

**DETERMINATION OF THE GENERALLY RECOGNIZED AS  
SAFE (GRAS) STATUS OF CALCIUM ACETATE**

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January 31, 2017

# DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF CALCIUM ACETATE

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**GRAS Conclusion  
Independent Determination**

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**PART 1 – SIGNED STATEMENTS AND CERTIFICATION**

**1.1. This GRAS conclusion has been reached in accordance with requirements in 21 CFR 170.220**

**1.2. Name and address of organization:**

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Prepared by:  
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**1.3. Name of substance:**

The name of the substance is calcium acetate. Calcium acetate is also known by the following synonyms: calcium ethanoate, calcium (II) acetate, calcium diacetate, acetic acid calcium salt, lime acetate, acetate of lime.

**1.4. Intended conditions of use of calcium acetate:**

Calcium acetate will be used in food as a firming agent as defined in § 170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; and texturizer as defined in § 170.3(o)(32) of this chapter in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice.

**1.5. Statutory Basis for GRAS conclusion:**

This GRAS conclusion is based on scientific procedures in accordance with 21 CFR 170.30(a) and 170.30(b).

**1.6. Exemption from Premarket approval requirements:**

Niacet Corporation has concluded that calcium acetate is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that calcium acetate, meeting the specifications cited herein, and when used as a firming agent as defined in §

170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; and texturizer as defined in § 170.3(o)(32) of this chapter, in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice at levels consistent with current good manufacturing practices (when not otherwise precluded by a Standard of Identity) in foods generally, as described in this dossier, and is GRAS and is therefore exempt from the premarket approval requirements.

It is Niacet's opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, Niacet has also concluded that calcium acetate, when used as described in this dossier, is GRAS based on scientific procedures.

**1.7. Availability of data and information:**

The data and information that are the basis for this GRAS conclusion will be made available to FDA upon request by contacting Niacet Corporation (Salvatore J. D'Angelo, Manager, Quality Assurance & Regulatory Affairs; address above), or EAS Consulting Group, LLC (Ed Steele; address above). The data and information will be made available to FDA in a form in accordance with that requested under 21 CFR 170.225(c)(7)(ii)(A) or 21 CFR 170.225(c)(7)(ii)(B).

**1.8. Data exempt from Disclosure:**

Niacet Corporation has identified all information that is trade secret and/or commercial or financial information that is privileged or confidential and has redacted this information from the dossier that can be made publicly available if warranted. A separate dossier containing the redacted information can be made available to FDA on request if warranted.

**1.9. Certification:**

Niacet Corporation certifies that, to the best of its knowledge, this GRAS conclusion is based on a complete, representative, and balanced, dossier that includes all available information both unfavorable and favorable that is known to Niacet Corporation and pertinent to the evaluation of the safety and GRAS status of the use of calcium acetate. Niacet Corporation accepts responsibility for the GRAS determination that has been made for calcium acetate as described in this dossier.

**1.10. Name and position/title of responsible person who signs dossier:**

Salvatore J. D'Angelo  
Manager, Quality Assurance & Regulatory Affairs  
Niacet Corporation  
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(b) (6)

February 14, 2017

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### 1.11. FSIS/USDA – Use in Meat and/or Poultry

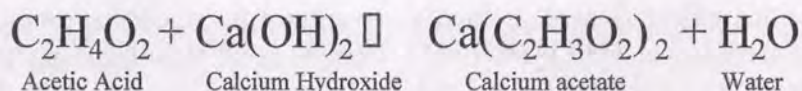
Niacet Corporation notes that calcium acetate is currently used in meat and poultry products for approved uses. These uses will not change. Therefore, 21 CFR 170.270 does not apply.

### 1.12. Background

Calcium acetate is the calcium salt of acetic acid. Calcium acetate is used in food processing for several physical and technical effects. Calcium acetate is naturally present in many fruits and is present in fermented products through bacterial fermentation. Calcium is a mineral essential for many cellular functions including nerve impulse transmission, muscle contraction, cardiac function, bone formation, and capillary and cell membrane permeability.

Calcium acetate is currently listed as GRAS for use as a sequestrant under 21 CFR 182.6197 (calcium diacetate) and is affirmed as GRAS at 21 CFR 184.1185 for several food uses and technical effects. Calcium acetate is intended for use as an ingredient in food products consistent with some uses and some technical effects permitted for other calcium salts as described in existing regulations and current practices. As such, it is intended for use as a substitute for existing calcium salts currently approved for use in food. Calcium acetate is also used as a source of calcium in dietary supplements (pre-DSHEA). Calcium acetate is also determined to be GRAS for use as a flavoring agent by FEMA (FEMA No. 2228).

Calcium acetate is prepared by reacting calcium hydroxide with acetic acid.



The molecular formula of calcium acetate is  $\text{CaC}_4\text{H}_6\text{O}_4$ ; its molecular weight is 158.2 g/mol. The CAS Registry Number is 62-54-4.

Calcium acetate is a white powder that is freely soluble in water and slightly soluble in ethanol. The content of calcium acetate is not less than 99.0% and not more than 100.5%, and the total calcium content is 25.3% (based on theoretical calculations). Calcium acetate is stable in foods. Specifications for calcium acetate are listed in the Food Chemicals Codex, 10<sup>th</sup> Ed. (Appendix I).

In this GRAS determination, Niacet is proposing to use calcium acetate in accordance with 21 CFR 184.1(b)(1) with no limitations other than current good manufacturing practice as a substitute for calcium-containing compounds that are currently approved and used in food products for various physical and technical effects. Therefore, the use of calcium acetate will not result in an increase of exposure in the daily calcium intake for consumers who currently consume food products containing calcium-containing substances.

### 1.13. Current Regulated Uses

Calcium acetate has numerous food uses in the U.S. and throughout the world. In the U.S., calcium acetate is affirmed as generally recognized as safe (GRAS) (21 CFR 184.1185) for use as a firming agent, pH control agent, processing aid, sequestrant, stabilizer and thickener and texturizer as well as a flavor enhancer (FEMA) and sequestrant (21 CFR 182.6197).

See regulation below:

#### § 184.1185 Calcium acetate.

(a) Calcium acetate ( $\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$ , CAS Reg. No. 62-54-4), also known as acetate of lime or vinegar salts, is the calcium salt of acetic acid. It may be produced by the calcium hydroxide neutralization of acetic acid.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 44, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: [http://www.archives.gov/federal\\_register/code\\_of\\_federal\\_regulations/ibr\\_locations.html](http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html).

(c) The ingredient is used as a firming agent as defined in §170.3(o)(10) of this chapter; pH control agent as defined in §170.3(o)(23) of this chapter; processing aid as defined in §170.3(o)(24) of this chapter; sequestrant as defined in §170.3(o)(26) of this chapter; stabilizer and thickener as defined in §170.3(o)(28) of this chapter; and texturizer as defined in §170.3(o)(32) of this chapter.

(d) The ingredient is used in food at levels not to exceed current good manufacturing practices in accordance with §184.1(b)(1). Current good manufacturing practices result in a maximum level, as served, of 0.2 percent for baked goods as defined in §170.3(n)(1) of this chapter; 0.02 percent for cheese as defined in §170.3(n)(5) of this chapter; 0.2 percent for gelatins, puddings, and fillings as defined in §170.3(n)(22) of this chapter; 0.15 percent for sweet sauces, toppings, and syrups as defined in §170.3(n)(43) of this chapter; and 0.0001 percent for all other food categories.

(e) Prior sanctions for this ingredient different from the uses established in this section or in part 181 of this chapter do not exist or have been waived.

[47 FR 27807, June 25, 1982]

Uses and the approved use levels for calcium acetate in select foods are summarized in Table 1.



**Table 1. Permitted uses of calcium acetate in food**

Category of Food	Maximum Level (%)
Baked goods § 170.3(n)(1)	0.2
Cheese § 170.3(n)(5)	0.02
Gelatins, puddings, and fillings § 170.3(n)(22)	0.2
Sweet sauces, toppings, and syrups § 170.3(n)(43)	0.15
Flavoring Agent FEMA	--
All other food categories.	0.001

FDA has developed a Food Additive Safety Profile (ASP # 1785) for calcium acetate which lists the regulations where calcium acetate is cited in title 21 of the Code of Federal Regulations below.

ASP	<u>1785</u>	CALCIUM ACETATE	62-54-4	§ 175.300
				§ 181.29
				§ 182.6197
				§ 184.1185

Calcium acetate is listed as a food additive by Codex Alimentarius in the Codex General Standard for Food Additives (GSFA) with the functional class designation including acidity regulator, preservative, and stabilizer. The list of GSFA Provisions for calcium acetate is summarized at GSFA Online (FAO/WHO Food Standards Codex Alimentarius <http://www.fao.org/gsfaonline/additives/details.html?id=317&print=true>). A copy of the uses is attached in Appendix II.

Calcium acetate is approved as a food additive (Group I) in the European Union (EU) for use in dehydrated milk, ripened cheese, canned or bottled fruit and vegetables, jams, jellies, marmalades and sweetened chestnut puree, and other similar fruit or vegetable spreads (E 263; <https://webgate.ec.europa.eu/sancofoods/main/index.cfm?event=substance.view&identifier=227>)

Calcium acetate is also approved for used by other international regulatory bodies for use in food for different technical effects and food applications. Because the use of calcium acetate is so broad, these regulatory bodies permit its use consistent with good manufacturing practice for the most part.

FDA has approved a number of calcium containing substances for use in food. Among the calcium salts that are listed in 21 CFR part 184 are: calcium acetate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium lactate, calcium panthothenate, calcium propionate, and calcium sulfate. Calcium diacetate (Syn.: calcium acetate) is also listed at 21 CFR 182.6197 for use as a sequestrant. In addition, calcium acetate and other calcium salts are

listed as FEMA GRAS and recognized by the FDA. Please note that the technical effects and food categories vary among these substances. In addition, FDA has received ten GRAS Notices (Appendix III) related to uses of calcium-containing substances, nine of which received “good day” letters from FDA for the notified use.

The calcium-containing substances affirmed as GRAS by FDA are shown in Table 2 below.

**Table 2. Calcium-containing Substances Affirmed As GRAS by FDA**

Substance	Regulation	Conditions for Use
Calcium acetate	21 CFR 184.1185	21 CFR 184.1(b)(1)
Calcium alginate	21 CFR 184.1187	21 CFR 184.1(b)(2)
Calcium carbonate	21 CFR 184.1191	21 CFR 184.1(b)(1)
Calcium chloride	21 CFR 184.1193	21 CFR 184.1(b)(1)
Calcium citrate	21 CFR 184.1195	21 CFR 184.1(b)(1)
Calcium gluconate	21 CFR 184.1199	21 CFR 184.1(b)(1)
Calcium glycerophosphate	21 CFR 184.1201	21 CFR 184.1(b)(1)
Calcium hydroxide	21 CFR 184.1205	21 CFR 184.1(b)(1)
Calcium iodate	21 CFR 184.1206	21 CFR 184.1(b)(2)
Calcium lactate	21 CFR 184.1207	21 CFR 184.1(b)(1)
Calcium oxide	21 CFR 184.1210	21 CFR 184.1(b)(1)
Calcium pantothenate	21 CFR 184.1212	21 CFR 184.1(b)(1)
Calcium propionate	21 CFR 184.1221	21 CFR 184.1(b)(1)
Calcium stearate	21 CFR 184.1229	21 CFR 184.1(b)(1)
Calcium sulfate	21 CFR 184.1240	21 CFR 184.1(b)(1)

Of special note, with the exception of calcium alginate and calcium iodate, all of the other calcium substances are approved for use under conditions of 21 CFR 184.1(b)(1) which states:

21 CFR 184.1

.....

(b) Any ingredient affirmed as GRAS in this part shall be used in accordance with current good manufacturing practice. For the purpose of this part, current good manufacturing practice includes the requirements that a direct human food ingredient be of appropriate food grade; that it be prepared and handled as a food ingredient; and that the quantity of the ingredient added to food does not exceed the amount reasonably required to accomplish the intended physical, nutritional, or other technical effect in food.

(1) If the ingredient is affirmed as GRAS with no limitations on its conditions of use other than current good manufacturing practice, it shall be regarded as GRAS if its conditions of use are consistent with the requirements of paragraph (b), (c), and (d) of this section. When the Food and Drug Administration (FDA) determines that it is appropriate, the agency will describe one or more current good manufacturing practice conditions of use in the regulation that affirms the GRAS status of the ingredient. For example, when the safety of an ingredient has been evaluated on the basis of limited conditions of use, the agency will describe in the regulation that affirms the GRAS status of the ingredient, one or more of these limited conditions of use, which may include the category of food(s), the technical effect(s) or functional use(s) of the ingredient, and the level(s) of use. If the ingredient is used under conditions that are significantly different from

those described in the regulation, that use of the ingredient may not be GRAS. In such a case, a manufacturer may not rely on the regulation as authorizing that use but shall independently establish that that use is GRAS or shall use the ingredient in accordance with a food additive regulation. Persons seeking FDA approval of an independent determination that a use of an ingredient is GRAS may submit a GRAS petition in accordance with § 170.35 of this chapter.

It is also recognized that many calcium-containing substances are used interchangeably. This can lead to confusion, especially when the same technical effects or food categories are not explicitly stated in the regulation. However, in many other countries, the use of calcium-containing substances is based on the principle of "*Quantum satis* (QS) which means "add as much of this ingredient as is needed to achieve the desired result, but no more." See Appendix II for FAO/WHO Food Standards for Calcium acetate.

This is contrasted with other affirmed GRAS regulations for other calcium-containing substances where different uses and technical effects are listed. Consider, for example, calcium propionate, 21 CFR 184.1221, below:

**§ 184.1221 Calcium propionate.**

(a) Calcium propionate ( $C_6H_{10}CaO_4$ , CAS Reg. No. 4075-81-4) is the calcium salt of propionic acid. It occurs as white crystals or a crystalline solid, possessing not more than a faint odor of propionic acid. It is prepared by neutralizing propionic acid with calcium hydroxide.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 60, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: [http://www.archives.gov/federal\\_register/code\\_of\\_federal\\_regulations/ibr\\_locations.html](http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html).

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an antimicrobial agent as defined in § 170.3(o)(2) of this chapter.

(2) The ingredient is used in the following foods at levels not to exceed current good manufacturing practice: baked goods as defined in § 170.3(n)(1) of this chapter; cheeses as defined in § 170.3(n)(5) of this chapter; confections and frostings as defined in § 170.3(n)(9) of this chapter; gelatins, puddings, and fillings as defined in § 170.3(n)(22) of this chapter; and jams and jellies as defined in § 170.3(n)(28) of this chapter.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[49 FR 13141, Apr. 3, 1984]

Please note that the regulation for calcium acetate lists six technical effects whereas the regulation for calcium propionate lists only one. Yet, these substances are used interchangeably and exhibit the same properties. Also, for calcium acetate, levels of use are listed for calcium acetate whereas no levels of use are listed for calcium propionate for the same food categories.

