# 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:**

Salvatore J. D'Angelo
Manager, Quality Assurance & Regulatory Affairs
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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
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**Niacet Corporation**
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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.

$$\underset{\text{Acetic Acid}}{C_2H_4O_2} + \underset{\text{Calcium Hydroxide}}{Ca(OH)_2} \rightarrow \underset{\text{Calcium acetate}}{Ca(C_2H_3O_2)_2} + \underset{\text{Water}}{H_2O}$$

The molecular formula of calcium acetate is $CaC_4H_6O_4$; 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, 10th 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 (Ca $(C_2H_3O_2)_2$, 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.*

(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 | 1785 | CALCIUM ACETATE | 62-54-4 | § 175.300<br>§ 181.29<br>§ 182.6197<br>§ 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.*

(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, 10th Ed.

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

| **Product Properties** | |
|---|---|
| Product Name | Calcium Acetate |
| Formula | (CH3COO)2Ca x H2O where x is ≤ 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, 10th 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**

| **Specifications Control Limits** | |
|---|---|
| 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, 10th 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 ).

### 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$^{th}$ 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.

# 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

**********

**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 is 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).

# GRAS Conclusion
# Independent Determination

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## PART 7 – LIST OF SUPPORTING DATA AND INFORMATION IN YOUR GRAS NOTICE

## 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. 9th 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.ilsi.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, 10th Ed. Therefore, no Certificates of analysis are attached.

Niacet

**CERTIFICATE OF ANALYSIS** **80015414** 1 (2)
80015414

18.11.2016
Customer's reference
4500019924
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).

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The Netherlands

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

IBAN NL61BOFA0266533965
Trade register Tiel
Registration no. 11044303
VAT NL807461817B01

80015414

18.11.2016

Customer's reference
4500019924

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 Analist Analytical Laboratory
Niacet b.v.
H. van den Hurk

Printing date:
18.11.2016

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Niacet

**CERTIFICATE OF ANALYSIS** **80014337** 1 (2)
80014337

21.10.2016
Customer's reference
4500017991
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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Trade register Tiel
Registration no. 11044303
VAT NL807461817B01

80014337

21.10.2016

Customer's reference
4500017991

Order no. / date
1000012592
24.08.2016

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:
Manager Analytical Laboratory
Niacet b.v.
G. Visser

Printing date:
21.10.2016

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Trade register Tiel
Registration no. 11044303
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Niacet

**CERTIFICATE OF ANALYSIS** **80012215** 1 (2)
80012215

19.04.2016
Customer's reference
4500014332
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**
30.03.2016

**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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IBAN NL61BOFA0266533965
Trade register Tiel
Registration no. 11044303
VAT NL807461817B01

80012215

19.04.2016

Customer's reference
4500014332

Order no. / date
1000010653
11.04.2016

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:
Manager Analytical Laboratory
Niacet b.v.
G. Visser

Printing date:
19.04.2016

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


Updated up to the 39th Session of the Codex Alimentarius Commission (2016)

### 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 |
|---|---|---|---|
| 13.2 | Complementary foods for infants and young children | GMP | Note 239 |
| 11.4 | Other sugars and syrups (e.g. xylose, maple syrup, sugar toppings) | GMP | Note 258 |

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

- 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

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

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

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

## APPENDIX IV. NIACET MSDS FOR CALCIUM ACETATE

Niacet

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

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### 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 47th Street Niagara Falls, NY
14304 USA
Telephone +1 716 285 1474 Telefax +1 716 285 1497 niacetcsr@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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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 | CAS-No. |
|---|---|
| EINECS-No. / ELINCS No. | |
| Calcium di(acetate) | 62-54-4 |
| 200-540-9 | |

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<br>Foam<br>Dry chemical<br>Carbon dioxide (CO2) |
| Unsuitable extinguishing media: | None. |

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





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/m³ |

440 - 700 kg/m³loose

| | |
|---|---|
| Lower explosion limit | no data available |
| Upper explosion limit | no data available |
| Vapour pressure | no data available |

Solubility(ies):

| | |
|---|---|
| Water solubility | 353 kg/m³ (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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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.





## 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/m³ (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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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 (Ca (C2H3O2)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.
(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.



• **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

$Ca(C_2H_3O_2)_2$ 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 $Ca(C_2H_3O_2)_2$.
**Acceptance criteria:** NLT 99.0% and NMT 100.5% of $Ca(C_2H_3O_2)_2$, 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*)
**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

$CaH_2P_2O_7$ Formula wt 216.04
CAS: [14866-19-4]
UNII: A7X6BBX98K [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. Prodedure**
**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.

