European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the re-evaluation of propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283) as food additives[1]

EFSA Panel on Food additives and Nutrient Sources added to Food (ANS)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The EFSA ANS Panel provides a scientific opinion re-evaluating the safety of propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283) which are authorised as food additives in the EU and have been previously evaluated by the SCF and JECFA. JECFA allocated an ADI "not limited". The SCF concluded that potassium propionate could be added to the list of preservatives and established an ADI "not specified". Propionates are naturally occurring substances in the normal diet. The Panel considered that forestomach hyperplasia reported in long-term studies in rodents is not a relevant endpoint for humans because humans lack this organ. Based on the reported presence of reversible diffuse epithelial hyperplasia in the oesophagus the LOAEL for a 90-day study in dogs was considered by the Panel to be 1 % propionic acid in the diet and the NOAEL to be 0.3 % propionic acid in the diet. The Panel considered that there is no concern with respect to genotoxicity and carcinogenicity. The Panel concluded that the present database did not allow allocation of an ADI for propionic acid - propionates. The overall mean and 95th percentile exposures to propionic acid - propionates resulting from their use as food additives (major contributor to exposure) ranged from 0.7-21.1 and 3.6-40.8 mg/kg bw/day, respectively. The Panel noted that the concentration provoking site of contact effect in the 90-day study in dogs (1 % propionic acid in the diet) is a factor of three higher than the concentration of propionic acid - propionates in food at the highest permitted level and concluded that for food as consumed, there would not be a safety concern from the maximum concentrations of propionic acid and its salts at their currently authorised uses and use levels as food additives.

[1] On request from the European Commission, Question No EFSA-Q-2011-00464, EFSA-Q-2011-00465, EFSA-Q-2011-00466, EFSA-Q-2011-00467, adopted on 3 July 2014.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group "A" Food Additives and Nutrient Sources (2011-2014): Pierre Galtier, Rainer Gürtler, Ursula Gundert-Remy, Claude Lambré, Jean-Charles Leblanc, Pasquale Mosesso, Dominique Parent-Massin, Ivan Stankovic, Christina Tlustos and Matthew Wright for the preparatory work on this scientific opinion and EFSA staff: Ana Rincon and Stavroula Tasiopoulou for the support provided to this scientific opinion.

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KEY WORDS

Propionic acid, CAS 70-09-4, E 280, sodium propionate, CAS 137-40-6, E 281, calcium propionate, CAS 4075-81-4, E 282, potassium propionate, CAS 327-62-8, E 283

SUMMARY

Following a request from the European Commission, the Panel on Food Additives and Nutrient Sources added to Food (ANS) of the European Food Safety Authority (EFSA) was asked to deliver a scientific opinion re-evaluating propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283) when used as food additives.

Propionic acid (E 280), sodium propionate (E 281), potassium propionate (E 282) and calcium propionate (E 283) are authorised food additive in accordance with Annex II of Regulation (EC) No 1333/2008 and have been previously evaluated by the EU Scientific Committee for Food (SCF) in 1974 and 1990, and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1973.

The JECFA allocated an acceptable daily intake (ADI) "not limited" for propionic acid and its sodium, potassium and calcium salts considering that propionate is a normal intermediary metabolite and a normal constituent of foods (JECFA, 1974).

In 1974, the SCF concluded that potassium propionate could be added to the list of preservatives permitted to be used in food (SCF, 1975). In 1990, the SCF concluded that there were no adverse health consequences to man from the present uses of propionic acid as a food additive (SCF, 1992). However, the SCF expressed the need to assess comparative studies with other short chain fatty acids and their salts. The SCF established an ADI "not specified".

Currently, propionic acid - propionates (E 280- 283) are authorised food additives in the EU with maximal permitted levels (MPLs) ranging from 1000 to 3000 mg/kg in foods.

Propionates are naturally occurring substances in the normal diet. Propionic acid is produced by certain bacteria and occurs in various food and feed stuffs as a result of microbial production.

The absorption of short chain fatty acids, including propionate, by the gastrointestinal has been studied both in rats and in humans. The absorption has been described to occur rapidly through the mammalian gastrointestinal tract. The Panel noted that sodium propionate, calcium propionate and potassium propionate will be dissociated in the gastrointestinal tract into propionate and their relevant cations. Therefore, the Panel considered that when assessing systemic (and genotoxic) endpoints, a group evaluation based on the propionate ion was appropriate for propionic acid and its salts. Overall, the ADME data of propionate indicated that oral exposure results in significant absorption. The distribution of the unchanged molecule is unknown whereas radioactivity from orally administered ^{14}C-sodium propionate is distributed in all organs. Propionate is extensively metabolised with approximately 80 % being oxidised to carbon dioxide and excreted by exhalation.

Investigations on in vivo toxicity of the propionates have shown that acute toxicity is low with oral LD_{50} values of 351-4290 mg/kg bw in rats. In repeated doses toxicity studies, propionic acid induced acanthosis and hyperkeratosis of the forestomach mucosa of rats at concentrations of 0.62 %. These lesions were not observed after the recovery period. From a 90-day study in dogs, the Panel identified a no observed adverse effect level (NOAEL) of 0.3 % propionic acid in the diet based on epithelial hyperplasia in the oesophagus in the 1% group that had resolved after a recovery period.

The Panel considered that although the number of reliable genotoxicity studies was limited, there was no concern with respect to genotoxicity for propionic acid, calcium propionate and sodium propionate. No genotoxicity data were available for potassium propionate. However, using a read-across approach, the Panel considered that this conclusion was also applicable to potassium propionate.

In long-term studies, forestomach lesions were reported. However, the Panel considered that forestomach hyperplasia in rodents is not a relevant toxicological endpoint for humans because humans lack this organ and there is an absence of a correlation between forestomach in rats and oesophageal lesions in humans. The Panel concluded that the long-term toxicity studies indicated that propionic acid and propionates were not of concern with respect to carcinogenicity.

Studies on reproductive toxicity of propionic acid and its salts were not available, however, in the 90-day studies in dogs and in rats histopathological investigations of the reproductive organs did not reveal any abnormalities. Developmental toxicity was not observed in rodents up to dose levels of 300 or 400 mg/kg bw/day, the highest dose levels tested. At the highest dose tested no maternal toxicity was observed.

For estimates derived using the MPL, mean exposure to propionic acid - propionates from their use as food additives ranged from 0.7-18.9 mg/kg bw/day in toddlers, 1.7-21.1 mg/kg bw/day in children, 1.4-10.9 mg/kg bw/day in adolescents, 1.3-7.8 mg/kg bw/day in adults and 0.8-8.3 mg/kg bw/day in the elderly. The high exposure to propionic acid - propionates using the MPL ranged from 3.6-36.3 mg/kg bw/day in toddlers, 5.5-40.8 mg/kg bw/day in children, 4.6-22.3 mg/kg bw/day in adolescents, 3.8-16.2 mg/kg bw/day in adults and 2.7-16 mg/kg bw/day in the elderly. The Panel noted that exposure estimates using reported use levels were similar to those from the use of MPLs due to the fact that no major differences were reported for food uses by industry.

The Panel estimated the exposure to propionic acid - propionates from others sources as natural food occurrence based on the levels in food reviewed from literature sources and for flavourings substances based on the data reported by JECFA (JECFA, 1998).

Total combined high exposure to propionic acid - propionates from all sources (food additive, flavouring and natural sources) across the five population groups ranged from 3.0 mg/kg bw/day in the elderly to 41.5 mg/kg bw/day in children. The Panel noted that their use as food additives is the major contributor to exposure.

The Panel noted that considering the differences in their respective molecular weights, it would be justified to establish different MPLs for propionic acid and for propionates.

The Panel concluded that the available toxicity database did not allow allocation of an ADI. The Panel considered that the overall exposure and toxicity data available were sufficient to base a risk assessment on a comparison of exposure and concentrations causing site of contact irritation. The Panel noted that in the 90-day study in dogs, 0.3 % propionic acid in the diet, did not provoke site of contact irritancy and this concentration was equal to the highest maximum permitted level of propionic acid - propionates (3000 mg/kg) in food, in the category of bread and rolls. The Panel noted that the concentration provoking site of contact effect in the 90-day study in dogs (1 % propionic acid in the diet) is a factor of three higher than the concentration of propionic acid - propionates in food at the highest permitted level.

Overall, taking into account of all these considerations including the natural occurrence in food, the Panel concluded that for food as consumed, there would not be a safety concern from the maximum concentrations of propionic acid - propionates [propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283)] at their currently authorised uses and use levels as food additives.

Furthermore, the Panel noted that the specifications for lead are different for propionic acid and its salts and there are specifications for iron and fluoride for the propionic salts but not for the propionic acid. In addition, the Panel further noted that boron trifluoride is used as a catalyst in the manufacturing process of propionic acid and residual amounts of the catalyst could be present in the final product. Therefore, the Panel considered that limits for fluoride and boron should be included in the specifications of propionic acid. The Panel also noted that the pH of a 10 % solution of calcium propionate in the EU specifications (range 6.0 to 9.0) and the JECFA specifications (range 7.5 to 10.5) are different, and the JECFA specifications is in agreement with the one reported in the Food Chemical Codex.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1333/2008[4] 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 Regulation (EU) No 257/2010[5]. 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[6] of 2001. The report "Food additives in Europe 2000[7]" 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.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

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.

[4] OJ L 354, 31.12.2008, p.16.
[5] OJ L 80, 26.03.2010, p.19.
[6] COM(2001) 542 final.
[7] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002:560.

ASSESSMENT

1. Introduction

The present opinion deals with the re-evaluation of the safety of propionic acid (E 280), sodium propionate (E 281), potassium propionate (E 282) and calcium propionate (E 283) when used as food additives.

Propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283) are authorised food additives in the EU in accordance with Annex II to Regulation (EC) No 1333/2008[8] and have been previously evaluated by the EU Scientific Committee for Food (SCF) in 1974 and 1990 (SCF, 1975, 1992) and in 1973 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (1974).

The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that became available since then and the data available following a public call for data.[9] The Panel noted that some original studies, on which previous evaluations were based, were not available for re-evaluation by the Panel.

2. Technical data

2.1. Identity of the substance

2.1.1. Propionic acid

Propionic acid (E 280) is an organic acid with the molecular formula $C_3H_6O_2$. Its molecular weight is 74.08 g/mol and its pKa is 4.6. The CAS Registry Number is 79-09-4 and the EINECS number is 201-176-3. The structural formula is presented in Figure 1.

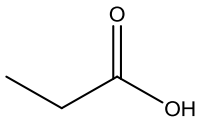

Figure 1: Structural formula of propionic acid

The most commonly known synonyms are propanoic acid, carboxyethane, ethylformic acid, ethanecarboxylic acid and methylacetic acid.

Propionic acid is miscible with water and ethanol (JECFA, 2006).

2.1.2. Sodium propionate

Sodium propionate (E 281) is an organic salt with the molecular formula $C_3H_5O_2Na$. Its molecular weight is 96.06 g/mol. The CAS Registry Number is 137-40-6 and the EINECS number is 205-290-4. The chemical name is sodium propanoate. The structural formula is presented in Figure 2.

[8] 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.

[9] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of preservatives and antioxidants. Published: 23 November 2009. Available online: http://www.efsa.europa.eu/en/dataclosed/call/ans091123a.htm

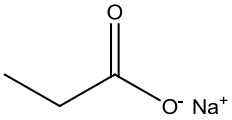

Figure 2: Structural formula of sodium propionate

The most commonly known synonyms are napropion, sodium ethanecarboxylate, propionic acid, sodium salt and propanoic acid, sodium salt.

Sodium propionate is freely soluble in water (1 g/mL, 25 ^{0}C) and soluble in ethanol (1 g/24 mL alcohol, 25 ^{0}C) (FCC, 2010-2011).

2.1.3. Calcium propionate

Calcium propionate (E 282) is an organic salt with the molecular formula $C_6H_{10}O_4Ca$. Its molecular weight is 186.22 g/mol. The CAS Registry Number is 4075-81-4 and the EINECS number is 223-795-8. The chemical name is calcium propanoate. The structural formula is presented in Figure 3.

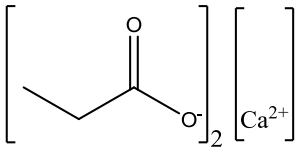

Figure 3: Structural formula of calcium propionate

The most commonly known synonyms are propionic acid, calcium salt and propanoic acid, calcium salt (2:1).

Calcium propionate is freely soluble in water (1 g/3 mL, 25 ^{0}C) (FCC, 2010-2011) and soluble in ethanol (JECFA, 2006).