Thus, there is no question of safety related to the use of these substances when used in accordance with current good manufacturing practice conditions of use as required by 21 CFR 184.1(b). In addition, we find that the conditions of use are consistent with the requirements listed under 21 CFR 184.1(b)(1). [See below.] As such, we do not believe a GRAS petition or other regulatory action is necessary.

# GRAS Conclusion Independent Determination

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## PART 2 – IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

## 2.1. Background

Calcium acetate is a substance that occurs naturally in many fruits and fermented products. Calcium acetate is a white, odorless crystalline powder that is used in many industrial, medicinal and food applications. As a food additive, it is used as a buffering agent, stabilizing or firming agent, leavening agent and as a nutrient. It is consumed orally to reduce phosphate levels in blood and is a registered biochemical pesticide (EPA) for use as an attractant for yellow jackets.

Calcium acetate is freely soluble in water and slightly soluble in ethanol. It is produced commercially by reacting acetic acid with calcium hydroxide.

Calcium acetate is affirmed as GRAS for use in food under 21 CFR 184.1185. See regulation above.

The physical and chemical properties of calcium acetate are shown in Table 3. It is noted that the physical and chemical properties of the two compounds used as starting materials to manufacture calcium acetate, acetic acid and calcium hydroxide, meet the specifications listed in the Food Chemicals Codex, 10<sup>th</sup> Ed.

**Table 3. Product Characteristics for Calcium acetate**

<b>Product Properties</b>	
Product Name	Calcium Acetate
Formula	$(\text{CH}_3\text{COO})_2\text{Ca} \cdot x \text{H}_2\text{O}$ where $x \leq 0.5$
Molecular weight (anhydrous)	158.17 g/mol
CAS No.	62-54-4
EINECS No.	2005409
HS Code US	2915.29.5000
HS Code EU	2915.29.00
Solubility in water	at 0°C 29.7 g/100 ml; at 25°C 35.3 g/100 ml; at 100°C 37.4 g/100 ml

Niacet has established specifications for its calcium acetate as indicated below in Table 4. Niacet's calcium acetate meets the specifications listed in the Food Chemicals Codex, 10<sup>th</sup> Ed. Certificates of Analyses on five non-consecutive lots are shown in Appendix I. Because calcium acetate is produced by means of a very simple procedure (i.e., reaction of food grade calcium hydroxide and food grade acetic acid), the potential for formation of contaminants, or for the introduction of impurities into the final product, is very low. However, Niacet has established internal specifications for heavy metals (arsenic, mercury, lead, cadmium) that are frequently analyzed to ensure that these contaminants are not present in the final product. The information in Table 4 is based on data provided by Niacet Corp.

**Table 4. Product Specification for Niacet Calcium Acetate**

<b>Specifications Control Limits</b>	
Purity (Dry Basis):	NLT 99% and NMT 100.5% (as Calcium Acetate)
Water	NMT 7.0%

pH of a 10% Aqueous Solution	6.3 - 9.0
Insolubles	0.1%, Maximum
Appearance	White Powder
Heavy metals	<5 ppm
Arsenic	<1 ppm
Lead	<1 ppm

All analyses are conducted using commonly accepted analytical, validated, methods consistent with the requirements of the Food Chemicals Codex, 10<sup>th</sup> Ed. The calcium acetate that is the subject of this document meets the specifications of the Food Chemicals Codex.

Niacet has also developed a Material Safety Data Sheet (MSDS) for its Calcium acetate. The MSDS is attached IN Appendix IV.

## 2.2. Intended Technical Effect

Calcium acetate is affirmed as GRAS under 21 CFR 184.1185 (above) for use as a firming agent, pH control agent, processing aid, sequestrant, stabilizer and thickener, texturizer, and flavoring agent (FEMA 2228). Other calcium-containing substances affirmed as GRAS lists the same, similar, other, or no food categories or technical effects at all. This is contrasted, e.g., with the regulations for calcium acetate and calcium propionate listed above.

Both are listed as Affirmed GRAS substances in accordance with 21 CFR 184.1(b)(1) which means that other uses (food categories) and technical effects may also be GRAS. However, calcium acetate lists some food categories and several technical effects whereas calcium propionate lists some food categories and only the antimicrobial technical effect. [See regulations above.] This often leads to confusion as some clients interpret these regulations to mean that calcium acetate cannot be substituted for calcium propionate unless the uses are identical and specifically stated in the regulation(s). In fact, in practice, the acid salts of calcium are used interchangeably throughout the industries, for a variety of reasons such as economic, availability, etc.

Calcium-containing substances that are affirmed as GRAS in 21 CFR part 184 are listed in Table 2 above. The technical effects, food categories, and levels of use vary among these substances

Since both calcium acetate and calcium propionate are regulated in accordance with 21 CFR 184.1(b)(1), we interpret this to mean that other uses and levels of use may also be considered to be GRAS consistent with current good manufacturing practice conditions of use. The use levels that we contemplate for calcium acetate are in line with use levels currently used for calcium propionate.

Given the interchangeable utility of the calcium-containing substances, and current industry practices, Niacet has determined that this practice is safe as there is no increase in exposure resulting from these practices. In addition, the counter anions associated with these calcium-containing substances are common species in the diet and do not present a safety concern. There

is no question of safety related to the use of these substances when used in accordance with current good manufacturing practice conditions of use as required by 21 CFR 184.1(b). In addition, we find that the conditions of use are consistent with the requirements listed under 21 CFR 184.1(b)(1). A model regulation that reflects the intended changes is provided in Appendix V.



# GRAS Conclusion Independent Determination

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## PART 3 – DIETARY EXPOSURE

### 3.1. Current Regulated Uses

Calcium acetate is affirmed as Generally Recognized As Safe (GRAS) (21 CFR 184.1155) for use as a firming agent, pH control agent, processing aid, sequestrant, stabilizer and thickener, texturizer, and flavoring agent (FEMA 2228). These uses and the approved use levels for calcium acetate in select foods are summarized in Table 1 above.

Calcium acetate has numerous food uses in the U.S. and throughout the world. Calcium acetate is listed as a food additive by Codex Alimentarius in the Codex General Standard for Food Additives (GSFA) with the functional class designation including firming agent, stabilizer, and thickener. The list of GSFA Provisions for calcium chloride is summarized at GSFA Online (FAO/WHO Food Standards Codex Alimentarius <http://www.fao.org/gsfaonline/additives/details.html?id=317&print=true>), Appendix II.

Calcium acetate is approved as a food additive (Group I) in the European Union (EU) for use in dehydrated milk, ripened cheese, canned or bottled fruit and vegetables, jams, jellies, marmalades and sweetened chestnut puree, and other similar fruit or vegetable spreads (E 263; [https://webgate.ec.europa.eu/sanco\\_foods/main/index.cfm?event=substance.view&identifier=227](https://webgate.ec.europa.eu/sanco_foods/main/index.cfm?event=substance.view&identifier=227)).

### 3.2. Proposed Use and Levels

Niacet intends to add calcium acetate to food as a firming agent as defined in § 170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; and texturizer as defined in § 170.3(o)(32) of this chapter in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice. This determination places the food uses of calcium acetate in line with the food uses of other regulated calcium-containing substances and reflects current industry practices.

Niacet intends to add calcium acetate to a variety of foods at levels consistent with current good manufacturing practices. As the new uses of calcium acetate will be substitutional for other calcium-containing substances, no increase in the overall exposure to calcium in the diets is anticipated from the consumption of calcium-containing substances. In addition, the counter anions associated with these calcium-containing substances are common species in the diet and do not present a safety concern.

In a GRAS Notice (GRN 634; available at: <http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf>), the submitter provided estimates from all food sources (page 30 of 100). These analyses indicated that the cumulative calcium intake at the 90<sup>th</sup> percentile from all sources was below the calcium upper limit (UL) established by the Institute of Medicine Upper Limit (IOM UL) for the majority of the age-based subpopulations as well as for all population groups of the European Food Safety Authority Upper Limits (EFSA ULs) established in 2012.

In summary, Niacet has concluded that, when used as intended, calcium acetate will not result in an increase in exposure to calcium.

Independent Determination  
GRAS Conclusion

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TABLE 1 - SELF-IDENTIFYING TYPES OF GRAS

# **GRAS Conclusion Independent Determination**

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## **PART 4 – SELF-LIMITING LEVELS OF USE**

#### **4.1. Self-limiting levels of use**

Calcium acetate is determined to be GRAS for use in food as a firming agent as defined in § 170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; and texturizer as defined in § 170.3(o)(32) of this chapter, and as a flavoring agent (FEMA 2228), in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice. Excessive levels of use will be controlled by economic factors and the possibility of introducing off-tastes or unwanted changes in the food matrix when current good manufacturing practices are exceeded.

**GRAS Conclusion  
Independent Determination**

\*\*\*\*\*

**PART 5 – EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE  
1958**

**5.1. Experience based on common use in food**

This GRAS determination is based on scientific procedures. We did not attempt to document common use in food prior to 1958. Notwithstanding this, it is reasonable to conclude that, since calcium acetate occurs naturally in food, it was present in food prior to 1958.

GRAS Conclusion  
Independent Determination

\*\*\*\*\*

PARTE - NARRATIVE

**GRAS Conclusion  
Independent Determination**

\*\*\*\*\*

**PART 6 – NARRATIVE**



## 6.1. Introduction

Calcium, an essential mineral, is known to play a wide range of biological roles. It is a major constituent of bone and teeth and is crucial for several functions such as muscle contraction, nerve conduction, the beating of the heart, blood coagulation, glandular secretion, energy production, maintenance of immune function, etc. (IOM, 2012). Calcium is an integral component of the skeleton; approximately 99% of the total body calcium is found in bones and teeth as calcium hydroxyapatite, where it has a major structural role. The remaining 1% of calcium found in the body acts as an essential intracellular messenger on cells and tissues. [Ref.: <http://efsa.europa.eu/en/efsajournal/pub/4101>].

The Office of Dietary Supplements (ODS) of the National Institutes of Health (NIH) has issued a detailed fact sheet regarding calcium as a nutrient and dietary supplement. This publication is attached in its entirety to this document in Appendix VI. While the document does not address calcium acetate specifically, it is relevant to the levels and properties of calcium in the body. As such, it provides the support for the need of additional calcium sources in human consumption because a large number of consumers do not receive an adequate amount of calcium through their diets and may be at risk for illnesses or ailments that could be prevented if the proper amounts of calcium were consumed.

The biological and toxicological effects of calcium deficiency as well as calcium excess have been extensively reviewed by both the Institute of Medicine (IOM, 2011) and the European Food Safety Authority (EFSA, 2012). Based on calcium excretion in young children and formation of kidney stones in older children and adults, the IOM (2011) established tolerable upper limits (ULs) for infants 0-6 months (1,000 mg/day), infants 6-12 months (1,500 mg/day), children 1- 8 y (2,500 mg/day), adolescents 9-18 y (3,000 mg/day), adults 19 – 50 y (2,500 mg/day), and older adults 51+ y (2,000 mg/day). The IOM (2011) concluded that there were insufficient data to determine a UL based on other effects, including increased risk of cardiovascular disease (CVD) among post-menopausal women and older men. In 2012, EFSA evaluated the safety of calcium and reached similar conclusions on the lack of adverse associations between calcium intake and CVD as well as other health endpoints but did not believe the available evidence required a revision of the UL of 2,500 mg/day for adults as previously established by the Scientific Committee on Food (SCF) in 2003. The literature published since the IOM review in 2011 provides no new evidence of a cause and effect that would alter the significant scientific consensus presented in the IOM (2011) or the EFSA (2012) reviews.

The NIH ODS Fact sheet on calcium states that: “Calcium, the most abundant mineral in the body, is found in some foods, added to others, is available as a dietary supplement, and is present in some medicines (such as antacids). Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling and hormonal secretion, though less than 1% of total body calcium is needed to support these critical metabolic functions [1]. Serum calcium is very tightly regulated and does not fluctuate with changes in dietary intakes; the body uses bone tissue as a reservoir for, and source of calcium, to maintain constant concentrations of calcium in blood, muscle, and intercellular fluids [1].

The remaining 99% of the body's calcium supply is stored in the bones and teeth where it supports their structure and function [1]. Bone itself undergoes continuous remodeling, with constant resorption and deposition of calcium into new bone. The balance between bone resorption and deposition changes with age. Bone formation exceeds resorption in periods of

growth in children and adolescents, whereas in early and middle adulthood both processes are relatively equal. In aging adults, particularly among postmenopausal women, bone breakdown exceeds formation, resulting in bone loss that increases the risk of osteoporosis over time.” [Ref.: NIH: Dietary Supplement Fact Sheet: Calcium. Available at: <https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/>. Accessed 06-27-2016].

As noted above, calcium acetate is affirmed as GRAS under 21 CFR 184.1155. It is also approved for use in food by many other international regulatory bodies. There is a large volume of publicly available information related to the safety of calcium acetate and other calcium-containing substances. As such, there is a recognized general consensus that calcium acetate is safe for use when used as described in this document.

The intended use of calcium acetate has been determined to be safe through scientific procedures as set forth in 21 CFR 170.30(b), thus satisfying the so-called “technical” element of the GRAS determination. Because this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called “common knowledge” element of a GRAS determination.

This determination of the safety and GRAS status of calcium acetate for addition to foods under its intended conditions of use has been made through the deliberations of an Expert Panel of individuals qualified by scientific training and experience to evaluate the safety of substances intended to be added to food. This panel has critically reviewed and evaluated the publicly available information summarized in this document and have individually and collectively concluded that calcium acetate produced consistent with Good Manufacturing Practice and meeting the specifications described herein, is safe under its intended conditions of use. The Panel further unanimously concludes that these uses of calcium acetate are GRAS based on scientific procedures, and that other experts qualified to assess the safety of foods and food ingredients would concur with these conclusions. The Panel’s GRAS opinion is included as Exhibit 1 to this document.

The safety of calcium acetate has been thoroughly reviewed by FDA, JECFA (Joint FAO/WHO Expert Committee on Food Additives) and other international regulatory bodies. All of these reviews have determined that calcium acetate is safe for use in food (Ref.: EFSA, 2009 and references cited therein). The EFSA Scientific Opinion on calcium acetate and other calcium-containing substances is listed in appendix VI.

For FDA, the safety of calcium acetate was reviewed by the Select Committee on GRAS Substances (SCOGS) where the SCOGS concluded:

**Calcium acetate:**

There is no evidence in the available information on calcium acetate, calcium chloride, calcium gluconate, and calcium phytate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future. [Available at: <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm260876.htm>].

In addition, FDA has received nine GRAS notices related to calcium-containing substances (Table 5) which discuss the safety of calcium as related to food uses, etc. All of these notices received “good day” letters from FDA. The safety related material and discussions in these documents are incorporated by reference into this document on calcium acetate.

