinetic factor of 0.22 by the default toxicodynamic factor of 2.5 would result in a total interspecies uncertainty factor of 0.55. As a conservative approach, the Panel decided to use an interspecies factor of 1. For the intraspecies factor, the Panel had no information regarding possible modification of this default factor and, therefore, the default factor of 10 was used. Accordingly, the resulting overall uncertainty factor used was 10 (1 × 10).

Applying the total uncertainty factor of 10 to the reference point of 3,100 mg sodium tartrate/kg bw per day (the highest dose tested), that is approximately 2,400 mg tartaric acid/kg bw per day, will

result in a group ADI for tartaric acid and tartrates (E 334-337 and E 354) of 240 mg/kg bw per day expressed as tartaric acid.

The difference between the ADI established by the SCF and the one derived in this opinion is due to the application of a chemical specific interspecies uncertainty factor instead of the default uncertainty factor used in previous evaluations.

Dietary to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives was calculated according to different exposure scenarios based on maximum permitted levels and the reported use levels, as described in Section 3.4. According to Annex II to Regulation N°1333/2008, tartaric acid and tartrates (E 334-337 and E 354) are authorised in 81 food categories of which 66 under Group I food additives.

Use levels were reported by industry for 17 food categories. Based on the information of the Mintel's GNPD, approximately 82% of the food products labelled with tartaric acid and tartrates (E 334-337 and E 354) in this database were considered in the exposure assessment. Together with the observation that the Panel assumed that 100% of the foods belonging to a food category included in the assessment contained the food additives, whereas the average percentage was 1% according to the Mintel's GNPD, and that the possible degradation of tartaric acid at high temperatures was not considered in the assessment, the Panel considered that the exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives according to Annex II to Regulation (EC) No 1333/2008 was overestimated in all exposure scenarios.

Tartaric acid and tartrates (E 334-337 and E 354) are used as 'acidity regulator' and are therefore not expected to change the organoleptic properties of the final food at the concentration used as a food additive. Therefore, the Panel considered the *non-brand-loyal scenario* covering the general population as most appropriate for risk characterisation. Dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) according to this exposure scenario was up to 91 mg/kg bw per day at the mean level and 174 mg/kg bw per day at the high (P95) level, both in infants. This exposure did not exceed the group ADI of 240 mg/kg bw per day, expressed as tartaric acid.

Since tartaric acid also occurs naturally in food, the Panel calculated the intake of tartaric acid from natural sources (non-processed fruits and vegetables and wine), based on the limited available information reported in the literature. This exposure was lower than the calculated exposure from the use of tartaric acid-tartrates as food additives, maximally 26 mg/kg bw per day in the elderly.

Exposure to tartaric acid, in addition to natural occurrence, can also occur by release from other food additives, including tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e), mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f), metatartaric acid (E 353) and stearyl tartrate (E 483). The Panel, therefore, also calculated the potential exposure to tartaric acid from these sources and combined it with the exposure to tartaric acid due to the use of tartaric acid and tartrates (E 334-337 and E 354). The non-brand loyal exposure scenario was considered for the exposure due to the use of food additives. The exposure to tartaric acid from stearyl tartrate (E 483) was not included in this assessment, as no reported use levels were available for this food additive. The highest P95 level of exposure was estimated for toddlers at 285 mg/kg bw per day. However, the Panel did not consider this exceedance to indicate a possible health concern, due to the overestimation of the exposure.

The Panel made some recommendations to be considered for possible revision of the EU specifications of these food additives

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1. Introduction

The present opinion document deals with the re-evaluation of L(+)-tartaric acid (E 334), monosodium tartrate (E 335 (i)), disodium tartrate (E 335 (ii)), monopotassium tartrate (E 336 (i)), dipotassium tartrate (E 336 (ii)), potassium sodium tartrate (E 337) and calcium tartrate (E 354) 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 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.

1.2. Information on existing authorisations and evaluations

L(+)-Tartaric acid (E 334), sodium tartrates (E 335), potassium tartrates (E 336), sodium potassium tartrate (E 337) and calcium tartrate (E 354) are authorised as food additives according to Regulation (EC) No 1333/2008 on food additives. Specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012[5] for L(+)-tartaric acid (E 334), monosodium tartrate (E 335(i)), disodium

[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.

[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 (Nordic Council of Ministers), 2002, 560.

[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.

tartrate (E 335(ii)), monopotassium tartrate (E 336(i)), dipotassium tartrate (E 336(ii)), potassium sodium tartrate (E 337) and calcium tartrate (E 354).

L(+)-Tartaric acid (E 334) is authorised to be used as a food additive (acidity regulator) in wine according to Regulation (EC) No 934/2019[6]. Dipotassium tartrate, monopotassium tartrate and calcium tartrate are authorised to be used as processing aids in wine according to Regulation (EC) No 934/2019.

L(+)-Tartaric acid (E 334) and its sodium and potassium salts (E 335, E 336,E 337), used as food additives, have previously been evaluated by the SCF in 1978, 1990 and 1992 (SCF, 1978, 1991a,b, 1994). Although not being actually evaluated, calcium tartrate was considered acceptable in weaning foods (SCF, 1994).

In 1978, the SCF stated that L(+)-tartaric acid and its sodium and potassium salts were acceptable for use in fine bakery wares (SCF, 1978). No detailed evaluation was performed, but it was stated that the Committee accepted, on a provisional basis, the ADI established by JECFA (1,800 mg/adult per day as total L(+)-tartaric acid from all sources, equal to 30 mg tartaric acid/kg bw for a 60 kg person).

In 1990, the SCF found L(+)-tartaric acid, sodium L(+)-tartrate and potassium L(+)-tartrate acceptable for use in weaning foods as raising agents in biscuits and rusks with a residue level of not more than 0.5 g/100 g (SCF, 1991a). In 1992, calcium L(+)-tartrate was also listed as acceptable in weaning foods with the same restriction (SCF, 1994).

In 1990, the SCF (SCF, 1991b) endorsed the group ADI of 30 mg/kg bw established previously by JECFA (1974a). The SCF report stated the following: '*the long-term study in rats with L(+)-tartrate showed no adverse effects at the highest level tested. Tartrates have been used medicinally for long periods. The evaluation of L(+)-tartrate can therefore be based on experimental data, the metabolic inertness of tartrates and the fact that they are normal constituents of food. Monosodium-L(+)-tartrate also produced no adverse effects in long-term studies. The available data were inadequate to assess the safety of DL-tartrate. The Committee agrees with the ADI of 30 mg/kg body weight established by JECFA for L(+) tartrate, while the DL-form is not acceptable.*'

L(+)-Tartaric acid and its sodium, potassium and sodium-potassium salts have been evaluated by JECFA in 1961, 1963, 1964, 1973, 1975 and 1977 (JECFA, 1962, 1964, 1965, 1974a,b, 1975, 1977, 1978).

In 1973, the JECFA established an acceptable daily intake (ADI) of 0–30 mg/kg bw (expressed as L(+)-Tartaric acid) for L(+)-tartaric acid and its potassium, potassium sodium and sodium salts (JECFA, 1974a).

In 1978, the JECFA evaluated tartaric acid and monosodium L(+)-tartrate and, on the ground of a new long-term study in rat, reconfirmed an ADI for L(+)-tartrate monosodium at 0–30 mg/kg bw expressed as tartaric acid.

In 2017, during the evaluation of metatartaric acid, JECFA reviewed two genotoxicity studies (Ishidate et al. (1984) and Hayashi et al. (1988)) and the publication (Hunter et al., 1977) of the unpublished report that was used to establish the ADI of L(+)-tartaric acid at its latest evaluation (1977). JECFA concluded that the body of evidence suggests no change to the group ADI previously established for L(+)-tartaric acid and its sodium, potassium and potassium–sodium salts, expressed as L(+)-tartaric acid (JECFA, 2017).

L(+)-Tartaric acid and its sodium, potassium and calcium salts were evaluated by the Nordic Council of Ministers in 2000 (TemaNord, 2002). A re-evaluation was not recommended provided that the exposure was below the ADI

EFSA evaluated the safety of the complexation product of sodium tartrates and iron(III) (FemTA) when used as a food additive (EFSA ANS Panel, 2015). FemTA is a mixture of sodium tartrates [DL-and *meso*-tartrates] with iron(III) chloride; where *meso*-tartrate represents approximately 65% of the total tartrate content. The ANS Panel concluded that the toxicity database was insufficient to establish an ADI for FemTA; however, considering the calculated MoS, it was also concluded that there is no safety concern for the use of FemTA only in salt and its substitutes, with a use level of 106 mg FemTA/kg salt as an anti-caking agent. Following this assessment, the food additive iron tartrate (E534) has been included in Annex II of Regulation (EC) No 1333/2008.

'L-carnitine-L-tartrate' is authorised to be added to food in the following food categories according to Regulation (EU) No 609/2013: Infant formula and follow on formula, food for special medical

[6] Commission Delegated Regulation (EU) 2019/934 of 12 march 2019 supplementing Regulation (EU) No 1308/2013 of the European Parliament and of the Council as regards wine-growing areas where the alcoholic strength may be increased, authorised oenological practices and restrictions applicable to the production and conservation of grapevine products, the minimum percentage of alcohol for by-products and their disposal, and publication of OIV files. OJ L 149, 7.6.2019, p. 1–52

purposes and total diet replacement for weight control. 'Choline bitartrate' (stereoisomeric composition of tartrate not specified) is also authorised to be used in the same food categories in addition to processed cereal-based food and baby food (Regulation (EU) No 609/2013).

Tartaric acid (FL 08.018) is a flavouring substance included in the Union list of flavourings (Commission Implementing Regulation (EU) No 872/2012).

L(+)-Tartaric acid and potassium sodium tartrate have been registered under the REACH Regulation 1907/2006[7] (ECHA, online).

L(+)-Tartaric acid (PM Ref. 92160) is included in the Union list of authorised substances that may be intentionally used in the manufacture of plastic materials which are intended to come into contact with food (Annex I to Commission Regulation (EU) No 10/2011[8]). Furthermore, L(+)-tartaric acid, disodium tartrate, dipotassium tartrate and potassium sodium tartrate are permitted as buffering substances in cosmetic products. Calcium tartrate is permitted as skin conditioner in cosmetic products (European Commission database-CosIng[9]).

2. Data and methodologies

Data

The FAF Panel was not provided with a newly submitted dossier. EFSA launched public call for data[10,11,12] to collect 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 January 2020. 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.

Food consumption data used to estimate the dietary exposure to tartaric acid-tartrates (E 334-337, 354) were derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database[13]).

The Mintel's Global New Products Database (GNPD) was used to verify the use of tartaric acid-tartrates (E 334-337, 354) in food and beverage products and food supplements within the EU's food market. The Mintel's GNPD is an online database that contains the compulsory ingredient information present on the label of numerous products.

Methodologies

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

The FAF Panel assessed the safety of L(+)-tartaric acid (E 334), monosodium tartrate (E 335 (i)), disodium tartrate (E 335 (ii)), monopotassium tartrate (E 336 (i)), dipotassium tartrate (E 336 (ii)), potassium sodium tartrate (E 337) and calcium tartrate (E 354) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the SCF (2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When in animal studies, the test substance was administered in the feed or in 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 is calculated by the Panel using the relevant default values. In case of rodents, the values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific

[7] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). OJ L 396, 30.12.2006.
[8] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1–89.
[9] Available online: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple
[10] Call for scientific data on miscellaneous food additives permitted in the EU and belonging to several functional classes. Published: 8 June 2010. Available from: http://www.efsa.europa.eu/en/dataclosed/call/ans100609
[11] Call for scientific data on L(+)-tartaric acid (E 334) and related food additives authorised in the EU. Published: 31 may 2016. Available from: https://www.efsa.europa.eu/sites/default/files/consultation/160531.pdf
[12] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 5). Available from: https://www.efsa.europa.eu/sites/default/files/consultation/160524.pdf
[13] Available online: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Committee, 2012) are applied. In the case of other animal species, the default values by JECFA (2000) are used. In these cases, the dose was expressed as 'equivalent to mg/kg bw per day'.

When relevant, the dose of the test substance as a salt of tartaric acid was calculated in mg of tartaric acid on the basis of the molecular weight of the corresponding salt of tartaric acid as indicated in the Regulation (EU) No 231/2012.

Dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives was estimated combining the food consumption data available within the EFSA Comprehensive Database with the maximum permitted levels and/or reported use levels submitted to EFSA following two calls for data. The exposure was estimated according to different exposure scenarios (see Section 3.4). Uncertainties in the exposure assessment were identified and discussed.

3. Assessment

3.1. Technical data

3.1.1. Identity of the substances

L(+)-Tartaric acid (E 334)

According to Commission Regulation (EU) No 231/2012 L(+), tartaric acid (E 334) has the chemical formula $C_4H_6O_6$; it is identified and defined as:

Chemical names:	L-tartaric acid; L-2,3-dihydroxybutanedioic acid; d-α,β-dihydroxy-succinic acid.
EINECS number:	201-766-0
Molecular weight:	150.09 g/mol
Description:	colourless or translucent crystalline solid or white crystalline powder
Melting range:	168–170°C
Specific rotation:	$[\alpha]_D^{20}$ between + 11.5° and + 13.5° (20% w/v aqueous solution).

According to JECFA specifications on solubility, L(+)-tartaric acid is very soluble in water and freely soluble in ethanol (JECFA, 2006).

The corresponding CAS number is 87-69-4; the melting point is 169°C (SRC), the boiling point is 95–97°C, the pK_a Value (predicted): 3.07 ± 0.34 (SciFinder[14], software). Structural formula is presented in Figure 1.

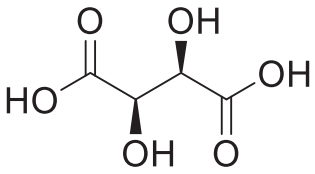

Figure 1: Structural formula of L(+) tartaric acid

Synonyms (SciFinder, software): (2R,3R)-2,3-dihydroxybutanedioic acid, butanedioic acid, 2,3-dihydroxy- [R-(R*,R*)]-; (+)-(2R,3R)-L(+)-tartaric acid; (+)-(R,R)-tartaric acid; (+)-tartaric acid; (2R,3R)-(+)- tartaric acid; (2R,3R)-2,3-Dihydroxysuccinic acid; (2R,3R)- tartaric acid; (R,R)-(+)- tartaric acid; (R,R)- tartaric acid; tartaric acid (+L).

Monosodium tartrate (E 335(i))

According to Commission Regulation (EU) No 231/2012, monosodium tartrate (E 335(i)) is identified and defined as:

Synonyms:	Monosodium salt of L(+)-tartaric acid
Chemical names:	monosodium salt of L(+)-tartaric acid; monosodium salt of L-2,3-dihydroxybutanedioic acid; monohydrated monosodium salt of L(+)-tartaric acid
Chemical formula:	$C_4H_5O_6Na{\cdot}H_2O$
Molecular weight:	194.05 g/mol
Description:	transparent colourless crystals

[14] SciFinder® the choice for chemistry researchTM.

The Panel noted that the molecular weight listed in Commission Regulation (EU) No 231/2012 is erroneous and should be corrected to '190.08 g/mol'.

The CAS Registry Number for monosodium L(+)-tartaric acid monohydrate is 6131-98-2 (SciFinder, software). No information on EC (EINECS) number. The structural formula for the anhydrous form is presented in Figure 2.

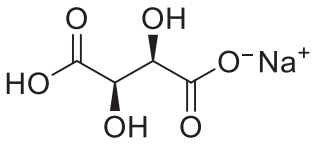

Figure 2: Structural formula of monosodium tartrate (anhydrous form)

Synonyms: sodium bitartrate monohydrate; butanedioic acid, 2,3-dihydroxy-(2R,3R)-, monosodium salt, monohydrate (1:1:1); butanedioic acid, 2,3-dihydroxy- (2R,3R)-, monosodium salt, monohydrate (9CI); sodium hydrogen (+)-tartrate monohydrate (SciFinder, software).

Disodium tartrate (E 335(ii))

According to Commission Regulation (EU) No 231/2012, disodium tartrate (E 335(ii)) is identified and defined as:

Chemical names:	disodium L-tartrate; disodium (+)-tartrate; disodium salt of (+)-2,3-dihydroxybutanedioic acid; dihydrated disodium salt of L(+)- tartaric acid
Chemical formula:	$C_4H_4O_6Na_2{\cdot}2H_2O$
Molecular weight:	230.8 g/mol
EINECS Number:	212-773-3
Description:	transparent colourless crystals
Solubility:	1 g is insoluble in 3 mL of water. Insoluble in ethanol

The Panel noted that the EINECS Number cited in Commission Regulation 231/2012 corresponds to the anhydrous form, while the authorised form is the dihydrate.

The Panel noted that in the description of solubility in water in the EU specification for disodium tartrate (E 335(ii)), the term 'insoluble' is incorrect and should be replaced by 'soluble'.

According to available information, the solubility in water for disodium L(+)-tartrate dihydrate is 290 g/L (20°C) (Sigmaldrich catalogue online[15]).

CAS Registry Number for disodium L(+)-tartaric acid dihydrate is 6106-24-7 (SciFinder, software); no EC/EINECS Number assigned to this CAS Number. The structural formula for the anhydrous form (CAS Number 868-18-8) is presented in Figure 3.

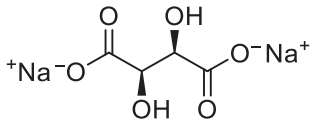

Figure 3: Structural formula of disodium tartrate (anhydrous form)

Synonyms: butanedioic acid, 2,3-dihydroxy- (2*R*, 3*R*)-, disodium salt, dihydrate (9CI); butanedioic acid, 2,3-dihydroxy-[*R*-(*R**,*R**)]-, disodium salt, dihydrate (SciFinder, software). In the JECFA specification for sodium L(+)-tartrate (INS No 335), sodium dextro-tartrate is mentioned as a synonym (JECFA, 2009).

Monopotassium tartrate (E 336 (i))

According to Commission Regulation (EU) No 231/2012, monopotassium tartrate (E 336(i)) is identified and defined as:

Synonyms:	Monobasic potassium tartrate
Chemical names:	Anhydrous monopotassium salt of L(+)-tartaric acid; Monopotassium salt of L-2,3-dihydroxybutanedioic acid
Chemical formula:	$C_4H_5O_6K$

[15] https://www.sigmaaldrich.com/catalog/product/mm/106664?lang=it&region=IT

Molecular weight:	188.17 g/mol
Description:	white crystalline or granulated powder
Melting point:	230°C

The CAS Registry Number for monopotassium L-(+)-tartaric acid is 868-14-4 (SciFinder, software). The EC Number assigned for this CAS Number is 212-769-1 (EC inventory, online); however, no indication of the stereochemistry is given in the EC inventory.

According to Kherici et al. (2015), the solubility of monopotassium tartrate in water is 5.78 g/L in 20°C. The structural formula is presented in Figure 4.