2.1.4. Potassium propionate

Potassium propionate (E 283) is an organic salt with the molecular formula $C_3H_5O_2K$. Its molecular weight is 112.17 g/mol. The CAS Registry Number is 327-62-8 and the EINECS number is 206-323-5. The chemical name is potassium propanoate. The structural formula is presented in Figure 4.

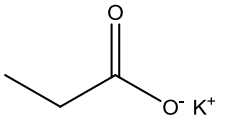

Figure 4: Structural formula of potassium propionate

Potassium propionate is freely soluble in water and soluble in ethanol (JECFA, 2006).

2.2. Specifications

Specifications of propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283) have been defined in Commission Regulation (EU) No 231/2012[10] and by JECFA (2006) (Table 1- 4).

[10] 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.

Table 1: Specifications for propionic acid (E 280) according to Commission Regulation (EU) No 231/2012 and to JECFA (2006)

	Commission Regulation (EU) No 231/2012	**JECFA (2006)**
Description	Colourless or slightly yellowish, oily liquid with a slightly pungent odour	An oily liquid with a slightly pungent odour
Melting point	-22°C	
Distillation range	138.5°C to 142.5°C	138.5 - 142.5°
Specific gravity	-	d^{20}_{20}:0.993-0.997
Solubility	-	Miscible with water and ethanol
Assay	Content ≥ 99.5 %	≥ 99.5 % on the dried basis
Non-volatile residue	≤ 0.01 % when dried at 140 °C to constant weight	≤ 0.01 % when dried at 140° to constant weight
Aldehydes	≤ 0.1 % (expressed as formaldehyde)	≤ 0.2 % (as propionaldehyde)
Arsenic	≤ 3 mg/kg	-
Lead	≤ 2 mg/kg	≤ 2 mg/kg
Mercury	≤ 1 mg/kg	-
Formic acid	-	≤ 0.1 %

Table 2: Specifications for sodium propionate (E 281) according to Commission Regulation (EU) No 231/2012 and to JECFA (2006)

	Commission Regulation (EU) No 231/2012	**JECFA (2006)**
Description	White crystalline hygroscopic powder, or a fine white powder	White or colourless, hygroscopic crystals with not more than a faint characteristic odor
Assay	Content ≥ 99 % after drying for two hours at 105 °C	≥ 99.0 % on the dried basis
Test for propionate	Passes test	Recognition of propionic acid by the odour when warmed with sulfuric acid.
Test for sodium		Passes test
Solubility	-	Freely soluble in water, soluble in ethanol
Test for alkali salt of organic acid	-	Ignite the sample. The alkaline residue effervesces with acid.
pH (10 % aqueous solution)	7.5-10.5	7.5-10.5
Loss on drying (105°, 2 h)	≤ 4 %	≤ 4 %
Water insolubles	≤ 0.1 %	≤ 0.1 %
Iron	≤ 50 mg/kg	≤ 50 mg/kg
Arsenic	≤ 3 mg/kg	-
Lead	≤ 5 mg/kg	≤ 5 mg/kg
Mercury	≤ 1 mg/kg	-

Table 3: Specifications for calcium propionate (E 282) according to Commission Regulation (EU) No 231/2012 and to JECFA (2006)

	Commission Regulation (EU) No 231/2012	**JECFA (2006)**
Description	White crystalline powder	White crystals, powder or granules with not more than a faint odor of propionic acid
Assay	≥ 99 %, after drying for two hours at 105 °C	≥ 98.0 % on the dried basis
Test for propionate	Passes test	Recognition of propionic acid by the odour when warmed with sulfuric acid
Test for calcium		Passes test
Solubility	-	Freely soluble in water, soluble in ethanol
Test for alkali salt of organic acid	-	Ignite the sample. The alkaline residue effervesces with acid
pH	6.0 - 9.0 (10 % aqueous solution)	7.5 - 10.5 (1 in 10 solution)
Loss on drying (105°, 2 h)	≤ 4 %	≤ 4 %
Water insolubles	≤ 0.3 %	≤ 0.3 %
Iron	≤ 50 mg/kg	≤ 50 mg/kg
Fluoride	≤ 10 mg/kg	≤ 30 mg/kg
Arsenic	≤ 3 mg/kg	-
Lead	≤ 5 mg/kg	≤ 5 mg/kg
Mercury	≤ 1 mg/kg	-

Table 4: Specifications for potassium propionate (E 283) according to Commission Regulation (EU) No 231/2012 and to JECFA (2006)

	Commission Regulation (EU) No 231/2012	**JECFA (2006)**
Description	White crystalline powder	White or colourless crystals
Assay	Content ≥ 99 % after drying for two hours at 105 °C	≥ 99 % on the dried basis
Test for propionate	Passes test	Recognition of propionic acid by the odour when warmed with sulfuric acid.
Test for potassium		Passes test
Solubility	-	Freely soluble in water, soluble in ethanol
Test for alkali salt of organic acid	-	Ignite the sample. The alkaline residue effervesces with acid.
pH	-	7.5 - 10.5 (1 in 10 solution)
Loss on drying (105°, 2 h)	≤ 4 %	≤ 4 % (
Water insolubles	≤ 0.1 %	≤ 0.1 %
Iron	≤ 30 mg/kg	≤ 30 mg/Kg
Fluoride	≤ 10 mg/kg	-
Arsenic	≤ 3 mg/kg	-
Lead	≤ 5 mg/kg	≤ 5 mg/kg
Mercury	≤ 1 mg/kg	-

The Panel noted that the pH range in the EU specifications (6.0 - 9.0 of a 10 % solution of calcium propionate) and the JECFA specifications (7.5 -10.5) are different. According to the Food Chemical

Codex (FCC, 2010-2011) the pH of a 10 % aqueous solution of calcium propionate is between 7.5 and 10.5.
The Panel noted that the specifications for lead are different for propionic acid and its salts and there are specifications for iron and fluoride for the propionic acid salts but not for the propionic acid. In addition, the Panel further noted that boron trifluoride is used as a catalyst in the manufacturing process of propionic acid and residual amounts of the catalyst could be present in the final product. Therefore, the Panel considered that limits for fluoride and boron should be included in the specifications of propionic acid.

2.3. Manufacturing process

2.3.1. Propionic acid

The industrial production of propionic acid is almost entirely by petrochemical routes. The acid can also be obtained from oxidation of propionaldehyde and very pure propionic acid can be obtained from propionitrile. The synthetic processes most used to produce propionic acid are via the Reppe process from ethylene, carbon monoxide and steam and via the Larson process from ethanol and carbon monoxide using boron trifluoride as catalyst (Boyaval and Corre, 1995). According to industry this latest process is used for the production of propionic acid (BASF, 2012).

In the literature, methods for producing propionic acid and propionates by microbial fermentation with *Propionibacterium* are described (Li et al., 2010, 2013), however according to Boyaval and Corre (1995) none of them is employed in the commercial manufacturing process.

2.3.2. Sodium propionate, calcium propionate and potassium propionate

Following a public call for data, industry submitted data on the manufacturing process in line with the already publically available information (Kemira, 2010). Sodium propionate (E 281) is produced from propionic acid and sodium hydroxide in hydrogen peroxide and water. After the reaction the product is filtered, spray dried, sieved and packed. Calcium propionate (E 282) is produced by the reaction of propionic acid and calcium oxide in water in the presence of a flocculant. The product is filtered, spray dried, sieved and packed. For potassium propionate, no description of manufacturing methods was readily retrievable.

2.4. Methods of analysis in food

Following a public call for data, industry submitted information on the use of an HPLC method for the analysis of organic acids (formic acid, acetic acid, sorbic acid and propionic acid) in animal feed (Kemira, 2010).

Several methods for the determination of propionates in food have been described: a simplified technique for the determination of propionates in bread by isolation using micro-diffusion (Karasz and Hallenbeck, 1972); a gas chromatographic method to determine the content of propionic acid in rye bread and margarine (Graveland, 1972); a gas chromatographic determination of propionic acid in "sweet oven products" or *prodotti dolciari al forno* (Cuzzoni, 1964); a gas chromatographic determination to determine the content of propionic acid in various types of bread and sourdough (Luck et al., 1975); an isothermal gas chromatographic determination of the propionic acid after mechanical extraction from bread and cake (Isshiki et al., 1981); a specific chromatographic method for the determination of propionate in white rye and whole grain bread (Lamkin et al., 1987); a gas chromatographic determination of propionic acid and propionates in bakery products (Khaldun et al., 2010).

Several publications in Chinese describe contemporary methods for the analysis of propionate. A method has been developed for the determination of eleven preservatives (including propionic acid) in food samples by GC-FIP (Gu et al., 2012). An HPLC method (hydrogen ion exchange column) for the simultaneous determination of ten organic acids (including propionic acid) has been described (Chen et al., 2012). An HPLC method for the quantitative determination of sodium propionate and calcium

propionate in different foodstuff (cake, dry soybean, sausage, noodle, etc.) has been described (Liang, 2009) and also quantitative determination of sodium propionate and calcium propionate (transformed into propionic acid) in food has been reported by capillary gas chromatography (Gao and Zhao, 2012). A new method for the quantitative determination of calcium propionate in cakes by ion chromatography with suppressed conductivity detection has been investigated (Dai et al., 2013).

2.5. Reaction and fate in food

No data have been found in relation to reaction and fate in food of propionic acid and its salts as food additives.

Following a public call for data, no information was obtained on the specific reactions and fate in food. However, information was provided by industry indicating that the stability of sodium or calcium propionate in their original packaging is 3 years. Industry also indicated that, when sodium or calcium propionate is used in the concentration range of 0.2-0.5 % for standard bread recipes, the odour of propionates may be noticed when the bread is still hot, but it rapidly disappears during cooling (Kemira, 2010).

2.6. Case of need and proposed uses

Maximum permitted levels (MPLs) of propionic acid - propionates (E 280, E 281, E 282 and E 283) have been defined in the Annex II of Regulation (EC) No 1333/2008 on food additives.

Currently, propionic acid - propionates are authorised food additives in the EU with MPLs ranging from 1000 to 3000 mg/kg in foods.

Table 5 summarises foods that are permitted to contain propionic acid - propionates and the corresponding MPLs as set by Annex II of Regulation (EC) No 1333/2008.

Table 5: MPLs of propionic acid - propionates in foods according to the Annex II of Regulation (EC) No 1333/2008

Category number	Foods	Restrictions/exceptions	MPL (mg/L or mg/kg as appropriate)
01.7.2	Ripened cheese	surface treatment only	*quantum satis*
01.7.6	Cheese products (excluding products falling in category 16)	only ripened products surface treatment	*quantum satis*
01.8	Dairy analogues, including beverage whiteners	only cheese analogues (surface treatment only)	*quantum satis*
07.1	Bread and rolls	only prepacked sliced bread and rye bread	3000[(a)]
07.1	Bread and rolls	only energy-reduced bread, partially baked prepacked bread and prepacked rolls and pitta, prepacked polsebrod, boller and dansk flutes	2000[(a)]
07.1	Bread and rolls	only prepacked bread	1000[(a)]
07.2	Fine bakery wares	only prepacked fine bakery wares (including flour confectionery) with a water activity of more than 0,65	2000[(a)]
16	Desserts excluding products covered in categories 1, 3 and 4	only *Christmas pudding*	1000[(a)]

[(a)] Propionic acid and its salts may be present in certain fermented products resulting from the fermentation process following good manufacturing practice.

The Panel noted that considering the differences in their respective molecular weights, it would be justified to establish different MPLs for propionic acid and for propionates.

Sodium propionate (E 281) is also permitted to be used as a food additive in food enzymes, according to Annex III of Regulation (EC) No 1333/2008. It may be used according to *quantum satis* in the enzyme preparation resulting in a maximum of *quantum satis* in the final food, except for beverages, where a maximum level of 50 mg/L sodium propionate (E 281) from the use in enzymes is authorised.

2.7. Reporting use levels or data on analytical levels of propionic acid - propionates

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. For those food additives where no MPL is set and which are authorised as *quantum satis*, information on actual use levels is required for performing an exposure assessment.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Regulation (EU) No 257/2010[11] regarding the re-evaluation of approved food additives, EFSA issued a public call[12] for scientific data on propionic acid - propionates (E 280, E 281, E 282 and E 283) including present use and use patterns (i.e. which food categories and subcategories, proportion of food within categories/subcategories in which it is used, actual use levels (typical and maximum use levels), especially for those uses which are only limited to *quantum satis*).

2.7.1. Summarised data on reported use levels in foods from industries and other sources

Appendix A provides data on the use levels of propionic acid - propionates in foods as reported by industry and on analysed levels. Appendix A also shows the levels used for the refined exposure assessment identified by the Panel and based on data for several food categories in finished products reported by industry or analytical data from other sources (Member States, scientific literature …).