**Table 5. GRAS Notices – Calcium-containing substances**

GRN 634 – Calcium chloride [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf>

GRN 573 – Calcium disodium ethylenediaminetetraacetate (EDTA) [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm456215.pdf>

GRN 451 – Calcium ascorbate with added threonate [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm337465.pdf>

GRN 420 – Calcium acid pyrophosphate [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm299333.pdf>

GRN 363 - Calcium disodium ethylenediaminetetraacetic acid (EDTA) and disodium EDTA

[Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm270270.pdf>

GRN 157 - Calcium propionate (alternative method of manufacture) [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264105.pdf>

GRN 136 – Calcium gluconate [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm267374.pdf>

GRN 28 – Seaweed-derived calcium [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm260968.pdf>

GRN 11 - Calcium casein peptone-calcium phosphate [Available at:

<http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264465.pdf>

An updated comprehensive literature search was conducted to obtain any publicly available information related to the safety of calcium acetate and related calcium-containing substances since 2010. No relevant animal or human safety studies were located.

In conclusion, Niacet has determined that there is a general consensus that calcium acetate is safe for use in food when used as described in this dossier.

Calcium acetate is produced by means of a very simple procedure (reaction of calcium hydroxide and acetic acid). As such, the potential for contamination or for the introduction of impurities into the final product is low. However, Niacet has established specifications for potential

contaminants, including heavy metals (arsenic, lead) to ensure that these substances are kept at sufficiently low levels in the finished products as not to present any safety concerns. Thus, there is no question of safety related to the use of these substances when used in accordance with current good manufacturing practice conditions of use as required by 21 CFR 184.1(b). In addition, we find that the conditions of use are consistent with the requirements listed under 21 CFR 184.1(b)(1). Calcium acetate produced by Niacet meets the specifications in the Food Chemicals Codex and JECFA specifications (Appendix VII).



## REFERENCES

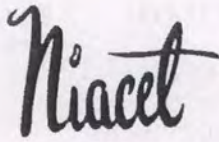
- European Food Safety Authority (EFSA). 2012. Scientific opinion on the tolerable upper intake level of calcium. EFSA Journal 10(7):2814.
- U.S. Food and Drug Administration Generally Recognized as Safe (GRAS) Database, SCOGS 45. 1975. Evaluation of the health aspects of certain calcium salts as food ingredients.
- Food Chemicals Codex (FCC). 2014. Calcium Acetate pp. 188-189. 9<sup>th</sup> Edition, U.S. Pharmacopeial (USP) Convention, Rockville, MD
- Institute of Medicine (IOM). Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. 1997. Washington, DC: National Academies Press.
- Institute of Medicine (IOM). Dietary Reference Intakes for Calcium and Vitamin D. 2011. Washington, DC: The National Academies Press.
- Joint FAO/WHO Expert Committee on Food Additives. 2001. Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1956-2001) (First through fifty-seventh meetings) Available at: <http://jecfa.ilsa.org/>

## **APPENDIX I. CERTIFICATES OF ANALYSIS FOR CALCIUM ACETATE**

The calcium acetate that is the subject of this document meets the specifications listed in the Food Chemicals Codex, 10<sup>th</sup> Ed. Therefore, no Certificates of analysis are attached.







CERTIFICATE OF ANALYSIS  
80015414

80015414 1 (2)

Customer's reference  
4500019924

18.11.2016  
Order no. / date  
1000013547  
03.11.2016

**Customer**

Niacet Corporation  
400 47th street  
NIAGARA FALLS, NY NY 14304  
USA

**Description**  
PROGUSTA CA POWDER 20KG

**Cust. No.:**  
52488

**Code**  
52026

**Gross Weight**  
5.256,720 KG

**Net Weight**  
5.040,000 KG

**Batch**  
2000034118

**Manufacturing date**  
13.11.2016

**Expiration date**  
13.11.2018

Characteristic	Result	Specification	Unit
Assay on dried material	100,0	99,0 - 100,5	%(m)
Mercury (Hg)*		< = 1	ppm
Oxidisable Impurities as Formic Acid	< 0,1	< = 0,1	%(m)
pH of 10% solution	6,3	6,0 - 9,0	
Water	5,9	< = 6,0	%(m)
Chloride	< 100	< = 500	ppm
Iron	< 2,0	< = 10,0	ppm
Appearance	White powder	White powder	
Insolubles in water	< 0,1	< = 0,1	%(m)
Lead*		< = 2	ppm
Fluoride*		< = 50	ppm
Heavy Metals (as Pb)*		< = 10	ppm
Arsenic*		< = 3	ppm
Sulphate	< 0,1	< = 0,1	%(m)

**Remarks:**

This Certificate of Analysis is based on batch specific analysis. Parameters marked with \* are not tested for every batch, but these are tested periodically. All our raw materials are obtained from only approved suppliers and match with our raw material specifications according to our ISO 9001 quality management system. Representative samples of each batch are retained for three years and the analysis results of each batch are archived for 10 years. Each sales order is directly linked to (a) batch number(s).

Niacet b.v.  
Papesteeg 91, 4006 WC Tiel  
P.O.Box 60, 4000 AB Tiel  
The Netherlands

Tel. + 31 344 615 224  
Fax + 31 344 611 475  
tiel@niacet.nl  
www.niacet.com

IBAN NL61BOFA0266533965  
Trade register Tiel  
Registration no. 11044303  
VAT NL807461817B01

CERTIFICATE OF ANALYSIS  
80015414

80015414 2 (2)

Customer's reference  
4500019924

18.11.2016  
Order no. / date  
1000013547  
03.11.2016

This CoA is only valid when the product is in its original undamaged packaging and when stored under the recommended conditions.

This Certificate of Analysis has been approved electronically and is valid without a signature.

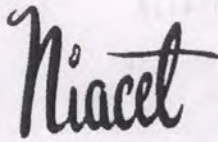
Approved by:  
Senior Analyst Analytical Laboratory  
Niacet b.v.  
H. van den Hurk

Printing date:  
18.11.2016

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Trade register Tiel  
Registration no. 11044303  
VAT NL807461817B01



CERTIFICATE OF ANALYSIS  
80014337

80014337 1 (2)

Customer's reference  
4500017991

21.10.2016  
Order no. / date  
1000012592  
24.08.2016

**Customer**

Niacet Corporation  
400 47th street  
NIAGARA FALLS, NY NY 14304  
USA

**Description**  
PROGUSTA CA GRANULAR 20KG

**Cust. No.:**  
52489

**Code**  
50276

**Gross Weight**  
8.216,000 KG

**Net Weight**  
8.000,000 KG

**Batch**  
2000032695

**Manufacturing date**  
06.10.2016

**Expiration date**  
06.10.2018

Characteristic	Result	Specification	Unit
Assay on dried material	99,8	99,0 - 100,5	%(m)
Mercury (Hg)*		< = 1	ppm
Oxidisable Impurities as Formic Acid	< 0,1	< = 0,1	%(m)
pH of 10% solution	7,3	6,0 - 9,0	
Water	5,5	< = 6,0	%(m)
Chloride	271	< = 500	ppm
Iron	< 2,0	< = 10,0	ppm
Appearance		White agglomerate	White agglomerate
Insolubles in water	< 0,1	< = 0,1	%(m)
Lead*		< = 2	ppm
Fluoride*		< = 50	ppm
Heavy Metals (as Pb)*		< = 10	ppm
Arsenic*		< = 3	ppm
Sulphate	< 0,1	< = 0,1	%(m)

**Remarks:**

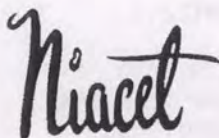
This Certificate of Analysis is based on batch specific analysis. Parameters marked with \* are not tested for every batch, but these are tested periodically. All our raw materials are obtained from only approved suppliers and match with our raw material specifications according to our ISO 9001 quality management system. Representative samples of each batch are retained for three years and the analysis results of each batch are archived for 10 years. Each sales order is directly linked to (a) batch number(s).

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CERTIFICATE OF ANALYSIS  
80012215

80012215 1 (2)

Customer's reference  
4500014332

19.04.2016  
Order no. / date  
1000010653  
11.04.2016

**Customer**

Niacet Corporation  
400 47th street  
NIAGARA FALLS, NY NY 14304  
USA

**Description**  
PROGUSTA CA GRANULAR 20KG

**Cust. No.:**  
52489

**Code**  
50276

**Gross Weight**  
4.108,000 KG

**Net Weight**  
4.000,000 KG

**Batch**  
2000026851

**Manufacturing date**  
30.03.2018

**Expiration date**  
30.03.2018

Characteristic	Result	Specification	Unit
Assay on dried matter	100,5	99,0 - 100,5	%(m)
Mercury (Hg)*		< = 1	ppm
Insoluble in water	< 1000	< = 1000	ppm
pH of 10% solution	7,2	6,0 - 9,0	
Sulphate	< 100	< = 1000	ppm
Water	5,9	< = 6,0	%(m)
Chloride	< 100	< = 500	ppm
Iron	< 2,0	< = 10,0	ppm
Appearance		White agglomerate	White agglomerate
Oxidisable impurities as H. Form	< 1000	< = 1000	ppm
Lead*		< = 2	ppm
Fluoride*		< = 50	ppm
Heavy Metals (as Pb)*		< = 10	ppm
Arsenic*		< = 3	ppm

**Remarks:**

This Certificate of Analysis is based on batch specific analysis. Parameters marked with \* are not tested for every batch, but these are tested periodically. All our raw materials are obtained from only approved suppliers and match with our raw material specifications according to our ISO 9001 quality management system. Representative samples of each batch are retained for three years and the analysis results of each batch are archived for 10 years. Each sales order is directly linked to (a) batch number(s).

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## APPENDIX II. FAO/WHO FOOD STANDARDS FOR CALCIUM ACETATE



### GSFA Online

Updated up to the 39<sup>th</sup> Session of the Codex Alimentarius Commission (2016)

FRANÇAIS | ESPAÑOL | 中文

### FOOD ADDITIVE DETAILS

#### Calcium acetate (263)

##### Functional Classes

- Acidity regulator
- Preservative
- Stabilizer

[Click here to search the FAO JECFA database for the specifications of additive\(s\) with INS No. 263](#)

[Click here to search the WHO JECFA database for evaluation of additive\(s\) with INS No. 263](#)

#### GSFA Provisions for Calcium acetate

Number	Food Category	Max Level	Notes
<sup>01</sup> 13.2	<a href="#">Complementary foods for infants and young children</a>		GMP <a href="#">Note 239</a>
<sup>01</sup> 11.4	<a href="#">Other sugars and syrups (e.g. xylose, maple syrup, sugar toppings)</a>		GMP <a href="#">Note 258</a>

Note: Unless otherwise specified, food additive provisions apply to the food category indicated (e.g. Dairy), as well as to all subcategories of that category (e.g. Cheese, Ripened Cheese, etc.).

#### GSFA Table 3 Provisions

**Calcium acetate** is a food additive that is included in [Table 3](#), and as such may be used in the following foods under the conditions of good manufacturing practices (GMP) as outlined in the Preamble of the Codex GSFA. Although not listed below, Calcium acetate could also be used in heat-treated butter milk of food category 01.1.1 and spices of food category 12.2.1. Note that food categories listed in the [Annex to Table 3](#) were excluded accordingly. **Calcium acetate** is






acceptable in foods conforming to the following commodity standards: CS 117-1981

Number	Food Category
01.1.4	<u>Flavoured fluid milk drinks</u>
01.3	<u>Condensed milk and analogues (plain)</u>
01.4.3	<u>Clotted cream (plain)</u>
01.4.4	<u>Cream analogues</u>
01.5	<u>Milk powder and cream powder and powder analogues (plain)</u>
01.6.1	<u>Unripened cheese</u>
01.6.2	<u>Ripened cheese</u>
01.6.4	<u>Processed cheese</u>
01.6.5	<u>Cheese analogues</u>
01.7	<u>Dairy-based desserts (e.g. pudding, fruit or flavoured yoghurt)</u>
01.8.1	<u>Liquid whey and whey products, excluding whey cheeses</u>
02.2.2	<u>Fat spreads, dairy fat spreads and blended spreads</u>
02.3	<u>Fat emulsions mainly of type oil-in-water, including mixed and/or flavoured products based on fat emulsions</u>
02.4	<u>Fat-based desserts excluding dairy-based dessert products of food category 01.7</u>
03.0	<u>Edible ices, including sherbet and sorbet</u>
04.1.2	<u>Processed fruit</u>
04.2.2.2	<u>Dried vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, and nuts and seeds</u>
04.2.2.3	<u>Vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), and seaweeds in vinegar, oil, brine, or soybean sauce</u>
04.2.2.4	<u>Canned or bottled (pasteurized) or retort pouch vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), and seaweeds</u>
04.2.2.5	<u>Vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g., peanut butter)</u>
04.2.2.6	<u>Vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed pulps and preparations (e.g. vegetable desserts and sauces, candied vegetables) other than food category 04.2.2.5</u>
04.2.2.8	<u>Cooked or fried vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), and seaweeds</u>
05.0	<u>Confectionery</u>
06.3	<u>Breakfast cereals, including rolled oats</u>
06.4.3	<u>Pre-cooked pastas and noodles and like products</u>
06.5	<u>Cereal and starch based desserts (e.g. rice pudding, tapioca pudding)</u>
06.6	<u>Batters (e.g. for breading or batters for fish or poultry)</u>

- 06.7 Pre-cooked or processed rice products, including rice cakes (Oriental type only)
- 06.8 Soybean products (excluding soybean-based seasonings and condiments of food category 12.9)
- 07.0 Bakery wares
- 08.2 Processed meat, poultry, and game products in whole pieces or cuts
- 08.3 Processed comminuted meat, poultry, and game products
- 08.4 Edible casings (e.g. sausage casings)
- 09.3 Semi-preserved fish and fish products, including mollusks, crustaceans, and echinoderms
- 09.4 Fully preserved, including canned or fermented fish and fish products, including mollusks, crustaceans, and echinoderms
- 10.2.3 Dried and/or heat coagulated egg products
- 10.3 Preserved eggs, including alkaline, salted, and canned eggs
- 10.4 Egg-based desserts (e.g. custard)
- 11.6 Table-top sweeteners, including those containing high-intensity sweeteners
- 12.2.2 Seasonings and condiments
- 12.3 Vinegars
- 12.4 Mustards
- 12.5 Soups and broths
- 12.6 Sauces and like products
- 12.7 Salads (e.g. macaroni salad, potato salad) and sandwich spreads excluding cocoa- and nut-based spreads of food categories 04.2.2.5 and 05.1.3
- 12.8 Yeast and like products
- 12.9 Soybean-based seasonings and condiments
- 12.10 Protein products other than from soybeans
- 13.3 Dietetic foods intended for special medical purposes (excluding products of food category 13.1)
- 13.4 Dietetic formulae for slimming purposes and weight reduction
- 13.5 Dietetic foods (e.g. supplementary foods for dietary use) excluding products of food categories 13.1 - 13.4 and 13.6
- 13.6 Food supplements
- 14.1.4 Water-based flavoured drinks, including "sport," "energy," or "electrolyte" drinks and particulated drinks
- 14.2.1 Beer and malt beverages
- 14.2.2 Cider and perry
- 14.2.4 Wines (other than grape)
- 14.2.5 Mead
- 14.2.6 Distilled spirituous beverages containing more than 15% alcohol
- 14.2.7 Aromatized alcoholic beverages (e.g. beer, wine and spirituous cooler-type beverages, low alcoholic refreshers)

 [15.0 Ready-to-eat savouries](#)

 [16.0 Prepared foods](#)

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Note: Unless otherwise specified, food additive provisions apply to the food category indicated (e.g. Dairy), as well as to all subcategories of that category (e.g. Cheese, Ripened Cheese, etc.).