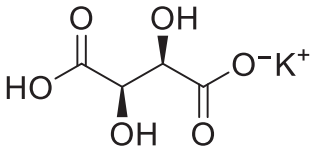

Figure 4: Structural formula of monopotassium tartrate

Synonyms: butanedioic acid, 2,3-dihydroxy-(2R,3R)-, monopotassium salt (9CI); L(+)-tartaric acid, monopotassium salt (8CI); potassium hydrogen L(+)-tartrate (SciFinder, software).

Dipotassium tartrate (E 336(ii))

According to Commission Regulation (EU) No 231/2012, dipotassium tartrate (E 336(ii)) is identified and defined as:

Synonyms:	dibasic potassium tartrate
Chemical names:	dipotassium salt of L-2,3-dihydroxybutanedioic acid; Dipotassium salt with half a molecule of water of L(+)-tartaric acid
EINECS Number:	213-067-8
Chemical formula:	$C_4H_4O_6K_2 \cdot ½H_2O$
Molecular weight:	235.2 g/mol
Description:	white crystalline or granulated powder

The Panel noted that the EINECS Number cited in Commission Regulation (EU) No 231/2012 corresponds to the anhydrous form, while the authorised form is the hemihydrate.

The CAS Registry Number for dipotassium L(+)-tartaric acid hemihydrate is 6100-19-2. The structural formula for the anhydrous form is presented in Figure 5.

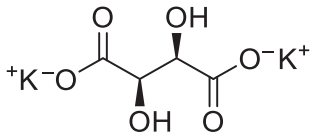

Figure 5: Structural formula of dipotassium tartrate (anhydrous form)

Synonyms (SciFinder, software): butanedioic acid, 2,3-dihydroxy-(2*R*,3*R*)-, dipotassium salt, hydrate (2:1); dipotassium tartrate hemihydrate.

Potassium sodium tartrate (E 337)

According to Commission Regulation (EU) No 231/2012, potassium sodium tartrate (E 337) is identified and defined as:

Synonyms:	potassium sodium L(+)-tartrate; Rochelle salt; Seignette salt
Chemical names:	potassium sodium salt of L-2,3-dihydroxybutanedioic acid; potassium sodium L(+)-tartrate
EINECS Number:	206-156-8
Chemical formula:	$C_4H_4O_6KNa \cdot 4H_2O$
Molecular weight:	282.23 g/mol
Description:	colourless crystals or white crystalline powder
Solubility:	1 g in 1 mL water; insoluble in ethanol
Melting point range:	70–80°C

The Panel noted that the EINECS Number cited in Commission Regulation (EU) No 231/2012 corresponds to the anhydrous form, while the tetrahydrate is the authorised form. The CAS Registry number for potassium sodium L(+)-tartrate tetrahydrate is 6381-59-5 (SciFinder, software). The structural formula for the anhydrous form is presented in Figure 6.

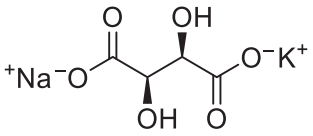

Figure 6: Structural formula of potassium sodium tartrate (anhydrous form)

Synonyms: butanedioic acid, 2,3-dihydroxy- (2*R*,3*R*-), monopotassium monosodium salt, tetrahydrate (9CI); tartaric acid, monopotassium monosodium salt, tetrahydrate, L(+)-(8CI) (SciFinder, software).

The Panel also noted that the chemical names and the synonyms listed in Commission Regulation (EU) No 231/2012 relate to the anhydrous form and may lead to misinterpretations of the authorised forms of the food additive.

Calcium tartrate (E 354)

According to Commission Regulation (EU) No 231/2012, calcium tartrate (E 354) is identified and defined as:

Synonym:	L-calcium tartrate
Chemical name:	calcium L(+)-2,3-dihydroxybutanedioate di-hydrate
Chemical formula:	$C_4H_4CaO_6 \cdot 2H_2O$
Molecular weight:	224.18 g/mol
Description:	fine crystalline powder with a white or off-white colour
Solubility:	slightly soluble in water, sparingly soluble in ethanol, slightly soluble in diethyl ether and soluble in acids
Specific rotation:	$[\alpha]_D^{20}$ +7.0° to + 7.4° (0.1% in a 1N HCl solution)

No information on the CAS Registry Number and the EC (EINECS) Number are available for calcium L(+)-tartrate dihydrate. The structural formula for the anhydrous form is presented in Figure 7.

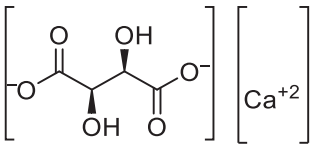

Figure 7: Structural formula of calcium tartrate (anhydrous form)

3.1.2. Specifications

Commission Regulation (EU) No 231/2012 on specifications for food additives lays down specifications for L(+)-tartaric acid (E 334), monosodium tartrate (E 335(i)), disodium tartrate (E 335 (ii)), monopotassium tartrate (E 336(i)), dipotassium tartrate (E 336(ii)), potassium sodium tartrate (E 337) and calcium tartrate (E 354) used as food additives (see Tables 1–7). JECFA has prepared specifications for L(+)-tartaric acid, disodium L(+)-tartrate and potassium sodium L(+)-tartrate (JECFA, 2006, 2009).

Table 1: Specifications for L(+)-tartaric acid (E 334) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Assay	Content not less than 99.5% on the anhydrous basis	Not less than 99.5% on the dried basis
Description	Colourless or translucent crystalline solid or white crystalline powder	Colourless or translucent crystals, or white, fine to granular, crystalline powder; odourless

	Commission Regulation (EU) No 231/2012	JECFA (2006)
Identification		
Melting range	Between 168°C and 170°C	–
Test for tartrate	Passes test	Passes test
Specific rotation	$[\alpha]_D^{20}$ between + 11.5° and + 13.5° (20% w/v aqueous solution)	[alfa] 20, D: Between + 11.5° and + 13.5°. A 1 in 10 solution is dextrorotatory
Solubility	–	Very soluble in water; freely soluble in ethanol
Purity		
Loss on drying	Not more than 0.5% (over P_2O_5, 3 h)	Not more than 0.5% (over P_2O_5, 3 h)
Sulfated ash	Not more than 1,000 mg/kg (after calcination at 800 ± 25°C)	Not more than 0.1%
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Oxalates	Not more than 100 mg/kg expressed as oxalic acid, after drying	[Test]
Sulfates	–	Not more than 0.05%

Table 2: Specifications for monosodium tartrate (E 335 (i)) according to Commission Regulation (EU) No 231/2012

	Commission Regulation (EU) 231/2012
Assay	Content not less than 99% on the anhydrous basis
Description	Transparent colourless crystals
Identification	
Test for tartrate	Passes test
Test for sodium	Passes test
Purity	
Loss on drying	Not more than 10.0% (105°C, 4 h)
Oxalates	Not more than 100 mg/kg (expressed as oxalic acid, after drying)
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg

Table 3: Specifications for disodium tartrate (E 335 (ii)) according to Commission Regulation (EU) No 231/2012 and JECFA (JECFA, 2009)

	Commission Regulation 231/2012	JECFA (2009)
Assay	Content not less than 99% on the anhydrous basis	Not less than 99% after drying
Description	Transparent, colourless crystals	Transparent, colourless and odourless crystals
Identification		
Test for tartrate	Passes test	Passes test
Test for sodium	Passes test	Passes test
Solubility	1 g is insoluble in 3 mL of water. Insoluble in ethanol	1 g is soluble in 3 mL of water; insoluble to ethanol
pH	Between 7.0 and 7.5 (1% aqueous solution)	–
Purity		
Loss on drying	Not more than 17.0% (105°C, 4 h)	Not more than 17.0% and not less than 14% (105°C, 3 h)
Oxalates	Not more than 100 mg/kg (expressed as oxalic acid, after drying)	(a)
Arsenic	Not more than 3 mg/kg	–

	Commission Regulation 231/2012	JECFA (2009)
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
pH	–	7.0–7.5 (1 in 10 solution)

(a): The Panel noted that JECFA describes an analytical test for oxalates.

Table 4: Specifications for monopotassium tartrate (E 336 (i)) according to Commission Regulation (EU) No 231/2012

	Commission Regulation 231/2012
Assay	Content not less than 98% on the anhydrous basis
Description	White crystalline or granulated powder
Identification	
Test for tartrate	Passes test
Test for potassium	Passes test
Melting point	230°C
pH	3.4 (1% aqueous solution)
Purity	
Loss on drying	Not more than 1.0% (105°C, 4 h)
Oxalates	Not more than 100 mg/kg (expressed as oxalic acid, after drying)
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg

Table 5: Specifications for dipotassium tartrate (E 336 (ii)) according to Commission Regulation (EU) No 231/2012

	Commission Regulation 231/2012
Assay	Content not less than 99% on the anhydrous basis
Description	White crystalline or granulated powder
Identification	
Test for tartrate	Passes test
Test for potassium	Passes test
pH	Between 7.0 and 9.0 (1% aqueous solution)
Purity	
Loss on drying	Not more than 4.0% (105°C, 4 h)
Oxalates	Not more than 100 mg/kg (expressed as oxalic acid, after drying)
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg

Table 6: Specifications for potassium sodium tartrate (E 337) according to Commission Regulation (EU) No 231/2012 and JECFA (JECFA, 2006)

	Commission Regulation 231/2012	JECFA (2006)
Assay	Content not less than 99% on the anhydrous basis	Not less than 99% after drying
Description	Colourless crystals or white crystalline powder	Colourless crystals, or as white, crystalline powder
Identification		
Test for tartrate	Passes test	Passes test
Test for potassium	Passes test	Passes test

	Commission Regulation 231/2012	JECFA (2006)
Test for sodium	Passes test	Passes test
Solubility	1 g is soluble in 1 mL of water, insoluble in ethanol	One gram is soluble in 1 mL of water; insoluble in ethanol
Melting range	70–80°C	–
pH	Between 6.5 and 8.5 (1% aqueous solution)	6.5–7.5 (1 in 10 solution)
Purity		
Loss on drying	Not more than 26.0% and not less than 21.0% (105°C, 3 h)	Not more than 26.0% and not less than 21.0% (105°C, 3 h)
Oxalates	Not more than 100 mg/kg (expressed as oxalic acid, after drying)	(a)
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–

(a): The Panel noted that JECFA describes an analytical test for oxalates.

Table 7: Specifications for calcium tartrate (E 354) according to Commission Regulation (EU) No 231/2012

	Commission Regulation 231/2012
Assay	Content not less than 98.0%
Description	Fine crystalline powder with a white or off-white colour
Identification	
Solubility	Slightly soluble in water. Solubility approximately 0.01 g/100 mL water (20°C). Sparingly soluble in ethanol. Slightly soluble in diethyl ether. Soluble in acids
Specific rotation	$[\alpha]_D^{20}$ + 7.0° to + 7.4° (0.1% in a 1N HCl solution)
pH	Between 6.0 and 9.0 (5% slurry)
Purity	
Sulphates	Not more than 1 g/kg (as H_2SO_4)
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg

The Panel noted that provisions of Appendix 1 'Tartaric acid ((L(+))-) and derived products' of Commission Regulation (EC) No 934/2019 only apply to the L(+)tartaric acid used in FC 14.2.2. The provisions of the above-mentioned Appendix 1 for tartaric acid do not have any application for the food additive L(+)-tartaric acid (E 334) in accordance with Regulation (EC) No 1333/2008 in food categories other than FC 14.2.2., which needs to comply with the specifications in Commission Regulation (EU) No 231/2012.

The Panel noted that, according to the EU specifications for monosodium tartrate (E 335 (i)), disodium tartrate (E 335 (ii)), monopotassium tartrate (E 336 (i)), dipotassium tartrate (E 336 (ii)), potassium sodium tartrate (E 337) and calcium tartrate (E 354), impurities of the toxic elements arsenic, lead and mercury are accepted up to concentrations of 3, 2 and 1 mg/kg, respectively. Moreover, according to the European Commission specifications for L(+)-tartaric acid (E 334), impurities of the toxic elements, lead and mercury are accepted up to concentrations of 2 and 1 mg/kg, respectively. Contamination at those levels could have a significant impact on the exposure, which are already close to the health-based guidance values or benchmark doses (lower confidence limits) established by EFSA (EFSA CONTAM Panel, 2009, 2010, 2012a,b, 2014).

The Panel noted that there is a provision for specific rotation only for L(+)-tartaric acid (E 334) and calcium tartrate (E 354). This provision is missing in the EU specifications for tartrates (E 335-337) and it should be introduced in order to ensure the exclusive use of the authorised L(+) stereoisomer.

3.1.3. Manufacturing process

L(+)-Tartaric acid

Information provided by industry

As a by-product of wine production

According to information provided by industry (NATEL, 2017 (Documentation provided to EFSA No. 9)), L(+) tartaric acid is produced from tartar, lees of wine and/or grape pomace. Usually, tartaric acid is present in these products as monopotassium tartrate (e.g. 80–90% in tartar) and, to a lesser extent, calcium tartrate.

From the workflow provided by industry (NATEL, 2017 (Documentation provided to EFSA No. 9)), tartar, lees and grape marc are neutralised by calcium hydroxide or calcium carbonate producing calcium tartrate after concentration and centrifugation. Calcium tartrate is further treated with sulfuric acid in a decomposing tank to produce tartaric acid that is purified by concentration and crystallisation. Similar information is available from the literature and patents (Dabul et al., 1963; Kassaian, 2012).

From chemical/microbiological production

L(+)-Tartaric acid is manufactured from maleic anhydride that is converted to disodium cis-epoxysuccinate solution (no detailed information on this step is provided by industry; catalysts contain alkali metal salts of tungstic acid and molybdic acid, such as sodium tungstate dihydrate and sodium molybdate dihydrate can be used for this reaction) (Documentation provided to EFSA No. 7).

Disodium cis-epoxysuccinate is converted to disodium L(+)-tartaric acid by bioconversion using cis-epoxysuccinate hydrolase produced by an immobilised microorganism. Interested parties have provided detailed information on the characterisation of two microorganisms declared to be used in this step for the manufacturing of L(+)-tartaric acid. Disodium L(+)-tartaric acid is transformed to calcium tartrate by treatment with a calcium salt. Calcium tartrate is converted to L(+)-tartaric acid by a procedure as described above, with the addition of a further step where DL-tartaric acid is removed by crystallisation from the crude L(+)-tartaric acid solution (Documentation provided to EFSA No. 7).

Information on maleic anhydride as a raw material

Maleic anhydride is the starting material converted enzymatically to L(+)-tartaric acid. Butane is partially oxidised to maleic anhydride in the presence of vanadyl-phosphate as catalyst. In the manufacturing process, azeotropic distillation is carried out at atmospheric pressure using xylene as dehydrated agent (Documentation provided to EFSA No. 7).

The Panel considered that the presence of heavy metals (such as vanadium, molybdenum and tungsten) in samples of L(+)-tartaric acid (Documentation provided to EFSA No. 8) can be due to the use of catalysts in the conversion of butane to maleic anhydride and maleic anhydride to disodium cis-epoxysuccinate solution. Therefore, maximum limits for heavy metals resulting from the use of any catalyst that could be present in L(+)-tartaric acid due to its manufacturing process should be included in the EU specifications for this food additive.

Rhodococcus sp strain USA-AN012 (Documentation provided to EFSA No. 6 and 7)

The L(+)-tartaric acid is obtained by biocatalysis using immobilised cells of the bacteria *Rhodococcus sp* strain USA-AN012. Phylogenetic analysis of the 16S rRNA gene situates this strain as probably belonging to *R. aetherovorans* (Gürtler et al., 2004; Frascari et al., 2006). *R. aetherovorans* is a Gram-positive soil bacterium which has not been associated to human infections. The strain is not genetically modified. No cytotoxicity was found in supernatants of the strain *Rhodococcus sp* strain USA-AN012 when tested on CHO-K1 (Chinese Hamster Ovary) cells.[16] The strain was tested for susceptibility to antimicrobials according to the EFSA Guidance (EFSA FEEDAP Panel, 2018) and resulted resistant to gentamycin compared with the reference values of minimum inhibitory concentration (MIC) provided for 'other gram-positives'.[17] The nature of the resistance remains unknown.

No viable microbial cells were found in three samples of L(+)-tartaric acid (1.3 g each, tested in triplicate), by plating on non-selective solid medium and incubating at 37°C for 3 days. Likewise, no DNA corresponding to a Polymerase Chain Reaction (PCR) based amplification of a region of the RbpA

[16] Appendix C.
[17] Appendix D.

gene from *Rhodococcus sp.* USA-AN012 was found when cells of this strain were suspended in 700 g/L of L(+)-L-tartaric acid and heated at 65°C for 8 h (conditions which mimic the crystallisation and concentration steps of the L(+)-tartaric acid). This indicates that the manufacturing conditions of L(+)-tartaric acid are sufficient to remove the production strain and to degrade its DNA, and therefore, the Panel considered the product to be free from the *Rhodococcus sp.* USA-AN012 and its DNA.

Rhodococcus ruber strain CM001 (Documentation provided to EFSA No. 3)

No information on the general manufacturing process of L(+)-tartaric acid using this microorganism was provided. The industry mentioned maleic anhydride as raw material; thus, the Panel assumed that they use a similar procedure as described above using *Rhodococcus sp* strain USA-AN012.

The L(+) tartaric acid is obtained by biocatalysis using immobilised cells of the bacteria *Rhodococcus ruber* strain CM001. The strain was identified as *R. ruber* by phylogenetic analysis of the 16S rRNA gene. *R. ruber* is a gram-positive soil bacterium which has not been associated with human infections. The strain is not genetically modified. *R. ruber* CM001 was tested for susceptibility to antimicrobials according to the EFSA Guidance (EFSA FEEDAP Panel, 2018) and resulted sensitive to all antimicrobials requested for 'other gram-positives'.

The Panel considered that the manufacturing process of L(+)-tartaric acid from chemical/microbiological production may result in impurities different from those that may be present in L(+)-tartaric acid as a by-product of wine production. The Panel, therefore, considered that separate specifications would be needed for L(+)-tartaric acid from chemical/microbiological production using *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012.

The Panel noted that in the peer-reviewed literature the manufacturing process of L(+)-tartaric acid using other microorganisms for the bioconversion are described (Tsurumi and Fujioka, 1978; Kamatani et al., 1987; Mikova et al., 1998; Rosenberg et al., 1999; Bucko et al., 2004; Willaert and De Vuyst, 2006; Cheng et al., 2014; Bao et al., 2015; E. Hoffmann et al., 2016; Hronska, 2017; Wang et al., 2017). However, no interested parties have indicated their use and, therefore, they have not been assessed by the Panel.

Monopotassium tartrate

From the workflow provided by industry (NATEL, 2017 (Documentation provided to EFSA No. 9)), monopotassium tartrate is produced by neutralisation of crude tartaric acid with potassium carbonate and it is purified by centrifugation and then dried.