Industry provided usage levels to EFSA for 2 out of the 6 food categories in which propionic acid - propionates are authorised. Information on the actual use levels of propionic acid - propionates in foods was made available to EFSA by Kemira (2010) for bread and rolls (FCS Category 7.1). Additional information on the actual use levels of propionic acid - propionates has been provided by FoodDrinkEurope (FDE, 2012) for the food categories of bread and rolls (FCS Category 7.1) and fine bakery wares (FCS Category 7.2).

Additionally, analytical data on the concentration of propionic acid - propionates in foods were made available by the Food Standards Agency (FSA, 1992; 1993) and the Food Safety Authority of Ireland (FSAI, 2011) for bread and rolls (FCS Category 7.1), fine bakery wares (FCS Category 7.2) and desserts (FCS Category 16 – desserts excluding products covered in FCS Categories 1, 3 and 4).

For the food categories: ripened cheese (FCS Category 1.7.2), cheese products (excluding products falling in FCS Category 16) (FCS Category 1.7.6) and dairy analogues, including beverage whiteners (FCS Category 1.8), where the use of propionic acid - propionates is authorised according to *quantum satis*, neither usage nor analytical data have been made available. Therefore, the value of 3000 mg/kg indicated in the Codex Alimentarius[13] has been considered for the exposure assessment.

2.8. Information on existing authorisations and evaluations

Propionic acid and its calcium, potassium and sodium salts are authorised as food additives in the EU in accordance with Annex II to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Propionic acid and its calcium, potassium and sodium salts were evaluated by JECFA in 1973 (JECFA, 1974). JECFA considered that propionate was a normal intermediary metabolite and a

[11] 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 133/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010.

[12] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of preservatives and antioxidants. Published 23 November 2009. http://www.efsa.europa.eu/en/dataclosed/call/ans091123a.pdf

[13] Available online: http://www.codexalimentarius.net/gsfaonline/additives/details.html?id=370

normal constituent of foods, and despite only one chronic toxicity study (1-year) being available (Graham et al., 1954), allocated an acceptable daily intake (ADI) for man "not limited"[14].

In 1974, the SCF concluded that potassium propionate could be added to the list of preservatives permitted to be used in food (SCF, 1975). In 1990, the SCF established an ADI "not specified"[15] (SCF, 1992).

Propionic acid and its salts have also been reviewed by BIBRA (1991) and TemaNord (2002).

According to the OECD Screening Information Data Set (OECD SIDS), propionic acid was evaluated in 2007 (OECD SIDS, 2007) and it was concluded that propionic acid was considered of low priority for human risk assessment.

The US Environmental Protection Agency (EPA) reviewed propionic acid and its calcium and sodium salts as active ingredients in pesticides (EPA, 2010).

EFSA has evaluated a mixture of sodium benzoate, propionic acid and sodium propionate as a feed additive and concluded that "*the additive is safe for the consumer and environment and for the user*" based on the consideration that propionic acid is a substance which occurs in the human body in the normal intermediate metabolism (EFSA FEEDAP Panel, 2011).

Propionic acid is a flavouring substance (FL-No. 08.003) included in the Union list of flavourings (Commission Implementing Regulation (EU) No 872/2012[16]. Propionic acid as flavouring substance was evaluated by JECFA in 1998 (JECFA, 1998) and therefore there is no need for its re-evaluation as a flavouring substance (Commission Regulation (EC) No 1565/2000[17])

Propionic acid and its salts, sodium and calcium propionate, are included in the Database of Select Committee on GRAS Substances[18] and they are food additives permitted for use in Canada[19]. The Panel noted that potassium propionate is not included in these lists.

Propionic acid has been registered under the REACH Regulation 1907/2006[20] (ECHA, online).

2.9. Dietary exposure assessment of propionic acid - propionates

2.9.1. Food consumption data used for the exposure assessment

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with data from national information on food consumption at a detailed

[14] A term no longer used by JECFA that has the same meaning as ADI "not specified". JECFA glossary of terms. Available online: http://www.who.int/foodsafety/chem/jecfa/glossary.pdf

[15] According to the SCF (1990) "*ADI not specified is a term used when, on the basis of the available toxicological, biochemical and clinical data, the total daily intake of the substance, arising from its natural occurrence and/or its present use or uses in food at the levels necessary to achieve the desired technological effect, will not represent a hazard to health. For this reason, the establishment of a numerical limit for the ADI is not considered necessary for these substances. Any additive allocated as "ADI not specified" must be used according to good manufacturing practice, i.e. it should be technological efficacious, should be used at the lowest level necessary to achieve its technological effect, should not conceal inferior quality or adulteration, and should not create a nutritional imbalance".*

[16] Commission implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting a list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012.

[17] Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council. OJ L 180, 19.7.2000.

[18] Available online:http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=259

[19] Available online: http://www.hc-sc.gc.ca/fn-an/securit/addit/diction/dict_food-alim_add-eng.php#p

[20] 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.

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 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a)).

The food consumption data gathered by EFSA were collected using different methodologies and thus direct country-to-country comparison should be made with caution.

For calculation of chronic exposure, intake statistics have been calculated based on individual average consumption over the total survey period, excluding surveys with only one day per subject. High level consumption was only calculated for those foods and population groups where the sample size was sufficiently large to allow calculation of the 95th percentile (EFSA, 2011a). The Panel estimated chronic exposure for the following population groups: toddlers, children, adolescents, adults and the elderly. Calculations were performed using individual body weights.

Thus, for the present assessment, food consumption data were available from 26 different dietary surveys carried out in 17 European countries as mentioned in Table 6.

Table 6: Population groups considered for the exposure estimates of propionic acid - propionates

Population	Age range	Countries with food consumption surveys covering more than one day
Toddlers	from 12 up to and including 35 months of age	Belgium, Bulgaria, Finland, Germany, Italy, Netherlands, Spain
Children[21]	from 36 months up to and including 9 years of age	Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden
Adolescents	from 10 up to and including 17 years of age	Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Italy, Latvia, Spain, Sweden
Adults	from 18 up to and including 64 years of age	Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Spain, Sweden, United Kingdom
The elderly[21]	from 65 years of age and older	Belgium, Denmark, Finland, France, Germany, Hungary, Italy

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 as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates.

For the calculation of the exposure estimates, the food categories in which the use of propionic acid – propionates is authorised were selected from the nomenclature of the Comprehensive Database (FoodEx classification system codes), at a detailed level (FoodEx classification levels 2-4) (EFSA, 2011b) (Appendix A).

2.9.2. Exposure to propionic acid - propionates from their use as food additives

Exposure to propionic acid - propionates from their use as food additives were calculated using MPLs as listed in Table 5 and data on reported use levels or data reported on analytical levels as listed in Appendix A (refined exposure assessment), combined with national consumption data for the five population groups (Table 6).

[21] The terms "children" and "the elderly" correspond respectively to "other children" and the merge of "elderly" and "very elderly" in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

Exposure estimates were derived based on individual food consumption data, at a refined level taking into consideration FoodEx classification levels 2-4, as appropriate.

However, the Panel noted that its estimates should be considered as being conservative as it was assumed that all processed foods contain the food additives propionic acid - propionates added at the MPLs or the maximum reported levels.

Table 7 summarises the estimated exposure to propionic acid - propionates from their use as food additives for all five population groups (Table 6).

Table 7: Summary of anticipated exposure to propionic acid - propionates from their use as food additives using MPLs and reported use levels or analytical data on use levels in five population groups (min-max across the dietary surveys in mg/kg bw/day)

	Toddlers (12-35 months)	Children (3-9 years)	Adolescents (10-17 years)	Adults (18-64 years)	The elderly (>65 years)
Estimated exposure using MPLs					
Mean	0.7-18.9	1.7-21.1	1.4-10.9	1.3-7.8	0.8-8.3
High level[22]	3.6-36.3	5.5-40.8	4.6-22.3	3.8-16.2	2.7-16
Estimated exposure using reported use levels or analytical data					
Mean	0.7-18.9	1.7-21.1	1.4-10.1	1.3-7.5	0.8-8.3
High level[22]	3.6-36.3	5.5-40.8	4.6-21.4	3.8-16.2	2.7-16

A summary of the total estimated exposure (using MPLs and data on reported use levels or data reported on analytical levels) detailed per age class and survey is presented in Appendix B.

2.9.3. Main food categories contributing to the exposure to propionic acid - propionates using MPLs and reported use levels or reported data on analytical levels

Table 8: Main food categories contributing to the exposure to propionic acid - propionates using MPLs and reported use levels or reported data on analytical levels (> 5 % to the total mean exposure) and number of surveys in which each food category is contributing

FoodEx Category Number[(a)]	Food Categories	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (Number of Surveys[(b)])				
A.01.04	Bread and rolls	18-80 (9)	15-89 (15)	48-90 (11)	6-83 (15)	8-87 (13)
A.01.07	Fine bakery wares	7-21 (8)	9-69 (15)	8-64 (11)	5-29 (12)	5-19 (7)
A.08.08	Cheese	6-82 (8)	6-85 (15)	6-36 (10)	9-94 (14)	14-92 (13)

(a) EFSA, 2011b.
(b) The total number of surveys may be greater than the total number of countries as listed in Table 6, as some countries submitted more than one survey for a specific age range.

2.9.4. Exposure via other sources

2.9.4.1. Via regular diet

Propionic acid is a naturally occurring carboxylic acid in milk products, and occurs as a product of bacterial fermentation. Organic acids occur in dairy products as a result of normal animal metabolism and breakdown of milk proteins, fat, lactose and citrate during manufacture and storage. Propionic acid is a major contributor to the characteristic nutty sweet flavour of Swiss-type cheeses, including Emmental, Gruyère, and Appenzeller, and, consequently, *Propionibacteria* play an important role in the production of propionic acid in cheese (Lee et al., 2010). The content of propionic acid occurring naturally in food was reported in the food categories listed in Appendix C.

[22] Typically 95th percentile of consumers only.

Information on natural occurrence of propionic acid in foods is also available from the Volatile Compounds in Food (VCF) database (TNO, 2009), giving a quantity range of 0 – 25 g/kg (see Appendix C).

The specific natural occurrence of propionic acid and propionates in certain foods over a broad range of food types makes estimation of exposure from natural occurrence difficult. A large variation in occurrence for the same type of food is also observed, which in many cases is likely dependent on the state of fermentation of the food.

To provide a crude estimate of intake of naturally occurring propionic acid, maximum mean values within each food category, or where appropriate for individual foods, have been used (Appendix C). Table 9 provides an overview of the so derived values used for estimating intake of propionic acid from natural sources and the food groups from the Comprehensive Database used for this estimate. Considering that only foods for which occurrence data were available have been taken into account in this estimate, the latter only serves as a crude "snap shot" intake estimate. The actual natural occurrence and the range of concentrations are assumed to be highly variable, therefore the magnitude of over- or under-estimation cannot be determined. Table 10 provides the anticipated exposure to propionic acid - propionates from natural occurrence in foods.

Table 9: Levels and Comprehensive Database (FoodEx) food categories used to estimate intake of "propionic acid"[23] from natural sources

FoodEx Level 1	FoodEx Level 2	FoodEx Level 3	Naturally occurring levels (mg/kg)
Vegetables and vegetable products	Tea and herbs for infusions (Solid)		0.5
	Coffee beans and coffee products (Solid) (excluding instant)		87.7
	Vegetable products	Sauerkraut	0.1
	Fungi, cultivated		4.4
	Fungi, wild, edible		4.4
Fruit and fruit products	Stone fruits	Plums	0.02
	Berries and small fruits	Strawberries	0.025
		Black-, Rasp- and Boysenberries	0.015
		Currants (red, black and white)	0.02
Fish and other seafood	Fish meat		3.5
	Fish products		3.5
	Crustaceans		97.4
	Water molluscs	Mussels	2.7
		Oyster	0.002
Milk and dairy products	Liquid milk		90
	Milk based beverages		90
	Concentrated milk		90
	Whey and whey products		90
	Cream and cream products		90
	Fermented milk products		21.6
	Cheese	Cheese, general	1565
		Cheese, blue	287
		Cheese, Cheddar	1620
		Cheese, Emmental (Swiss)	3105
Sugar and confectionary	Honey		0.2

[23] The Panel considered that the term "propionic acid" may cover also propionates.

FoodEx Level 1	FoodEx Level 2	FoodEx Level 3	Naturally occurring levels (mg/kg)
Fruit and vegetable juices	Fruit juice	Juice, Arctic bramble	0.15
Non-alcoholic beverages (excluding milk based beverages)	Tea (Infusion)		0.005[(a)]
	Coffee (Beverage)		4.87[(b)]
Alcoholic beverages	Beer and beer-like beverage		3.2
	Wine		10
	Fortified and liqueur wines	Sherry	0.1
	Wine-like drinks	Cider	1
	Spirits	Brandy	5.5
		Whisky	8
		Rum	2.1
Herbs, spices and condiments	Condiment	Wine and apple vinegar	70
		Soy sauce	10.6
	Savoury sauces	Fish sauce	23

[(a)] A dilution factor of 100 has been applied in the exposure calculations (tea as consumed).