 [printer-friendly version](#)

[GSFA Home](#) [Food Categories](#) [Food Additives](#) [Search](#) [Functional Classes](#)  
[Glossary](#)

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**APPENDIX III. GRAS NOTICES RECEIVED BY FDA (ACCESSED 10-12-2016)**

<b>GRN No.</b> (sorted Z-A)	<b>Substance</b>	<b>Date of closure</b>	<b>FDA's Letter</b>
634	Calcium chloride		Pending
573	Calcium disodium ethylenediaminetetraacetate (EDTA)	Oct 22, 2015	FDA has no questions <sup>7</sup>
451	Calcium ascorbate with added threonate	Aug 5, 2013	FDA has no questions <sup>8</sup>
420	Calcium acid pyrophosphate	Aug 10, 2012	FDA has no questions <sup>9</sup>
363	Calcium disodium ethylenediaminetetraacetic acid (EDTA) and disodium EDTA	Jun 6, 2011	FDA has no questions <sup>10</sup>
157	Calcium propionate (alternative method of manufacture)	Dec 13, 2004	FDA has no questions <sup>11</sup>
136	Calcium gluconate	Feb 5, 2004	FDA has no questions <sup>12</sup>
52	Whey mineral concentrate	Jan 30, 2001	FDA has no questions <sup>13</sup>
28	Seaweed-derived calcium	Apr 21, 2000	FDA has no questions (additional correspondence available) <sup>14</sup>
11	Calcium casein peptone-calcium phosphate	Jan 29, 1999	FDA has no questions <sup>15</sup>

## APPENDIX IV. NIACET MSDS FOR CALCIUM ACETATE



Ref.50274/1.1/REG\_EU/EN

### SAFETY DATA SHEET

Calcium acetate

Revision Date: 14.11.2014

Previous date: 11.06.2013

Print Date: 14.11.2014

#### 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

Product information

**Commercial Product Name**

Chemical name: Calcium acetate

Registration number:

01-2119987569-11-0001

Relevant identified uses of the substance or mixture and uses advised against Use of the Substance/Mixture

Food additive, Preservative, Pharmaceutical, Active substance

Recommended restrictions on use

Reserved for industrial and professional use.

Details of the supplier of the safety data sheet

Niacet b.v.

P.O. Box 60 4000 AB Tiel NETHERLANDS

Telephone +31 344-615224, Telefax. +31 344-611475 Tiel@Niacet.nl

Niacet Corporation 400 47<sup>th</sup> Street Niagara Falls, NY

14304 USA

Telephone +1 716 285 1474 Telefax +1 716 285 1497 niacetsr@niacet.com

Emergency telephone number

For Niacet b.v.Tiel, The Netherlands products: +31 344-615224 For Niacet Corporation, Niagara Falls, U.S.A. products:  
Chemtrec +1 (800) 424 9300, +1 (703) 527 3887

## 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

## 2. HAZARDS IDENTIFICATION

Classification of the substance or mixture

Classification according to Regulation (EU) 1272/2008(CLP)

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

Classification according to EU Directives 67/548/EEC or 1999/45/EC

Not a hazardous substance or mixture according to EC-directives 67/548/EEC or 1999/45/EC.

Label elements

Labelling (REGULATION (EC) No 1272/2008)

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

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## SAFETY DATA SHEET

Calcium acetate

Revision Date: 14.11.2014

Previous date: 11.06.2013

Print Date: 14.11.2014

### 2.3 Other hazards

This substance is not considered to be persistent, bioaccumulating nor toxic (PBT).

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

### 3.1 Substances

Chemical Name  
EINECS-No. / ELINCS No.  
Calcium di(acetate)  
200-540-9

CAS-No.  
62-54-4

Concentration [%]  
<= 100

## FIRST AID MEASURES

Description of first aid measures

Inhalation

Remove to fresh air. Keep patient warm and at rest. In case of feeling unwell consult a physician.

Skin contact

Rinse with water.

Eye contact

Rinse with plenty of water. If symptoms persist, call a physician.

Ingestion

Rinse mouth with water. Obtain medical attention.

Most important symptoms and effects, both acute and delayed

Symptoms: May cause mild irritation.

Indication of immediate medical attention and special treatment needed, if necessary

Treatment: No information available.

## 5. FIRE-FIGHTING MEASURES

Extinguishing media

Special hazards arising from the substance or mixture

No hazards to be specially mentioned.

Extinguishing media:	Water spray
Foam	
Dry chemical	
Carbon dioxide (CO <sub>2</sub> )	
Unsuitable	None.
extinguishing media:	

Niacet

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## SAFETY DATA SHEET

Calcium acetate

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Special protective actions for fire-fighters  
Standard equipment for firefighting.

Specific methods  
The product is flammable but not readily ignited.

### 6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures  
Use personal protective equipment. For personal protection see section 8.

Environmental precautions  
Try to prevent the material from entering drains or water courses.

Methods and materials for containment and cleaning up  
Take up mechanically and collect into suitable containers for disposal. After cleaning, flush away traces with water

### HANDLING AND STORAGE

Precautions for safe handling  
Keep container tightly closed. Avoid contact with skin, eyes and clothing. Ensure adequate ventilation.

Conditions for safe storage, including any incompatibilities  
Keep tightly closed in a dry and cool place. Materials for packaging Suitable material: original container

Materials to avoid:  
no data available



Specific end uses

Food additive, Pharmaceutical, Active substance, Preservative

**EXPOSURE CONTROLS/PERSONAL PROTECTION**

Exposure Limit Values

Contains no substances with occupational exposure limit values.

Exposure controls

Appropriate engineering controls

Handle in accordance with good industrial hygiene and safety practice. In case of insufficient ventilation, wear suitable respiratory equipment.

Individual protection measures, such as personal protective equipment

Hand protection

Glove material: PVC

Glove material: Rubber gloves

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The logo for Niacel, featuring the word "Niacel" in a stylized, blue, cursive font.

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**SAFETY DATA SHEET**

Calcium acetate

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Eye protection

Tightly fitting safety goggles.

Skin and body protection

Work clothing.

Respiratory protection

Respirator must be worn if exposed to dust.

## 9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties General Information (appearance, odour)

Physical state	solid, powder, granules
Colour	white
Odour	odourless

Important health safety and environmental information

pH 7 - 8 (1 %)

Flash point  
no data available

Explosive properties:

Density 1.500 kg/m<sup>3</sup>  
440 - 700 kg/m<sup>3</sup> loose

Lower explosion limit  
no data available

Upper explosion limit  
no data available

Vapour pressure  
no data available

Solubility(ies):  
Water solubility 353 kg/m<sup>3</sup> (25 °C)

Thermal decomposition > 200 °C

9.2 Other data

## 10. STABILITY AND REACTIVITY

Reactivity

No dangerous reaction known under conditions of normal use.

Chemical stability

Stable under normal conditions.

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## SAFETY DATA SHEET

Calcium acetate

Revision Date: 14.11.2014

Previous date: 11.06.2013

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Possibility of hazardous reactions

Hazardous reactions: None known.

Conditions to avoid

Conditions to avoid: Stable under recommended storage conditions.

Incompatible materials

Materials to avoid: no data available

Hazardous decomposition products

Thermal decomposition: >200 °C

### 11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects Acute toxicity

LD50/Oral/rat: 4.280 mg/kg

Irritation and corrosion

Skin:

Not classified as irritating for skin.

Eyes:

Not classified as irritating for eyes.

Sensitization

no data available

Long term toxicity

Other information

no data available

Human experience

Inhalation

Exposure to dust at high concentrations.,

May cause irritation of the mucous membranes. May cause irritation of respiratory tract.

Skin contact

Repeated or prolonged exposure, may cause mild irritation.

Eye contact

May cause mild irritation.

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**SAFETY DATA SHEET**

Calcium acetate

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**12. ECOLOGICAL INFORMATION**

Ecotoxicity effects

Aquatic toxicity

no data available

Toxicity to other organisms

no data available

Persistence and degradability

Biological degradability:  
Readily biodegradable

Bioaccumulative potential

Bioaccumulation is unlikely.

Mobility in soil Mobility  
Water solubility: 353 kg/m<sup>3</sup> (25 °C)

Water soluble. Stays in water phase. non-volatile

Results of PBT and vPvB assessment

This substance is not considered to be persistent, bioaccumulating nor toxic (PBT).

12.6 Other adverse effects  
no data available

### **13. DISPOSAL CONSIDERATIONS**

13.1 Waste treatment methods

Product: Dispose of in compliance with local and national regulations.

### **14. TRANSPORT INFORMATION**

14.1 UN number

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## SAFETY DATA SHEET

Calcium acetate

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Land transport

Not classified as dangerous in the meaning of transport regulations.

Sea transport

Not classified as dangerous in the meaning of transport regulations.

Air transport

### 14.6 Special precautions for user

Not classified as dangerous in the meaning of transport regulations.

Not classified as dangerous in the meaning of transport regulations.

## 15. REGULATORY INFORMATION

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

Water contaminating class (Germany)

WGK 1 slightly water endangering

15.2 Chemical Safety Assessment

No Chemical Safety Assessment has been carried out.

## 16. OTHER INFORMATION

### Training advice

Read the safety data sheet before using the product.

### Further information

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

### Sources of key data used to compile the Safety Data Sheet

Regulations, databases, literature, own tests.

### Additions, Deletions, Revisions

Relevant changes have been marked with vertical lines.

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## APPENDIX V. MODEL REGULATION (184.1155) FOR CALCIUM ACETATE – NIACET

Sec. 184.1185 Calcium acetate.

(a) Calcium acetate ( $\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$ , CAS Reg. No. 62-54-4), also known as acetate of lime or vinegar salts, is the calcium salt of acetic acid. It may be produced by the calcium hydroxide neutralization of acetic acid.

(b) The ingredient meets the specifications of the Food Chemicals Codex, Eighth Ed. (2012), p.160-161, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: [http://www.archives.gov/federal\\_register/code\\_of\\_federal\\_regulations/ibr\\_locations.html](http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html).

(c) In accordance with 184.1(b)(1), the ingredient is used in food with no limitation other than good manufacturing practice. The affirmation of this ingredient as generally regarded as safe (GRAS) as a direct human food ingredient is based upon the following good manufacturing condition of use:

(1) The ingredient is used as an antimicrobial agent as defined in 170.3(o)(2) of this chapter; a firming agent as defined in 170.3(o)(10) of this chapter; flavor enhancer as defined in 170.3(o)(11) of this chapter; nutrient supplement as defined in 170.3(o)(20) of this chapter; pH control agent as defined in 170.3(o)(23) of this chapter; processing aid as defined in 170.3(o)(24) of this chapter; sequestrant as defined in 170.3(o)(26) of this chapter; stabilizer and thickener as defined in 170.3(o)(28) of this chapter; and texturizer as defined in 170.3(o)(32) of this chapter.

(2) The ingredient is used in the following foods at levels not to exceed current good manufacturing practice: baked goods as defined in 170.3(n)(1) of this chapter; cheeses as defined in 170.3(n)(5) of this chapter; gelatins, puddings, and fillings as defined in 170.3(n)(22) of this chapter; sweet sauces, toppings, and syrups as defined in 170.3(n)(43) of this chapter; and all other food categories.

(d) Prior sanctions for this ingredient different from the uses established in this section or in part 181 of this chapter do not exist or have been waived.



## APPENDIX VI. FCC AND JECFA SPECIFICATIONS FOR CALCIUM ACETATE.

FCC 9

- **READILY CARBONIZABLE SUBSTANCES**, Appendix IIB  
Sample solution: Dissolve 500 mg of sample in 5 mL of 95% sulfuric acid.  
Acceptance criteria: The color of the resulting Sample solution is no darker than that of Matching Fluid D.
- **RESIDUE ON IGNITION (SULFATED ASH)**, Appendix IIC  
Sample: 2 g  
Acceptance criteria: NMT 0.1%
- **WATER**, Water Determination, Appendix IIB  
Acceptance criteria  
Anhydrous: NMT 0.5%  
Hydrous: NMT 8.5%

### OTHER REQUIREMENTS

- **LABELING**: Indicate whether it is anhydrous or hydrous.

### Calcium Acetate

First Published: Prior to FCC 6

$\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$  Formula wt 158.17  
INS: 263 CAS: [62-54-4]  
UNII: Y882YXF34X [calcium acetate]

### DESCRIPTION

Calcium Acetate occurs as a fine, white, bulky powder. It is freely soluble in water and slightly soluble in alcohol.

**Function**: Buffer; stabilizer; firming agent

**Packaging and Storage**: Store in well-closed containers.

### IDENTIFICATION

- **ACETATE**, Appendix IIIA  
Sample solution: 100 mg/mL  
Acceptance criteria: Passes tests
- **CALCIUM**, Appendix IIIA  
Sample solution: 100 mg/mL  
Acceptance criteria: Passes tests

### ASSAY

- **PROCEDURE**  
Sample: 300 mg  
Analysis: Dissolve the Sample in 150 mL of water containing 2 mL of 2.7 N hydrochloric acid. While stirring, preferably with a magnetic stirrer, add about 30 mL of 0.05 M disodium EDTA from a 50-mL buret. Then add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue indicator and continue the titration to a blue endpoint. Each mL of 0.05 M disodium EDTA is equivalent to 7.909 mg of  $\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$ .  
Acceptance criteria: NLT 99.0% and NMT 100.5% of  $\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$ , calculated on the anhydrous basis

### IMPURITIES

#### Inorganic Impurities

- **CHLORIDE**, Chloride and Sulfate Limit Tests, Chloride Limit Test, Appendix IIIB  
Sample: 40 mg  
Control: 20 µg chloride (2 mL of Standard Chloride Solution)

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- Acceptance criteria: Any turbidity produced by the Sample does not exceed that produced by the Control. (NMT 0.05%)
- **FLUORIDE**, Fluoride Limit Test, Method III, Appendix IIIB  
Analysis: Use 10 mL of 1 N hydrochloric acid instead of water to dissolve the sample.  
Acceptance criteria: NMT 0.005%
- **LEAD**, Lead Limit Test, Flame Atomic Absorption Spectrophotometric Method, Appendix IIIB  
Sample: 10 g  
Acceptance criteria: NMT 2 mg/kg
- **SULFATE**, Chloride and Sulfate Limit Tests, Sulfate Limit Test, Appendix IIIB  
Sample: 200 mg  
Control: 200 µg sulfate (20 mL of Standard Sulfate Solution)  
Acceptance criteria: Any turbidity produced by the Sample does not exceed that by the Control. (NMT 0.1%)

### SPECIFIC TESTS

- **WATER**, Water Determination, Appendix IIB  
Acceptance criteria: NMT 7.0%

### Calcium Acid Pyrophosphate

First Published: Prior to FCC 6

$\text{CaH}_2\text{P}_2\text{O}_7$  Formula wt 216.04  
CAS: [14866-19-4]  
UNII: A7X68BX98K [calcium acid pyrophosphate]

### DESCRIPTION

Calcium Acid Pyrophosphate occurs as a fine, white, acidic powder. It is insoluble in water, but it is soluble in dilute hydrochloric and nitric acids.