According to Blair and DeFraties (2000), monopotassium tartrate can be produced:

- from argols (which are the crystalline crusts that form in the vats in the secondary fermentation period) after a treatment with sodium carbonate;
- from a solution of L(+) tartaric acid with the addition of a liquor of potassium sodium tartrate (also cited by Kassaian (2012));
- from of a water suspension of the argols after the saturation with sulfur dioxide.

The precipitated potassium tartrate is recovered by centrifugation, washed, dried and ground. The substance so obtained is 99.9% pure (Blair and DeFraties (2000) and Kassaian (2012)).

Kherisi et al. (2015) described a process for manufacturing monopotassium tartrate from wine tartar (lees) followed by purification.

Potassium sodium tartrate

From the workflow provided by industry (NATEL, 2017 (Documentation provided to EFSA No. 9)), tartar, lees and grape marc are neutralised by sodium hydroxide or sodium carbonate. Sodium potassium tartrate is purified by filtration, centrifugation and dried.

According to Kassaian (2012), potassium sodium tartrate is manufactured using monopotassium tartrate with a low content (about 68%) of tartaric acid as starting material. Tartar, diluted in water, is brought to pH 8 by adding sodium carbonate or sodium hydroxide. The precipitate so obtained is decolourised with activated coal, washed, filtered, centrifuged, evaporated (at 100°C to specific gravity of 1.41), and allowed to crystallise on slow cooling to produce potassium sodium tartrate.

Calcium tartrate

As mentioned above, calcium tartrate is the starting material for the production of tartaric acid (NATEL, 2017 (Documentation provided to EFSA No. 9)).

A short description of the production of calcium tartrate is given in the papers by Audinos and Paci (1992) and Blair and DeFraties (2000). In the process, potassium bitartrate contained in the lees of wine reacted with calcium hydroxide and calcium sulfate according to the following reaction,

$2\ KHC_4H_4O_6 + Ca(OH)_2 + CaSO_4 \rightarrow 2\ CaC_4H_4O_6 + K_2SO_4 + 2H_2O$

Calcium tartrate is insoluble and precipitates.

No information on the manufacturing process of disodium tartrate and dipotassium tartrate was available to the Panel.

3.1.4. Methods of analysis in food

According to the International Organisation of Vine and Wine (OIV), which is the recommended basis for analytical methods in wines (Regulation 1308/2013), the reference method (OIV-MA-AS313-05A) for the determination of L(+)-tartaric acid in wine consists of a precipitation step followed by gravimetric measurement (OIV, online).

A range of chromatographic techniques for the analysis of L(+)-tartaric acid and its sodium, potassium and calcium salts in food have been described in the published literature. These include:

High-Performance Liquid Chromatography (HPLC)

There are a number of publications with various chromatographic conditions, which are all based on Reversed Phase HPLC separation: 1. Radin et al. (1994) with UV-detection at 210 nm in wine, partially validated; 2. Scherer et al. (2012) used UV-detection at 210 nm in fruits and juices with a limit of detection (LOD) of 0.72 mg/L; 3. Paredes et al. (2006) used three different detectors coupled with the HPLC and demonstrated three different LODs 3.1 mg/L (ICP-AES for carbon), 1.2 mg/L (Refractive Index) and 17 mg/L (UV-detection) in juices, wines and non-alcoholic drinks; 4. Rhaghav et al. (2012), used a UV detection at 214 nm to measure tartaric acid in juices, where no information on the validation of the method was available; 5. Mortera et al. (2017) analysed tartaric acid by using a diode-array (DAD) detector and measured it at 210 nm together with an identification of the peak; 6. Park et al. (2017) used UV detection at 210 nm and analysed wine and beer with no further information on the validation of the method; 7. Restuccia et al. (2017) used an Electronic Light Scattering Detector to analyse, among others organic acids, tartaric acid in juices with a LOD of 3.18 mg/L.

Ion chromatography

Kupina et al. (1991) analysed grape juice and wines, where recovery rates were estimated but no further information on the validation of the method is reported. Castro et al. (2002) compared the results of the analysis of tartaric acid in sherry wine vinegar via Ion Exclusion Chromatography with those obtained via Capillary Electrophoresis (CE) and concluded that both methods are applicable for this purpose. Jin et al. (2010) presented a validated method of Ion Chromatography combined with ElectroSpray Ionisation and MS detection reaching a Limit of Quantification (LOQ) of 0.05 mg/L in wines and beverages.

Capillary electrophoresis (CE)

Kandl and Kupina (1999) used CE equipped with a DAD detector to analyse tartaric acid in wines and fruit juices, where the partial validation of the method was demonstrated and the results were compared with the ones obtained via Ion Chromatography. Karovicova et al. (1990) used CE to analyse tartaric acid in red wines but no information on the validation of the method was available. Treilhou et al. (2001) presented a CE analytical method with indirect UV detection for wine and beverages, with a LOQ of 0.28 mg/L. Kodoma et al. (2001) demonstrated the analytical separation and measurement of D(-) and L(+) tartaric acid via CE equipped with UV detector in various food items (e.g. sake, candies, grape juice and red wine). Vickers et al. (2007) developed a method to separate and detect the two chiral isomers of tartrates in spiked samples matrices (e.g. cocoa, jam, lemonade, sugar syrup) with a LOD of 10 mg/L, based on the calibration curve.

Capillary zone electrophoresis (CZE) coupled to ESI/QTOF-MS has been reported as a method for quantitative determination of tartaric acid, together with other five organic acid, in red wine (Ivanova-Petropulos et al., 2018). The validation parameters, including linearity of concentration curve, LOQ (0.038 mM, equivalent to 5.7 mg/L), recovery, repeatability and reproducibility, were determined for each acid.

Other methodologies

Chine et al. (1994) demonstrated that isotachophoresis can be applied for the analysis of tartaric acid in juices and soft drinks. The method has been only partially validated. Fourier Transform IR (FTIR) analysis has been used by Le Thahn et al. (2000) to estimate the tartaric acid content in soft drinks after a solid phase extraction step, without any information on the validation of the method. Ayora-Cañada et al. (2000) also used flow injection analysis (FIA)-FTIR with a pH modulation for the analysis of tartaric acid in soft drinks.

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

The stability of the food additive L(+) tartaric acid (E 334) over a period of 3 years as a packaged food additive regarding its compliance with the purity criteria (appearance and physical/chemical parameters) under the recommended storage temperature has been reported without change in the assay (%) or specific rotation (CMBEC, 2017 (Documentation provided to EFSA No. 2)).

Tartaric acid and its salts (potassium bitartrate and calcium tartrate) are naturally present in wine. The Panel noted that in wine, during alcoholic fermentation and during storage, potassium bitartrate and/or calcium tartrate precipitate or crystallise. The stability (solubility) of the tartrates depends on the alcohol content, pH and temperature as well as interactive effects of the solution matrix with the cations (K and Ca) and the bitartrate/tartrate anions (Zoecklein et al., 1990; Gerbaud et al., 2010). According to Marchal and Jeandet (2009), free tartaric acid can be complexed with proteins and polyphenols in certain wines, thus inhibiting potassium bitartrate crystal formation.

The Panel noted that tartaric acid has been reported to decompose at temperatures above 180°C (Chattaway and Ray, 1921); however, no data were identified on the fate of tartaric acid during food processing such as baking.

In view of the de-acidification of wines, Gao and Fleet (1995) examined the ability of high-density cell suspensions of several yeast species to degrade L(+)-tartaric acids and L(+)-malic in view of the de-acidification of wines. Data show that weak or no degradation of tartaric acid occurred.

3.2. Authorised uses and use levels

Maximum levels of tartaric acid and tartrates (E 334-337; E 354) have been defined in Annex II to Regulation (EC) No 1333/2008[18] on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, tartaric acid and tartrates (E 334-337 and E 354) are authorised in the EU at *quantum satis* (QS) in almost all food categories (FCs) listed in Table 8. In FCs 13.1.3 and 13.1.5.2, tartaric acid and tartrates (E 334-337 and E 354) are permitted at an MPL of 5,000 mg/kg. Tartaric acid and tartrates (E 334-337 and E 354) are included in the Group I of food additives. Table 8 summarises the food categories that are permitted to contain tartaric acid and tartrates (E 334-337 and E 354) and the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.

Table 8: MPLs of tartaric acid and tartrates (E 334-337 and E 354) in foods according to the Annex II to Regulation (EC) No 1333/2008

Food category number	Food category name	E-number/ Group	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
01.3	Unflavoured fermented milk products, heat treated after fermentation	Group I		*quantum satis*
01.4	Flavoured fermented milk products including heat-treated products	Group I		*quantum satis*
01.6.3	Other creams	Group I		*quantum satis*
01.7.1	Unripened cheese excluding products falling in category 16	Group I	Except mozzarella	*quantum satis*
01.7.5	Processed cheese	Group I		*quantum satis*

[18] 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.

Food category number	Food category name	E-number/ Group	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
01.7.6	Cheese products (excluding products falling in category 16)	Group I		*quantum satis*
01.8	Dairy analogues, including beverage whiteners	Group I		*quantum satis*
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Group I		*quantum satis*
02.3	Vegetable oil pan spray	Group I		*quantum satis*
03	Edible ices	Group I		*quantum satis*
04.2.1	Dried fruit and vegetables	Group I		*quantum satis*
04.2.2	Fruit and vegetables in vinegar, oil or brine	Group I		*quantum satis*
04.2.3	Canned or bottled fruit and vegetables	E 334 / E 335 / E 336 / E 337		*quantum satis*
04.2.4.1	Fruit and vegetable preparations excluding compote	Group I		*quantum satis*
04.2.5.1	Extra jam and extra jelly as defined by Directive 2001/113/EC	E 334 / E 335		*quantum satis*
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut purèe as defined by Directive 2001/113/EC	E 334 / E 335		*quantum satis*
04.2.5.3	Other similar fruit or vegetable spreads	E 334 / E 335		*quantum satis*
04.2.5.4	Nut butters and nut spreads	Group I		*quantum satis*
04.2.6	Processed potato products	Group I		*quantum satis*
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	Group I	Only energy-reduced or with no added sugar	*quantum satis*
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	E 334		5,000
05.2	Other confectionery including breath freshening microsweets	Group I		*quantum satis*
05.3	Chewing gum	Group I		*quantum satis*
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Group I		*quantum satis*
06.2.2	Starches	Group I		*quantum satis*
06.3	Breakfast cereals	Group I		*quantum satis*
06.4.1	Fresh pasta	E 334		*quantum satis*
06.4.2	Dry pasta	Group I	Only gluten free and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	*quantum satis*
06.4.3	Fresh pre-cooked pasta	E 334		*quantum satis*
06.4.4	Potato Gnocchi	Group I	Except fresh refrigerated potato gnocchi	*quantum satis*
06.4.4	Potato Gnocchi	E 334	Only fresh refrigerated potato gnocchi	*quantum satis*

Food category number	Food category name	E-number/ Group	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
06.4.5	Fillings of stuffed pasta (ravioli and similar)	Group I		*quantum satis*
06.5	Noodles	Group I		*quantum satis*
06.6	Batters	Group I		*quantum satis*
06.7	Pre-cooked or processed cereals	Group I		*quantum satis*
07.1	Bread and rolls	Group I	Except products in 7.1.1 and 7.1.2	*quantum satis*
07.2	Fine bakery wares	Group I		*quantum satis*
08.3.1	Non-heat-treated meat products	Group I		*quantum satis*
08.3.2	Heat-treated meat products	Group I	Except *foie gras, foie gras entier, blocs de foie gras, Libamàj, libamàj egèszben, libamàj tömbben*	*quantum satis*
08.3.3	Casings and coatings and decorations for meat	Group I		*quantum satis*
09.2	Processed fish and fishery products including molluscs and crustaceans	Group I		*quantum satis*
09.3	Fish roe	Group I	Only processed fish roe	*quantum satis*
10.2	Processed eggs and egg products	Group I		*quantum satis*
11.2	Other sugars and syrups	Group I		*quantum satis*
11.4.2	Table-Top sweeteners in powder form	E 336		*quantum satis*
11.4.3	Table-top sweeteners in tablets	E 334/E 335/ E 336		*quantum satis*
12.1.2	Salt substitutes	Group I		*quantum satis*
12.2.2	Seasonings and condiments	Group I		*quantum satis*
12.3	Vinegars and diluted acetic acid (diluted with water to 4–30% by volume)	Group I		*quantum satis*
12.4	Mustard	Group I		*quantum satis*
12.5	Soups and broths	Group I		*quantum satis*
12.6	Sauces	Group I		*quantum satis*
12.7	Salads and savoury-based sandwich spreads	Group I		*quantum satis*
12.8	Yeast and yeast products	Group I		*quantum satis*
12.9	Protein products, excluding products covered in category 1.8	Group I		*quantum satis*
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/ 125/EC2006/125/EC	E 334/E 335/E 336	only biscuits and rusks and baby foods	5,000[(a)]
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC2006/125/EC	E 354	only biscuits and rusks	5,000[(a)]
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 334/E 335/ E 336	Only biscuits and rusks and baby foods	5,000[(a)]
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 354	Only biscuits and rusks	5,000[(a)]

Food category number	Food category name	E-number/ Group	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	Group I		*quantum satis*
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	Group I		*quantum satis*
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Group I	Including dry pasta	*quantum satis*
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Group I	Only vegetable juices	*quantum satis*
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	E 336	Only grape juice	*quantum satis*
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	Group I	Only vegetable nectars	*quantum satis*
14.1.4	Flavoured drinks	Group I		*quantum satis*
14.1.5.2	Other	Group I	Excluding unflavoured leaf tea; including flavoured instant coffee	*quantum satis*
14.2.3	Cider and perry	Group I		*quantum satis*
14.2.4	Fruit wine and made wine	Group I		*quantum satis*
14.2.5	Mead	Group I		*quantum satis*
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Group I	Except whisky or whiskey	*quantum satis*
14.2.7.1	Aromatised wines	Group I		*quantum satis*
14.2.7.2	Aromatised wine-based drinks	Group I		*quantum satis*
14.2.7.3	Aromatised wine-product cocktails	Group I		*quantum satis*
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol	Group I		*quantum satis*
15.1	Potato-, cereal-, flour- or starch-based snacks	Group I		*quantum satis*
15.2	Processed nuts	Group I		*quantum satis*
16	Desserts excluding products covered in categories 1, 3 and 4	Group I		*quantum satis*
17.1	Food supplements supplied in a solid form, excluding food supplements for infants and young children	Group I		*quantum satis*
17.2	Food supplements supplied in a liquid form, excluding food supplements for infants and young children	Group I		*quantum satis*
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	Group I		*quantum satis*

MPL: maximum permitted level.
(a): As a residue (Regulation (EC) No 1333/2008), with the intention to have not more than 5,000 mg/kg as a residue for all tartrates.

The Panel considered that 'residue' as mentioned in footnote (Table 8) corresponds to the total amount of tartrate in the food resulting from the added tartaric acid and tartrates (E 334-337 and E 354) as food additives and the presence of tartaric acid from natural origin.

The Panel noted that the restriction applicable to FC 13.1.5.2 'Only L(+)-form; only biscuits and rusks and baby foods' excludes the use of E 334, E 335, E 336 and E 354 as food additives in food for infants under the age of 16 weeks.

In addition to the authorised uses in accordance with Annex II, Part E of Regulation (EC) No 1333/2008 (Table 8), (L)-tartaric acid (E 334) is authorised to be used as a food additive (acidity regulator) in wine according to Regulation (EC) No 934/2019. Limits for acidification or de-acidification using any of the oenological compounds listed as acidity regulators in Regulation (EC) No 934/2019 are established in Regulation (EU) No 1308/2013.[19]

Tartaric acid and tartrates (E 334-337 and E 354) are also authorised according to Annex III of Regulation (EC) No 1333/2008.

According to Annex III, Part 2 of Regulation (EC) No 1333/2008, tartaric acid and tartrates (E 334-337 and E 354) are authorised as food additives in food additives having a function other than a carrier with a maximum level in the products (beverages or not) at QS.

According to Annex III, Part 3 of Regulation (EC) No 1333/2008, tartaric acid and tartrates (E 334-337 and E 354) are authorised as food additives in food enzymes with a maximum level in the products (beverages or not) at QS.

According to Annex III, Part 4 of Regulation (EC) No 1333/2008, tartaric acid and tartrates (E 334-337 and E 354) are authorised as food additives including carriers in all food flavourings with a maximum level in the products (beverages or not) at QS.

In addition, according to Annex III, Part 5, Section A of Regulation (EC) No 1333/2008, tartaric acid and tartrates (E 334-337 and E 354) are authorised in all nutrients with a maximum level in the nutrient at QS.

3.3. Exposure data

3.3.1. Reported use levels or data on analytical levels of tartaric acid-tartrates (E 334-337, 354)

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives for which no MPL is set and which are authorised according to *QS*.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued two public calls[20,21] for occurrence data (use level and/or concentration data) on tartaric acid and tartrates (E 334-337 and E 354). In response to these calls, both types of data on tartaric acid and tartrates (E 334-337 and E 354) were submitted to EFSA by industry and Member States, respectively.

Summarised data on reported use levels in foods provided by industry

Industry provided EFSA with data on use levels (n = 83) of tartaric acid and tartrates (E 334-337 and E 354) in foods for 17 out of the 81 food categories in which these food additives are authorised according to Regulation (EC) No 1333/2008. Furthermore, use levels of tartaric acid (E 334) and monopotassium tartrate (E 336) for sparkling wines and vermouth were provided by CEEV (Comité Européen des Entreprises Vins), as according to Commission Regulation (EC) No 934/2019.

Updated information on the actual use levels of tartaric acid and tartrates (E 334-337 and E 354) in foods was made available to EFSA by the Association of the European Self-Medication Industry (AESGP), European Dairy Association (EDA), European Snacks Association/SNACMA (ESA), Food Drink Europe (FDE), Food Supplements Europe (FSE), HiPP-Werk Georg Hipp OHG (HIPP), IMACE, International Chewing Gum Association (ICGA), ROSHEN and Specialised Nutrition Europe (SNE).

[19] Regulation (EU) No 1308/2013 of the European Parliament and of the Council of 17 December 2013 establishing a common organisation of the markets in agricultural products and repealing Council Regulations (EEC) No 922/72, (EEC) No 234/79, (EC) No 1037/2001 and (EC) No 1234/2007. OJ L 347, 20.12.2013, p. 671–854.

[20] http://www.efsa.europa.eu/sites/default/files/consultation/ans15062010%2C0.pdf

[21] http://www.efsa.europa.eu/sites/default/files/consultation/160524.pdf

Industry reported 67 levels for E 334, 1 for E 335, 13 for E 336 and 2 for E 337. No use levels were reported for E 354. The Panel noted that 14 use levels referred to niche products. These levels are only considered if no other use levels are available for the food categories to which the niche products belong. In the current assessment, the 14 use levels were not included in the refined assessment. Use levels in niche products were considered in the maximum level exposure scenario, if those levels were higher than the other use levels reported within the food category.