[(b)] A dilution factor of 18 has been applied in the exposure calculations (coffee as consumed).

Table 10: Summary of anticipated exposure to propionic acid - propionates from natural sources using occurrence data reported in the literature in five population groups (min-max across the dietary surveys in mg/kg bw/day)

	Toddlers (12-35 months)	Children (3-9 years)	Adolescents (10-17 years)	Adults (18-64 years)	The elderly (>65 years)
Mean	1.4 - 5.8	0.6 - 3.8	0.5 - 1.9	0.4 - 1.4	0.7 - 1.3
High level[24]	4 - 10	2.4 - 8.9	1.3 - 4.2	0.9 - 3.2	1.7 - 3.2

2.9.4.2. Propionic acid used as a flavouring substance

Exposure estimates of propionic acid from its use as a flavouring substance were derived in 1998 by JECFA (JECFA, 1998) and are shown in Table 11. Estimates provided are based on the maximised survey-derived daily intake (MSDI) approach.

Table 11: Annual production and estimated per capita intake of propionic acid as a flavouring substance in the USA and Europe (JECFA, 1998)

Propionic acid	Most recent annual production volume[(a)] tonnes	Daily Per Capita Intake[(b)] ("eaters only")	
		µg/day (mg/day)	µg/kg bw/day (mg/kg bw/day)
USA	27	5200 (5.2)	86 (0.09)
Europe	8	1100 (1.1)	19 (0.02)

(a) USA: National Academy of Science (NAS, 1987). Evaluating the safety of food chemicals. Washington, DC. Europe: International Organization of the Flavour Industry (IOFI, 1995). European inquiry on volume of use. Private communication to FEMA.

(b) Intake calculated as follows: [[(annual volume, kg) x (1 x 109 µg/kg)]/ [population x 0.6 x 365 days]], where population (10%, "eaters only") = 24 x 106 for the USA and 32 x 106 for Europe; 0.6 represents the assumption that only 60% of the

[24] Typically 95th percentile of consumers only

flavour volume was reported in the survey (NAS, 1987; IOFI, 1995). Intake (µg/kg bw/day) calculated as follows: [µg/day/body weight], where body weight = 60 kg. Slight variations may occur from rounding off.

2.9.5. Total estimated exposure to propionic acid - propionates from all sources (food additive, flavouring and natural sources)

Table 12 provides an overview of the data considered for the estimation of the total exposure to propionic acid - propionates from their use as food additives, as flavouring substance and from natural occurrence. It further provides an estimate of the combined exposure from these sources.

Table 12: Total estimated exposure to propionic acid - propionates from all sources (food additive, flavouring substance and natural sources) in five population groups (min-max across the dietary surveys in mg/kg bw/day)

Estimated range of exposure from:	Toddlers		Children		Adolescents		Adults		The elderly	
	Mean	High level	Mean	High level	Mean	High level	Mean	High level	Mean	High level
Use as food additives [(a)]	0.7-18.9	3.6-36.3	1.7-21.1	5.5-40.8	1.4-10.1	4.6-21.4	1.3-7.5	3.8-16.2	0.8-8.3	2.7-16
Natural occurrence in food	1.4-5.8	4 - 10	0.6 -3.8	2.4- 8.9	0.5- 1.9	1.3-4.2	0.4- 1.4	0.9- 3.2	0.7- 1.3	1.7- 3.2
Use as flavouring substance in food (MSDI) [(b)]	0.02		0.02		0.02		0.02		0.02	
Combined exposure range from all sources[(c)(d)]	3.5-19.3	10.1-37	3.2-21.7	8.6-41.5	2.1-10.4	5.4-22.1	1.7-7.7	4.3-16.4	1.2-8.5	3-16.3

[(a)] Estimated exposure using reported use levels or analytical data (Table 7).
[(b)] Based on per capita intake
[(c)] For combined estimation of occurrence in cheese, it was assumed that natural occurrence (if any) and/or use as additive (if any), singly or in combination would on average not exceed 3000 mg/kg, i.e. the maximum permitted level set by Codex Alimentarius (2008, 2010).
[(d)] Calculated in combination, using individual raw data. Minimum and maximum intake values of the range of means reported for food additive intake only and from natural sources only do not refer to the same countries, therefore the minimum and maximum values reported here do not correspond to summed up minimum and maximum values for the separately calculated components of the combined estimate.

Total combined mean exposure to propionic acid - propionates from all sources was estimated up to 19.3 mg/kg bw/day in toddlers, 21.7 mg/kg bw/day in children, 10.4 mg/kg bw/day for adolescents, 7.7 mg/kg bw/day in adults and 8.5 mg/kg bw/day in the elderly.

Total combined high exposure to propionic acid - propionates from all sources across the five population groups ranged from 3.0 mg/kg bw/day in the elderly to 41.5 mg/kg bw/day in children.

Table 13: Percentage contribution to propionic acid - propionates intake from their use as food additives, flavouring substance and from natural food occurrence to the total combined mean exposure from all sources in five population groups (min-max in %)

	Toddlers	Children	Adolescents	Adults	The elderly
	% Min-Max (of mean exposure)				
Food additive	19-96	41-97	70-98	77-99	68-98
Natural sources	7-90	6-80	5-43	6-65	12-66
Flavouring	0.1-0.6	0.1-0.6	0.2-1.0	0.3-1.2	0.2-1.6

2.9.6. Uncertainty analysis

Uncertainties in the exposure assessment of propionic acid - propionates have been discussed above. According to 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 below:

Table 14: Qualitative evaluation of influence of uncertainties

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies / representativeness / under reporting / misreporting / no portion size standard	+/-
Use of data from food consumption survey of few days to estimate long-term (chronic) exposure	+
Correspondence between reported use levels and food items in the consumption database: uncertainties on which precise types of food the use levels refer	+/-
MSDI approach to estimate exposure from food flavouring use	-
Natural fluctuation leads to large variation of observed natural occurrence of propionic acid levels across all relevant foodgroups	-/+
Occurrence data: maximum reported use levels considered applicable for all items within the entire food category, exposure calculations based on the maximum reported use levels	+
Uncertainty in possible national differences in food additive use levels within food categories, concentration data not fully representative of the foods on the EU market	+/-

(a): + = uncertainty with potential to cause over-estimation of exposure; - = uncertainty with potential to cause underestimation of exposure.

The Panel considered that the uncertainties identified would tend to an overestimate of the real exposure to propionic acid - propionates as food additives in European countries.

3. Biological and toxicological data

The biological properties of propionate have been evaluated previously by JECFA (1974) and the SCF (1992). The present opinion briefly reports the major studies evaluated in these reports. Additional information has been identified from the literature and the call for data.

3.1. Absorption, distribution, metabolism and excretion

3.1.1. Absorption

Kozuka et al. (1981) reported that 77% of the radioactivity was excreted by exhalation, within three days after a single oral dose of [2-^{14}C]sodium propionate in rats. The Panel, therefore, considered that at least 77% of propionate ingested was absorbed and systemically available.

In rats, absorption of short chain fatty acids (acetate, propionate and butyrate) was studied in vivo by measuring their disappearance from the caecum (Fleming et al., 1991). The absorption, expressed as µmol/min/g dry tissue, was independent of the chain length. During absorption, increases in pH, total carbon dioxide (CO_2) and bicarbonate (HCO_3^-) were observed, but no change in pCO_2. The authors suggested that short chain fatty acids were absorbed mainly via diffusion involving anionic exchange with HCO_3^-. The same result was found in isolated caecum from mice tested in vitro in Ussing chambers (Kawamata et al., 2007). It was shown that short chain fatty acid absorption in the large intestine followed two distinct pathways, i.e., the HCO_3^- dependent and non- HCO_3^- dependent. The HCO_3^- dependent pathway is very likely to be mediated by an electroneutral, carbonic anhydrase-dependent short-chain fatty acid HCO_3^- exchange mechanism.

In humans, the absorption of short chain fatty acids (acetic acid, propionic acid, butyric acid, *iso*-butyric acid, valeric acid, *iso*-valeric acid, caproic acid) by the gastrointestinal tract has been studied by Dawson et al. (1964). Neither extent nor rate of absorption were given and only the absorption rate relative to propionate- which was set as 1- was reported. The authors showed that the relative rate of absorption correlated with their octanol/water partition coefficient (K_{ow}) (Dawson et al., 1964). The absorption of short chain fatty acids from the human ileum was investigated in 8 volunteer subjects by perfusion technique (Schmitt et al., 1977). Absorption of each short chain fatty acid was found to be rate-limited with an apparent Michaelis constant (K_m) between 22 and 27 mM and a V_{max} between 0.54 and 0.82 mmol/h per cm. Water, sodium, and chloride transport were not affected, whereas significant stimulation of bicarbonate secretion and a rise in intraluminal pH were consistently observed. The authors indicated that the results were compatible with either of two mechanisms for short chain fatty acid absorption: an anion exchange between bicarbonate (or hydroxyl) and short chain fatty acid ions, or protonation of the short chain fatty acid anion at the mucosal surface followed by simple diffusion of nonionized short chain fatty acids into the absorbing cell.

3.1.2. Distribution

In order to evaluate the distribution of the remaining radioactivity in the body of rats, the levels of [2-^{14}C]sodium propionate were determined in rat tissues three days after a single oral administration at a time point at which 84 % of the total radioactivity was excreted (Kozuka et al., 1981). There was no marked difference in the radioactivity detected in the different organs investigated (liver, spleen, gastrointestinal tract, kidney and brain).

3.1.3. Metabolism

^{14}C-labelled propionate fed to fasted rats excreted 50 % of the radioactivity as expired CO_2 within two hours, the rest being incorporated into glucose, glycogen, succinate, malate, fumarate and proteins (Buchanan et al., 1943; Lorber et al., 1950; Pritchard and Tove, 1960). 77 % of the radioactivity was exhaled after three days (Kozuka et al., 1981).

The major pathway of propionate oxidation in animal tissues involves activation to propionyl-CoA, conversion to methyl-malonyl-CoA followed by conversion to succinate and further metabolism into the Krebs cycle (Beck et al., 1957; Flavin and Ochoa, 1957). Propionic acid administered to rats appeared to be metabolised to glycogen, glucose, lipids, amino acids, and proteins (OECD SIDS, 2007: USDA, 2008). In addition, propionic acid is found naturally in humans as a normal intermediary metabolite that represents up to 4 % of the normal total plasma fatty acids (Clayton and Clayton, 1994, as referred to by OECD SIDS, 2007).

3.1.4. Excretion

In rats, radioactivity was measured in excreta over 24 hours after intravenous injection of [1-^{14}C] and [3-^{14}C]sodium propionate (Cherruau et al., 1980). The authors reported that most of the radioactivity was eliminated by exhalation. Fecal and urinary elimination was low 24 hours after ^{14}C-propionate injection.

The excretion of [2-^{14}C] sodium propionate in rats after a single oral administration was investigated (Kozuka et al., 1981). Half of the administered radioactivity was exhaled as $^{14}CO_2$ within 4 hours of administration and, within 3 days, 77 % of the radioactivity had been expired. Fecal and urinary excretion also occurred for about 7 % of the radioactivity during 3 days, of which unchanged ^{14}C-propionate accounted for only a trace.

Overall, the ADME data of propionate indicated that oral exposure results in significant absorption. The Panel noted that in the gastrointestinal tract, sodium propionate, calcium propionate and potassium propionate will be dissociated into sodium ion, potassium ion or calcium ion and propionate ion. The distribution of the unchanged molecule is unknown whereas radioactivity from orally

administered ^{14}C-sodium propionate is distributed in all organs. Propionate is extensively metabolised with approximately 80 % being oxidised to CO_2 and excreted by exhalation.

3.2. Toxicological data

3.2.1. Acute oral toxicity

Groups of five non-fasted rats were given propionic acid as a 10 % aqueous solution at doses of 0, 2000, 4000 or 8000 mg/kg bw by oral gavage (Union Carbide, 1957). The LD_{50} for the 10 % solution of propionic acid in rats was determined to be 4290 mg/kg bw. Necropsy of dead animals showed haemorrhagic and congested lungs and gastrointestinal tract, and "burned" surfaces of kidney, liver, spleen and adrenal gland where contact was made with the gastrointestinal tract. A similar LD_{50} value was reported for male rats (Smyth et al., 1962)

Rats (5/sex/group and 10/sex in the group receiving 3177 mg/kg bw) received diluted propionic acid (20 % and 30 % respectively) in doses of 1986, 2483, 3177, 3972, 4965 and 6355 mg/kg bw by oral intubation (BASF, 1969). All except one death occurred within 24 hours of dosing. The LD_{50} was determined to be 3466 mg/kg bw for both sexes. Clinical signs included squatting posture, agitation or apathy, dyspnea, cyanosis, and ruffled fur. Necropsy of animals that died during the study showed large amount of liquid in the abdomen and discolouration around the snout.