**Function**: Leavening agent; nutrient

**Packaging and Storage**: Store in well-closed containers.

### IDENTIFICATION

- **A. PROCEDURE**  
Sample: 100 mg  
Analysis: Dissolve the Sample by warming it in a mixture of 5 mL of 2.7 N hydrochloric acid and 5 mL of water. Add dropwise, while shaking, 2.5 mL of 6 N ammonium hydroxide and then add 5 mL of ammonium oxalate TS.  
Acceptance criteria: A white precipitate forms.
- **B. PROCEDURE**  
Sample solution: Dissolve 100 mg of sample in 100 mL of 1.7 N nitric acid.  
Analysis:  
Mixture A: Add 0.5 mL of the Sample solution to 30 mL of quimociac TS.

Monographs

## JECFA SPECIFICATIONS CALCIUM ACETATE

Prepared at the 17th JECFA (1973), published in FNP 4 (1978) and in FNP 52 (1992). Metals and arsenic specifications revised at the 63rd JECFA (2004). An ADI 'not limited' was established at the 17th JECFA (1973)

### SYNONYMS

INS No. 263

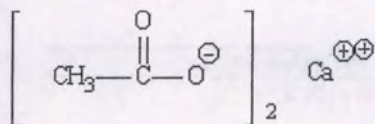
### DEFINITION

Chemical names Calcium acetate

C.A.S. number 62-54-4

Chemical formula Anhydrous:  $C_4H_6CaO_4$   
Hydrates:  $C_4H_6CaO_4 \cdot H_2O$ ;  $C_4H_6CaO_4 \cdot xH_2O$  ( $x < 1$ )

### Structural formula



Formula weight Anhydrous: 158.17; Monohydrate: 176.18

Assay Not less than 98% after drying

**DESCRIPTION** White, hygroscopic, bulky, crystalline solid; a slight odour of acetic acid may be present; the monohydrate may be needles, granules or powder.

**FUNCTIONAL USES** Antimold and antirope agent, stabilizer, buffer

### CHARACTERISTICS

### IDENTIFICATION

Solubility (Vol. 4) Freely soluble in water, insoluble in ethanol

Test for acetate (Vol. 4) Passes test

Test for calcium (Vol. 4) Passes test

### PURITY

Loss on drying (Vol. 4)	Not more than 11% (155o to constant weight; monohydrate)
pH (Vol. 4)	6 - 9 (1 in 10 soln)
Water insolubles	Not more than 0.3% Dissolve 10 g of the sample, weighed to the nearest mg, in 100 ml of hot water. Filter through a Gooch crucible, tared to an accuracy of $\pm 0.2$ mg, and wash any residue with water. Dry the crucible for 2 h at 105o. Cool, weigh and calculate as percentage. (The weight of the dried residue should not exceed 30 mg).
Formic acid and oxidizable impurities	Not more than traces Dissolve 1 g of the sample in 5 ml of water. Add 2.5 ml of 0.1 N potassium dichromate and 6 ml of sulfuric acid and allow to stand for 1 min. Add 20 ml of water, cool to 15o and add 1 ml of potassium iodide TS. A faint yellow or brown color should be produced immediately.
Aldehydes	Not more than traces Dissolve 2 g of the sample in 10 ml of water and distil. To the first 5 ml of the distillate, add 10 ml of mercuric chloride TS and make alkaline with N sodium hydroxide. Allow to stand for 5 min, and acidify with dilute sulfuric acid TS. The solution should show no more than a faint turbidity.
Lead (Vol. 4)	Not more than 2 mg/kg Determine using an atomic absorption technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the method described in Volume 4, "Instrumental Methods."

## METHOD OF ASSAY

### 1. Calcium content:

Dissolve in a beaker 2.5 g of the sample, weighed to the nearest mg, in 5 ml of hot dilute hydrochloric acid TS. Cool, transfer to a 250-ml volumetric flask, dilute to volume with water, and mix. Transfer 50 ml of the solution to a 400ml beaker, add 100 ml of water, 25 ml of sodium hydroxide TS, 40 mg of murexide indicator preparation (an alternative indicator is hydroxynaphthol blue, of which 0.25 g is used - in this case the naphthol green TS is omitted), and 3 ml of naphthol green TS. Titrate with 0.05 M disodium ethylenediamine-tetraacetate until the solution is deep blue in colour. Each ml of 0.05 M disodium ethylenediaminetetraacetate is equivalent to 7.909 mg of  $C_4H_6CaO_4$ .

### 2. Acid content:

Half fill a chromatographic column (1.5 cm in diameter, 20 cm long) with a strong cation-exchange resin (Amberlite IR 120, Amberlite IR 100, Duolite C III, Dorvex 50, Lewatit KS, Ion

Exchanger I Merck). Add 0.1 N hydrochloric acid through the top of the column, with the outflow orifice closed until the resin is completely covered and let stand 1-2 h. Drain the acid and rinse the column with water (about 1 liter) until 20 ml of eluate forms a red colour, when one drop each of 0.02 N sodium hydroxide and phenolphthalein TS is added. Weigh, to the nearest mg, 0.05 g of the sample, previously dried at 155o to constant weight, into a flask. Dissolve in 15 ml of water and pour slowly on to the column. Wash the flask and the column with about 200 ml of water and collect the total filtrate in a conical flask. Add two drops of phenolphthalein TS and titrate with 0.1 N sodium hydroxide using a microburette. Each ml of 0.1 N sodium hydroxide is equivalent to 7.909 mg of C<sub>4</sub>H<sub>6</sub>CaO<sub>4</sub>.

## APPENDIX VII. EFSA SCIENTIFIC OPINION ON CALCIUM ACETATE AND OTHER CALCIUM-CONTAINING SUBSTANCES



European Food Safety Authority

*The EFSA Journal* (2009) 1088, 1-25

### SCIENTIFIC OPINION

**Calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate magnesium succinate and potassium malate added for nutritional purposes to food supplements 1**

**Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (ANS)**

**(Question No EFSA-Q-2005-131, EFSA-Q-2005-136, EFSA-Q-2005-137, EFSA-Q-2005-141; EFSA-Q-2006-230; EFSA-Q-2008-025)**

**Adopted on 13 May 2009**

### PANEL MEMBERS

F. Aguilar, U.R. Charrondiere, B. Dusemund, P. Galtier, J. Gilbert, D.M. Gott, S. Grilli, R. Guertler, G.E.N. Kass, J. Koenig, C. Lambré, J-C. Larsen, J-C. Leblanc, A. Mortensen, D. Parent-Massin, I. Pratt, I. Rietjens, I. Stankovic, P. Tobback, T. Verguieva, R. Woutersen.

### SUMMARY

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Additives and Nutrient Sources (ANS) added to Food was asked to provide a scientific opinion on the safety of calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate, magnesium succinate and potassium malate added for nutritional purposes as sources of calcium, magnesium and potassium in food supplements and on the bioavailability of magnesium, calcium and potassium from these sources.

Although no data were provided by the petitioners, human and animal studies indicate that magnesium and calcium are readily absorbed from orally ingested soluble organic salts. The Panel expects the bioavailability of calcium from the less soluble pyruvate and succinate salt sources to be comparable to that of readily soluble salts, given that the absorption of calcium from the gastrointestinal tract is primarily determined by food components, especially organic acids. Similarly, potassium from potassium malate is readily absorbed from the gastrointestinal tract.

<sup>1</sup> For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate magnesium succinate and potassium malate added for nutritional purposes to food supplements following a request from the European Commission. *The EFSA Journal* (2009) 1088, 1-25.

No data were provided on the metabolic fate of calcium, magnesium, potassium, succinate, pyruvate, acetate and malate. However, the Panel noted that succinate, pyruvate, acetate and malate are normal constituents of the body with well documented biochemical fates in the Krebs cycle or the glycolytic pathway.

No specific toxicological data were provided by the petitioners on the succinate, pyruvate and acetate salts of calcium or magnesium. No specific toxicological data were provided by the petitioner on the malate salt of potassium. Studies that have investigated the effect of calcium pyruvate supplementation (daily doses of 13-25 g calcium pyruvate for 6 weeks in hyperlipidaemic subjects) during physical training, on body fat and metabolic responses to exercise did not describe any adverse effects, except for one study where adverse changes in serum lipid composition were documented following administration of 10 g daily for 30 days. DL-malic acid and potassium malate are permitted food additives with the numbers E296 and E351, respectively. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated malic acid and derived, on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food by adults, a group Acceptable Daily Intake (ADI) not specified for DL-malic acid and potassium DL-malate.

The petitioner for calcium succinate and calcium pyruvate proposes that the quantity of calcium to be added to food supplements as calcium succinate or calcium pyruvate will be up to 800 mg calcium/day. The petitioner for calcium acetate proposes its use as tablets containing 110 mg or 167 mg calcium; however, it is not clear from the dossier what the proposed daily exposure to calcium acetate would be. The Panel considered, as for others calcium sources, (calcium succinate or calcium pyruvate) that the quantity of calcium to be added to food supplements as calcium acetate will be also estimated to provide up to 800 mg calcium/day.

In the case of the 97.5 percentile European dietary calcium intakes for the adult population, the Panel noted that the total anticipated exposure to calcium from users of calcium succinate, calcium pyruvate or calcium acetate supplements with the proposed use levels may exceed the Tolerable Upper Intake Level (UL) defined by the Scientific Committee on Food (SCF) of 2500 mg/day.

The UL for magnesium supplements, as defined by the SCF, for adults is 250 mg/day. The petitioner states that the quantity of magnesium succinate or magnesium pyruvate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply adults with up to 250 mg magnesium/day.

No UL has been established for potassium, but it was stated by EFSA's Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) that long-term supplementary intake of up to 3 g/day, in addition to intake from food, has been shown not to have an adverse effect in adults. The petitioner proposes that the quantity of potassium malate to be added to food supplements will supply up to 350 mg potassium/day.

No ULs have been established by the SCF for succinate, pyruvate, acetate and malate. Based on an anticipated intake of 800 mg calcium/day in food supplements, as indicated by the petitioner, the maximum exposure to succinate, pyruvate and acetate from the respective sources as proposed by the petitioners would be 2, 3.4 and 2.4 g/day, respectively. The maximum exposure to malate from potassium malate would be 1.5 g/day. Combined intake of succinate and pyruvate salts from the proposed sources of calcium and magnesium would increase the exposure to these anions to 3.2 and 5.2 g/day, respectively. No adverse effects have been reported for the proposed use levels for succinate, acetate and malate. A daily exposure of up to 46 g pyruvate has been shown in two studies to have no adverse effects although one study reported an increase in

fasting serum levels of very low density lipoproteins and triglycerides in subjects exposed to 10 g pyruvate/day.

The Panel concludes the following:

- Calcium is expected to be bioavailable from the three sources of calcium (calcium succinate, calcium pyruvate and calcium acetate) to be used as nutritional substances in food supplements;
- Magnesium is expected to be bioavailable from the two sources of magnesium (magnesium succinate and magnesium pyruvate) to be used as nutritional substances in food supplements;
- Potassium is expected to be bioavailable from potassium malate which is to be used as a nutritional substance in food supplements;
- The use of calcium acetate, calcium succinate, calcium pyruvate, magnesium succinate, magnesium pyruvate and potassium malate, as sources of calcium, magnesium and potassium, in food supplements for the uses and at the use levels proposed by the petitioners is not of safety concern, provided that the UL for intake of the cations is not exceeded. However, the Panel noted that when the dietary intake is also taken into consideration, with supplementation of calcium succinate, calcium pyruvate or calcium acetate at the proposed daily use levels of up to 800 mg calcium, the UL defined by the SCF for calcium would be exceeded for the 97.5 percentile European adult population;
- The intake of pyruvate, succinate, malate and acetate from the corresponding sources is not of safety concern.

**Key words:**

Food supplements, foods, magnesium succinate, magnesium pyruvate, calcium pyruvate, calcium succinate, calcium acetate, potassium malate, CAS Registry Numbers 556-32-1, 140-99-8, 18983-79-4, 52009-14-0, 62-54-4, 585-09-1.

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## **BACKGROUND AS PROVIDED BY THE COMMISSION**

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of magnesium succinate, calcium succinate, magnesium pyruvate, calcium pyruvate, calcium acetate, and potassium malate added for nutritional purposes to food supplements. The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements<sup>2</sup>.

## **TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION**

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of magnesium succinate, calcium succinate, magnesium pyruvate, calcium pyruvate, calcium acetate, and potassium malate added for nutritional purposes in food supplements.

## **ACKNOWLEDGEMENTS**

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## **ASSESSMENT**

### 1. Introduction

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<sup>2</sup> OJL 183, 12.7.2002, p.51.



The present opinion deals only with the safety of calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate, magnesium succinate and potassium malate added for nutritional purposes in food supplements and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium and potassium themselves, in terms of the amounts that may be consumed, is outside the remit of this Panel.

## **2. Technical data**

### **2.1. Chemistry**

#### ***Magnesium succinate***

The molecular formula of magnesium succinate is  $MgC_4H_4O_4$ , its molecular weight is 140.39 g/mol and its CAS Registry Number is 556-32-1 (Technical dossier, 2005a).

Synonyms proposed by the petitioner are magnesium butanedioate, and butanedioic acid magnesium salt.

#### ***Calcium succinate***

The molecular formula of calcium succinate is  $CaC_4H_4O_4$ , its molecular weight is 140.4 g/mol and its CAS Registry Number is 140-99-8 (Technical dossier, 2005b). The synonym proposed by the petitioner is butanedioic acid calcium salt.

#### ***Magnesium pyruvate***

The molecular formula of magnesium pyruvate is  $MgC_6H_6O_6$ , its molecular weight is 198.4 g/mol and its CAS Registry Number is 18983-79-4 (Technical dossier, 2005c).

The synonym proposed by the petitioner is pyruvic acid magnesium salt.

#### ***Calcium pyruvate***

The molecular formula of calcium pyruvate is  $CaC_6H_6O_6$ , its molecular weight is 214.2 g/mol and its CAS Registry Number is 52009-14-0 (Technical dossier, 2005d).

The synonym proposed by the petitioner is pyruvic acid calcium salt.

#### ***Calcium acetate***

The molecular formula of calcium acetate is  $CaC_4H_6O_4$ , its molecular weight is 158.2 g/mol and its CAS Registry Number is 62-54-4 (Technical dossier, 2005e).

The synonym proposed by the petitioner is acetic acid calcium salt.

#### ***Potassium D,L-malate***

The molecular formula of potassium malate is  $K_2C_4H_6O_5$ , its molecular weight is 210.3 g/mol and its CAS Registry Number is 585-09-1 (Technical dossier, 2008).