Appendix A provides an overview of the use levels of tartaric acid and tartrates (E 334-337 and E 354) in foods as reported by industry.

Summarised data on analytical results in food submitted by Member States

In total, 1212 analytical results were reported to EFSA by one Spanish laboratory. This laboratory provided analytical data of samples obtained from four countries: Germany (n = 310), Hungary (n = 302), Spain (n = 304) and UK (n = 296). These data were mainly for snack food (FC 15.1) and flavoured drinks (FC 14.1.4). The other data were on other confectionery including breath freshening micro-sweets (FC 05.2), fruit juices (FC 14.1.2) and fruit nectars (FC 14.1.3). Foods were all sampled in 2013. All samples were analysed for sodium tartrate through a capillary (zone) electrophoresis (CE or CZE) method, performed in an accredited laboratory.

Overall, 92% of the analytical results on tartaric acid and tartrates (E 334-337 and E 354) were not quantified (< LOQ, left-censored). All analytical results were left-censored for the FCs 14.1.3 Fruit nectars as defined by Directive 2001/112/EC and vegetable juices and 14.1.4 Favoured drinks. The LOQs ranged from 50 to 2,875 mg/L (kg).

The Panel considered the analytical data unsuitable for the estimation of the exposure to tartrates that occur naturally in the diet, due to the high percentage of left-censored data, the high limit of quantification (up to 2,875 mg/kg for some samples) and because these data do not allow the estimation of the exposure from natural sources only.

Appendix B shows the analytical results of tartaric acid and tartrates (E 334-337 and E 354) in foods as reported by 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 3 million food and beverage products of which more than 1,100,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 25 out of its 28 Member Countries and Norway presented in the GNPD.[22]

For the purpose of this Scientific Opinion, Mintel's GNPD[23] was used for checking the labelling of food and beverages products and food supplements for tartaric acid and tartrates (E 334-337 and E 354) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to Mintel's GNPD, tartaric acid and tartrates (E 334-337 and E 354) were labelled on around 4,700 products between January 2014 and November 2019.

Appendix C.1 lists the percentage of the products labelled with tartaric acid and tartrates (E 334-337 and E 354) out of the total number of products per food subcategory according to Mintel's GNPD food classification. The percentages ranged from less than 0.1% in many food subcategories to 19.3% in food subcategory 'Baby Biscuits & Rusks' and 'Standard & Power Mints'. The average percentage of foods labelled with tartaric acid and tartrates (E 334-337 and E 354) was 1.0%.

The Panel noted that according to Mintel's GNPD, tartaric acid (E 334) was used most frequently (almost 60%) in food products labelled with tartaric acid and tartrates (E 334-337 and E 354). The Panel also noted that only one food product (from the subcategory 'Baking ingredients and mixes') was reported to be labelled with calcium tartrate (E 354).

Some food products for which no use levels were provided to EFSA were labelled with tartaric acid and tartrates (E 334-337 and E 354), such as desserts (frozen, chilled and shelf-stable), sweeteners and chocolate products. In total, 76 products were labelled with two different additives belonging to tartaric acid and tartrates (E 334-337 and E 354) out of the 4730 products labelled with at least one additive (Appendix C.2).

[22] Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.
[23] http://www.gnpd.com/sinatra/home/ accessed on 28/11/2019.

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 considered in this assessment.[13]

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons may not be appropriate. 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 infants, toddlers, children, adolescents, adults and the elderly were used in the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 9).

Table 9: Population groups considered for the exposure estimates of tartaric acid and tartrates (E 334-337 and E 354)

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

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

Food categories considered for the exposure assessment of tartaric acid and tartrates (E 334-337 and E 354)

The 17 food categories, for which MPL or use levels of tartaric acid and tartrates (E 334-337 and E 354) were available, 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).

For the following food categories, the restrictions/exceptions which apply to the use of tartaric acid and tartrates (E 334-337 and E 354) could not be considered, and therefore, the whole food category

was considered in the exposure assessment. This applied to two food categories and may have resulted in an overestimation of the exposure:

- 07.1 Bread and rolls; except products in 7.1.1 and 7.1.2;
- 13.1.3 Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/E and 13.1.5.2 Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC, only L(+)-form; only biscuits and rusks and baby foods.

Since a specific limit for (L)-tartaric acid is not defined in Regulation (EU) No 1308/2013, the use of (L)-tartaric acid (E 334) as a food additive in wine (FC 14.2.2) was not considered in the *maximum level exposure assessment scenario* (see Section 3.4.1).

For the FCs 17.1/17.2 Food supplements supplied in a solid or liquid form, excluding food supplements for infants and young children, the form cannot be differentiated in the EFSA Comprehensive Database, and therefore, the levels provided for the FCs 17.1 and 17.3[24] were used for the whole FC 17.

Overall, 17 food categories were included in the present exposure assessment to tartaric acid and tartrates (E 334-337 and E 354) (Appendix D).

3.4. Exposure estimates

3.4.1. Exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives

The Panel estimated the chronic dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Based on information from the Mintel's GNPD, the Panel considered that tartaric acid and tartrates (E 334-337 and E 354) are not likely to be used in combination in the same food product and, therefore, the exposure assessment of tartaric acid and tartrates (E 334-337 and E 354) was performed considering the highest reported use level for either E 334, E 335, E 336, E 337 or E 354 per food category.

Dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) was calculated by multiplying the concentrations of tartaric acid and tartrates (E 334-337 and E 354) per food category (Appendix D) 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 as 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 was not estimated.

The exposure assessment to tartaric acid and tartrates (E 334-337 and E 354) was carried out by the FAF Panel based on two different sets of concentration data: (1) MPLs combined with maximum reported use levels *(defined as the maximum level exposure assessment scenario)*; and (2) typical/maximum reported use levels (defined as the *refined exposure assessment scenario*). These two scenarios are discussed in detail below.

These scenarios do not consider the exposure to tartaric acid and tartrates (E 334-337 and E 354) from the consumption of food supplements. This exposure source was covered in an additional scenario detailed below (*food supplements consumers only scenario*).

A possible additional exposure to tartaric acid and tartrates (E 334-337 and E 354) as food additives from their use in food additives, food enzymes, food flavourings and in nutrients in accordance with Annex III to Regulation (EC) No 1333/2008 (Parts 2, 3, 4 and 5A, respectively) was not considered in any of the exposure assessment scenarios, as no data were available reflecting this use.

[24] Call for data on tartaric acid and tartrates (E 334-337 and E 354) was launched during batch 5, with deadline January 2017. At the time, food additives legislation foresaw 3 food categories of food supplements (17.1, 17.2 and 17.3) depending on their forms. In October 2018, Regulation (EC) No 1333/2008 was modified and food supplements are now subdivided into 2 food categories of 17.1 and 17.2 (as mentioned in Table 8).

Most of the reported use levels referred to tartaric acid (E 334) (n = 67 out of the 83 use levels). The other levels were for sodium tartrate (E 335), potassium tartrate (E 336) and sodium potassium tartrate (E 337). No reported use levels were submitted for calcium tartrate (E 354), which corresponds with the information from Mintel GNPD. The use levels reported for its salts were converted to tartaric acid. Therefore, the estimated exposure to tartaric acid and tartrates (E 334-337 and E 354) was expressed as mg tartaric acid/kg bw per day.

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. As tartaric acid and tartrates (E 334-337 and E 354) are authorised according to *QS* in almost all food categories (Table 8), the 'maximum level exposure assessment' scenario was based on the maximum reported use levels provided by industry and the MPL for FCs 05.1 and 13.1.3, according to the EFSA Conceptual framework (EFSA ANS Panel, 2014).

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 maximum reported use levels over a longer period of time.

Refined exposure assessment scenario

The refined exposure assessment scenario for tartaric acid and tartrates (E 334-337 and E 354) was based on use levels reported by the food industry, as the analytical data provided by the Member States were considered unsuitable for this scenario (Section 3.3.1). Appendix D summarises the levels used in this scenario. This exposure scenario can consider only food categories for which these data were available to the Panel.

Based on the available data set, the Panel calculated two refined exposure estimates based on two model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long term to tartaric acid and tartrates (E 334-337 and E 354) present at the maximum reported use level for one food category. This exposure estimate is calculated as follows:
  - Combining food consumption with the maximum of the reported use levels for the main contributing food category at the individual level.
  - Using the mean of the typical reported use levels for the remaining food categories.
- The non-brand-loyal consumer scenario: It was assumed that a consumer is exposed long term to tartaric acid and tartrates (E 334-337 and E 354) present at the mean reported use levels in food. This exposure estimate is calculated using the mean of the typical reported use levels for all food categories.

'Food supplement consumers only' scenario

Tartaric acid and tartrates (E 334-337 and E 354) are authorised in FCs 17.1 and 17.2 Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children. As exposure via food supplements may deviate largely from that via food, and the number of food supplement consumers may be low depending on populations and surveys, an additional scenario was calculated to reflect additional exposure to tartaric acid and tartrates (E 334-337 and E 354) from food supplements. This additional exposure was estimated assuming that consumers of food supplements were exposed to tartaric acid and tartrates (E 334-337 and E 354) present at the maximum reported use level in food supplements on a daily basis. For the remaining food categories (14/81 categories), the mean of the typical reported use levels was used.

As FCs 17.1 and 17.2 do not consider food supplements for infants and toddlers as defined in the legislation, exposure to tartaric acid and tartrates (E 334-337 and E 354) from food supplements was not estimated for these two population groups.

This scenario included 19 food categories (Appendix D).

Dietary exposure to tartaric acid and tartrates (E 334-337 and E 354)

Table 10 summarises the estimated exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives in six population groups (Table 9) according to the different exposure scenarios. Detailed results per population group and survey are presented in Appendix E.

Table 10: Summary of dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg tartaric acid/kg bw per day)

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Maximum level exposure assessment scenario						
• Mean	1–214	5–146	21–130	15–90	16–42	14–27
• 95th percentile	7–436	17–362	70–251	42–187	37–102	30–57
Refined estimated exposure assessment scenario						
Brand-loyal scenario						
• Mean	< 1–101	3–100	17–96	12–68	12–32	11–19
• 95th percentile	2–194	11–273	54–188	34–142	25–80	23–42
Non-brand-loyal scenario						
• Mean	< 1–91	3–65	9–56	6–39	11–21	10–15
• 95th percentile	2–174	9–130	28–107	20–74	23–45	19–27

In the *maximum level exposure assessment scenario*, mean exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives ranged from 1 mg/kg bw per day to 214 mg/kg bw per day, both in infants. The 95th percentile of exposure to tartaric acid and tartrates (E 334-337 and E 354) ranged from 7 to 436 mg/kg bw per day, again in infants.

In the *brand-loyal refined estimated exposure scenario*, mean exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives ranged from less than 1 to 101 mg/kg bw per day in infants. The high exposure to tartaric acid and tartrates (E 334-337 and E 354) ranged from 2 mg/kg bw per day in infants to 273 mg/kg bw per day in toddlers. In the *non-brand-loyal scenario*, mean exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives ranged from below 1 to 91 mg/kg bw per day in infants. The 95th percentile of exposure to tartaric acid and tartrates (E 334-337 and E 354) ranged from 2 to 174 mg/kg bw per day in infants.

In the *food supplements consumers only scenario*, mean exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives ranged from 8 mg/kg bw per day in adolescents to 99 mg/kg bw per day in children. The 95th percentile of exposure to tartaric acid and tartrates (E 334-337 and E 354) ranged from 19 mg/kg bw per day in adolescents to 93 mg/kg bw per day in children. Detailed results per population group and survey for the *food supplements consumers only scenario* are presented in Appendix G.

Tartaric acid and tartrates (E 334-337 and E 354) are used as 'acidity regulator' and are therefore not expected to change the organoleptic properties of the final food at the concentration used as a food additive. For this reason, the Panel considered the *non-brand-loyal scenario* covering the general population as the most appropriate scenario for risk characterisation.

Main food categories contributing to exposure to tartaric acid and tartrates (E 334-337 and E 354)

FC 07.1 Bread and rolls was the major contributor to the mean exposure in all scenarios and population groups. Other food categories that contributed significantly to the exposure in some population groups were:

- In infants and toddlers:
  - FC 13.1.3 Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC.
  - FC 01.2 Unflavoured fermented milk products, including natural unflavoured buttermilk (excluding sterilised buttermilk) non heat-treated after fermentation.
- In children and adolescents:
  - FC 05.2 Other confectionery including breath freshening microsweets.

- In all population groups, except infants.
  - FC 07.2 Fine bakery wares.
- In all population groups, except infants and the elderly:
  - FC 15.1. Potato-, cereal-, flour- or starch-based snacks in all population groups, except infants and the elderly.
  - FC 14.1.4 Flavoured drinks.

For the actual contributions per exposure scenario and population group, see Appendix F.

Uncertainty analysis

Potential sources of uncertainty in the exposure assessment of tartaric acid and tartrates (E 334-337 and E 354) 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	+/–
Methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Correspondence of reported use levels and analytical data to the food items in the EFSA Comprehensive Database: uncertainties to which types of food the levels refer	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Concentration data:– use levels considered applicable to all foods within the entire food category, whereas on average 1% of the foods, belonging to food categories with foods labelled with additive, was labelled with the additive	+
Possible degradation of tartaric acid at high temperatures (e.g. during baking) not considered in the exposure assessment	+
The 17 food categories included in the refined exposure assessment scenarios out of all authorised food categories (n = 81) corresponded to 4% to 94% of the amount (g of foods by body weight) of food consumption documented in the EFSA Comprehensive Database	–
Food categories selected for the exposure assessment: inclusion of food categories without considering the restriction/exception (n = 2 for all scenarios out of 81 food categories)	+
Maximum level exposure assessment scenario:– exposure calculations based on MPLs and the maximum reported use levels (reported use from industries)	+
Refined exposure assessment scenarios:– exposure calculations based on the maximum or mean reported use levels (reported use from industry)	+/–

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

Tartaric acid and tartrates (E 334-337 and E 354) are authorised as a Group I food additive in 66 food categories and have a specific authorised use in 15 food categories (Table 8). Since the majority of food categories correspond to the general Group I food additives authorisation, the food additives may not be used in all of these food categories. This may explain why reported use levels of tartaric acid and tartrates (E 334-337 and E 354) were only available for 17 food categories. For the 15 food categories with a specific use of these food additives, use levels were only reported for one food category (FC 13.1.3). Furthermore, the Panel noted that the information from Mintel's GNPD (Appendix C.1) supported the observation that the food additives may not be used in all food categories in which they are authorised.

The Panel also noted that of the 105 food subcategories, categorised according to Mintel's GNPD nomenclature and in which at least one food was labelled with tartaric acid and tartrates (E 334-337 and E 354), 42 were included in the exposure assessment. These 42 food subcategories represented approximately 82% of the food products labelled with tartaric acid and tartrates (E 334-337 and E 354) in Mintel's GNPD. In the remaining 63 food subcategories, the main food category not included in the exposure assessment was desserts (see Appendix C.1).

The Panel noted further that the percentage of foods per subcategory labelled to contain tartaric acid and tartrates (E 334-337 and E 354) was maximally about 20% in the food subcategory Baby Biscuits & Rusks (78 out of 388 products in total) (Appendix C.1), with an average percentage of 1% among all subcategories. In the exposure assessment, it was assumed that 100% of the foods belonging to an authorised food category contained the additive.

Additionally, the possible degradation of tartaric acid at high temperatures (e.g. during baking) was not considered in the exposure assessment due to the absence of data (Section 3.1.5).

Given these observations, the Panel considered that the uncertainties identified have resulted in an overestimation of the exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives according to Annex II to Regulation N°1333/2008 in European countries considered in the EFSA Comprehensive Database for all three exposure scenarios.

The Panel noted that food categories which may contain tartaric acid and tartrates (E 334-337 and E 354) due to carry-over (Annex III, Parts 2, 3, 4, 5A) were not considered in the current exposure assessment and this may have resulted in an underestimation of the exposure to these additive from all authorised sources (Annex II and Annex III).

3.4.2. Exposure from natural occurrence

L(+)-Tartaric acid is the primary non-fermentable soluble acid in grapes and the principal acid in wine. In grapes, the synthesis of tartaric acid starts in the early stages of berry development, resulting in the accumulation of tartaric acid in their pulp. Furthermore, tartaric acid is present in many other fruit and vegetables. In some of them, the presence of tartaric acid is the result of L-ascorbic acid catabolism.

To estimate the exposure to naturally occurring tartaric acid, levels of tartaric acid reported in the literature were used (Appendix H). Only the exposure via the consumption of wine (FC 14.2.1) and non-processed fruits and vegetables (corresponding to FC 04.1) was considered:

- For fruits: grapes, berries and pome fruits.
- For vegetables: root vegetables, bulb vegetables, fruiting vegetables, brassica vegetables, leaf vegetables, stem vegetables and legumes vegetables.

The presence of tartaric acid in wine could come from natural occurrence and from the addition to wine as a food additive according to Regulation (EU) 934/2019.

For the other products from the diet for which levels of tartaric acid were reported in the literature, no distinction could be made between added and naturally occurring tartaric acid. These products were therefore excluded from this exposure assessment (Appendix H).

Table 12 summarises the estimated exposure to tartaric acid from its natural occurrence in the diet.

Table 12: Summary of dietary exposure to tartaric acid from its natural occurrence in the diet, in six population groups (minimum–maximum across the dietary surveys in mg tartaric acid/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)
Natural sources scenario						
• Mean	0.4–1.6	0.5–4.8	0.3–3.4	0.3–1.9	1.2–6.1	1.3–8.7
• 95th percentile	1.0–6.8	1.5–22	1.2–25	0.7–17	7.9–20	9.0–26

The mean exposure to tartaric acid ranged from 0.3 mg/kg bw per day in children and adolescents to 8 mg/kg bw per day in the elderly. The 95th percentile of exposure to tartaric acid ranged from 0.7 mg/kg bw per day in adolescents to 26 mg/kg bw per day in the elderly.

For infants, toddlers and children, the main contributing food category to the total mean exposure estimates of tartrates from natural sources was unprocessed fruit and vegetables. For the older age groups, unprocessed fruit and vegetables and alcoholic beverages, including alcohol-free and low-alcohol counterparts, contributed most to the mean exposure.

Detailed results per population group and survey for the dietary exposure to tartaric acid from its natural occurrence in the diet are presented in Appendix I.

3.4.3. Exposure to tartaric acid from the use of tartaric acid-tartrates (E 334-337 and E 354) and related food additives (tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e), mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f), metatartaric acid (E 353) and stearyl tartrate (E 483))

The Panel noted that in addition to the exposure to tartaric acid from the use of tartaric acid and tartrates (E 334-337 and E 354), tartaric acid can be released from the use of other food additives, i.e. tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e), mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) (EFSA FAF Panel, 2020a), metatartaric acid (E 353) (EFSA FAF Panel, 2020b) and stearyl tartrate (E 483) (EFSA FAF Panel, 2020c).