The OECD SIDS report (2007) reported a LD_{50} for females rats of 351 mg/kg bw after oral administration of undiluted propionic acid (dose range and number of rats per group was unknown). As the data are coming from a report (Union carbide, 1974 as referred to by OECD SIDS, 2007) which is not available to the Panel the value could not be independently confirmed.

The Panel noted that in the study reports the doses were sometimes given in volumes and not weight units. When calculating the LD_{50}, conversion has been made in some of the reports without considering that the substance was applied as a diluted solution. The Panel recalculated the doses considering the dilution factor. The Panel noted that the LD_{50} values varied between 351 mg/kg bw and 4290 mg/kg bw, the lowest LD_{50} value has been observed in a study where undiluted propionic acid has been tested in female rats.

3.2.2. Short-term and subchronic toxicity

3.2.2.1. Short-term toxicity studies

Rats

Four groups of one control and two weanling test rats were pair-fed for four to five weeks on diets containing 1 % sodium or calcium propionate and 3 % sodium or calcium propionate (concentration equal to 0.75 g/kg bw/day or 2.2 g propionic acid/kg bw/day) (Harshbarger, 1942). No effect on growth as the only endpoint measured was observed.

Rats were fed with 4 % propionic acid (equivalent to 480 mg/kg bw/day) in powdered diet for 9-27 days (Rodrigues et al., 1986). Rats fed propionic acid for 27 days showed thickening of the mucosa (i.e. acanthosis and hyperkeratosis along the lesser curvature of the forestomach). Changes in the mucosa were also accompanied by oedema and infiltration of eosinophils and lymphocytes. A two-fold increase in [methyl-^{3}H]thymidine incorporation into cells was observed only in the mid region of the forestomach epithelium but did not become apparent before day 27.

3.2.2.2. Subchronic toxicity studies

Rats

In a study by Bueld and Netter (1993), 24 male Wistar rats were fed powder diet supplemented with 4 % (equivalent[25] to 3600 mg/kg bw/day) propionic acid for 12 weeks. When the content of the food was controlled at the time of use by chemical analysis, the concentration was 4.4 % at the time of filling the food reservoir, 3.5 % 6 hours thereafter and 2.9 % after 24 hours. The dose of 3600 mg/kg bw/day caused severe hyperplasia and ulcerations of the forestomach. The authors did not explicitly indicate that the fed powder was prepared every day but did measure the propionate content of feed up to 24 hours so that it might be concluded that the powder feed was freshly prepared every day. The Panel considered that the study did not allow identification of a no observed adverse effect level (NOAEL).

In an unpublished study (BASF, 1971a), Sprague Dawley rats (20/sex/dose) were fed a diet containing 0, 6200, 12 500, 25 000 or 50 000 mg/kg diet propionic acid (equivalent[25] to 558, 1125, 2250, 4500 mg/kg bw/day) for approximately 3 months (91 days). An additional 10 animals were assigned in the control, 6200 and 50 000 mg/kg diet groups (equivalent to 558 mg/kg bw/day and 4500 mg/kg bw/day, respectively) and fed the control diet for 6 weeks. During the treatment period, there was no mortality and no clinical signs of toxicity. Food consumption was slightly reduced and mean body weights were reduced compared to controls in males in the high-dose group (equivalent to 4500 mg/kg bw/day). There were no significant changes in haematology, clinical chemistry parameters and absolute organ weights that could be attributed to the test material. Relative kidney weights were decreased by 12 % in high-dose male group. In high-dose female group, there were increases in the relative weights of the heart (5 %) and liver (9 %). Examination of tissues revealed no lesions except point-of-contact changes of the mucosa of the forestomach (e.g. acanthosis, hyperkeratosis, and proliferation of the epithelium) in rats in the high treatment group equivalent to 4500 mg/kg bw/day. These changes were not observed after the recovery period, and there were no differences in relative or absolute organ weights. Based on these results, the authors considered that the effects on the forestomach observed in the high-dose group (4500 mg/kg bw/day) were clearly substance related. The Panel noted, however, that these effects were also observed in animals in the dose groups of 1125 and 2250 mg/kg bw/day (in low intensity in the 1125 mg/kg bw/day group in 4/20 males and in 3/20 females; in low intensity in the 2250 mg/kg bw/day group in 2/20 males and in 2/20 females; and in high intensity in the 4500 mg/kg bw/day group in 8/20 males and 9/20 females). The Panel considered the NOAEL to be equivalent to 558 mg propionic acid/kg bw/day.

Dogs

Propionic acid was included in the diet to male and female Beagle dogs for 90 days (BASF, 1988). Groups of dogs (8/sex) received 0, 0.3, 1.0, or 3.0 % (equivalent to 0, 201, 669, and 2007 mg/kg bw/day in males, and 0, 208, 695, and 2084 mg/kg bw/day in females) propionic acid in the diet. Eight additional animals from the high-dose group and 8 additional animals from the control group (4/sex) were observed over a 6-week recovery period. The authors gave no mean dose over the time period of 90 days but a mean daily dose for every week for male and female dogs. The administered dose to male dogs in the 3 % dose group ranged between 2491 and 1848 mg/kg bw/day, whereas the mean daily dose administered to high-dose female group ranged between 2209 and 1832 mg/kg bw/day. The Panel calculated the median dose as 2007 mg/kg bw/day in males and 2084 mg/kg bw/day in females. During the treatment period, there was no mortality and dogs did not show clinical signs of toxicity. Dogs in the high-dose group experienced a decrease in appetite, attributed by the authors to the unpleasant taste of the test material; however, the decrease in food consumption was reversible and did not significantly alter body weights or body weight gains. There were no significant changes in haematology, urinalysis or clinical chemistry parameters that could be attributed to the test material. Necropsy of dogs after the treatment period revealed no gross lesions and examination of tissues showed no lesions except point-of-contact diffuse epithelial hyperplasia of the mucosa of the

[25] Calculated by the Panel according to EFSA Scientific Committee (2012)

oesophagus in three dogs in the high-dose group. At the end of the recovery period, the incidence of lesions of the oesophagus was the same in control and high-dose animals. The incidence of focal epithelial hyperplasia in lower dose animals was comparable to controls. The authors set the "dose without effect" at a dose level between 1 % and 3 %. The Panel did not agree with the dose without effect determined by the authors. Based on the reported presence of diffuse epithelial hyperplasia in the oesophagus, the lowest observed adverse effect level (LOAEL) for this study was considered by the Panel to be 1 % propionic acid in the diet and the NOAEL to be 0.3 % propionic acid in the diet, corresponding to doses of 210 and 226 mg/kg bw/day for male dogs and female dogs, respectively.

Overall, propionic acid has a local effect at the first site of contact with the body. In repeated doses toxicity studies, propionic acid did show lesions in the forestomach of rats with NOAELs of 558 mg/kg bw/day (90-day study) and 900 mg/kg bw/day (28-day study). From a 90-day study in dogs, the Panel identified a NOAEL of 210 mg/kg bw/day based on epithelial hyperplasia in the oesophagus.

3.2.3. Genotoxicity

3.2.3.1. In vitro

In an unpublished study report (Litton Bionetics, 1974a) calcium propionate was tested for mutagenicity in *Salmonella typhimurium* tester strains G-46 and TA1530 and for recombinogenic properties in *Saccharomyces cerevisiae* strain D3. In the *Salmonella* reversion assay calcium propionate was added to plates either in the form of a microdrop onto a small filter paper disk or a small crystal applied directly to the agar. In the assay with *Saccharomyces cerevisiae*, cells at appropriate dilutions were shaken with test compound and plated at 50 % survival or above. Red colonies were then scored and the frequency calculated after adequate incubation time. Negative results were reported for these assays. The Panel noted that these studies have some shortcomings due to the poorly reported concentration levels and experimental designs.

Negative results for calcium propionate were reported when assayed for gene mutation in the Ames test with *Salmonella typhimurium*, tester strains TA1535, TA1537, and TA1538 and for gene conversion with *Saccharomyces cerevisiae,* tester strain D4, both in the absence and presence of exogenous mouse, rat and monkey liver S9 metabolism (Litton Bionetics, 1974b). The Panel noted that these studies have some shortcomings due to the poorly reported concentration levels and experimental designs.

Khoudokormoff et al. (1978) assessed the DNA-modifying effects of calcium propionate at a dose-level of 10 mg/mL by the Rec-assay (DNA repair test) using the *Bacillus subtilis* mutant strain M45 rec-, unable to repair DNA damage and the wild type strain H17 rec+ as control. Negative results were obtained. No details about use of an exogenous metabolism and cytotoxicity were reported.

Similarly Ohta et al. (1980) assessed the DNA-modifying effects of calcium propionate by the Rec-assay (DNA repair test) using the *Bacillus subtilis* mutant strain M45 rec^-, unable to repair DNA damage and the wild type strain H17 rec^+ as control and its mutagenicity in the reverse mutation assay with *Escherichia coli* WP2 hcr trp tester strain and TA1535, TA1537, TA1538, TA98 and TA100 *Salmonella typhimurium* tester strains, using of a top-agar overlay method both in the absence and presence of an exogenous rat liver S9 metabolism (Arochlor-induced). Negative results were reported in both assays.

In the study by Ishidate et al. (1984) calcium and sodium propionate were assessed for their mutagenicity in the reverse mutation assay using *Salmonella typhimurium* strains TA 1535, TA1537, TA92, TA94, TA98 and TA100 according to the method of Ames by the pre-incubation method both in the absence and presence of rat liver S9 metabolism. Six dose-levels of either sodium or calcium propionate were used and the maximum dose-levels selected were 5 and 10 mg/mL respectively. Both sodium and calcium propionate were negative in the reversion mutation assay.

Basler et al. (1987) investigated the in vitro genotoxicity of propionic acid in the bacterial DNA repair assay with *Escherichia coli* strains WP2, WP67 uvrA$^-$, polA$^-$ and CM871 uvrA$^-$, recA$^-$ and lexA$^-$, in the SOS-chromotest using the *Escherichia coli* PQ37 tester strain, in the Salmonella/microsome test with *Salmonella typhimurium* tester strains TA1535, TA1537, TA98 and TA100 both in the absence and presence of rat liver S9 metabolism (Arochlor-induced). All assays performed were exhaustively conducted with dose-levels adequately selected. Negative results were obtained in all assays employed with the exception of bacterial DNA repair assay with *Escherichia coli* strains WP67 and CM871 where positive effects were observed. It should be noted that the effect was not dose-related and was not observed in similar DNA repair studies with *Bacillus subtilis* (Khoudokormoff et al., 1978; Ohta et al., 1980)

In the study by Von Houten et al. (1988), genotoxicity of propionic acid was investigated in the SOS-chromotest using the *Escherichia coli* PQ37 tester strain both in the absence and presence of rat liver S9 metabolism at dose-levels of 0.3, 1.0, 3.3, 10.0 and 33.3 mM. Slight increases in the SOS induction factor were observed which turned positive at the higher (33.3 mM) dose-level assayed. However, this dose-level was considered by the Panel not physiological in in vitro studies where the highest recommended dose-level is 10 mM. On this basis, the outcome of the study was considered not biologically relevant by the Panel.

In a survey with 311 chemicals tested in the Salmonella mutagenicity assay using a preincubation protocol in the absence and presence of an exogenous liver S9 metabolism from Arochlor-induced Sprague-Dawley rats and Syrian hamsters, Zeiger et al. (1992) analysed the mutagenicity of propionic acid at dose-levels of 100, 333, 1000, 3333 and 10 000 µg/plate in *Salmonella typhimurium* tester strains TA1535, TA1537, TA98, TA100, TA102, TA104. Negative results were obtained. The Panel noted that performance was essentially in compliance with OECD Guideline 471.

In the study by Litton Bionetics (1974a) calcium propionate was tested for clastogenicity in a human embryonic lung (WI-38) cell line by observing cells in anaphase. Main end points observed were bridges, pseudochiasmata, multipolar cells and acentric fragments. In the anaphase mammalian cell assay dose-levels of 0.4, 4 and 40 µg/mL were selected from preliminary toxicity tests where cytotoxic and mitotic inhibition effects were monitored. Anaphase collection was performed at 24-48 hours from beginning of treatment and negative results were reported. However, the Panel noted that the assay of chromosome aberration in anaphase has not been validated and it is no longer employed for genotoxicity assessment. On this basis, the Panel considered this study not relevant for hazard characterisation.