The synonyms proposed by the petitioner include the following: hydroxiethane-1,2-dicarboxylic acid potassium salt, malic acid potassium salt, hydroxybutanedioic acid dipotassium salt, and potassium  $\alpha$ -hydroxysuccinate.

### **2.2. Specifications**

The petitioner stated the following on the specifications:

#### ***Magnesium succinate***

Magnesium succinate is a white powder that is soluble in water, its purity is not less than 97.0% and the total magnesium content is 17.3% (based on theoretical calculations). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

***Calcium succinate***

Calcium succinate is a fine white powder, with a characteristic odour, that is slightly soluble in water. Its purity is not less than 97.0% and the total calcium content is 28.5% (based on theoretical calculations). The petitioner states that the source exists as calcium succinate monohydrate. The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

***Magnesium pyruvate***

Magnesium pyruvate is a white powder that is soluble in water. Its purity is not less than 98.0% and the total magnesium content is 12.2% (based on theoretical calculations). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

***Calcium pyruvate***

Calcium pyruvate is a white to off-white powder that is slightly soluble in water. Its purity is not less than 97.0% and total calcium content is 18.7% (based on theoretical calculations). The petitioner states that the source exists as hydrated calcium pyruvate (CaC<sub>6</sub>H<sub>6</sub>O<sub>6</sub> 2.5 H<sub>2</sub>O). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

***Calcium acetate***

Calcium acetate is a white powder that is freely soluble in water and slightly soluble in ethanol. The content of calcium acetate is not less than 99.0% and not more than 100.5%, and the total calcium content is 25.3% (based on theoretical calculations). The limits for impurities are as follows: chlorides 0.05%, fluorides 0.005%, sulphates 0.06%, arsenic not more than 3 mg/kg, lead not more than 10 mg/kg and heavy metals not more than 25 mg/kg.

***Potassium D,L-malate***

Potassium D,L-malate is a white powder that is soluble in water. Its purity is not less than 97.0% and total potassium content is 18.6% (based on theoretical calculations). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of lead, mercury and cadmium in food supplements as sold should be 3 mg/kg, 0.1 mg/kg and 1 mg/kg, respectively (EC, 2008).

**2.3. Manufacturing processes**

***Magnesium succinate***

Magnesium succinate is synthesised from magnesium carbonate and succinic acid.

***Calcium succinate***

Calcium succinate is synthesised from a calcium salt (identity not specified by petitioner) and succinic acid.

***Magnesium pyruvate***

Magnesium pyruvate is synthesised by the reaction of a magnesium carbonate with pyruvic acid.

***Calcium pyruvate***

Calcium pyruvate is synthesized by the reaction of a soluble calcium salt (identity not specified by petitioner) with pyruvic acid.

***Calcium acetate***

Calcium acetate is precipitated by the reaction of acetic acid and calcium hydroxide.

***Potassium D,L-malate***

Potassium D,L-malate is synthesized by the reaction of potassium hydroxide with D,L-malic acid.

**2.4. Methods of analysis in food**

***Magnesium succinate, magnesium pyruvate, calcium succinate and calcium pyruvate***

The petitioner listed AAS and ICP-AES as instrumental techniques for the determination of the food content of magnesium and calcium after appropriate extraction and preparation.

***Calcium acetate***

The petitioner described a titration method with calcon carbonic acid as an indicator.

***Potassium D,- malate***

The petitioner did not provide any analytical methods.

***Succinate, pyruvate, acetate and malate anions of the sources***

The petitioner did not provide any analytical methods.

**2.5. Reaction and fate in foods to which the source is added**

Magnesium succinate and magnesium pyruvate, calcium succinate, calcium pyruvate, calcium acetate and potassium malate are described by the petitioners as stable in foods. However, no specific information was provided.

**2.6. Case of need and proposed use levels**

Calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate, magnesium succinate, and potassium malate are intended to be used as sources of the respective nutrient cations.

The petitioners proposed the following uses for each of the salts:

Magnesium succinate, magnesium pyruvate, calcium succinate, calcium pyruvate and potassium malate are to be used by food supplement manufacturers as ingredients in tablets, caplets,

capsules, chewable tablets, effervescent powders and liquids that are food supplements. Calcium acetate is proposed only to be used in tablet form. The method of incorporation of the source into the nutrient supplement is determined by the individual manufacturers as appropriate for the particular type of finished products.

The petitioners for calcium succinate and calcium pyruvate state that the quantity of calcium to be added to food supplements as calcium succinate or calcium pyruvate will be determined by individual formulators, but it is normally the quantity necessary to supply up to 800 mg calcium/day. The petitioner for calcium acetate proposes its use as tablets containing 110 mg or 167 mg calcium although no specification for the use levels as a food supplement was provided. The Panel considered that as for others calcium supplements (calcium succinate and calcium pyruvate), the quantity of calcium to be added to food supplements as calcium acetate will be determined by individual formulators, but it is normally the quantity necessary to supply up to 800 mg calcium/day

The petitioner states that the quantity of magnesium succinate or magnesium pyruvate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply adults with up to 250 mg magnesium/day. The petitioner states that the quantity of potassium as potassium malate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply up to 350 mg potassium/day.

## **2.7. Information on existing authorizations and evaluations**

Calcium acetate and potassium malate are permitted food additives with the numbers E263 and E351, respectively. Calcium acetate is licensed in Germany as a medical product.

The SCF established a Tolerable Upper Intake Level (UL) for calcium from all sources of 2500 mg/day for adults, and pregnant and lactating women (SCF, 2003). In 2001, the SCF established a UL for magnesium from supplements of 250 mg/day for adults (SCF, 2001).

The SCF has issued an opinion on the UL of potassium (EFSA, 2005b). No UL could be established for potassium but it was stated by EFSA's Scientific Panel on Dietetic products, Nutrition and Allergies (NDA) that long-term supplementary intake of up to 3 g/day, in addition to intake from foods, has been shown not to have an adverse effect.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated malic acid and derived, on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food, a group Acceptable Daily Intake (ADI) not specified for DL-malic acid and sodium, potassium and calcium DL-malate (JECFA 1980, 1986). The SCF agreed with this group ADI for adults (SCF, 1990), but considered only the L-isomer acceptable for use in foods prepared for infants and young children (SCF, 1992).

The Scientific Panel on Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) evaluated a citrate malate source of calcium (EFSA, 2007) and concluded that its use as source of calcium in foods for Particular Nutritional Uses (PARNUTS) and foods for the general population (including food supplements) is of no safety concern.

The Population Reference Intake (PRI) for adults are in the order of 3.1-3.5 g/day for potassium, for calcium 700 mg/day (range 400-1200 mg/day depending on age), and for magnesium in the order of 150-500mg/day depending on age (SCF, 1993; SCF, 2001).

## 2.8. Exposure

This section deals with the calcium intake and anticipated exposure to succinic acid, pyruvic acid and acetic acid from calcium succinate, calcium pyruvate and calcium acetate, magnesium intake and anticipated exposure to succinic acid and pyruvic acid from magnesium succinate or magnesium pyruvate, and potassium intake and anticipated exposure to malic acid from potassium malate.

The body synthesises succinic acid, pyruvic acid and malic acid during the process of metabolising carbohydrates to energy. Some berries and some food products contain succinic acid, specifically those, whose preparation involves anaerobic processes. However, many everyday food products are devoid of succinic acid. Additional exposure comes from the use of succinic acid esters in food supplements (e.g. vitamin E acid succinate), as flavouring agents (e.g. succinic acid monomethyl ester) and also a small amount can come from carbohydrates produced in the gut. However, no data on total dietary exposure to succinate are available. Pyruvate is readily found in foods, including apples, beer and red wine, with concentrations up to 7 mg/100g ([Souci et al., 2008](#)) but the daily amount consumed through an average diet is difficult to quantify. In addition, pyruvate supplements providing up to 2 g per tablet are readily available. It is also difficult to quantify the daily amount of malate consumed through an average diet as it is present in many foods and sold in many supplements. Concentrations typically ranging from 0.1 to 2 g/100g have been detected in fruits and wines ([Antonelli et al., 2008](#); [Souci et al., 2008](#)) and the daily human consumption of malic acid from vegetables, fruits and their juices is calculated to be in the order of 1.5 to 3 g (JECFA, 1966). Acetate is synthesised by the body and is present in many foods. The amount of acetate present in 1 g of calcium acetate is equivalent to 15 mL vinegar. This amount of acetate is rapidly metabolised to water and carbon dioxide. Overall, the total consumption of succinic acid, pyruvic acid, acetic acid and malic acid by the general population is difficult to assess.

### 2.8.1. Exposure to calcium succinate, calcium pyruvate and calcium acetate

Foods particularly rich in calcium are milk (1200 mg/kg), cheese (730-12000 mg/kg) and other dairy products (except butter), green leafy vegetables (except spinach), soybean products, bread and other baked goods made from calcium fortified flour (variable levels), almonds (2400 mg/kg), brazil nuts (1700 mg/kg) and hazelnuts (1400 mg/kg). In European diets 45 to 70% of calcium intake is from milk and dairy products (SCF, 2003).

According to the SCF and the UK Total Diet Study, the average and high percentile calcium intakes from food for adults in European countries vary from 683 to 944 mg/day and from 1308 to 1970 mg/day, respectively (SCF, 2003; [Ysart et al., 1999](#)).

Table 1 summarizes the information on calcium intake from food in European countries, anticipated exposure to calcium by using supplements as proposed by the petitioners, and ULs.

The Panel noted that the additional exposure of 800 mg of calcium/day from the proposed use of calcium succinate, calcium pyruvate and calcium acetate in food supplements would result in an anticipated total average exposure for adults of 1483 to 1744 mg/day and at the high percentile, a total exposure for adults of 2108 to 2770 mg/day.

Assuming a mean dietary calcium intake for children in Europe in the range of 804 to 809 mg/day and a high percentile intake range of 1338 to 1442 mg/day, the Panel estimated that daily consumption of an additional food supplement containing 800 mg calcium/day would result in a

total anticipated exposure between 1604 and 1609 mg/day at the average level and a total anticipated exposure between 2138 and 2242 mg/day at the high level.

Based on an anticipated intake of 800 mg calcium/day in food supplements, as indicated by the petitioner, the equivalent intake of succinic, pyruvic and acetic acid would be 2, 3.4 and 2.4 g/day, respectively. Except for the pyruvate salts, used at high levels by athletes and body builders (their potential pyruvate intake may be up to 46 g/day ([Stanko et al., 1992](#)), no potential high intake groups have been identified.

**Table 1. Summary information on calcium intake and anticipated exposure to succinic acid, pyruvic acid and acetic acid from calcium succinate/pyruvate/acetate**

Nutrient: calcium	Intake (mg/day)		References
Recommended Intake for adults	700		SCF, 1993
Recommended Intake for children	500-800 (up to 7 years) 1200-1300 (older children and adolescents)		SCF, 2003
Tolerable Upper Intake Level for adults (including pregnant and lactating women)	2500		SCF, 2003
Tolerable Upper Intake Level for children	Insufficient data		SCF, 2003
Nutrient: Calcium	Average intake (mg/day)	High intake (95th or 97.5th) (mg/day)	References
Intake range from food in Europe for adults	683-944	1308-1970	SCF, 2003; Ysart et al., 1999
Intake range from food in Europe for children (3-17 years)	804-809	1338-1442	SCF, 2003; AFSSA, 2009
Amount of calcium added to supplements from calcium succinate/pyruvate/acetate as indicated by the petitioners	800	800	Technical dossier, 2005b; Technical dossier, 2005d; Technical dossier, 2005e
Source: Calcium succinate/pyruvate/acetate			
Total anticipated exposure to calcium from supplement and food intake <sup>1</sup> for adults.	1483-1744	2108-2770	calculation by Panel

Total anticipated exposure to calcium from supplement and food intake <sup>2</sup> for children (3-17 years).	1604-1609	2138-2242	calculation by Panel
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1 calculation based on proposed use level of 800 mg/day plus average dietary intake of 683-944 mg/day and high dietary intake of 1308-1970 mg/day for adults

2 calculation based on proposed use level of 800 mg/day plus average dietary intake of 804-809 mg/day and high dietary intake of 1338-1442 mg/day for children

### 2.8.2. Exposure to magnesium succinate and magnesium pyruvate

Magnesium is ubiquitous in foods, but its content varies substantially. Leafy vegetables, as well as grains and nuts, generally have higher magnesium contents (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). Fats, refined sugars and pure alcohol are free of magnesium. Meat, most kinds of fish, fruit, most vegetables and dairy products contain less than 250 mg magnesium/kg. Cacao and bitter chocolate, conches, shrimps, soybeans, butter beans, and beet greens contain over 1000 mg magnesium/kg. The magnesium content of grain and grain products largely depends on processing: high concentrations (1100-1800 mg/kg) are found in whole barley, whole rye or wheat flour or brown rice (EVM, 2003, SCF, 2001).

According to the SCF, the average and the 97.5 percentile of magnesium intakes from food for adults in European countries vary from 208 to 353 mg/day and from 350 to 628 mg/day, respectively (SCF, 2001). In children, the average and the 97.5 percentile of magnesium intakes from food vary from 196 to 227 mg/person/day and from 298 to 387 mg/day, respectively (AFSSA, 2009; SCF, 2001).

Table 2 summarizes the information on magnesium intake from food in European countries, anticipated exposure to magnesium by using supplements as proposed by the petitioner and ULs.

**Table 2. Summary information on magnesium intake and anticipated exposure to succinic acid and pyruvic acid from magnesium succinate or magnesium pyruvate.**

Nutrient: Magnesium	Intake (mg/day)		References
Acceptable range of intake for adults	150-500		SCF, 1993
Tolerable Upper Intake Level for adults and children from 4 years on	250*		SCF, 2001
Nutrient: Magnesium	Average intake (mg/day)	High intake (95th or 97.5th) (mg/day)	References
Intake range from food in Europe for adults	208-353	350-628	SCF, 2001
Intake range from food in Europe for children (3-17 years)	196-227	298-387	SCF, 2001; AFSSA, 2009,

Amount of magnesium added to supplements from succinate/pyruvate as indicated by the petitioner	250	250	Technical dossier, 2005a; Technical dossier, 2005c
Source: Magnesium succinate/pyruvate			
Total anticipated exposure to magnesium from supplement and food intake <sup>3</sup> for adults.	458-603	600-878	calculation by Panel
Total anticipated exposure to magnesium from supplement and food intake <sup>4</sup> for children (3-17 years).	446-477	898-1265	calculation by Panel

\* This UL is established for readily dissociable magnesium salts and compounds like magnesium oxide and does not include magnesium normally present in foods and beverages

The Panel noted that the additional exposure of 250 mg of magnesium/day from the proposed use of magnesium succinate and magnesium pyruvate in food supplements would result in an anticipated total average exposure for adults ranging from 458 to 603 mg/day and at the high percentile of 600 to 878 mg/day.