The Panel estimated the chronic dietary exposure to tartaric acid from the use of these food additives. Reported use levels were available for their exposure assessment except for stearyl tartrate (E 483), which was therefore not considered for this assessment (Appendix J)

Food categories considered for the exposure assessment of tartaric acid

The food categories for which use levels of all food additives releasing tartaric acid were provided 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).

In total 22 food categories were included in the exposure assessment. For four of these categories, the restrictions/exceptions which apply to the use of food additives releasing tartaric acid could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to four food categories and may have resulted in an overestimation of the exposure:

- 05.1 Cocoa and chocolate products as covered by Directive 2000/36/EC, only energy-reduced or with no added sugar. The whole food category was taken into account as it is not possible to separate energy-reduced or with no added sugar cocoa and chocolate products from regular cocoa and chocolate products;
- 07.1 Bread and rolls, except products in 7.1.1 and 7.1.2. The whole food category was taken into account as it is not possible to exclude products belonging to FCs 7.1.1 and 7.1.2;
- 13.1.3 Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC, only biscuits and rusks and baby foods. The whole food category was considered as it is not possible to only select biscuits and rusks and baby foods;
- 14.1.5.2 Other (i.e. chicory extracts, tea, herbal- and fruit-infusions; coffee substitutes, coffee mixes and mixes for 'hot beverages'), excluding unflavoured leaf tea; including flavoured instant coffee.

Exposure estimates

To estimate the exposure to tartaric acid, the amount of tartaric acid released from the different additives needs to be established. The Panel used for this the total amount of tartaric acid in the additives (% by weight) according to the EU specifications for these food additives (Commission Regulation (EU) No 231/2012). According to these specifications, E 472d contains maximally 40%, E 472e and E 472f maximally 50% and E 483 maximally 40% tartaric acid. Metatartaric acid (E 353) was assumed to be hydrolysed to an approximately equivalent amount of tartaric acid (EFSA FAF Panel, XX). The Panel used these released amounts as the maximum release on which exposure to tartaric acid was estimated.

The different additives considered in this exposure assessment have different functions in foods and can therefore be used together in the same food. For instance, metatartaric acid (E 353) is used to avoid the precipitation of tartaric acid (E 334) so both can be used together.

Considering the above, the use levels provided for each food additive and food category (or a percentage of these levels depending of the hydrolysis of the food additive into tartaric acid) were summed to get a total 'potential' concentration of tartaric acid in all foods within a food category. These levels were then used to estimate the chronic dietary exposure to tartaric acid.

Dietary exposure to tartaric acid was calculated as described in Section 3.4.1. Added to the uncertainties described in Table 11, estimates are based on the maximum possible amount of tartaric acid released from the other food additives and all food additives were considered present together in the same food.

Detailed results per population group and survey are presented in Appendix K. For the actual contributions per population group and food categories, see Appendix L.

Table 13 summarises the estimated exposure to tartaric acid from the use of E 472d, E 472e, E 472f, tartaric acid and tartrates (E 334-337 and E 354) and metatartaric acid (E 353) as food additives in the non-brand loyal refined exposure scenario.

Table 13: Summary of dietary exposure to tartaric acid from the use of E 472d, E 472e, E 472f, tartaric acid and tartrates (E 334-337 and E 354) and metatartaric acid (E 353) as food additives in the non-brand loyal refined exposure scenario, in six population groups (minimum–maximum across the dietary surveys in mg tartaric acid/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)
• Mean	2–122	7–127	20–113	13–74	14–38	13–28
• 95th percentile	7–235	20–278	54–221	31–145	29–83	29–53

Mean exposure to tartaric acid from the use of several food additives ranged from 2 mg/kg bw per day in infants to 127 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 7 mg/kg bw per day in infants to 278 mg/kg bw per day in toddlers.

Compared to the mean dietary exposure to only tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives, mean estimates including all food additives releasing tartaric acid are higher by a factor of approximately 1.3 up to 2 among the populations.

FC 07.1 Bread and rolls was the major contributor to the mean exposure in all scenarios and population groups except infants for whom the major contributor was FC 13.1.3 Processed cereal-based foods and baby foods for infants and young children. The 2nd food category that contributed significantly to the exposure in toddlers, children, adolescents and adults was FC 14.1.4 Flavoured drinks.

Exposure to tartaric acid from the use of several additives is an overestimation, due to the uncertainties described for tartaric acid and tartrates (E 334-337 and E 354) (Table 11). Additionally, for the food categories for which there were reported use levels for more than one food additive, it was assumed that these food additives were present together in the same food while the information from the Mintel GNPD indicated that this is not frequently the case.

When the total exposure to tartaric acid from all sources of food additives and natural sources is calculated using the methodology described in Section 3.4.1, the mean exposure ranged from 2 mg/kg bw per day in infants to 130 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 8 mg/kg bw per day in infants to 285 mg/kg bw per day in toddlers. Taking into account the uncertainties described above, this exposure estimate is also an overestimation.

3.5. Biological and Toxicological data

The Panel considered that sodium, potassium and calcium salts of tartaric acid are expected to dissociate in the gastrointestinal tract into tartrate and their corresponding cations. The resulting sodium, potassium and calcium cations will enter their normal physiological processes. The toxicity of the corresponding cations was therefore not addressed in the opinion.

3.5.1. Absorption, distribution, metabolism and excretion

Although only the L(+)-form of tartaric acid and tartrates is authorised as a food additive in the EU, when in some studies the racemic (DL-form) or the D(-)-form were used for comparison with the L(+)-form, these data have also been reported in this opinion.

In vitro *studies*

Chadwick et al. (1978) studied the metabolism of **sodium D(-)- and L(+)-tartrate** in a faecal incubation system. Sodium D(-)- or L(+)-tartrate (30 mL of 250 mmol/L) was incubated anaerobically at 37°C for 24 h with fresh faeces from five healthy subjects. Tartrate was measured at 0, 3, 6, 7.5 and 24 h. The percentages (± SEM) of tartrate still present in the samples were 45 ± 13, 32 ± 14 and < 25% for L(+)-tartrate after 3, 6 and 7.5–24 h, respectively; and 91 ± 7, 87 ± 9, 64 ± 8 and 34 ± 16% for D(-)-tartrate after 3, 6, 7.5 and 24 h, respectively (due to the insensitivity of the method used for analysis of tartrate, it was not possible to accurately measure tartrate concentrations

below 25% of the initial dose). When tartrate concentrations were plotted logarithmically against time, 50% loss was recorded after approximately 4 h for L(+)-tartrate and 20 h for D-tartrate indicating that the natural isomer L(+)-tartrate was metabolised five times more rapidly than the D-tartrate.

The metabolism of **DL-[1,4-^{14}C]tartrate** by intestinal bacteria was also investigated in the same study by Chadwick et al. (1978). Pure cultures of aerobic (Enterobacteria, Enterococci, Micrococci and Bacillus sp.) and anaerobic (Clostridia, gram-positive non-sporing bacilli and gram-negative non-sporing bacilli) bacteria were incubated anaerobically for 48 h at 37°C with 0.1 μCi of DL-[1,4-14C]tartrate/mL. The percentages of metabolised tartrate (mean ± SD) were 36.5 ± 20.2, 15.7 ± 13.6, 12.5 ± 8.9 and 7.1% after incubation with Enterobacteria, Enterococci, Micrococci and Bacillus sp., respectively. The percentages of metabolised tartrate (mean ± SD) were 18.5 ± 6.5, 7.5 ± 7 and 4 ± 3.9 after incubation with Clostridia, gram-positive non-sporing bacilli and gram-negative non-sporing bacilli, respectively. On several occasions more than 50% of the radioisotopic label was converted into CO_2, showing, according to the authors, that both L(+) and D(-)-forms of tartrate were metabolised by human intestinal bacteria.

In vivo

Animal studies

L(+)-tartaric acid

Sourkes and Koppanyi (1950) compared the rate of excretion of tartaric acid in dogs gavaged with 500 mg tartaric acid/kg (in water) and given either as tartaric acid (n = 2) or tartaric acid esters of mixed mono- and diglycerides (n = 4). Twelve hours after administration of tartaric acid, up to 60% of the administered dose was found in urine, whereas only 6–18% was found in animals receiving tartaric acid esters of mixed mono- and diglycerides. The rapid and large excretion of tartaric acid in dogs receiving this compound was associated with histopathological nephrotic changes, which were not found in animals receiving tartaric acid esters of mixed mono- and diglycerides. The authors concluded that the toxicity of tartaric acid was correlated with a high rate of renal excretion whereas tartaric acid esters of mixed mono- and diglycerides, which is well absorbed but slowly excreted showed no renal toxicity.

Fasted Wistar rats (5 animals/sex), guinea pigs (11 females) and Danish Landrace pigs (3 females) were given 1,000, 1,000 and 500 mg/kg bw, respectively, of **L(+)-tartaric acid** by gavage (Gry and Larsen, 1978). The percentages of L(+)-tartaric acid recovered in urine after 48 h were (mean ± SD): 72.9 ± 15.7, 3.6 ± 3.1 and 26 (17–43) (mean (range)), for the rats, guinea pigs and pigs, respectively. In addition, L(+)-tartaric acid was incubated at concentrations of 10 mg/mL for up to 24 h in caecal extracts from either rat or guinea pig and there were no differences in the ability to metabolise L(+)-tartaric acid between the species. The authors also looked at the excretion of D-tartaric acid administered to the animals under the same conditions. The rats had a lower recovery in urine of the D(-)-form compared to the L(+)-form (52% and 73%, respectively). The authors noted that: 'the low recovery of both isomers in guinea pigs was associated with marked kidney damage while this effect was not found in the rat after administration of the L(+)-form' and considered that 'some correlation exists between low recovery of unchanged tartrate in urine, which reflects some absorption in the small intestine, and kidney damage'. The authors considered that the percentage recovery in the urine of pigs (26%) is close to the one reported for humans (20%).

Potassium tartrate

Male Wistar rats (8 animals/group, 6 weeks old, weighing ca. 180 g) were given for 21 days **potassium tartrate** (stereoisomeric composition not specified) at a concentration of 47.9 g/kg diet, or a control diet (Sabboh et al., 2007). During the last 4 days of the experiment, the feed intake was determined and urine was collected and analysed for tartrate. Mean (SEM) feed intake was 17.31 (0.79) and 17.65 (0.62) g/day in the potassium tartrate and control group, respectively. Mean (SEM) urinary excretion of tartrate was 2.2 (0.25) mmol/24 h in the potassium tartrate group, which was reported by the authors to correspond approximately to 50% of the tartrate intake. Caecum content of tartrate was 4.7 mmol/g. Caecum content was analysed for acetate, propionate, butyrate, lactate and succinate.

Sodium tartrate

In a study investigating the absorption and biotransformation of **monosodium L(+)-tartrate**, adult Sprague-Dawley CFY rats (3 males and 3 females, weighing 200–250 g) were dosed by gavage with monosodium ^{14}C-L(+)-tartrate at a dose level of 400 mg/kg bw in water (Chasseaud et al., 1977). Urine, faeces and expired air ($^{14}CO_2$) were collected and the rats were sacrificed after 2 days. Excretion of radioactivity was almost completed within 12 h and in the expired air within 24 h. At 48 h

after dosing, 70.1 ± 4.1%, 13.6 ± 7.3% and 15.6 ± 2.7% had been excreted in the urine, faeces and expired air, respectively, indicating that L(+)-tartrate was extensively absorbed and that a part was metabolised to carbon dioxide.

In a study with the purpose of investigating the renal and bone uptake of **monosodium L(+)-tartrate**, a total of 10 male Sprague Dawley CFY rats (weighing 160–180 g) were given by gavage 2,730 mg/kg bw per day monosodium L(+)-[^{14}C] tartrate for 7 days (Down et al., 1977). One animal was sacrificed immediately before the 7th day's dose and the remaining animals were sacrificed at intervals during the following 12 days. Blood was sampled immediately before sacrifice. Carcasses were subjected to whole-body autoradiography and the nature of radioactivity in bone was determined. Radioactivity was observed in whole-blood, plasma, bone and kidneys. Peak concentrations (μg equivalents of L(+)-tartaric acid) of radioactivity were 176 μg/mL, 279 μg/mL, 787 μg/g and 3,983 μg/g, respectively, 1 h after the 7th dose. After 12 days concentrations had declined to 23 μg/mL, 2 μg/mL, 208 μg/g and 38 μg/g, respectively. The radioactivity in plasma declined biophysically with half-lives of about 3 and 53 h after the last dose. Localisation of radioactivity in bone persisted for at least 8 days after the last dose. The amount of radioactivity in bone was estimated to be 0.4% of the total administered dose, whereas the L(+)-form was not retained in the kidney. On the contrary, in animals that had received the same dose of calcium DL-tartrate, retention of this DL-form was observed in the kidney. According to the authors, this was due to the DL-form being less soluble than the L(+)-form and could be a possible explanation for the higher nephrotoxic effect of the DL-form as compared to the L(+)-form.

In the Chadwick et al. (1978) study, rats (200–250 g) were given by gavage 20 μCi of **sodium DL-[1,4-^{14}C]tartrate** (with 18.8 mg/kg L(+)-tartrate as carrier). The specific radioactivity of labelled CO_2 in breath was measured every 30 minutes for 6 h and urinary excretion of [^{14}C]tartrate was measured over 24 h; faeces were not collected. The recovery of $^{14}CO_2$ in expired air and [^{14}C]tartrate in urine was (mean ± SEM) 21.8 ± 1.4 and 51.0 ± 4.5%. Absorption of tartrate from the intestine was calculated as 81% of the dose; urinary radioactivity amounted to 70% with the difference between absorption and urinary excretion representing metabolism in body tissues.

Potassium sodium tartrate

Underhill et al. (1931a) reported on the metabolism of **potassium sodium L(+)-tartrate** (Rochelle salt) in rats, guinea pigs and dogs administered by gavage or subcutaneously; rabbits were administered by gavage or intramuscularly. Tartrate was determined in the urine by a colorimetric method. According to the authors, the guinea pig was unique among the laboratory animals examined as only a small portion (16%) of the tartrate reappeared in the urine when administered by gavage, and tartrate could not be detected in the faeces. They also concluded that during its passage in the gastrointestinal tract of the guinea pig, tartrate was altered (oxidised?) so that it no longer responded to the tartrate test. This was supported by the observation that 96–100% of the administered dose of tartrate was recovered in urine when it was injected subcutaneously to the guinea pigs. Such a change in the percentage of tartrate recovered in urine was not observed under the same conditions in rats, dogs and rabbits. In addition, the authors reported that the dog was more resistant to the nephropathic action of tartrate (depression of renal function as assessed by the phenolsulfonphthalein test, and renal necrosis at doses above 200 mg/kg bw), than the rabbit (see also Section 3.4.2).

Human studies

A total of four subjects (two young men and two young women) were given diets supplemented with **L(+)-tartaric acid or potassium sodium tartrate** (Rochelle salt) (Underhill et al., 1931b). Urine and faeces were collected in 24-h periods. After 7.8–9.4 g of L(+)-tartaric acid, the urinary recovery was between 12 and 18.7%. After 10 g of potassium sodium tartrate (corresponding to 5.3 g tartaric acid), the urinary recovery ranged between 12.8 and 15.4%. No trace of tartrate was present in the faeces. The dosing was repeated in six subjects (two young men and two young women) but with a smaller quantity of tartrate. Here the amount of L(+)-tartaric acid ingested was between 2.3 and 4.5 g and the urinary recovery was between 8.7 and 20.4%. The amount of tartaric acid ingested from potassium sodium tartrate was 5.3 g (as in the first dosing), but the urinary recovery ranged between 2.4 and 5%. An additional study with 2 men showed no recovery of L(+)-tartaric acid in urine less than 10 h after ingestion of 2.5 g L(+)-tartaric acid. To investigate the fate of L(+)-tartaric acid in the gastrointestinal tract, fresh faeces were diluted with water and mixed with 20 mg of L(+)-tartaric acid, L(+)-tartaric acid neutralised or potassium sodium tartrate. Samples were subsequently kept at 37.5°C or 0°C for up to 8 h. After 8 h of incubation with L(+)-tartaric acid, the amount of recovered L

(+)-tartaric acid was 0 and 10–12 mg after 37.5 and 0 °C, respectively. When potassium sodium tartrate was incubated with faeces at 37.5°C for 4 h the recovery of L(+)-tartaric acid was 0 mg, but 10 mg after incubation for 6 h at 0°C. After 4 h of incubation with potassium sodium tartrate, the amount of recovered L(+)-tartaric acid was 0 after 37.5°C. In addition, L(+)-tartaric acid was incubated at 37.5°C with intestinal contents obtained through a fistula in the caecum. After 4.5, 7.5, 10.5 and 24 h, the decomposition of L(+)-tartaric acid was 0, 23.5, 73.5 and 100%, respectively.

A group of 12 men were given 2 g '**D-tartaric acid**' as sodium tartrate in two capsules of 1 g each, and allowed to drink as much water as desired. Urine was collected for a minimum of 12 h (Finkle, 1933). Recovery of tartrate in urine ranged from 11.5 to 24.7% with an average of 17.4% after oral administration. In another group of 10 individuals receiving sodium tartrate by intramuscular injection (1 g), tartrate was almost completely recovered in the urine within 12 h. The authors concluded that: '*with the low doses employed in our observations on human beings, renal damage did not occur, and it is therefore possible to recover practically all of the injected tartrate in the urine and to demonstrate that none of this fruit acid is utilised by human beings*'.

After ingestion of **sodium L(+)-tartrate** (2 g expressed as tartaric acid, repeated on four occasions, 1 week apart), between 0.4 and 12.2% L(+)-tartaric acid was recovered in the urine (collected for a minimum of 12 h) in a single subject (Bauer and Pearson, 1957). It was reported that L(+)-tartaric acid was metabolised when given in small amounts by per-oral administration, as well as by intramuscular injection (ca. 750 mg). The same conclusion was reach with D(-)- and DL-tartrates.

Two subjects (A and B, gender not specified) were given **sodium L(+)-tartrate** in three oral doses of a total of 1.5 mmol/kg per day (corresponding to 346 mg tartaric acid/kg bw per day) for 2 (subject A) or 4 (subject B) days (Chadwick et al., 1978). Excreted tartrate was measured in urine from subject B and hydrogen ion excretion and pH were measured in urine from both subjects. These analyses were also performed on several days before and after the dosing. Subject B was on a constant diet. Subjects A and B received a daily total of 130.5 and 104.5 mmol sodium L(+)-tartrate (corresponding to 30 and 24 g sodium L(+)-tartrate, respectively, calculated on the basis of the molecular weight of disodium tartrate (230.8 g/mol)). Urinary pH from subject A was 5.8 before and 7.69 after the dosing and similar from subject B. Urinary tartrate excretion from subject B was between 8.9 and 10.3 mmol during the dosing period equivalent to 7.4% of the total administered dose.