In a chromosome aberration assay on 242 food additives, calcium and sodium propionate were assayed for their clastogenic properties in a Chinese hamster lung (CHL) cell line (Ishidate et al., 1984). Treatments were performed for 24 or 48 hours at three different dose-levels. The maximum dose level employed for both sodium and calcium propionate was 2 mg/mL, selected in a preliminary toxicity test as the dose causing 50 % cell-growth inhibition. Results obtained indicate negative findings for sodium propionate and an equivocal clastogenic response for calcium propionate. However, the Panel noted that for calcium propionate the reported finding was only observed at the 48 hours sampling time (considered excessively long). On this basis, the equivocal results obtained for calcium propionate were considered not biologically relevant.

In the study by Basler et al. (1987), propionic acid was investigated for its genotoxicity in a sister chromatid exchange (SCE) assay both in the absence and presence of rat liver S9 metabolism in a Chinese hamster V79 cell line. The study included two independent experiments which were exhaustively conducted with dose-levels adequately selected. Negative results were obtained.

In a comparative analysis of data on the clastogenicity of 951 chemical substances tested in mammalian cell cultures (Ishidate et al., 1988) calcium and sodium propionate did not show clastogenic activity in CHL cell assay although assayed at dose-levels exceeding 10 mM, the highest recommended dose-level in in vitro studies.

In the study by Sipi et al. (1992), propionic acid was studied for its genotoxicity in an in vitro SCE's assay in human lymphocytes. Propionic acid was tested at dose-levels of 0.2 – 20 mM and cytogenetic analyses performed at 1.25, 2.50 and 5.00 mM. Statistically significant increases in SCE's were only observed at 2.5 mM. However, the Panel noted that the observed increases although statistically significant were small and were not dose-related. Furthermore, this effect was accompanied by a concurrent reduction of pH which is known to be associated with enhancement of genotoxic effects. On this basis, the Panel considered the results of this study not biologically relevant.

3.2.3.2. In vivo

In an unpublished study report (Litton Bionetics, 1974a) calcium propionate was assessed for its genotoxic properties in:

a) The Host-Mediated assay in vivo in mice

b) The rat bone marrow chromosomal aberration assay

c) The rat Dominant Lethal assay

In all assays performed, the treatment regime used consisted of three dose levels 50, 500 and 5000 mg/kg bw administered by oral gavage as single dose. In addition, the same dosages have been administered daily for five consecutive days.

In the Host-Mediated assay, a total of 10 male ICR random-bread mice were allocated to each of the five groups; three dose levels as described above and positive and negative controls for both single and repeated treatments (5 mice per group). The indicator organisms used in this study were two histidine auxotroph *Salmonella typhimurium* strains (his G-46, TA1530) for induction of reverse mutation and a diploid strain (D3) of *Saccharomyces cerevisiae* for mitotic recombination. In the single treatment, all animals, immediately after treatment received 2 mL of indicator organism by intraperitoneal injection containing 3 x 10^8 cells for *Salmonella* and 5 x 10^8 cells for *Saccharomyces*. Three hours later animals were sacrificed, indicator organisms removed from peritoneal cavity and appropriately plated for scoring of mutant colonies.

Results obtained indicate that calcium propionate induced significant increases in the reversion frequency of *Salmonella* strain G-46 in the repeated treatment groups. The Panel noted that increases were not dose-related and close to the two higher dose levels in the single treatment. The *Salmonella typhimurium* TA1530 tester strain did not show any statistically significant increase in reversion both in the single and repeated treatments. The Panel noted that positive findings observed in the *Salmonella* strain G-46 were not reproduced in single and repeated treatments and in the TA1530 tester strain and therefore the outcome was considered not biologically relevant.

For *Saccharomyces cerevisiae* D3 tester strain calcium propionate did not induce mitotic recombination both in the single and repeated treatments.

In the rat bone marrow chromosomal aberration assay a total of 59 animals in the single treatment and 18 in the repeated treatment were employed. In the single treatment, animals were sacrificed 6, 24 and 48 hours after dosing and in the repeated treatment 6 hours after the last dose. Fifty metaphase spreads for animal were scored for chromosomal aberration and at least 500 cells (interphases and metaphases) for mitotic index determination. Calcium propionate did not induce statistically significant increases of chromosomal aberrations at any dose level and sampling time employed both in the single and repeated treatments.

In the rat Dominant Lethal assay a total of 10 male random-bred rats were allocated to each of the five groups, (e.g. three dose levels as described above and positive and negative control) for both single and repeated treatments (5 rats per group). Following treatments the males were sequentially mated to 2 untreated virgin females per five days/week for eight weeks. At the end of five days, females were

removed from the males and housed separately until sacrifice. Females were sacrificed at 14 days after separation from males and at necropsy the uteri were analysed for early and late fetal deaths and total implantations. Results were clearly negative.

In the study by Basler et al. (1987) propionic acid was assayed in the bone marrow micronucleus assay in male and female Chinese hamsters at the maximum tolerated dose of 124 mg/kg bw administered intraperitoneally as a single dose (2.5 % solution of propionic acid). Animals were sacrificed at 12, 24, or 48 hours after dosing and bone marrow collected and evaluated for the presence of micronucleated immature (polychromatic) erythrocytes. Propionic acid did not induce any significant increase in micronucleated polychromatic erythrocytes, indicating absence of clastogenicity and aneugenicity in vivo under the reported experimental conditions.

The Panel considered that based on the available data there was no concern with respect to genotoxicity for propionic acid, calcium propionate and sodium propionate. Using a read-across approach, the Panel considered that this conclusion was also applicable to potassium propionate.

3.2.4. Chronic toxicity and carcinogenicity

3.2.4.1. Rats

Male Wistar rats were fed 0, 4, or 40 g propionic acid/kg diet (equivalent[26] to 0, 270, 2700 mg/kg bw/day) for 20 weeks or their lifetime (Griem, 1985). Among animals receiving 270 mg propionic acid/kg bw/day there were no gross changes in the forestomach, however hyperplasia and hyperkeratosis were observed histologically. No changes were observed in the mucosa of the glandular stomach. In rats receiving 2700 mg/kg bw/day, forestomach epithelial changes (i.e. hyperplasia and hyperkeratosis) were observed after 20 weeks. In addition, erosive changes were also seen in the glandular stomach. At 270 mg/kg bw/day group, hyperplasia of the mucosa was observed. The Panel considered that in this study, 270 mg propionic acid/kg bw/day was a LOAEL.

In a study by Bueld and Netter (1993), Wistar rats were fed propionic acid in food of different forms, either as pellets or a powder. In the first part of the study, propionic acid was incorporated into food pellets whereby the concentration was 8 % when the food was prepared. Six male rats fed for 24 weeks showed no effects on the forestomach mucosa. No macroscopic and histopathological changes were observed. It was reported that the content of the food pellets was controlled by chemical analysis; after 4 days of storage the concentration was reduced to 3.1 % and after 10 days of storage was only 2.4 %. The authors reported that the pellets were stored for not longer than 10 days so that the content of the pellets declined to 2.4 % and that the content of the pellets at the time of the consumption was between 2 % and 3 %.

In a study in Charles River CD rats (40/sex/group) lasting for 104 weeks, the rats were fed diets containing 2.05 % sodium propionate, equivalent[27] to 1025 mg/kg bw/day (Owen et al., 1978a). There were no adverse effects upon bodyweight gain, food consumption, haematology, blood chemistry, organ weights or mortality by comparison with control rats receiving the basal diet. Water consumption, urinary volume and sodium excretion were increased and this appeared to be reflected in an increased incidence and earlier onset of spontaneous subepithelial basophilic deposits in the renal pelvis among treated rats. Focal mineralization at the renal corticomedullary junction occurred with equal frequency in the treated and control groups. There were no other histological findings mentioned. The organs evaluated by histopathology have not been mentioned in detail.

3.2.4.2. Dogs

Beagle dogs (5/sex) were fed for 104 weeks a diet containing 5.13 % sodium propionate (equivalent[27] to 1282.5 mg/kg bw/day) (Owen et al., 1978b). There were no adverse effects upon bodyweight gain, food consumption, general behaviour, ECG, ophthalmological findings, haematology, blood

[26] Calculated by the Panel according to EFSA Scientific Committee (2012).

chemistry, organ weights or mortality by comparison with control dogs receiving the basal diet. Urinary volume and sodium excretion were slightly raised in dogs receiving sodium propionate, but the ability to concentrate urine was unimpaired. The authors stated that no clinical and morphological changes were detected, that could be attributed to the administration of sodium propionate, but did not mention in detail which organs were evaluated.

Overall, most of the studies did not report any effects apart from reactions observed in the forestomach of rats.

3.2.5. Reproductive and developmental toxicity

3.2.5.1. Reproductive toxicity

Reproductive toxicity studies of propionic acid and its salts were not available.

3.2.5.2. Developmental toxicity

Calcium propionate was fed to pregnant CD-1 mice and Wistar rats (n= 24 per group) during gestation days 6-15 at dose levels of 3, 14, 65 and 300 mg/kg bw/day and to pregnant rabbits (n = 15-26 per group) and hamsters (n= 20-22 per group) at doses of 0, 4, 19, 86 and 400 mg/kg bw/day during gestation days 6-18 (rabbits) and 6-10 (hamsters) (FDRL, 1972). Body weights, food and water intake and other measures of appearance and behaviour of dams were taken at several intervals during gestation. Dams were sacrificed on gestation day 17 (mice), 20 (rats), 14 (hamsters) and 29 (rabbits). Numbers of implantation and resorption sites, and live and dead fetuses were recorded. Body weights of live fetuses were also recorded. All fetuses were examined grossly for external congenital abnormalities. Detailed visceral examinations were undertaken in one-third of the fetuses of each litter; two-thirds were examined for skeletal defects. In all species, no effect on maternal or fetal survival or on fetal or litter size was reported. No increase in fetal or skeletal abnormalities was noted. In conclusion, developmental toxicity was not observed in mice and rats up to dose levels of 300 mg/kg bw/day, and in hamsters and rabbits up to doses of 400 mg/kg bw/day. The Panel noted that the NOAELs were 300 mg calcium propionate/kg bw/day in rats and mice and 400 mg calcium propionate/kg bw/day in hamsters and rabbits, the highest doses tested.

3.2.6. Hypersensitivity, allergenicity, intolerance

In a double-blind study (Veien, 1987), 101 Danish patients with a history of food-associated dermatitis were administered orally 140 mg of sodium propionate in capsule form. Over the following 3 days, 27 of the patients reported reappearance of dermatitis after administration of sodium propionate, but the incidence was not statistically significantly higher compared with the placebo (16 reactions).

In a study conducted by Malanin and Kalimo (1989), in order to test the possible correlation between the results of skin tests and different food additives (9 food preservatives, scratch test) and colours (9 food colours, prick test), reproducible positive scratch test responses to a 5 % aqueous solution of propionic acid was found in 3 out of 91 patients suffering from chronic urticaria. In the controls (247 subjects), there were 24 positive results. The Panel considered that the significant bias identified in the study together with the limited statistical significance of the results did not allow to identify by skin testing, a sensitizing potential of propionic acid.

Overall, the Panel considered that the few human data available do not indicate that propionic acid and its salts used as food additives may represent a concern as regards hypersensitivity, allergenicity and intolerance.

3.2.7. Other studies

3.2.7.1. Human studies

A controlled trial of cumulative behavioural effects of a common bread preservative was performed in the Northern Territory (Australia) in 56 children having behavioural problems according to their parents and according to a score which was at the 85th percentile or higher on the Rowe Behaviour Rating Inventory (RBRI), a validated behavioural test (Dengate and Ruben, 2002). After a 3-week period on an elimination diet, in which 50 additives, natural salicylates, amines and glutamates were excluded, the RBRI scores declined in 33 children finishing the study by 25 points or more. Twenty seven children that had completed the open part of the study participated in the double-blind, placebo-controlled part of the study. Each child ate 4 slices of bread daily for 3 days, either without preservatives or with calcium propionate at the maximum permitted level in Australia, in a cross over design. Using the RBRI weighted scores, the results were inconclusive with increases in the score after calcium propionate containing bread but also decreases. The difference (33 %) between those participants with increased and decreased scores was statistically significant (95 % confidence intervals of the difference was 14-60 %). However, no statistically significant difference was seen when the results were tested by an appropriate statistical test (ANOVA).

The Panel noted that the evidence for an effect of calcium propionate on the behaviour of children is limited because of shortcomings of the study design (cross over) and that the results have not been confirmed when using appropriate statistical testing. The Panel also noted that there is not a plausible biological explanation for such an effect.

4. Discussion

The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations and reviews, additional literature that became available since then and the data available following a public call for data. The Panel noted that some original studies, on which previous evaluations were based, were not available for re-evaluation by the Panel.

Propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283) are authorised food additives in accordance with Annex II of Regulation (EC) No 1333/2008 and have been previously evaluated by the SCF (SCF, 1992) and JECFA (JECFA, 1974).

JECFA allocated an ADI "not limited" for propionic acid and its sodium, potassium and calcium salts considering that propionate is a normal intermediary metabolite and a normal constituent of foods (JECFA, 1974).

In 1974, the SCF concluded that potassium propionate could be added to the list of preservatives permitted to be used in food (SCF, 1975). In 1990, the SCF concluded that there were no adverse health consequences to man from the present uses of propionic acid as a food additive (SCF, 1992). However, the SCF expressed the need to assess comparative studies with other short chain fatty acids and their salts. The SCF established an ADI "not specified".

Propionates are substances occurring in the normal diet. Propionic acid is produced by certain bacteria and occurs in various food and feed stuffs as a result of microbial production.

The absorption of short chain fatty acids, including propionate, by the gastrointestinal tract, has been studied to a limited extent both in rats and in humans. Short chain fatty acids are absorbed in the mammalian gastrointestinal tract (Dawson et al., 1964). In rats the extent of absorption is at least 77 % (Kozuka et al., 1981).

The Panel noted that sodium propionate, calcium propionate and potassium propionate will be dissociated in the gastrointestinal tract into propionate and their relevant cations. Therefore, the Panel

considered that when assessing systemic (and genotoxic) endpoints, a group evaluation based on the propionate ion was appropriate for propionic acid and its salts.

Overall, the ADME data of propionate indicated that oral exposure results in significant absorption. The distribution of the unchanged molecule is unknown whereas radioactivity from orally administered ^{14}C-sodium propionate is distributed in all organs. Propionate is extensively metabolised with approximately 80 % being oxidised to CO_2 and excreted by exhalation.

The Panel noted that in the available acute oral toxicity studies, the administered doses were sometimes given in volumes and not weight units. Overall, the LD_{50} values varied between 351 mg/kg bw and 4290 mg/kg bw. The former LD_{50} value was observed in a study using undiluted propionic acid in female rats.

In repeated dose toxicity studies, propionic acid induced acanthosis and hyperkeratosis of the forestomach mucosa of rats at concentrations of 0.62 %. These lesions were not observed after the recovery period. From a 90-day study in dogs (BASF, 1988), the Panel identified a NOAEL of 0.3 % propionic acid in the diet based on epithelial hyperplasia in the oesophagus in the 1% group that had resolved after a recovery period.

With regard to genotoxicity, the Panel considered that although the number of reliable studies was limited, there was no concern with respect to genotoxicity for propionic acid, calcium propionate and sodium propionate. No genotoxicity data were available for potassium propionate. However, using a read-across approach, the Panel considered that this conclusion was also applicable to potassium propionate.

In long-term studies, forestomach lesions were reported. However, the Panel considered that forestomach hyperplasia in rodents is not a relevant toxicological endpoint for humans because humans lack this organ and there is an absence of a correlation between forestomach in rats and oesophageal lesions in humans as reported in the review by Wester and Kroes (1988) and Proctor et al. (2007). The Panel noted that the available long-term studies had some limitations, e.g. no blood chemistry parameters, limited information on blood counts. However, the Panel concluded that the long-term toxicity studies indicated that propionic acid and propionates were not of concern with respect to carcinogenicity.

Studies on reproductive toxicity were not available. However, in dog and in rat 90-day studies (BASF, 1988, 1971a) histopathological investigations of the reproductive organs did not reveal any abnormalities. The NOAEL for effects on the gonads was 3 % propionic acid in the diet, equivalent to 2007 mg/kg bw/day and 2084 mg/kg bw/day for male and female dogs, respectively; and 5 % propionic acid in the diet for rats equivalent to 4500 mg/kg bw/day.

From a developmental toxicity study (FDRL, 1972), the Panel identified the NOAELs of 300 mg calcium propionate/kg bw/day in rats and mice and of 400 mg calcium propionate/kg bw/day in hamsters and rabbits, the highest doses tested. At the highest dose tested no maternal toxicity was observed.

The Panel concluded that an ADI should not be derived because the only reported adverse effect to propionic acid exposure was observed at the site of contact and was a consequence of its irritating property. There was significant absorption of propionate anion but, despite some limitations in the available toxicological database, no systemic effects were reported in the toxicity studies. The Panel considered that the overall exposure and toxicity data available were sufficient to base a risk assessment on a comparison of exposure and concentrations causing site of contact irritation.

Exposure estimates were derived based on individual food consumption data, at a refined level taking into consideration FoodEx classification levels 2-4, as appropriate. However, the Panel notes that its estimates should be considered as being conservative as it was assumed that all processed foods

contain the food additives propionic acid - propionates added at the MPLs or the maximum reported use levels.

For estimates derived using the MPL, mean exposure to propionic acid - propionates from their use as food additives ranged from 0.7-18.9 mg/kg bw/day in toddlers, 1.7-21.1 mg/kg bw/day in children, 1.4-10.9 mg/kg bw/day in adolescents, 1.3-7.8 mg/kg bw/day in adults and 0.8-8.3 mg/kg bw/day in the elderly. The high exposure to propionic acid - propionates using the MPL ranged from 3.6-36.3 mg/kg bw/day in toddlers, 5.5-40.8 mg/kg bw/day in children, 4.6-22.3 mg/kg bw/day in adolescents, 3.8-16.2 mg/kg bw/day in adults and 2.7-16 mg/kg bw/day in the elderly. The Panel noted that exposure estimates using reported use levels were similar to those from the use of MPLs due to the fact that no major differences were reported for food uses by industry.

The Panel estimated the exposure to propionic acid - propionates from others sources as natural food occurrence based on the levels in food reviewed from literature sources (see Table 13) and for flavourings substances based on the data reported as such by JECFA (1998).

Total combined mean exposure to propionic acid - propionates from all sources (food additive, flavouring substance and natural sources) was estimated to be up to 19.3 mg/kg bw/day in toddlers, 21.7 mg/kg bw/day in children, 10.4 mg/kg bw/day for adolescents, 7.7 mg/kg bw/day in adults and 8.5 mg/kg bw/day in the elderly. Total combined high exposure to propionic acid - propionates from all sources across the five population groups ranged from 3.0 mg/kg bw/day in the elderly to 41.5 mg/kg bw/day in children. The Panel noted that their use as food additives is the major contributor to exposure.

The Panel noted that considering the differences in their respective molecular weights, it would be justified to establish different MPLs for propionic acid and for propionates.

Results of acute toxicity testing studies were supportive for site of contact irritation as a mode of action. Notably, in rats, the lowest LD_{50} value was from a study where undiluted propionic acid was given, whereas a ten-fold higher LD_{50} value was derived when propionic acid was given in a 10 % diluted form. From a 90-day study in dogs the concentration of 1 % propionic acid in the diet was identified as a concentration at which a site of contact effect in the oesophagus was induced. The Panel noted that this adverse effect was reversible, as it was not observed in the recovery group. The Panel considered that in the case of propionic acid, the mode of action was related to its concentration, and not the dose. The Panel evaluated the highest concentration permitted in food and the concentration in the animal diet provoking irritant effects. The Panel noted that in the 90-day study in dogs, 0.3% propionic acid in the diet did not provoke site of contact irritancy and that this concentration was equal to the highest maximum permitted level of propionic acid - propionates (3000 mg/kg) in food, the category of bread and rolls. The concentration in the 90-day study in dogs (1% propionic acid in the diet) resulting in reversible site of contact irritancy was three-fold higher than the highest permitted level. The Panel was not aware of any differences in sensitivity to acids at the site of contact between humans and dogs and, therefore, the concentration at which irritancy was reported in dogs was considered to be relevant to humans. The Panel considered that the site of contact irritancy was due to propionic acid.

Furthermore, in a 1-year study in dogs, no effects were reported at the single concentration of 5.0 % sodium propionate in the diet suggesting that sodium propionate, and also calcium and potassium propionates were less irritating than propionic acid. Any assessment based on propionic acid concentration in food would represent a worst case scenario.

Thus, taking into account of all these considerations including the natural occurrence in food, the Panel concluded that for food as consumed there would not be a safety concern from the maximum concentrations of propionic acid - propionates at their currently authorised uses and use levels as food additives.

Furthermore, the Panel noted that the specifications for lead are different for propionic acid and its salts and there are specifications for iron and fluoride for the propionic acid salts but not for the propionic acid. In addition, the Panel further noted that boron trifluoride is used as a catalyst in the manufacturing process of propionic acid and residual amounts of the catalyst could be present in the final product. Therefore, the Panel considered that limits for fluoride and boron should be included in the specifications of propionic acid. The Panel also noted that the pH of a 10 % solution of calcium propionate in the EU specifications (range 6.0 to 9.0) and the JECFA specifications (range 7.5 to 10.5) are different, and the JECFA specifications is in agreement with the one reported in the Food Chemical Codex (2011).

CONCLUSIONS

The Panel concluded that the available toxicity database did not allow allocation of an ADI. The Panel considered that the overall exposure and toxicity data available were sufficient to base a risk assessment on a comparison of exposure and concentrations causing site of contact irritation. The Panel noted that in the 90-day study in dogs, 0.3 % propionic acid in the diet, did not provoke site of contact irritancy and this concentration was equal to the highest maximum permitted level of propionic acid - propionates (3000 mg/kg) in food, in the category of bread and rolls. The Panel noted that the concentration provoking site of contact effect in the 90-day study in dogs (1 % propionic acid in the diet) is a factor of three higher than the concentration of propionic acid - propionates in food at the highest permitted level.

Overall, taking into account of all these considerations including the natural occurrence in food, the Panel concluded that for food as consumed, there would not be a safety concern from the maximum concentrations of propionic acid - propionates [propionic acid (E 280), sodium propionate (E 281), calcium propionate (E 282) and potassium propionate (E 283)] at their currently authorised uses and use levels as food additives.

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APPENDICES

Appendix A. Summary of levels (mg/kg) propionic acid - propionates (E 280-E 283) used in the exposure estimates (mg/kg or mg/L)

FCS Category No	Food categories	Matching FoodEx Food codes	Refinement at FoodEx Level 3 and 4	MPL	Restrictions/exception	Reported use level from industry				Analytical data				Level used for calculation	
						FDE (2012)			Kemira (2010)						
						Typical	Maximum	Comments	Typical	FSAI (2011)	FSA (1992)	FSA (1993)	Comments	mg/kg	Comments
01.7.2	Ripened cheese	A.08.08 Cheese	Cheese	*q.s.*	surface treatment only									3000	Source: Codex Alimentarius (2008, 2010)
01.7.6	Cheese products (excluding products falling in category 16)			*q.s.*	only ripened products surface treatment										
01.8	Dairy analogues, including beverage whiteners			*q.s.*	only cheese analogues (surface treatment only)										
07.1	Bread and rolls	A.01.04 Bread and rolls	Bread	3000	only prepacked sliced bread and rye bread	2000	3000	FDE: Representative for the Dutch market. Limited representation for the French market	796-1989	20-670	<50-1110			3000	Highest reported use level is equal to MPL
				1000	prepacked bread	1000	1000	FDE: Representative for the European market Kemira: Reported levels expressed as propionic acid and based on assumption of 50 % flour content of standard bread recipe							
				2000	partially baked prepacked bread										
				2000	prepacked polsebrod, boller and dansk flutes										
				2000	only energy-reduced bread										
			Rolls and Pitta	2000	prepacked rolls and pitta	500	600	FDE: Partly representative for the UK market. Used typically in rolls		<20		<10-1480		600	
				2000	pitta					410-2510	975-2675	<10-925			
07.2	Fine bakery wares	A.01.07 Fine bakery wares	Pastries and cakes (excluding waffles and baklava)	2000	only prepacked fine bakery wares, (including flour confectionery) with a water activity of more than 0,65	400-900	2000	FDE: Representative for the European market. Typical use in pancakes reported up to 1100 mg/kg				<10-650	analytical <10[#]	2000	Highest reported use level is equal to MPL
16	Desserts excluding products covered in categories 1, 3 and 4			1000	only Christmas pudding							<10-335			

Appendix B. Summary of total estimated exposure (using MPLs and reported use levels or analytical data) per age class and survey[(a)]: mean and high level (mg/kg bw/day)