The Panel estimated that daily consumption of an additional food supplement containing 250 mg magnesium/day would result in a total anticipated exposure for children between 446 to 477 mg/day at the average level and a total anticipated exposure between 898 to 1265 mg/day at the high level.

Based on an anticipated intake of 250 mg magnesium/day in food supplements, as indicated by the petitioner, the equivalent intake of succinic and pyruvic acid would be 1.2 and 1.8 g/day, respectively.

### 2.8.3. Exposure to potassium malate

Important potassium sources include potatoes, fruit and berries, vegetables, milk products (excluding cheese) and nuts. Potassium occurs in foods, mainly associated with weak organic acids. Potassium is also found in mineral, spring, and table waters, but the content varies considerably. Some mineral waters available on the market can, when consumed in large quantities, contribute significantly to the daily intake of potassium.

The average and the 97.5 percentile of potassium intakes from food for adults in European countries vary from 2.7 to 4.4 g/day and from 4.2 to 5.5 g/day, respectively (EFSA, 2005b). In

<sup>3</sup> calculation based on proposed use level of 250 mg/day plus average dietary intake of 208-353 mg/day and high dietary intake of 350-628 mg/day for adults

<sup>4</sup> calculation based on proposed use level of 250 mg/day plus average dietary intake of 196-227 mg/day and high dietary intake of 297.8-387.4 mg/day for children



children, the average and the 97.5 percentile of potassium intakes from food vary from 2.1 to 3.0 g/day and from 2.4 to 4.4 g/day, respectively (EFSA, 2005b)

Table 3 summarizes the information on potassium intake from food in European countries, anticipated exposure to potassium by using supplements as proposed by the petitioner and ULs. The Panel noted that the additional exposure of 0.35 g of potassium/day from the proposed use of potassium malate in food supplements would for adults, result in an anticipated total average exposure of 3.05-4.35 g/day and an anticipated total exposure of 4.55-5.85 g/day at the high percentile.

The Panel estimated that daily consumption of an additional food supplement containing 0.35 g of potassium would for children aged 3-7 years, result in a total anticipated exposure of 2.45-3.35 g/day at the average level and a total anticipated exposure of 2.75-4.75 g/day at the high level.

Based on a potential intake of 0.35 g potassium/day in food supplements, as indicated by the petitioner, the equivalent intake of malic acid would be 1.5 g/day. No potential high intake groups of malic acid have been identified.

**Table 3. Summary information on potassium intake and anticipated exposure to malic acid from potassium malate**

Nutrient: Potassium	Intake (g/day)		References
Acceptable range of intake adult	3.1-3.5		EFSA, 2005b
Tolerable Upper Intake Level (UL)	No UL, no observed effects at 3 g/d in addition to diet		EFSA, 2005b
Nutrient: Potassium	Average intake (g/day)	High intake (95th or 97.5th) (g/day)	References
Intake range from food in Europe for adults	2.7-4.0	4.2-5.5	EFSA, 2005b
Intake range from food in Europe for children (3-17 years)	2.1-3.0	2.4-4.4	EFSA, 2005b
Amount of potassium added to supplements from potassium malate as indicated by petitioner (g/d)	0.35	0.35	Technical dossier, 2008
Source: Potassium malate			
Total anticipated exposure to potassium from supplement and food intake <sup>1</sup> for adults.	3.05-4.35	4.55-5.85	calculation by Panel
Total anticipated exposure to potassium from supplement and food intake <sup>2</sup> for children (3-17 years).	2.45-3.35	2.75-4.75	calculation by Panel

1 calculation based on proposed use level of 0.35 g/day plus average dietary intake of 2.7-4.0 g/day and high dietary intake of 4.2-5.5 g/day for adults

2 calculation based on proposed use level of 0.35 g/day plus average dietary intake of 2.1-3.0 g/day and high dietary intake of 2.4-4.4 g/day for children

### **3. Biological and toxicological data**

#### **3.1. Absorption, distribution, metabolism and excretion**

No data on the bioavailability of magnesium and potassium from the different sources were provided by the petitioners. Magnesium succinate and magnesium pyruvate are highly soluble in water. Similarly, potassium malate is highly soluble in water and dissociates in the gastrointestinal tract. The Panel therefore assumed that magnesium and potassium are readily absorbed from these sources within the gastrointestinal tract.

Although calcium acetate is highly soluble in water, its succinate and pyruvate salts are only slightly to sparingly soluble in water. However, it has been shown that the solubility of a calcium source does not appear to correlate with its bioavailability from the human gastrointestinal tract ([Heaney et al., 1990](#)). Instead, the absorption of calcium from the gastrointestinal tract is primarily determined by food components, especially organic acids, and hence bioavailability is difficult to predict ([Greenwald, 1938](#); [Heaney et al., 1990](#)).

The absorptions and metabolic fates of calcium, magnesium and potassium cations have been thoroughly described previously by the SCF and the European Food Safety Authority (EFSA) (SCF, 2001; SCF, 2003; EFSA, 2004; EFSA, 2005a; EFSA, 2005b; EFSA, 2006).

The absorption and metabolic fate of succinic, pyruvic, acetic and malic acid as intermediary metabolites of glucose in glycolysis and the Krebs cycle have been well described. The available evidence shows that D(+)-malate is metabolised without difficulty and there is no clear evidence for a need to distinguish between the enantiomers when malate is used in food (SCF, 1990). Recently, a cell surface receptor for succinic acid has been identified. The cognate receptor G protein-coupled receptor-91 (GPR91) in neurons has a major role in retinal angiogenesis, and extracellular succinate may be involved in revascularisation ([Sapieha et al., 2008](#)).

#### **3.2. Toxicological data**

No specific toxicological data were provided by the petitioners neither on the succinate, pyruvate and acetate salts of calcium or magnesium, nor on the malate salt of potassium.

The Panel reviewed an acute oral toxicity study of calcium pyruvate; three Wistar rats of each sex dosed by oral gavage with 2000 mg/kg bw showed no mortality and no clinical or macroscopic signs of toxicity. Furthermore, in vitro genotoxicity tests using four *S. typhimurium* strains with up to 5 mg calcium pyruvate/plate were negative (Technical dossier, 2009).

Numerous human studies have investigated the effect of high level calcium pyruvate supplementation during physical training, on body fat and metabolic responses to exercise.

Early studies indicated that calcium pyruvate and sodium pyruvate supplementation enhances weight and fat loss and improves exercise capacity primarily in overweight individuals ([Stanko et al., 1992](#); [Stanko et al., 1994](#)). Hence, pyruvate has recently become a popular weight-loss supplement and a performance enhancing aid. However, these findings remain unconfirmed and the consensus opinion is that calcium pyruvate supplementation during physical training does not

significantly affect body composition or exercise performance ([Ebersole et al., 2000](#); [Koh-Banerjee et al. 2005](#); [Morrison et al., 2000](#)).

In a study, twenty-three untrained women were matched and assigned to ingest in a double blind and randomized manner either 5 g of calcium pyruvate or a placebo twice daily for 30 days while participating in a supervised exercise program (Koh-Banerjee et al., 2005). The subjects who used calcium pyruvate showed an increase in fasting serum levels of very lowdensity lipoprotein cholesterol and triacylglycerol, whereas levels of high-density lipoprotein (HDL) cholesterol were significantly decreased. The 10 g of calcium pyruvate administered daily during this study is well above the levels recommended by the petitioner. However, two other studies on 40 and 34 hyperlipidaemic subjects, using daily doses of 13-25 g calcium pyruvate for 6 weeks in 40, showed no change in plasma HDL and triglyceride levels ([Stanko et al., 1992](#); 1994) and a 5% decrease ([Stanko et al., 1992](#)) or no change (Stanko et al. 1994) in plasma cholesterol levels as compared to controls.

DL-malic acid as well as sodium malate, potassium malate and calcium malate are permitted food additives with the numbers E296, E350, E351 and E352i, respectively, and are therefore considered not to be of safety concern (EFSA, 2006). However, whilst the SCF agrees that DL-malic acid can be used for food supplements for adults, it considered only the L-isomer acceptable for use in foods prepared for infants and young children (SCF, 1992).

The toxicities of the cations magnesium, calcium and potassium has been evaluated by the SCF, UK Expert Group on Vitamins and Minerals (EVM) and EFSA (SCF, 2001; SCF, 2003; EVM, 2003). The succinate anion occurs in nature and plays a role as an intermediate metabolite in the Krebs cycle. It also participates in glucose and fatty acid synthesis. Although no systematic toxicological studies are available, it has been shown that consumption of succinic acid by rats results in a decreased weight increment of adult animals kept on an abundant sugar diet (Saakjan et al., 1994). The results from a 1990 study on the toxicity/carcinogenicity of monosodium succinate had shown neither toxicity nor carcinogenic activity in F344 rats after continuous administration at levels of 1 or 2% in the drinking-water for 2 years ([Maekawa et al., 1990](#)). From this study it appears that succinic acid has no carcinogenic properties.

The malate anion is a normal component of foods and plays a role as an intermediate metabolite in the Krebs cycle. No systematic toxicological studies are available. Foods containing malic acid have been consumed by man for centuries. The toxicity of malate has been evaluated by EFSA (EFSA, 2006) and JECFA (JECFA, 1969).

Pyruvate and acetate occur in nature. Pyruvate has a role as a final metabolite in glycolysis from where it can be converted to either acetyl CoA for further metabolism in the Krebs cycle or to lactate during anaerobic metabolism. Acetate is formed during ethanol metabolism and is a precursor in fatty acid synthesis. No systematic toxicological studies are available.

#### 4. Discussion

Although no data were provided by the petitioners, human and animal studies indicate that magnesium and calcium are readily absorbed from orally ingested soluble organic salts. The Panel expects the bioavailability of calcium from the less soluble pyruvate and succinate salt sources to be comparable to that of readily soluble salts given that the absorption of calcium from the gastrointestinal tract is primarily determined by food components, especially organic

acids. Similarly, potassium from potassium malate is readily absorbed from the gastrointestinal tract.

No data were provided by the petitioners on the metabolic fate of calcium, magnesium, potassium, succinate, pyruvate, acetate and malate. However, the Panel noted that succinate, pyruvate, acetate and malate are normal constituents of the body with well documented biochemical fates in the Krebs cycle or the glycolytic pathway.

No specific toxicological data were provided by the petitioners on the succinate, pyruvate and acetate salts of calcium or magnesium, nor on the malate salt of potassium. Studies in humans that have investigated the effect of calcium pyruvate supplementation during physical training on body fat and metabolic responses to exercise (with daily doses of 13-25 g calcium pyruvate for 6 weeks in hyperlipidaemic subjects) did not describe any adverse effects except for one study where adverse changes in serum lipid composition at 10 g daily were documented. An acute oral toxicity study of calcium pyruvate in three Wistar rats of each sex dosed by oral gavage with 2000 mg/kg bw showed no mortality and no clinical or macroscopic signs of toxicity. Furthermore, in vitro genotoxicity tests on four *S. typhimurium* strains with up to 5 mg calcium pyruvate/plate were negative. DL-malic acid and potassium malate are permitted food additives with the numbers E296 and E351, respectively. JECFA evaluated malic acid, and derived on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food by adults, a group ADI not specified for DL-malic acid and potassium DL-malate.

The toxicities of the cations magnesium, calcium and potassium have been evaluated by the SCF, the EVM and EFSA.

The petitioner, for calcium succinate and calcium pyruvate, proposed that the quantity of calcium to be added to food supplements as calcium succinate or calcium pyruvate will be up to 800 mg calcium/day. The petitioner for calcium acetate proposed its use as tablets containing 110 mg or 167 mg calcium; however, it is not clear from the dossier what the proposed daily exposure to calcium acetate would be. The Panel considered as for others calcium supplements (calcium succinate or calcium pyruvate) that the quantity of calcium to be added to food supplements as calcium acetate will also provide up to 800 mg calcium/day. In the case of the 97.5 percentile European dietary calcium intake population, the Panel noted that the total anticipated exposure to calcium for users of calcium succinate, calcium pyruvate or calcium acetate with the use levels proposed by the petitioners more food intake may exceed at the high percentile intake the UL of 2500 mg/day for calcium, established for adults by the SCF.

The UL for magnesium supplements defined by the SCF for adults is 250 mg/day. The petitioner states that the quantity of magnesium succinate or magnesium pyruvate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply adults with up to 250 mg magnesium/day, as defined by SCF.

No UL has been established for potassium but it was stated by EFSA's NDA Panel that long term supplementary intake of up to 3 g/day, in addition to intake from foods, has been shown not to have an adverse effect in adults. The petitioner proposes that the quantity of potassium malate to be added to food supplements will supply up to 350 mg potassium/day.

No ULS have been defined by the SCF for succinate, pyruvate, acetate and malate. Based on an anticipated intake of 800 mg calcium/day in food supplements, as indicated by the petitioner, the maximum exposure to succinate, pyruvate and acetate from the respective sources as proposed by the petitioners would be 2, 3.4 and 2.4 g/day, respectively. The maximum exposure to malate from potassium malate would be 1.5 g/day. Combined intake of succinate and pyruvate salts

from the proposed sources of calcium and magnesium would increase the exposure to these anions to 3.2 and 5.2 g/person/day, respectively. No adverse effects for the proposed quantities of succinate, acetate and malate have been reported. A daily exposure of up to 46 g pyruvate has been shown in two studies to have no adverse effects although one study reported an increase in fasting serum levels of very low density lipoproteins and triglycerides in subjects exposed to 10 g pyruvate/day.

## CONCLUSIONS

The present opinion deals only with the safety of magnesium succinate, calcium succinate, magnesium pyruvate, calcium pyruvate, calcium acetate, and potassium malate added for nutritional purposes in food supplements and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium and potassium themselves, in terms of amounts that may be consumed, is outside the remit of this Panel.

The Panel noted that the proposed supplementation with calcium succinate, calcium pyruvate, calcium acetate, magnesium succinate and magnesium pyruvate, will not exceed the ULs for calcium and magnesium, established for adults in Europe. However, the total anticipated exposure to calcium with the use levels proposed by the petitioners may exceed the UL of 2500 mg/day for calcium at the high percentile dietary intake established for adults.

The Panel concludes the following:

- Calcium is expected to be bioavailable from the three sources of calcium (calcium succinate, calcium pyruvate and calcium acetate) to be used as nutritional substances in food supplements;
- Magnesium is expected to be bioavailable from the two sources of magnesium (magnesium succinate and magnesium pyruvate) to be used as nutritional substances in food supplements;
- Potassium is expected to be bioavailable from potassium malate which is to be used as a nutritional substance in food supplements;
- The use of calcium acetate, calcium succinate, calcium pyruvate, magnesium succinate, magnesium pyruvate and potassium malate, as sources of calcium, magnesium and potassium, in food supplements for the uses and at the use levels proposed by the petitioners is not of safety concern, provided that the UL for intake of the cations is not exceeded. However, the Panel notes that when the dietary intake is also taken into consideration, with supplementation of calcium succinate, calcium pyruvate or calcium acetate at the proposed daily use levels of up to 800 mg calcium, the UL defined by SCF for calcium would be exceeded for the 97.5 percentile European adult population;
- The intake of pyruvate, succinate, malate and acetate from the corresponding sources is not of safety concern.