In the same study by Chadwick et al. (1978), five healthy human subjects (28–45 years old) were given 5 μCi of **sodium DL-[1,4-^{14}C]tartrate** (with sodium L(+)-tartrate as carrier) in three different doses: 2.5, 5 or 10 g. The specific radioactivity of labelled CO_2 in breath and urinary [^{14}C]tartrate excretion was measured every hour for 7 h. Stools were weighed and analysed immediately after they were passed. There were no differences in percentages of excreted ^{14}C between the doses, so the results from all five subjects were pooled. The percentage recovery of ^{14}C (mean ± SEM) of the administered dose was 46.2 ± 8.1, 12 ± 1.2 and 4.9 ± 1.7% in the breath, urine and faeces, respectively. The concentration of $^{14}CO_2$ in expired air peaked after 4 h consistent with, according to the authors, the time for sodium DL -[1,4-^{14}C]tartrate to reach the colon and be exposed to colonic bacteria. The concentration of [^{14}C]tartrate in urine peaked 1–2 h after ingestion of sodium DL-[1,4-^{14}C]tartrate. A single subject received 10 μCi of DL-[1,4-^{14}C]tartrate intravenously (with 125 mg sodium L(+)-tartrate as carrier). The specific radioactivity of labelled CO_2 in breath and urinary [^{14}C]tartrate excretion was measured every hour for 8 h. The percentage recovery of ^{14}C of the injected dose was 18 and 63.8% in the breath and urine, respectively. The concentration of $^{14}CO_2$ in expired air peaked after 1 h suggesting, according to the authors, a rapid metabolism by tissue enzymes. From the differences in the urinary excretion of labelled tartrate after oral and parenteral administration, absorption of tartrate from the intestine was calculated as 18% of the dose and urinary radioactivity amounted to 14% of the dose.

Thirteen healthy subjects (seven males and six females; 27–65 years of age) were fed 5 g cream of tartar (monopotassium tartrate) or 120 g sun dried raisin, both equal to approximately 2 g tartaric acid, per day for 9 weeks, divided into 3-week cycles (Spiller et al., 2003). The experimental diets were fed in a crossover design after an initial control period. Faeces were collected for the last 4 days of each cycle for analysis of Short Chain Fatty Acids (SCFA). The authors indicated that tartaric acid was fermented by colonic bacteria, which utilise it for the production of SCFA, the concentration of faecal SCFA remained unchanged during the study, which is likely indicative of an absorption of SCFA in the colon.

Overall, the metabolism of L(+)-tartaric acid and its potassium sodium salt was shown to be species-dependent. In rats, after oral administration, up to 81% of labelled tartrate was absorbed (Underhill et al., 1931a; Chadwick et al., 1978; Gry and Larsen, 1978). In rats, L(+) and D(-)-tartrate were excreted differently in urine after gavage, the L(+)-form being more efficiently excreted than the D(-)-form (Gry

and Larsen, 1978). Up to 10% of labelled parenteral tartrate was expired as CO_2 within 6 h and 63% was found in the urine over 24 h, which indicated significant metabolism by tissues (Chadwick et al., 1978). High rate of renal excretion (up to 60% within 12 h) was reported in dogs receiving tartaric acid (Sourkes and Koppanyi, 1950). Underhill et al. (1931a) found that after parenteral injection of tartrate, recovery ranged from 70% in rabbits, dogs and rats to almost 100% in guinea pigs. Therefore, tissue metabolism could not be excluded in these species; however, it played a minor role in disposal of tartrate.

In man, only 12% of tartrate administered orally appeared in the urine; as this was unrelated to dose absorption was likely passive (Chadwick et al., 1978). The difference in urinary excretion after an oral dose (12%) or an intravenous dose (66%) suggested that only a fraction of the oral dose was systemically available (approximately 18% according to Chadwick et al., 1978). Finkle (1933) found that 91% of an intramuscular dose of unlabelled tartrate was recovered in the urine, which according to the authors, indicated that the human body cannot metabolise tartrate. It must be noted, however, that in the intramuscular part of the study, D-tartrate was most probably used because the author described D-tartrate in the oral part of the study. After an intravenous injection of ^{14}C-L-tartrate, Chadwick et al. (1978) reported that 66% of the radioactivity was excreted in the urine in 22 h, and that 18% was excreted as $^{14}CO_2$ over 8 h. The concentration of $^{14}CO_2$ in expired air peaked after 1 h and contained 7% of the dose suggesting, a rapid metabolism by tissue enzymes. The Panel considered that the different recoveries of 91 and 66% may be due to the different stereospecific forms. However, these recoveries are not directly comparable because radioactivity was measured in one study while unlabelled tartrate was analysed in the other study. Tartrate was fermented by colonic bacteria, with L(+)-tartrate being metabolised faster than D(-)-tartrate (Chadwick et al., 1978). Spiller et al. (2003) reported that tartaric acid/tartrate were fermented by colonic bacteria to SCFAs, which then can be absorbed in the colon.

The Panel noted that no information on the ADME of calcium tartrate was available.

3.5.2. Acute toxicity

Mice

Mice (reported to be white, of mixed strain and sex, average weight 22–23 g) were administered by gavage with a single dose of a 25% solution in water of **disodium tartrate** (stereoisomeric composition not specified) in doses of 12 (30 animals), 20 (35 animals) or 30 (51 animals) mmol/kg (corresponding to 2,770, 4,616 or 6,924 mg/kg bw, respectively). An LD_{10} was established at 4,385 mg/kg bw (Locke et al., 1942).

Rabbits

Fasting rabbits (1–5 males/group) were orally administered **potassium sodium tartrate** or tartaric acid (stereoisomeric composition not specified) in single doses corresponding to 26–300 mg/kg bw of tartaric acid (Underhill et al., 1931a). According to the authors, renal performance was assessed by the phenolsulfonphthalein test before and after administration and nitrogen was measured in urine. The animals were killed and the kidneys were examined histologically 3–4 days after administration. Diarrhoea was observed in animals given the highest dose of potassium sodium tartrate (300 mg/kg as tartaric acid). The renal performance test showed decreased kidney function at all doses. Changes in urinary nitrogen were not associated with kidney injury.

Rabbits (New Zealand White males) were administered by gavage with a single dose of a 25% solution in water of **disodium tartrate** (stereoisomeric composition not specified). Three out of seven rabbits died after an average oral dose of 5,308 mg tartaric acid/kg bw, while six out of six rabbits survived an average dose of 3,693 mg tartaric acid/kg bw (Locke et al., 1942).

Dogs

Fasting dogs (1–4 animals/group (sex unspecified)) were gavaged with single doses of 100, 200, 400, 600, 1,000, 1,500 or 2,000 mg/kg bw tartaric acid given as **potassium sodium tartrate** (stereoisomeric composition not specified) (Underhill et al., 1931a). The animals were killed 3 days after and kidney sections were examined microscopically. According to the authors, renal performance was assessed by the phenolsulfonphthalein test before and after the administration. Diarrhoea and slight to medium (highest dose only) renal changes (not further specified) were observed in dogs given tartaric acid as potassium sodium tartrate in doses of 400–2,000 mg/kg bw. Renal tests showed decreased kidney function at doses of 600–2,000 mg/kg bw.

Overall, only outdated studies were available, they reported that disodium tartrate has a low acute toxicity in mice. Impaired kidney function was observed in rabbits and dogs after a single oral dose of potassium sodium tartrate higher than 50 and 600 mg/kg bw, respectively, and renal changes were observed in dogs at doses above 400 mg/kg bw.

3.5.3. Short-term and subchronic toxicity

Rats

A total of 10 male CFY rats (weighing 160-180 g) were given 2,730 mg/kg bw per day **monosodium L(+)-[^{14}C] tartrate** for 7 days by gavage. One animal was sacrificed immediately before the 7th day's dose and the remaining animals were sacrificed at intervals during the following 12 days (Down et al., 1977). Liver and kidneys were weighed and examined macroscopically. No adverse effects were observed. In the same study, the authors reported that when DL-form was administered under the same conditions, the liver of the animals was not affected; however, kidneys had changes consistent with crystalluria. Main findings were focal chronic and mixed inflammation of the interstitium and small number of tubules containing birefringent crystals.

In the Inoue et al. (2015) study, groups (n = 10) of male and female F344/DuCrj rats were fed for 90 days a diet containing 0, 0.125%, 0.5% and 2% **monopotassium DL -tartrate** (equivalent to 0, 75, 150 and 600 mg/kg bw per day expressed as potassium hydrogen DL-tartrate or approximately to 0, 60, 120 and 480 mg/kg bw per day if expressed as tartaric acid). The study was conducted in accordance with official Japanese Test Guidelines and GLP. The test compound was described by the authors as a mixture containing equal amounts of D(-)- and L(+)- monopotassium tartrate, plus small amounts of mesotartaric acids. Microscopic findings were irregular dilation of the distal tubule lumen, foreign body giant cells, inflammatory cell infiltration. Regeneration of renal tubules was observed in the renal cortex and/or medulla in the 0.5% and higher dose groups. The severity of these lesions was dose dependent. In urine, an increase in protein and white blood cells together with the concentration of tartaric acid was found from the 0.5% dosage groups of both sexes. However, blood biochemical analysis did not indicate any failure of renal function. No other treatment-related changes in other organs were reported. According to the authors, these results indicated that the monopotassium DL-tartrate induced obstructive nephropathy in rats. The Panel identified an NOAEL of 0.125% in the diet (equal to 75 mg and 82 mg monopotassium DL-tartrate/kg bw per day, or to 60 and 68 mg DL-tartaric acid/kg bw per day, in males and females, respectively).

The Panel noted that the authors (Inoue et al., 2015) stated that the tested compound (monopotassium DL-tartrate) is registered as a food additive, however, in the EU, only the L(+)-form of monopotassium tartrate (E 335 (i)) is authorised as a food additive.

Rabbits

Male rabbits (n = 15) were fed 0 or 7.7% **sodium tartrate** (stereoisomeric composition not specified) in their diet for up to 150 days (Packman et al., 1963). Food consumption and mean body weights were recorded at 4, 8, 16 and 22 weeks, the calculated intake was approximately 550 mg/kg bw per day. After 60 days, blood samples from five treated animals and six control animals were examined (erythrocyte, leucocyte and differential leucocyte counts, blood sugar and non-protein nitrogen determinations). Urine samples from an equal number of animals were also examined (colour, appearance, specific gravity, sugar, albumin, alkalinity and microscopic constituents). After 30 days (2 animals from each group) and 60 days (1 animal from each group), gross pathological examinations were performed, organs (adrenals, bladder, brain, heart, kidneys, liver, lung, prostate, spleen, stomach, testes and thyroid) were weighed and testes were examined histologically. After 100 days, similar examinations were performed on one-half of the surviving animals of each group, as well as histological examination of the liver and kidney. After 150 days, all surviving animals were sacrificed and examined macroscopically and microscopically. No treatment-related adverse effects were observed.

Dogs

Four dogs were given a daily oral dose of 990 mg/kg bw (in two gelatine capsules about 6 h apart) of **tartaric acid** (stereoisomeric composition not specified) for a period of 90–114 days (Krop and Gold, 1945). The general appearance and behaviour of dogs were observed during the entire experiment. Weight was measured and urine and blood were collected on a weekly basis. Urine was analysed for specific gravity, pH, albumin and blood cells. Blood was analysed for non-protein nitrogen (NPN) and creatinine. At 3-week intervals, the serum CO_2 combining power and kidney function were

determined. Tests were carried out more frequently in dogs showing signs of poisoning. All animals underwent gross post-mortem examinations and liver, kidney and lung tissue from 1 dog was prepared for histological examination. Weight changes varied from a gain of 30% to a loss of 32%. Casts appeared in the urine from 3 dogs after 19, 38 and 89 days, respectively. No changes in the measured parameters were observed except in one dog, which had increased blood NPN, creatinine and albumin (azotemia) after 88 days and died after 90 days. Histopathological examination showed advanced tubular degeneration of the kidney. No other adverse effects were observed.

Overall, no adverse effects were observed in rats given 2,730 monosodium L-tartrate/kg bw per day. In the same study, DL-tartaric acid was shown to cause kidney effects. Furthermore, in a 90-day study in rats, an NOAEL of 60 mg/kg bw per day was identified for monopotassium DL-tartrate, based on kidney histological alterations (obstructive nephropathy) reported at higher doses.

In rabbits given 550 mg monosodium tartrate/kg bw per day acid (stereoisomeric composition not specified), no adverse effects were observed. Advanced tubular degeneration of the kidneys and increased blood NPN, creatinine and albumin were observed in one out of the four dogs given 990 mg/kg bw per day tartaric acid (stereoisomeric composition not specified), the only dose tested.

The Panel considered that the renal effects reported with tartrates were most likely due to the presence of the D-form of tartaric acid only.

3.5.4. Genotoxicity

In vitro

L(+)-tartaric acid, monosodium tartrate and monopotassium tartrate (stereo-isomeric composition not specified) (purity 99.0, 99.5 and 100.0%, respectively) were tested in the *Salmonella*/microsome test using Salmonella typhimurium strains TA 92, TA 94, TA 98, TA 100, TA 1535 and TA 1537 (with and without metabolic activation) in the pre-incubation assay. All three substances were reported to be negative in the *Salmonella*/microsome test (Ishidate et al., 1984). The Panel noted that the reliability of this study was limited (the bacterial strains TA102 or E. coli WP2 were not used, the substances were tested only on duplicate plates, and the results were not reported in detail since the publication is a compilation of results obtained with many substances).

Potassium sodium tartrate (purity not reported; stereoisomer not reported but based on the reported CAS Number (304-59-6) the test material was potassium sodium L(+)-tartrate) was tested for mutagenicity in the *Salmonella*/microsome test using Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 (with and without metabolic activation) and in *Escherichia coli* strain WP2 in the plate-incorporation assay in concentrations up to 10 mg/plate. Potassium sodium tartrate was reported to be negative in both tests. In one experiment, unusual high numbers of histidine revertants were observed with strains TA1535 and TA100. According to the authors, this was due to an excessive amount of ethylene oxide used by the manufacturer in the sterilisation of the Petri plates. In a subsequent experiment performed with these strains, no such unusually high numbers of revertants were observed (Simons and Eckford, 1979; Prival et al., 1991). The Panel noted that the reliability of this study was limited (the substance was tested only in duplicate plates, historical control values were not reported, and unusually high numbers of revertants were observed with strains TA1535 and TA100 in one out of two experiments

L(+)-tartaric acid (purity not reported) was tested for mutagenicity in the *Salmonella*/microsome test using Salmonella typhimurium strains TA 97a, TA 98, TA 100 and TA 102 (with and without metabolic activation) in the plate-incorporation assay in concentrations up to 5 mg/plate (CMBEC, 2004 (Documentation provided to EFSA No. 1)). L(+)-tartaric acid did not induce mutagenicity in this assay. The Panel noted that this study was mainly consistent with the OECD guideline 471 (except that strain TA 1535 was not used and purity, individual plate counts, signs of toxicity and historical control data were not reported). The study can be considered reliable with limitations.

L(+)-tartaric acid, monosodium tartrate and monopotassium tartrate (stereoisomeric composition not specified) (purity 99.0, 99.5 and 100.0%, respectively) were tested in the *in vitro* chromosomal aberration test using a Chinese hamster fibroblast cell line (without metabolic activation) at concentrations up to 1.0, 15.0 and 2.0 mg/mL, respectively (the mid and low concentrations were not reported) (Ishidate et al., 1984). L(+)-tartaric acid and monopotassium tartrate were reported to be negative. Monosodium tartrate was reported to be positive. The Panel noted that this could be due to the high concentration used which exceeded the recommended maximum concentration (2 mg/L) according to the OECD Guideline 473. The Panel considered that the reliability of this study was limited (gaps were not excluded from the evaluation, different types of chromosomal aberrations were not

reported separately, only 100 metaphases were analysed per concentration, the substances were tested only in the absence of metabolic activation, and the results were not reported in detail since the publication is a compilation of results obtained with many substances).

In vivo

L(+)-tartaric acid (purity not reported) was tested in the bone marrow micronucleus assay at doses of 0, 598, 1,075 and 2,150 mg/kg bw in male mice and 0, 395, 790 and 1,580 mg/kg bw in female ICR mice (five animals per group) (CMBEC, 2004 (Documentation provided to EFSA No. 2)). It was given by gavage twice with 24-h interval. The mice were sacrificed 6 h after the second gavage. The frequency of micronucleated cells was analysed in 1,000 polychromatic erythrocytes per animal and the proportion of immature among total erythrocytes was analysed by counting 200 PCEs and all NCEs. No obvious toxic effects were observed and the PCE/NCE ratio was not changed. No statistically significant differences in the frequency of micronucleated cells were observed in the treated groups compared to the negative control groups. The Panel noted that the study deviated from the current OECD guideline 474 concerning the sampling time and the number of erythrocytes analysed. Additionally, there was no indication for exposure of the bone marrow. Therefore, the reliability of this study was limited.

L(+)-tartaric acid (purity not reported) was tested for induction of chromosomal aberrations in primary spermatocytes in male ICR mice at doses of 0, 598, 1,075 and 2,150 mg/kg bw (five animals per group) (CMBEC, 2004 (Documentation provided to EFSA No. 1)). The test item was given by gavage once a day, for five consecutive days. A colchicine solution (4 mL/kg bw, concentration not reported) was injected 6 h before sacrifice. The mice were sacrificed on the 12th day of the experiment, the spermatocytes were isolated from testes and prepared and stained for microscopic investigation (stain and conditions of preparation not reported). The frequency of chromosomal aberrations was analysed in 100 cells per animal. No statistically significant differences in the frequency of 'cell aberration' were observed in the treated groups compared to the negative control groups. The Panel noted that the study deviated from the current OECD guideline 483 with respect to the study design (treatment schedule and sampling time), the number of cells analysed and the reporting (e.g. it is unclear if the result is expressed as chromosomal aberrations per cell or as percentage of cells bearing chromosomal aberrations; the types of chromosomal aberrations were not reported, unclear if gaps were excluded). Therefore, the reliability of this study is insufficient.

In silico analysis using the OECD QSAR Toolbox (version 4.2) revealed one structural alert for in vivo micronucleus induction ('Hacceptor-path3-Hacceptor') for tartaric acid and the three tartrates, while no structural alerts were revealed for DNA binding, protein binding, carcinogenicity, 'DNA alerts for Ames by OASIS' and 'DNA alerts for CA and MNT by OASIS'. The 'Hacceptor-path3-Hacceptor' alert is an indicator for non-covalent substance/DNA interactions such as intercalation (Snyder et al., 2006). It is, however, noted by Snyder et al. (2006) that DNA intercalation in the absence of covalent addition is not necessarily a genotoxic event. Moreover, according to Benigni et al. (2010), the positive predictivity (i.e. probability for a substance with structural alert to result in a positive experimental outcome) of this structural alert for the in vivo micronucleus assay is only low (34%).