	MPL		Use levels	
	Mean	**High level**	**Mean**	**High level**
Toddlers				
Bulgaria (Nutrichild)	18.5	36.3	18.5	36.3
Finland (DIPP)	0.7	3.6	0.7	3.6
Germany (Donald 2006_2008)	6.6	19.5	6.5	19.1
The Netherlands (VCP_Kids)	13.0	33.3	13.0	33.3
Spain (enKid)	6.8		6.8	
Belgium (Regional_Flanders)	18.9		18.9	
Italy (INRAN_SCAI_2005_06)	14.7		14.7	
Children				
Belgium (Regional_Flanders)	15.6	28.6	15.6	28.6
Bulgaria (Nutrichild)	21.1	40.8	21.1	40.8
Czech Republic (SISP04)	13.5	27.5	11.3	25.4
Denmark (Danish Dietary Survey)	17.4	29.0	16.8	28.4
Finland (DIPP)	1.7	5.5	1.7	5.5
Finland (STRIP)	10.3	19.6	10.3	18.7
France (INCA 2)	15.4	29.3	15.4	29.3
Germany (Donald 2006_2008)	6.1	16.0	5.9	15.7
Greece (Regional_Crete)	3.5	9.7	3.5	9.7
Italy (INRAN_SCAI_2005_06)	16.1	35.0	16.1	35.0
Latvia (EFSA_TEST)	10.0	25.6	10.0	25.6
The Netherlands (VCP_Kids)	11.3	26.9	11.3	26.7
Spain (enKid)	9.3	21.2	9.3	21.2
Spain (Nut_Ink05)	2.0	7.2	2.0	7.2
Sweden (NFA)	5.3	12.6	4.8	11.9
Adolescents				
Belgium (Diet_National_2004)	7.3	15.1	6.8	14.9
Cyprus (Childhealth)	3.9	9.5	3.9	9.5
Czech Republic (SISP04)	10.9	22.3	9.3	20.3
Denmark (Danish Dietary Survey)	9.1	17.3	8.8	16.8
France (INCA 2)	8.7	17.4	8.7	17.4
Germany (National_Nutrition_Survey_II)	6.8	16.2	6.0	15.0
Italy (INRAN_SCAI_2005_06)	10.1	21.4	10.1	21.4
Latvia (EFSA_TEST)	9.2	21.2	9.2	21.2
Spain (AESAN_FIAB)	6.8	12.9	6.8	12.9
Spain (enKid)	8.2	21.3	8.2	21.3
Spain (Nut_Ink05)	1.4	4.6	1.4	4.6
Sweden (NFA)	3.4	8.9	3.1	8.8
Adults				
Belgium (Diet_National_2004)	6.5	14.2	6.1	13.7

	MPL		Use levels	
	Mean	**High level**	**Mean**	**High level**
Czech Republic (SISP04)	7.8	15.5	6.8	14.3
Denmark (Danish_Dietary_Survey)	7.2	12.8	6.9	12.3
Finland (FINDIET_2007)	1.3	3.8	1.3	3.8
France (INCA2)	7.5	15.1	7.5	15.1
Germany (National_Nutrition_Survey_II)	6.3	13.6	5.6	12.8
Hungary (National_Repr_Surv)	5.9	12.9	5.2	12.1
Ireland (NSIFCS)	6.7	12.4	6.7	12.4
Italy (INRAN_SCAI_2005_06)	7.4	14.1	7.4	14.1
Latvia (EFSA_TEST)	7.2	16.2	7.2	16.2
The Netherlands (DNFCS_2003)	7.2	14.4	6.7	13.8
Spain (AESAN)	5.2	11.5	5.2	11.5
Spain (AESAN_FIAB)	5.2	11.3	5.2	11.3
Sweden (Riksmaten_1997_98)	3.5	7.6	3.5	7.6
United Kingdom (NDNS)	4.8	9.3	4.5	8.9
The elderly				
Belgium (Diet_National_2004)	6.65	13.28	6.49	13.10
Denmark (Danish_Dietary_Survey)	6.96	11.94	6.67	11.69
Finland (FINDIET_2007)	0.83	2.71	0.83	2.71
France (INCA2)	8.19	14.94	8.19	14.94
Germany (National_Nutrition_Survey_II)	6.82	13.99	6.48	13.82
Hungary (National_Repr_Surv)	5.51	11.14	4.88	10.65
Italy (INRAN_SCAI_2005_06)	7.43	15.09	7.43	15.09

(a): The different methodologies of European dietary surveys included in the EFSA Comprehensive Database are fully described in the Guidance on the use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment (EFSA, 2011a). A summary is available p.11, Table 1 of the guidance

Appendix C. Naturally occurring propionic acid concentrations reported in the literature

Food category	Propionic acid range (mg/kg) [a]	Data source	Average (mg/kg [b][c])
Alcoholic Beverages			
Apple Brandy	1	VCF (TNO, 2009)	1.0
Beer	1.3-5	VCF (TNO, 2009)	3.2
Cider	1	VCF (TNO, 2009)	1.0
Cocoa Liquor	qualitative	VCF (TNO, 2009)	
Grape Brandy	1.08-10	VCF (TNO, 2009)	5.5
Plum Brandy	qualitative	VCF (TNO, 2009)	
Rum	0-4.2	VCF (TNO, 2009)	2.1
Sake	qualitative	VCF (TNO, 2009)	
Sherry	0.05-0.06	VCF (TNO, 2009)	0.1
Tequila	qualitative	VCF (TNO, 2009)	
Whisky	0.04-16	VCF (TNO, 2009)	8.0
Wine	0.05-20	VCF (TNO, 2009)	**10.1**
Red wine	ND	Lee et al, 2010	
Cereals and cereal products			
Bread and Bread Preferment	qualitative	VCF (TNO, 2009)	
Rye Bread	qualitative	VCF (TNO, 2009)	
Wheaten Bread	0.7	VCF (TNO, 2009)	
Buckwheat	qualitative	VCF (TNO, 2009)	
Cassava	qualitative	VCF (TNO, 2009)	
Malt	qualitative	VCF (TNO, 2009)	
Rice	qualitative	VCF (TNO, 2009)	
Cereal	ND	Lee et al, 2010	
Dairy and dairy products			
Cheddar Cheese	0-3240	VCF (TNO, 2009)	1620.0
Cheese, various	trace-3130	VCF (TNO, 2009)	1565.0
Swiss Cheese	0.7-6210	VCF (TNO, 2009)	**3105.4**
Blue Cheese	3-570	VCF (TNO, 2009)	286.5
Milk /milk products	trace-180	VCF (TNO, 2009)	**90.0**
Fermented milk	ND–43.2	Lee et al, 2010	**21.6**
Meat and meat products			
Beef	qualitative	VCF (TNO, 2009)	
Chicken	qualitative	VCF (TNO, 2009)	
Lamb and Mutton	<0.05	VCF (TNO, 2009)	
Pork	qualitative	VCF (TNO, 2009)	
Sukiyaki	qualitative	VCF (TNO, 2009)	
Nuts, Seeds and Spices			
Peanut	qualitative	VCF (TNO, 2009)	
Pecan	qualitative	VCF (TNO, 2009)	
Sesame seed, roaster	qualitative	VCF (TNO, 2009)	
Cardamom	qualitative	VCF (TNO, 2009)	
Vanilla	qualitative	VCF (TNO, 2009)	
Vegetables and Legumes			
Allium species	qualitative	VCF (TNO, 2009)	
Mushroom	4.4	VCF (TNO, 2009)	**4.4**
Potato	qualitative	VCF (TNO, 2009)	
Potato Chips	qualitative	VCF (TNO, 2009)	
Sauerkraut	0.1	VCF (TNO, 2009)	0.1
Tomato	qualitative	VCF (TNO, 2009)	
Shoyu (fermented soya hydrolysate)	qualitative	VCF (TNO, 2009)	
Soybean (Glycine max. L. merr.)	qualitative	VCF (TNO, 2009)	
Processed vegetable	ND	Lee et al, 2010	
Fruit			
Apple	qualitative	VCF (TNO, 2009)	
Apple, processed	qualitative	VCF (TNO, 2009)	
Arctic Bramble	0.15 in juice	VCF (TNO, 2009)	
Banana	qualitative	VCF (TNO, 2009)	
Black Currants	0.02	VCF (TNO, 2009)	0.02
Citrus Fruit	qualitative	VCF (TNO, 2009)	

Food category	Propionic acid range (mg/kg) [a]	Data source	Average (mg/kg[b][c])
Cloudberry	trace in juice	VCF (TNO, 2009)	
Coconut	qualitative	VCF (TNO, 2009)	
Dalieb, Palmyra Palm Fruit	84 edible part	VCF (TNO, 2009)	
Elderberry	qualitative	VCF (TNO, 2009)	
Papaya	qualitative	VCF (TNO, 2009)	
Pineapple	qualitative	VCF (TNO, 2009)	
Plum	0.02	VCF (TNO, 2009)	0.02
Raspberry, Blackberry, Boysenberry	trace-0.03	VCF (TNO, 2009)	0.02
Strawberry	trace-0.05	VCF (TNO, 2009)	**0.025**
Vaccinum species	trace	VCF (TNO, 2009)	
Fish and Seafood			
Fish	3-4	VCF (TNO, 2009)	**3.5**
Katsuobushi(dried bonito)	qualitative	VCF (TNO, 2009)	
Mussels	2.73	VCF (TNO, 2009)	2.7
Oysters	0.002	VCF (TNO, 2009)	0.002
Scallops	qualitative	VCF (TNO, 2009)	
Shellfish	ND–194.7	Lee et al, 2010	**97.4**
Salted and fermented fish sauce	ND–45.9	Lee et al, 2010	23.0
Salted and fermented fish	ND–37.7	Lee et al, 2010	18.9
Tea, Coffee, Cocoa			
Rooibos Tea	qualitative	VCF (TNO, 2009)	
Tea	0.3-0.6	VCF (TNO, 2009)	0.5
Cocoa	qualitative	VCF (TNO, 2009)	
Coffee	49.6-125.8	VCF (TNO, 2009)	**87.7**
Mate	qualitative	VCF (TNO, 2009)	
Other			
Kumazasa (Sasa albo-marginata)	qualitative	VCF (TNO, 2009)	
Artocarpus spc.	qualitative	VCF (TNO, 2009)	
Chinese quince	qualitative	VCF (TNO, 2009)	
Laurel	qualitative	VCF (TNO, 2009)	
Licorice	qualitative	VCF (TNO, 2009)	
Honey	0-0.4	VCF (TNO, 2009)	0.2
Vinegar	83-25000	VCF (TNO, 2009)	12542
Sauce	ND	Lee et al, 2010	
Fermented soybean paste	ND–14.5	Lee et al, 2010	7.3
Korean hot pepper paste	ND	Lee et al, 2010	
Soy sauce	ND–21.2	Lee et al, 2010	10.6
Seasoned soybean paste	ND–8.1	Lee et al, 2010	4.1
Chunggukjang (Natto)	ND–27.6	Lee et al, 2010	13.8
Vinegar[d]	ND–140.0	Lee et al, 2010	70.0

[a] Qualitative indicates un-quantified presence of propionic acid.
[b] Averages have been calculated assuming a normal distribution of the reported range. Where single values are reported, no transformation was performed.
[c] Figures in bold were used in the exposure assessment.
[d] Due to the very large variation in values reported for vinegar and absence of detailed food consumption data, this food category has not been taken into account in the overall estimate of intake of propionic acid from natural occurrence.

GLOSSARY AND ABBREVIATIONS

ADI	Acceptable daily intake
ANOVA	Analysis of Variance
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
BIBRA	The British Industrial Biological Research Association
bw	Body weight
CAS	Chemical Abstract Service
CHL	Chinese hamster lung
EC	European Commission
ECG	Electrocardiography
ECHA	European Chemical Agency
EFSA	European Food Safety Authority
EP	Enviromental Protection Agency
EU	European Union
EINECS	European Inventory of Existing Commercial chemical Substances
FAIM	Food additives intake model
FAO/WHO	Food and Agriculture Organisation/World Health Organisation
FCC	Food Chemical Codex
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FDE	FoodDrinkEurope
FDRL	Food and Drug Research Laboratories, Inc
FSA	Food Standards Agency
FSAI	Food Safety Authority of Ireland
GC	Gas chromatographic
HPLC	High-performance liquid chromatography
IOFI	International Organization of the Flavor Industry
JECFA	Joint FAO/WHO/Expert Committee on Food Additives
K_m	Michaelis constant
K_{ow}	Octanol/water partition coefficient
LD_{50}	Lethal dose, 50 %, i.e. dose that causes the death of 50% of treated animals
LOAEL	Lowest observed adverse effect level
MSDI	Maximised survey-derived daily intake
MPL	Maximum permitted level
NAS	National Academy of Sciences
NOAEL	No observed adverse effect level

OECD	Organisation for Economic Co-operation and Development
pCO_2.	Partial pressure of carbon dioxide
QS	*Quantum satis*
RBRI	Rowe behaviour rating inventory
SCE	Sister chromatid exchange
SCF	Scientific Committee for Food
TNO	Netherlands Organisation for Applied Scientific Research
USDA	United States Department of Agriculture
V_{max}	Maximal velocity