## DOCUMENTATION PROVIDED TO EFSA

1. Technical dossier, 2005a. Dossier on Magnesium Succinate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. June, 2005. Submitted by Health Food Manufacturers Association UK.

2. Technical dossier, 2005b. Dossier on Calcium Succinate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. May, 2005. Submitted by Health Food Manufacturers Association UK.
3. Technical dossier, 2005c. Dossier on Magnesium Pyruvate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. June, 2005. Submitted by Health Food Manufacturers Association UK.
4. Technical dossier, 2005d. Dossier on Calcium Pyruvate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. May, 2005. Submitted by Health Food Manufacturers Association UK.
5. Technical dossier, 2005e. Submission for use of calcium acetate in nutritional supplements. July, 2005. Submitted by Fresenius Medical Care Deutschland GmbH, Germany.
6. Technical dossier, 2008. Dossier on Potassium Malate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. February, 2008. Submitted by BioCare Ltd, UK.

#### **ADDITIONAL INFORMATION PROVIDED TO EFSA**

1. Technical dossier, 2009. Supporting information on Calcium Pyruvate. February 2009. Submitted by PhytoLab GmbH & KG. Germany.

#### **REFERENCES**

AFSSA (Agence française de sécurité sanitaire des aliments), 2009. AFSSA, report of the 2006/2007 individual and national study on food consumption 2 (INCA2, coordinator L. Lafay), February 2009. Available at: [www.afssa.fr](http://www.afssa.fr).

[Antonelli ML, Spadaro C, Tomelli RF, 2008. A microcalorimetric sensor for food and cosmetic analyses: L-Malic acid determination. Talanta 74 \(5\), 1450-1454.](#)

[Ebersole KT, Stout JR, Eckerson JM, Housh TJ, Evetovich TK, Smith DB, 2000. The effect of pyruvate supplementation on critical power. Journal of Strength and Conditioning Research 14, 32-134.](#)

[EC \(European Commission\), 2008. Commission Regulation \(EC\) No 629/2008 of 2 July 2008 amending Regulation \(EC\) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs. Official Journal of the European Union L 173, 03.07.2008, p. 6.](#)

EFSA (European Food Safety Authority), 2004. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from

the Commission related to Calcium Sulphate as a mineral substance in foods intended for the general population. The EFSA Journal 112, 1-10.

EFSA(European Food Safety Authority), 2005a. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Magnesium Aspartate as a mineral substance when used as a source of magnesium in dietary foods for special medical purposes. The EFSA Journal 167, 1-6.

EFSA (European Food Safety Authority), 2005b. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Potassium. The EFSA Journal 193, 1-19.

EFSA (European Food Safety Authority), 2006. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium, Magnesium and Zinc Malate added for nutritional purposes to food supplements as sources for Calcium, Magnesium and Zinc and to Calcium Malate added for nutritional purposes to foods for particular nutritional uses and foods intended for the general population as source for Calcium. The EFSA Journal 391a,b,c,d, 1-6.

EFSA (European Food Safety Authority), 2007. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium citrate malate as source for calcium for use in foods for Particular Nutritional Uses and in foods for the general population (including food supplements). The EFSA Journal 612, 1-2.

EVM (Expert Group on Vitamins and Minerals), 2003. Safe upper levels for vitamins and minerals, Food Standards Agency, London (2003). ISBN 1-904026-11-7.

[Greenwald I. 1938. The dissociation of some calcium salts. Journal of Biological Chemistry 124, 437-452.](#)

[Heaney RP, Recker RR, Weaver CM, 1990. Absorbability of calcium sources: The limited role of solubility. Calcified Tissue International 46, 300-304.](#)

JECFA, 1966. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. FAO Nutrition Meetings Report Series No. 40A,B,C. WHO/Food Add./67.29. Available at:  
<http://www.inchem.org/documents/jecfa/jecmono/40abcj01.htm>

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1969. Evaluations of D,Lmalic acid. INS: 296. NMRS 46/TRS 445-JECFA 13/16

[JECFA \(Joint FAO/WHO Expert Committee on Food Additives\), 1980. Evaluation of certain food additives \(Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives\). WHO Technical Report Series No. 648.](#)

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1986. Evaluation of certain food additives and contaminants (Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 733,

Koh-Banerjee PK, Ferreira MP, Greenwood M, Bowden RG, Cowan PN, Almada AL, Kreider RB, 2005. Effects of calcium pyruvate supplementation during training on body composition, exercise capacity, and metabolic responses to exercise. *Nutrition* 21, 3123-19.

Maekawa A, Todate A, Onodera H, Matsushima Y, Nagaoka T, Shibutani M, Ogasawara H, Kodama Y, Hayashi Y, 1990. Lack of Toxicity Carcinogenicity of Monosodium Succinate in F344 Rats. *Food and Chemical Toxicology* 28, 235-241.

Morrison MA, Spriet LL, Dyck DJ, 2000. Pyruvate ingestion for 7 days does not improve aerobic performance in well-trained individuals. *Journal of Applied Physiology* 89, 549-556.

Saakjan MR, Kondrashova MN, Visochina IV, 1994. Correction of Internal Media in Animals and Man by Adding Succinic Acid with Food. *Izvestiya Akademii Nauk Seriya Biologicheskaya*, 596-604.

Sapieha P, Sirinyan M, Hamel D, Zaniolol K, Joyal JS, Cho JH, Honore JC, KermorvantDuchemin E, Varma DR, Tremblay S, Leduc M, Rihakova L, Hardy P, Klein WH, Mu XQ, Mamer O, Lachapelle P, Di Polo A, Beausiour C, Andelfinger G, Mitchell G, Sennlaub F, Chemtob S, 2008. The succinate receptor GPR91 in neurons has a major role in retinal angiogenesis. *Nature Medicine* 14, 1067-1076.

SCF (Scientific Committee for Food), 1990. First series of food additives of various technological functions (Opinion expressed on 18 May 1990).

SCF (Scientific Committee for Food), 1992. Minutes of the 86th meeting of the Scientific Committee for Food held on 8-9 October 1992.

SCF (Scientific Committee for Food), 1993. Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food, Thirty First Series. European Commission, Luxembourg.

SCF (Scientific Committee for Food), 2001. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Magnesium. Expressed on 26 September 2001. SCF/CS/NUT/UPPLEV/54 Final. 11-10-2001.

SCF (Scientific Committee for Food), 2003. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium. Expressed on 4 April 2003. SCF/CS/NUT/UPPLEV/64 Final. 23-4-2003.

Souci SW, Fachman W, Kraut H, 2008. Food composition and nutrition tables. *Medpharm*.



Stanko RT, Reynolds HR, Lonchar KD, Arch JE, 1992. Plasma-Lipid Concentrations in Hyperlipidemic Patients Consuming A High-Fat Diet Supplemented with Pyruvate for 6Wk. American Journal of Clinical Nutrition 56, 950-954.

Stanko RT, Reynolds HR, Hoyson R, Janosky JE, Wolf R, 1994. Pyruvate Supplementation of A Low-Cholesterol, Low-Fat Diet -Effects on Plasma-Lipid Concentrations and BodyComposition in Hyperlipidemic Patients. American Journal of Clinical Nutrition 59, 423-427.

Ysart G, Miller P, Crews H, Robb P, Baxter M, De L'Argy C, Lofthouse S, Sargent C, Harrison N. 1999. Dietary exposure estimates of 30 elements from the UK Total Diet Study. Food Additives and Contaminants 16, 391-403.

## **GLOSSARY / ABBREVIATIONS**

AAS	Atomic Absorption Spectroscopy
ADI	Acceptable Daily Intake
AFC	Scientific Panel on Additives, Flavourings, Processing Aids and Materials in Contact with Food
AFSSA	Agence Française de Sécurité Sanitaire des Aliments
ANS	Scientific Panel on Additives and Nutrient Sources
BW	Body Weight
CAS	Chemical Abstracts Service
EC	European Commission
EFSA	European Food Safety Authority
GPR91	G Protein-coupled Receptor -91
HDL	High-Density Lipoprotein
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectrophotometry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
PARNUTS	Foods prepared for Particular Nutritional Uses
PRI	Population Reference Intake
SCF	Scientific Committee on Food
UL	Tolerable Upper Intake Level
WHO	World Health Organisation

## EXHIBIT 1. REPORT OF THE EXPERT PANEL

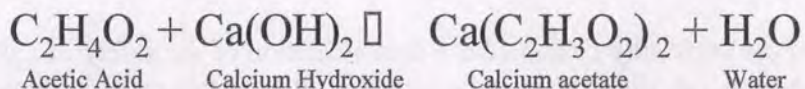
### EXPERT PANEL OPINION THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF THE PROPOSED CHANGES IN USE OF CALCIUM ACETATE

The undersigned, an independent panel of experts, qualified by their scientific training and expertise, to evaluate the safety of food and food ingredients (the Expert Panel), was convened on behalf of Niacet to specifically evaluate the safety and "generally recognized as safe" ("GRAS") status of the proposed use of calcium acetate in food as a firming agent as defined in § 170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; texturizer as defined in § 170.3(o)(32) of this chapter; and as a flavoring agent (FEMA 2228) in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice.

Calcium acetate is the calcium salt of acetic acid. Calcium acetate is also used in food processing for several physical and technical effects. Calcium acetate is naturally present in many fruits and is present in fermented products through bacterial fermentation. Calcium is a mineral essential for many cellular functions including nerve impulse transmission, muscle contraction, cardiac function, bone formation, and capillary and cell membrane permeability.

Calcium acetate is currently listed as GRAS for use as a sequestrant under 21 CFR 182.6197 (calcium diacetate) and is affirmed as GRAS at 21 CFR 184.1185 for several food uses and technical effects. Calcium acetate is intended for use as an ingredient in food products consistent with uses and technical effects permitted for other calcium salts as described in existing regulations and current practices. As such, it is intended for use as a substitute for existing calcium salts currently approved for use in food. Calcium acetate is also used as a source of calcium in dietary supplements (pre-DSHEA). Calcium acetate is also determined to be GRAS for use as a flavoring agent by FEMA (FEMA No. 2228).

Calcium acetate is prepared by reacting calcium hydroxide with acetic acid.



The molecular formula of calcium acetate is  $\text{CaC}_4\text{H}_6\text{O}_4$ , its molecular weight is 158.2 g/mol.

The CAS Registry Number is 62-54-4.

The safety of calcium acetate has been evaluated by FDA and several other international regulatory bodies. There is a large volume of publicly available information that addresses the safety and food uses of calcium acetate and other calcium-containing substances. As such, there is a recognized general consensus that calcium acetate is safe for use in food when used in the manner described in this document. In summary, the findings and conclusions of the public documents supports the fact that:

1. Calcium acetate is not mutagenic;
2. Calcium acetate is not genotoxic;
3. Calcium acetate is not a carcinogen;
4. Calcium acetate is a bioavailable source of calcium;
5. There is no evidence of adverse safety events associated with the food use of calcium acetate when used consistent with current good manufacturing practices.

Published documents that address the safety of calcium acetate by regulatory bodies are attached in Appendices III, VI and VII.

Niacet performed a comprehensive search of the scientific literature through September 2016 relating to the safety of calcium acetate and calcium for human consumption. No new safety information was uncovered that would point to a safety concern for the use of calcium acetate as described in this document.

Because calcium acetate will be used as a substitute product for other calcium-containing substances, there is not expected to be an increase in the consumption of calcium. Even if there is a slight increase in the consumption of calcium, this can be considered to be a beneficial effect as most consumers are calcium deficient in the diet.

Because calcium acetate is produced by means of a very simple procedure (i.e., reaction of food grade calcium hydroxide with food grade acetic acid), the potential for the introduction of impurities into the final product is low. The calcium acetate produced by Niacet meets the specifications listed in the Food Chemicals Codex, 10th Ed. However, Niacet has specifications established for potential contaminants, including heavy metals (arsenic, lead) to ensure that these substances are kept at sufficiently low levels in the finished product.

The Expert Panel critically evaluated the documentation of the safety of calcium acetate in this document and other available data and information that members of the Expert Panel deemed to be pertinent to the safety of calcium acetate under the conditions of its intended use. In addition, the Expert Panel critically evaluated the specifications for calcium acetate, analytical data confirming compliance with appropriate food-grade specifications and consistency of production, the conditions of its intended use as a component of the food production process, and

the estimated dietary exposure to calcium and calcium acetate. After an independent review, the Expert Panel convened on January 27, 2017, thoroughly discussed the document, and agreed to the suggested revisions and edits. The Expert Panel then independently, jointly, and unanimously concluded that the intended use of calcium acetate, when used in food consistent with current good manufacturing practices, meeting appropriate food-grade specifications, is safe and GRAS, based on scientific procedures. It is also the opinion of the Expert Panel that other qualified experts would concur with these conclusions.

In conclusion, the intended use of calcium acetate in food as a firming agent as defined in § 170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; texturizer as defined in § 170.3(o)(32) of this chapter; and, as a flavoring agent (FEMA 2228) in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice, is determined to be safe based on the following:

1. Calcium acetate will be used in food generally consistent with 21 CFR 184.1(b)(1) with no limitations except current good manufacturing practices, and, in some cases, will be used as a substitute for existing regulated calcium-containing products;
2. Calcium acetate will be used in foods at levels consistent with current good manufacturing practices. These uses are not expected to result in any significant increase in the overall exposure to calcium.
3. Many calcium salts, including calcium acetate, are dietary and supplemental sources of calcium;
4. Calcium acetate produced by Niacet meets the specifications in the Food Chemicals Codex, 10th Ed.
5. This action more closely aligns the use of calcium acetate with other regulated calcium-containing substances.

## CONCLUSION

We, the undersigned expert panel members have, individually and collectively, critically evaluated the information described in this document, and other pertinent information and data, related to the safety of the proposed use of calcium acetate in food, as a firming agent as defined in § 170.3(o)(10) of this chapter; flavor enhancer as defined in § 170.3(o)(11) of this chapter; nutrient supplement as defined in § 170.3(o)(20) of this chapter; pH control agent as defined in § 170.3(o)(23) of this chapter; processing aid as defined in § 170.3(o)(24) of this chapter; sequestrant as defined in § 170.3(o)(26) of this chapter; stabilizer and thickener as defined in § 170.3(o)(28) of this chapter; texturizer as defined in § 170.3(o)(32) of this chapter; and, as a flavoring agent (FEMA 2228) in accordance with § 184.1(b)(1) with no limitations other than current good manufacturing practice, and unanimously conclude that the intended use of calcium acetate is safe and GRAS based on scientific procedures.

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that calcium acetate, when used as described, is GRAS.

### Signatures

(b) (6)

Robert L. Martin, Ph.D.

Feb. 2, 2017

Date

(b) (6)

Stanley M. Tarka, Jr., Ph.D., F.A.T.S.

01 February 2017

Date

(b) (6)

Madhusudan G. Soni, Ph.D., F.A.C.N., F.A.T.S.

Feb. 2, 2017

Date