Overall, L(+)-tartaric acid, monosodium, monopotassium and potassium sodium tartrates did not show a mutagenic potential in several strains of Salmonella typhimurium and *Escherichia coli*. The Panel noted that all studies had shortcomings, however, considering the available data in a weight of evidence approach, there was no concern for these compounds with respect to a potential for induction of gene mutations. Concerning structural and numerical chromosome aberrations, there are no reliable in vitro data available and one in vivo study was of limited reliability. However, based on these data, there was at least no indication for structural or numerical chromosomal aberrations. Taking also into account that tartaric acid and tartrates do not have a structural alert that would have to be regarded as highly predictive for genotoxicity, the Panel considered that there is no concern for genotoxicity for tartaric acid and its sodium and potassium salts.

3.5.5. Chronic toxicity and carcinogenicity

Rats

Weanling Osborne-Mendel rats (21 days old, 12 animals/sex/group) were given a diet containing 0, 0.1, 0.5, 0.8 or 1.2% **tartaric acid** (stereoisomeric composition not specified) (equivalent to 0, 50, 250, 400 and 600 mg/kg bw per day) for 2 years (Fitzhugh and Nelson, 1947). A group of 48 animals was used as control. Weight and feed consumption were determined weekly (first year). Mortality was assessed at 18 months and 2 years. Histopathological examinations were performed on the lung,

heart, liver, spleen, pancreas, stomach, small intestine, kidney, adrenal, testis, colon, bone marrow, leg bones, leg muscles, lymph nodes, uterus, ovary, thyroid and parathyroid. There were no adverse treatment-related effects observed on any of the investigated parameters (Fitzhugh and Nelson, 1947).

CFY rats (4 weeks old, 35 animal/sex per group) were given a commercial diet containing **monosodium L(+)-tartrate** at levels of 0, 25 600, 42,240, 60,160 or 76,800 mg/kg diet (equal to 0, 890, 1,620, 2,200 and 3,100 mg monosodium L(+)-tartrate/kg bw per day for males, and equal to 0, 1,190, 2,050, 3,030 and 4,100 mg monosodium L(+)-tartrate/kg bw per day for females) for 104 weeks (Hunter et al., 1977). Urine was collected from five animals/sex from the control group and the highest dose group during weeks 4, 8, 12, 24, 52, 77 and 103 and analysed for pH, specific gravity, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen and haemoglobin. At the same period of time, blood was collected from a total of 15 animals/sex from the control group and the highest dose group. Packed cell volume, haemoglobin, red cell count, white cell count, mean corpuscular haemoglobin and mean cell volume was determined in 10 animals/sex, and plasma urea, plasma glucose, total serum proteins, serum alkaline phosphatase, serum glutamic pyruvic transaminase and electrolyte levels were determined in five animals/sex. The animals sacrificed at the end of the study were subjected to a detailed macroscopic examination. The aorta, lungs, thymus, cervical and mesenteric lymph nodes, pancreas, stomach, caecum, ileum, duodenum, femur, eyes, urinary bladder, salivary gland, trachea, oesophagus, muscle, skin and seminal vesicles were preserved and the brain, pituitary, thyroids, spleen, heart, liver, kidneys, adrenals, testes and ovaries were preserved and weighed. Microscopic examinations were performed on tissues from 15 animals/sex from the high-dose group and 10 animals/sex from the control group. After 2 years, a dosage-related reduction of body weight (15–20% as compared to controls) was observed in male and female rats at the three highest dose levels compared to controls. According to the authors, this may be partially due to the slightly reduced food intake (at most 8%), but the Panel noted that the presence of up to 8% tartaric acid in the diet may have resulted in a nutritional imbalance. There were no treatment-related adverse effects observed in the urinary, haematological or clinical chemistry parameters, or in the ophthalmic examinations. Statistically significant relative organ weight changes included: brain, heart, liver, kidney, uterus and gonad. These increased relative organ weights were mainly due to decreased body weights. Therefore, the Panel considered these increased relative organ weights not of toxicological significance. Histopathological examination did not reveal a difference between treated animals and controls. The Panel considered that monosodium L(+)-tartrate was not carcinogenic and identified an NOAEL of 3,100 mg monosodium tartrate/kg bw per day, the highest dose tested.

Overall, from the two available toxicity studies in rats, the Panel considered that monosodium L+ tartrate was not carcinogenic and identified an NOAEL of 3,100 mg monosodium tartrate/kg bw per day, the highest dose tested.

3.5.6. Reproductive and developmental toxicity

Reproductive toxicity

No studies available.

Developmental toxicity studies

In all studies performed by the Food and Drug Res. Lab. (FDRL, 1973 (Documentation provided to EFSA No. 5)) with tartaric acid (stereoisomeric form not specified) described below, body weights were recorded at regular intervals during gestation and all animals were observed daily for appearance and behaviour. To test the methodology and the sensitivity of the laboratory animals, positive controls were tested. All dams were subjected to caesarean section, and the numbers of implantation sites, resorption sites, live and dead fetuses and body weights of live fetuses were recorded. All fetuses were examined grossly for sex distribution and for external abnormalities (one-third detailed visceral examination and two-third stained and examined for skeletal defects).

Mice

Groups of 20-–22 pregnant CD-1 mice received on gestation day (GD) 6 to 15 dose levels of 0, 2.74, 12.7, 59.1 or 274 mg tartaric acid/kg bw per day by gavage (vehicle was water; dose volume 10 mL/kg bw) (FDRL, 1973 (Documentation provided to EFSA No. 5)). Body weight was determined at GD 0, 6, 11, 15 and 17. All dams were subjected to Caesarean section at GD 17. No maternal or developmental toxicity was detected up to 274 mg tartaric acid/kg bw per day.

Rats

Groups of 19–24 pregnant Wistar rats received on GD 6 to 15 dose levels of 0, 1.81, 8.41, 39.1 or 181 mg tartaric acid/kg bw per day by gavage (vehicle was water; dose volume 1 mL/kg bw) (FDRL, 1973 (Documentation provided to EFSA No. 5)). Body weight was determined at GD 0, 6, 11, 15 and 20. A Caesarean section was carried out on GD 20. The fetal body weight was increased by 11–16% in all treated groups. At fetal examination of the skeletons, the number of fetuses and litters with wavy ribs was increased in all groups dosed with tartaric acid. The Panel considered the effects on wavy ribs not as adverse as there was no dose relationship and normally wavy ribs are associated with lower fetal weights and not as in this study with higher fetal weights. Furthermore, no treatment-related maternal or developmental toxicity was detected up to 181 mg tartaric acid/kg bw per day. No statistical analysis of the data was performed.

Hamsters

Groups of 20–23 pregnant golden hamsters received dose levels of 0, 2.25, 10.45, 48.35 or 225 mg tartaric acid/kg bw per day by gavage (vehicle was water; dose volume 1 mL/kg bw) from GD 6 to 10 (FDRL, 1973). Body weight was determined at GD 0, 8, 10 and 14. On GD 14, a Caesarean section was carried out. There was no evidence for maternal or developmental toxicity up to 225 mg tartaric acid/kg bw per day.

Rabbits

Groups of 15–19 inseminated Dutch-belted rabbits (10–11 pregnant does/group) received via gavage dose levels of 0, 2.15, 10, 46.4 or 215 mg tartaric acid/kg bw per day by gavage (vehicle was water; dose volume 1 mL/kg bw) from GD 6 to 18 (FDRL, 1973 (Documentation provided to EFSA No. 5)). Body weight was determined at GD 0, 6, 12, 18 and 29. On GD 29, a Caesarean section was performed. Fetal weight of the groups dosed with tartaric acid was decreased with approx. 7, 9, 9 and 15% in the 2.15, 10, 46.4 or 215 mg tartaric acid/kg bw per day groups compared to the control group. Furthermore, there was no evidence for maternal or developmental toxicity up to 215 mg tartaric acid/kg bw per day. No statistical analysis was performed.

Overall, no maternal or developmental effects were reported in mice, rats, hamsters or rabbits administered tartaric acid during organogenesis at the highest dose tested (mice: 274 mg/kg bw per day, rats: 181 mg/kg bw per day, hamsters: 225 mg/kg bw per day or rabbits: 215 mg/kg bw per day for 13 days). No studies for reproductive toxicity were available.

3.5.7. Hypersensitivity, allergenicity and food intolerance

No data were available.

3.5.8. Other studies

Sodium tartrate has been used as a laxative (Gold and Zahm, 1943). Forty-three patients with pre-existing constipation were given for 379 days a daily dose of 10 g of sodium tartrate. In this study, 1.6% of the patients experienced nausea and/or vomiting and 2.1% had abdominal cramps.

Potassium sodium tartrate (Rochelle salt) has been used medically as an osmotic laxative in doses of 10 g (corresponding to 143 mg potassium sodium tartrate/kg bw per day for an adult (70 kg)) (Fingl, 1965). This therapeutic use, which corresponds to the bolus intake of a large dose of potassium sodium tartrate in drinking water, was not applicable to the assessment of this tartrate salt as a food additive.

A fatal case was reported of a man having accidentally ingested an aqueous solution containing tartaric acid. (approximately 30 g) (Robertson and Lonnell, 1968). Due to the uncertainties in this report (e.g. composition of the aqueous solution, exact dose ingested, pre-existing health status of the man,…) together with the bolus ingestion of the solution, the Panel considered that this observation was not relevant for the assessment of tartaric acid as a food additive.

Two subjects (A and B, gender not specified) were given sodium L(+)-tartrate in three oral doses of a total of 1.5 mmol/kg per day (corresponding to 285 mg/kg bw per day) for 2 (Subject A) or 4 (Subject B) days (Chadwick et al., 1978). Changes in plasma total CO_2 was measured in subject B and pH, protein and creatinine were measured in urine from both subjects. Urine pH from subject A and B was 5.8 and 7.69 before and at the end of the dosing, respectively. There was no proteinuria, and creatinine clearance did not change after tartrate administration. A slight purgative effect was observed in both subjects and the urine output from subject B rose to 3,500 mL/day during the dosing. The total CO_2 content of venous plasma from subject B was 31.4 mmol/L on the last day

before the dosing; 34 mmol/L on the last day of dosing and 30.3 mmol/L on day 4 after the dosing showing, according to the authors '*that the alkaline urine caused by tartrate was not a consequence of renal damage impairing the mechanism of urinary acidification, but a normal renal response to the mild systemic alkalosis caused by the conversion of ingested sodium tartrate into bicarbonate*'

Potassium tartrate was given in the form of Cal-K® tablets (Somapharm, Lachine, Que.) to 20 healthy volunteers (8 men and 12 women, mean weight 64.6 ± 10.6 kg) for 2 days (Whiting et al., 1991). The daily dose of potassium tartrate was 34 mmol (corresponding to 85–119 mg/kg bw per day). Urine was collected throughout the study. The urinary creatinine excretion did not vary significantly for any subject during the study and no adverse side-effects were reported.

Naqvi (2017) reported four cases of acute tubular necrosis in patients who had consumed 'large amounts of tartaric acid' without specifying the form of tartaric acid (L(+)-, D(-)-, or DL-). In addition, the Panel noted that according to the authors: 'most of patients cannot describe the amount of substances taken'. Therefore, the Panel could not consider this report in the evaluation of tartaric acid and its salts used as food additives (E 334-337).

Using a data-driven computational in silico approach to evaluate the gut microbial metabolites that may affect (i.e. promote or protect) ColoRectal Cancer (CRC), Wang et al. (2018) reported that tartaric acid was associated with a number of genes and suggested that through its fermentation products (e.g. SCFAs), it could play significant roles by participating in many biological functions including cytokines and inflammatory response during the development of CRC. For instance, the SCFA butyrate has a role in the suppression of inflammation and colorectal cancer. The Panel noted that these hypotheses deserved further investigation.

Several case reports and one case series were published on patients diagnosed with kidney or bladder stones consisting of calcium tartrate tetrahydrate (Kleinguetl et al., 2017, 2019). According to Kleinguetl et al. (2019) who identified the cases from a search in the Mayo Clinic patient databank, the incidence of calcium tartrate tetrahydrate stone formation is extremely rare (around 0.007%; 7 cases of calcium tartrate tetrahydrate stones in 100,000 stone patients). Three of the patients diagnosed with calcium tartrate tetrahydrate stones declared they consumed daily for a long period of time, large amounts of vitamin and amino acid supplement energy drink/powders containing, among several other components, 'L-carnitine-L-tartrate' and 'choline bitartrate'. According to Klurfeld (2002), kidney and bladder stones and renal failure observed in rats was associated with the consumption of choline bitartrate in rodent diet due to the substitution of L(+)-tartrate by DL-tartrate that was used for the production of choline bitartrate as an ingredient or due to a toxic contaminant at trace levels introduced into the product at some step in the process, possibly during synthesis of DL-tartaric acid (Klurfeld, 2002). The Panel noted that the formation of kidney stones in rats was also associated with the consumption of racemic choline bitartrate (Kankesan et al., 2003; Newland et al., 2005). The Panel also noted that Le Bail et al. (2009) demonstrated that racemic tartrate was a constituent of the stones observed in rats. The Panel considered that the observations from these studies underline the difference in toxicity between the D(-)- and L(+)- form of tartaric acid.

3.6. Discussion

L(+)-tartaric acid (E 334), sodium tartrate (E 335 (i)), disodium tartrate (E 335 (ii)), potassium tartrate (E 336 (i)), dipotassium tartrate (E 336 (ii)), potassium sodium tartrate (E 337) were previously evaluated by JECFA several times, the latest in 1977 (JECFA, 1962, 1964, 1965, 1974a,b, 1975, 1977, 1978, 1983) and the SCF in 1990 (SCF, 1991b). Both committees established a group ADI of 30 mg/kg bw per day for L(+)-tartaric acid and its potassium and sodium salts.

Information on the manufacturing process of L(+)-tartaric acid using immobilised cells of the bacteria *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012 was submitted.

Rhodococcus ruber has not been reported to be pathogenic to humans. *Rhodococcus sp* strain USA-AN012 shows resistance to gentamycin for which a genetic basis has not been identified. In addition, the strain carries a gene which has been involved in resistance to vancomycin, although the strain was sensitive to this antimicrobial. Since no viable cells from *Rhodococcus sp* USA-AN012 remained in the final product, and the manufacturing conditions were shown able to fully degrade DNA, the use of immobilised cells of the bacteria *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012 was not considered to pose a safety concern.

The Panel considered that the manufacturing process of L(+)-tartaric acid from chemical/microbiological production may result in impurities different from those that may be present in L(+)-tartaric acid as a by-product of wine production. The Panel, therefore, considered that separate

specifications would be needed for L(+)-tartaric acid from chemical/microbiological production using *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012.

The specifications for L(+)-tartaric acid from chemical/microbiological production should include parameters relevant for these specific manufacturing processes:

- proper definition to describe the manufacturing process and the two bacteria, *Rhodococcus ruber* strain CM001 or *Rhodococcus sp* strain USA-AN012, assessed in the current evaluation.
- The absence of DNA in the final product demonstrated (EFSA CEP, 2019).
- The absence of viable cells in the final product demonstrated, using an analytical method (testing at least 1 g of product) (EFSA CEP, 2019).
- maximum limits for heavy metals (e.g. vanadium, molybdenum and tungsten) resulting from the use of any catalyst.

The metabolism of L(+)-tartaric acid and its potassium sodium salt was shown to be species-dependent. In rats, after oral administration, up to 81% of labelled tartrate was absorbed (Underhill et al., 1931a; Chadwick et al., 1978; Gry and Larsen, 1978). In rats, L(+) and D(-)-tartrate were excreted differently in urine after gavage, the L(+)-form being more efficiently excreted than the D(-)-form (Gry and Larsen, 1978). Up to 10% of labelled parenteral tartrate was expired as CO_2 within 6 h and 63% was found in the urine over 24 h, which indicated significant metabolism by tissues (Chadwick et al., 1978). High rate of renal excretion (up to 60% within 12 h) was reported in dogs receiving tartaric acid (Sourkes and Koppanyi, 1950). Underhill et al. (1931a) found that after parenteral injection of tartrate, recovery ranged from 70% in rabbits, dogs and rats to almost 100% in guinea pigs. Therefore, tissue metabolism could not be excluded in these species; however, it played a minor role in disposal of tartrate.

In humans, only 12% of tartrate administered orally appeared in the urine; as this was unrelated to dose absorption was likely passive (Chadwick et al., 1978). The difference in urinary excretion after an oral dose (12%) or an intravenous dose (66%) suggested that only a fraction of the oral dose was systemically available (approximately 18% according to Chadwick et al., 1978). Finkle (1933) found that 91% of an intramuscular dose of unlabelled tartrate was recovered in the urine, which according to the authors, indicated that the human body cannot metabolise tartrate. It must be noted, however, that in the intramuscular part of the study, D-tartrate was most probably used because the author described D-tartrate in the oral part of the study. After an intravenous injection of ^{14}C-L-tartrate, Chadwick et al. (1978) reported that 66% of the radioactivity was excreted in the urine in 22 h, and that 18% was excreted as $^{14}CO_2$ over 8 h. The concentration of $^{14}CO_2$ in expired air peaked after 1 h and contained 7% of the dose suggesting, a rapid metabolism by tissue enzymes. The Panel considered that the different recoveries of 91 and 66% may be due to the different stereospecific forms. However, these recoveries are not directly comparable because radioactivity was measured in one study while unlabelled tartrate was analysed in the other study. Tartrate was fermented by colonic bacteria, with L(+)-tartrate being metabolised faster than D (-)-tartrate (Chadwick et al., 1978). Spiller et al. (2003) reported that tartaric acid/tartrate were fermented by colonic bacteria to SCFAs, which then can be absorbed in the colon (Dawson et al., 1964).

It is necessary to consider whether the hazard could only be due to the parent compounds. In this respect, the metabolic products originating from the metabolism of the unabsorbed tartaric acid/tartrate by the microbiome in the lower part of the gastrointestinal tract have to be evaluated. In the study by Chadwick et al. (1978), the authors confirmed that tartrate is not metabolised to oxalate, a potential metabolite with toxic properties for the kidney; most of the ^{14}C- label was recovered as $^{14}CO_2$. Hence, from the ADME data, it can be concluded that the metabolites would not cause potential side effects.

An LD_{10} value for disodium tartrate above 4,000 mg/kg bw in mice was indicative of a low oral toxicity of tartrate in this species (Locke et al., 1942). Acute renal toxicity was seen in rabbits and dogs after a single oral dose of tartaric acid or Rochelle salt (potassium sodium tartrate) from 26.6 and 600 mg/kg bw (expressed as tartaric acid), respectively (Underhill et al., 1931a).

No adverse effects were observed in rats given 2,730 monosodium L-tartrate/kg bw per day. In the same study, DL-tartaric acid was shown to cause kidney effects. Furthermore, in a 90-day study in rats, an NOAEL of 60 mg/kg bw per day was identified for monopotassium DL-tartrate, based on kidney histological alterations (obstructive nephropathy) reported at higher doses. In rabbits given 550 mg monosodium tartrate/kg bw per day acid (stereoisomeric composition not specified), no adverse effects were observed. Advanced tubular degeneration of the kidneys and increased blood NPN, creatinine and albumin were observed in one out of the four dogs given 990 mg tartaric acid/kg bw per day (stereoisomeric composition not specified), the only dose tested. The Panel considered that the renal effects reported with tartrates were most likely due to the presence of the D(-)-form of tartaric acid only.

L(+)-tartaric acid, monosodium, monopotassium and potassium sodium tartrates did not show a mutagenic potential in several strains of Salmonella typhimurium and *Escherichia coli*. The Panel noted that all studies had shortcomings, however, considering the available data in a weight of evidence approach, there is no concern with respect to a potential for induction of gene mutations. Concerning structural and numerical chromosome aberrations, there are no reliable in vitro data available and one in vivo study was of limited reliability. However, based on these data, there was no indication for structural or numerical chromosomal aberrations. Taking also into account that tartaric acid and tartrates do not have a structural alert for genotoxicity, the Panel considered that, overall, there was no concern for genotoxicity for tartaric acid and its sodium and potassium salts.

A dosage-related reduction of body weight and higher relative weights for a number of organs were reported for rats fed monosodium tartrate at doses equal to or above 1,620 and 2,050 mg/kg bw per day for males and females, respectively, for 2 years (Hunter et al., 1977). These increased relative organ weights were mainly due to decreased body weights. The Panel considered that the decrease in body weights was due to a nutritional imbalance likely due to palatability effect, and therefore, considered these increased relative organ weights not of toxicological significance. Histopathological examination did not reveal a difference between treated animals and controls. From the available chronic and carcinogenicity studies (Fitzhugh and Nelson, 1947; Hunter et al., 1977), the Panel considered that monosodium L(+)-tartrate was not carcinogenic and identified an NOAEL of 3,100 mg monosodium tartrate/kg bw per day, the highest dose tested. The Panel noted that the current ADI of 30 mg/kg bw per day, expressed as tartaric acid and established by the SCF, was derived from this study which was performed with monosodium tartrate.

No maternal or developmental effects were reported at the highest dose tested (mice: 274 mg/kg bw per day, rats: 181 mg/kg bw per day, hamsters: 225 mg/kg bw per day or rabbits: 215 mg/kg bw per day for 13 days). The Panel noted that the doses used in these studies were low; the authors of the report did not explain why they selected these doses; it could be due to the low pH of tartaric acid, which limited the possible amount of this acid to be administered by gavage; it was also noted that in the only toxicity study where tartaric acid and not one of its salt was administered to the animals, the highest dose added to the feed corresponded to only 600 mg/kg bw per day. The Panel considered that there was no indication of maternal or developmental effects from these studies and that owing to the low doses used, the NOAELs that could be identified were not relevant for the derivation of an ADI.

No studies for reproductive toxicity were available, however, no histopathological findings were reported in testes, ovaries and uterus in various studies: Inoue et al. (2015) rats up to 480 mg tartaric acid/kg bw per day for 90 days, Fitzhugh and Nelson (1947) rats up to 600 mg/kg bw per day 2 years, Hunter et al. (1977) rats up to 2400 mg/ kg bw per day for 2 years. In addition, in the CMBEC report (2004), in mice given up to 2,150 mg L(+) tartaric acid/kg bw per day by gavage for 5 days, no statistically significant differences in the frequency of 'cell aberration' in primary spermatocytes were observed in the treated groups compared to the negative control groups.

In humans, sodium tartrate has been used as a laxative; in the Gold and Zahm study (1943), 43 patients with pre-existing constipation were given doses of 10 g of sodium tartrate (daily or once or twice a week, number of doses varying from 1 to 100) and 1.6% of the patients experienced nausea and/or vomiting and 2.1% had abdominal cramps. The Panel noted that sodium tartrate was given as a bolus dose in water for a prolonged period of time and that the symptoms were poorly described. In addition, according to the authors, the study population had chronic constipation and comprised 'patients with heart disease among other health problems'. Accordingly, the Panel considered this observation not relevant for the risk assessment of tartaric acid/tartrates as food additives. Naqvi (2017) reported four cases of acute tubular necrosis in patients who had consumed 'large amounts of tartaric acid'; the amount and form of tartaric acid absorbed were not specified. The Panel noted that adverse effects of tartrate or tartaric acid were observed only after ingestion of high bolus doses of tartaric acid in water, and the form of tartaric acid consumed was not indicated

Derivation of an ADI using a chemical-specific uncertainty factor for tartaric acid-tartrates

A group ADI of 30 mg/kg bw per day was established by JECFA (1974a) and later endorsed by the SCF (SCF, 1991b). This ADI was derived from an NOAEL of 3,000 mg monosodium tartrate/kg bw per day, the highest dose tested in a chronic toxicity study in rats (Hunter et al., 1977), and applying an uncertainty factor of 100.

The Panel considered whether this uncertainty factor would be appropriate given the fact that the absorption of tartaric acid/tartrate is greater in rats than humans. Whereas in the rat the systemic availability was 81%, the systemic availability in humans amounted to 18% (Chadwick et al., 1978).

The Panel decided that the available data on systemic availability were robust enough to derive a chemical-specific uncertainty factor instead of the usual default uncertainty factor of 100.

The default uncertainty factor of 100 is composed of a factor of 10 accounting for the difference between animal and human and a second factor of 10 accounting for the variability in the human population. The two factors consist of two components, one component describing the toxicokinetic difference and variability, respectively, and the other component describing the toxicodynamic difference and variability, respectively. For the toxicokinetic component of the interspecies factor a value of 4 is used when extrapolation is made from the rat to the human (EFSA Scientific Committee, 2012). This factor of 4 is based on allometric scaling from rat to humans. The remaining factor of 2.5 is attributed to the toxicodynamic interspecies difference. The human factor of 10 accounting for the variability in the human population is subdivided into two factors of 3.2 accounting for toxicokinetic and toxicodynamic variability.

In 2004, the IPCS/WHO proposed a framework indicating how chemical-specific toxicokinetic and/or toxicodynamic data can be used to replace the default factors or its subfactors (WHO, 2004).

When considering the systemic toxicity of the parent compounds tartaric acid/tartrates, toxicity is related to the amount, which is given as the internal dose. Accordingly, the external (administrated) dose can be adjusted to the internal dose by taking into account how much is absorbed and systemically available after oral administration. In humans, 18% of the dose is systemically available whereas in rats the figure is 81%. Furthermore, it is to be noted that the rate of metabolism is similar between rats and humans as measured by the rate of expired CO_2. The usual default value for the toxicokinetic differences between rats and humans is 4 assuming that in general the internal human exposure is four times higher than in the rat with the same external dose. In case of tartrate, the situation is reverse; in humans, the internal exposure is 22% of that in rats. Hence, when considering the different absorption in rats and humans, together with the similar rate of metabolism, the interspecies toxicokinetic factor may be reduced to 0.22 instead of 4.

Multiplying this interspecies toxicokinetic factor of 0.22 by the default toxicodynamic factor of 2.5 would result in an interspecies uncertainty factor of 0.55. As a conservative approach, the Panel decided to use an interspecies factor of 1. For the intraspecies factor, the Panel had no information allowing possible modification of the default factor and, therefore, the default factor of 10 was used. Accordingly, the resulting overall uncertainty factor would be 10 (1×10).

Applying the uncertainty factor of 10 to the reference point of 3,100 mg sodium tartrate/kg bw per day, approximately 2,440 mg tartaric acid/kg bw per day, will result in a group ADI for tartaric acid and tartrates (E 334-337 and E 354) of 240 mg/kg bw per day expressed as tartaric acid.

The difference between the ADI established by the SCF and the one derived in this opinion is due to the application of a chemical-specific interspecies uncertainty factor instead of the default uncertainty factor used in previous evaluations.

Dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives was calculated according to different exposure scenarios based on MPLs and the reported use levels, as described in Section 3.4. According to Annex II to Regulation N°1333/2008, tartaric acid and tartrates (E 334-337 and E 354) are authorised in 81 food categories of which 66 under Group I food additives.

For tartaric acid and tartrates (E 334-337 and E 354), use levels were reported by industry for 17 food categories. Based on the information of the Mintel's GNPD, approximately 82% of the food products labelled with tartaric acid and tartrates (E 334-337 and E 354) in this database were considered in the exposure assessment. Based on the observations that

- 100% of the foods belonging to a food category included in the assessment were assumed to contain tartaric acid, whereas the average percentage was 1% according to Mintel's GNPD;
- the possible degradation of tartaric acid at high temperatures was not addressed in the assessment,

the Panel considered that the exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives according to Annex II to Regulation (EC) No 1333/2008 was overestimated in all exposure scenarios (Section 3.4.1).

Tartaric acid and tartrates (E 334-337 and E 354) are used as 'acidity regulator' and are therefore not expected to change the organoleptic properties of the final food at the concentration used as a food additive. For this reason, the Panel considered the *non-brand-loyal scenario* covering the general

population as the most appropriate scenario for risk characterisation. Dietary exposure to tartaric acid and tartrates (E 334-337 and E 354) according to this exposure scenario was up to 91 mg/kg bw per day at the mean level and 174 mg/kg bw per day at the high (P95) level in infants.

A consumer's only scenario including the exposure to tartaric acid-tartrates (E 334-337 and E 354) through the intake of food supplements was also calculated. High (P95) level exposure was up to 93 mg/kg bw per day in children.

Since tartaric acid also occurs naturally in food, the Panel calculated the intake of tartaric acid from natural sources (non-processed fruits and vegetables (corresponding to FC 04.1) and wine), based on the limited available information reported in the literature. This exposure was lower than the calculated exposure from the use of tartaric acid-tartrates as food additives, maximally 26 mg/kg bw per day in the elderly.

Exposure to tartaric acid in addition to via natural occurrence, can also occur by release from other food additives, including tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e), mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f), metatartaric acid (E 353) and stearyl tartrate (E 483). The Panel, therefore, also calculated the potential exposure to tartaric acid from these sources and combined it with the exposure to tartaric acid due to the use of tartaric acid and tartrates (E 334-337 and E 354). The non-brand-loyal exposure scenario was considered for the exposure due to the use of food additives. The exposure to tartaric acid from stearyl tartrate (E 483) was not included in this assessment, as no reported use levels were available for this food additive. The highest P95 level of exposure was estimated for toddlers at 285 mg/kg bw per day.

The Panel noted that the exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use according the Annex III (Parts 2, 3, 4 and 5A) was not considered in the exposure assessment.

The Panel also noted that the refined exposure estimates are based on reported levels of use of tartaric acid and tartrates (E 334-337 and E 354). If actual practice changes, these refined estimates may no longer be representative and should be updated.

Overall, the Panel considered that:

- Only L(+)-tartaric acid and its sodium, potassium and calcium salts are authorised as food additives in the EU and, therefore, the only subject of this assessment.
- L(+)-tartaric acid is naturally present in many fruits (e.g. grapes, apples).
- In many biological studies, the stereoisomeric form of the tartaric acid/tartrate salt used was not specified.
- In humans, salts of tartaric acid although not digested in the small intestine are fermented in the colon to SCFAs, and once absorbed, these SCFAs follow their natural degradation pathway.
- No toxic effects were observed in toxicological studies in which the L(+)-form was tested. In contrast, nephrotoxicity was reported in studies in which the DL-form has been tested and, therefore, it can be associated with the D(-)-form.
- There was no indication for a genotoxic potential of tartaric acid and its sodium and potassium salts.
- There was no indication for carcinogenicity of monosodium L(+)-tartrate at the highest dose tested (3,100 mg /kg bw per day).
- The available studies for maternal or developmental toxicity did not report any relevant effects, no studies for reproductive toxicity were available and no effects on reproductive organs were observed in the chronic toxicity study.
- A total uncertainty factor of 10 was derived by applying a total interspecies uncertainty factor of 1 instead of 10, based on data showing lower internal exposure to tartaric acid in humans compared to rats.
- Applying the total uncertainty factor of 10 to the reference point of 3,100 mg sodium tartrate/kg bw per day, that is approximately 2,440 mg tartaric acid/kg bw per day, will result in a group ADI for tartaric acid and tartrates (E 334-337 and E 354) of 240 mg/kg bw per day expressed as tartaric acid.
- In the various populations, exposure estimates to tartaric acid and tartrates (E 334-337 and E 354) in the non-brand loyal exposure scenario ranged from less than 1 to 91 mg/kg bw per day at the mean and from 2 to 174 mg/kg bw per day at the 95th percentile.
- For calcium tartrate (E 354), no use was reported and only one food was reported to be labelled with this food additive in Mintel's GNPD.

- In the various populations, the combined exposure estimates to tartaric acid from the use of tartaric acid and tartrates (E 334-337 and E 354) and other relevant food additives (E472d, E472f, E472e, E 354), using the non-brand loyal exposure scenario, and natural occurrence ranged from 2 to 130 mg/kg bw per day at the mean and from 8 to 285 mg/kg bw per day at the 95th percentile.
- The calculated exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives according to Annex II to Regulation N°1333/2008, as well as the calculated exposure to tartaric acid from the use of the different relevant food additives (E472d,e,f and E 353) and natural sources are overestimates.

4. Conclusions

The Panel concluded that the data on systemic availability were robust enough to derive a chemical-specific uncertainty factor instead of the usual default uncertainty factor of 100. Therefore, a total uncertainty factor of 10 was derived by applying a total interspecies uncertainty factor of 1 instead of 10, based on data showing lower internal exposure in humans compared to rats.

The Panel established a group ADI for L(+)-tartaric acid and tartrates (E 334-337 and E 354) of 240 mg/kg bw per day, expressed as tartaric acid, by applying the total uncertainty factor of 10 to the reference point of 3,100 mg sodium tartrate/kg bw per day (the highest dose tested), that is approximately 2,440 mg tartaric acid/kg bw per day. Accordingly, the current ADI of 30 mg/kg bw per day is withdrawn.

The group ADI of 240 mg/kg bw per day, expressed as tartaric acid, does not apply to D(-)-,DL- or meso-tartrate.

The exposure estimates for L(+)-tartaric acid and tartrates (E 334-337 and E 354) for the different population groups for the refined non-brand-loyal exposure scenario, which was considered by the Panel as the most relevant scenario, did not exceed the group ADI of 240 mg/kg bw per day, expressed as tartaric acid.

Considering additionally the exposure to tartaric acid from the use of tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e), mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) and metatartaric acid (E 353) and natural occurrence, the P95 level of exposure in toddlers would exceed the group ADI. However, the Panel did not consider this exceedance to indicate a possible health concern, due to the overestimation of the exposure.

Recommendations

The Panel recommended that the European Commission considers:

- Revising the authorisation of DL-tartaric acid as a processing aid (stabilising agent) in wine, according to Commission Regulation (EC) No 934/2019, in the light of the observed nephrotoxic effect of DL-tartaric acid.
- Establishing separate specifications for L(+)-tartaric acid from chemical/microbiological production in Commission Regulation (EU) No 231/2012.
- Revising the EU specifications for monosodium tartrate (E 335(i)), disodium tartrate (E 335(ii), monopotassium tartrate (E 336(i)), dipotassium tartrate (E 336(ii)) and potassium sodium tartrate (E 337) in order to introduce a provision for specific rotation to ensure the exclusive use of the authorised L(+)-stereoisomer in these food additives.
- Revising the EU specifications for disodium tartrate (E 335(ii) in order to correct the mistake where this compound is indicated as 'insoluble' whereas it is soluble.
- Revising the EU specifications for sodium tartrate (E 335(i)) in order to correct the molecular weight to '190.08 g/mol'.
- Harmonising the name for the food additive E 337 in Commission Regulation (EU) No 231/2012 and in the Regulation (EC) No 1333/2008 on food additives. Both Regulations should use the name potassium sodium tartrate for E 337.
- Setting lower maximum limits for toxic elements (lead, mercury and arsenic) in the EU specification for L(+)-tartaric acid (E 334), monosodium tartrate (E 335 (i)), disodium tartrate (E 335 (ii)), monopotassium tartrate (E 336 (i)), dipotassium tartrate (E 336 (ii)), potassium sodium tartrate (E 337) and calcium tartrate (E 354) in order to ensure that their use as food additives will not be a significant source of exposure to these toxic elements in food.

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Abbreviations

ADME	absorption, distribution, metabolism, excretion
ADI	acceptable daily intake
AESGP	Association of the European Self-Medication Industry

ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
bw	body weight
CAS	Chemical Abstracts Service
CONTAM	EFSA Panel on Contaminants
ECHA	European Chemical Agency
EDA	European Dairy Association
ESA	European Snacks Association/SNACMA
EINECS	European Inventory of Existing Commercial Chemical Substances
FAF	EFSA Panel on Food Additives and Flavourings
FC	food category
FCS	food categorisation system
FDE	Food Drink Europe
FIA	flow injection analysis
FSE	Food Supplements Europe
FTIR	Fourier Transform IR
HIPP	HiPP-Werk Georg Hipp OHG
HPLC	high-performance liquid chromatography
ICGA	International Chewing Gum Association
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	lethal dose, median
LOD	limit of detection
LOQ	limit of quantification
MPL	maximum permitted level
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
QS	*quantum satis*
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCF	Scientific Committee on Food
SNE	Specialised Nutrition Europe
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
UPLC-Q/TOF-MS	ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry
WHO	World Health Organization

Appendix A – Summary of the reported use levels (mg/kg or mg/L as appropriate) of tartaric acid and tartrates (E 334-337 and E 354) provided by industry

Appendix B – Summary of analytical results (mg/kg or mg/L as appropriate) of tartaric acid and tartrates (E 334-337 and E 354) provided by Member States

Appendix C –

1. Number and percentage of food products labelled with tartaric acid and tartrates (E 334-337 and E 354) out of the total number of food products present in the Mintel GNPD per food subcategory between 2014 and 2019

2. Number of food products labelled with two food additives: tartaric acid and tartrates (E 334-337 and E 354) out of the total number of food products present in the Mintel GNPD per food subcategory between 2014 and 2019

Appendix D – Concentration levels of tartaric acid and tartrates (E 334-337 and E 354) used in the exposure assessment scenarios (mg/kg or mL/kg as appropriate)

Appendix E – Summary of total estimated exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix F – Main food categories contributing to exposure to tartaric acid and tartrates (E 334-337 and E 354) using the maximum level exposure assessment scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendix G – Summary of total estimated exposure to tartaric acid and tartrates (E 334-337 and E 354) from their use as food additives for the food supplements consumers only exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix H – Summary of tartaric acid levels (mg/kg or mg/L as appropriate) in food as found in literature

Appendix I – Summary of total estimated exposure to tartaric acid from its natural occurrence in the diet, per population group and survey: mean and 95th percentile (mg tartaric acid/kg bw per day)

Appendix J – Concentration levels used in the exposure assessment

Appendix K – Summary of total estimated exposure to tartaric acid from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix L – Main food categories contributing to exposure to tartaric acid using the maximum level exposure assessment scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)