**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

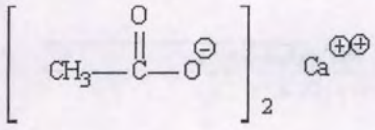
**DEFINITION**

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%<br>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 ±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<br>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<br>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<br>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 hydroxynaphtol 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 C4H6CaO4.

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, Duolit 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 C4H6CaO4.

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


*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.

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[1] 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 supplements2.

## 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

The European Food Safety Authority wishes to thank the members of the Working Group A on Food Additives and Nutrient Sources of the ANS Panel for the preparation of this opinion:
F. Aguilar, N. Bemrah, P. Galtier, J. Gilbert, S. Grilli, R. Guertler, G.E.N. Kass, C. Lambré, J.C. Larsen, J.-C. Leblanc, A. Mortensen, I. Pratt, I. Stankovic.

## ASSESSMENT

1. Introduction

[2] OJ L 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 MgC4H4O4, 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 CaC4H4O4, 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 MgC6H6O6, 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 CaC6H6O6, 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 CaC4H6O4, 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 K2C4H6O5, 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, hydroxybutanodioic acid dipotassium salt, and potassium α-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 (CaC6H6O6 2.5 H2O). 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)<br>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;<br>Ysart et al., 1999 |
| Intake range from food in Europe for children (3-17 years) | 804-809 | 1338-1442 | SCF, 2003;<br>AFSSA, 2009 |
| Amount of calcium added to supplements from calcium succinate/pyruvate/acetate as indicated by the petitioners | 800 | 800 | Technical dossier, 2005b;<br>Technical dossier, 2005d ;<br>Technical dossier, 2005e |
| Source: Calcium succinate/pyruvate/acetate | | | |
| Total anticipated exposure to calcium from supplement and food intake1 for adults. | 1483-1744 | 2108-2770 | calculation by Panel |

| | | | |
|---|---|---|---|
| Total anticipated exposure to calcium from supplement and food intake2 for children (3-17 years). | 1604-1609 | 2138-2242 | calculation by Panel |

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 intake3 for adults. | 458-603 | 600-878 | calculation by Panel |
| Total anticipated exposure to magnesium from supplement and food intake4 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

[3] 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

[4] 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 intake1 for adults. | 3.05-4.35 | 4.55-5.85 | calculation by Panel |
| Total anticipated exposure to potassium from supplement and food intake2 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.

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

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## 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.

$$\underset{\text{Acetic Acid}}{C_2H_4O_2} + \underset{\text{Calcium Hydroxide}}{Ca(OH)_2} \rightarrow \underset{\text{Calcium acetate}}{Ca(C_2H_3O_2)_2} + \underset{\text{Water}}{H_2O}$$

The molecular formula of calcium acetate is CaC4H6O4, 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

# GRAS Notice (GRN) No. 712 amendments

**From:** Salvatore DAngelo
**To:** Morissette, Rachel
**Cc:** Robert Martin; Minsk, Alan G.
**Subject:** RE: GRN 000712 questions
**Date:** Tuesday, December 12, 2017 3:28:29 PM
**Attachments:** image007.png
image001.png
Niacet - GRN 712- Calcium Acetate- Responses to FDA queries 12-12-2017_signed.pdf

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Dear Dr. Morissette,

Attached are our responses to the questions referenced below. We trust you will find the responses complete and to FDA's satisfaction. Please contact me if you have any questions or require additional information.

Best Regards,

Salvatore J. D'Angelo
Manager, Quality Assurance & Regulatory Affairs
**Niacet Corporation**
400 47th Street | Niagara Falls, NY 14304
P: 716-285-1474 | F: 716-285-1497
www.niacet.com

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**From:** Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
**Sent:** Tuesday, November 28, 2017 1:16 PM
**To:** Salvatore DAngelo <SDAngelo@niacet.com>
**Subject:** GRN 000712 questions

Dear Mr. D'Angelo,

Please see attached the questions from FDA for GRN 000712 (calcium acetate). As we discussed during our November 16, 2017 phone call, you will have 10 business days from receipt of this email to respond to our reviewers' questions/comments. Though FDA advised during the meeting that Niacet request that we cease our evaluation of this notice on the basis that it did not meet the general recognition standard and would require a significant rewrite, Dr. Martin indicated that Niacet would like to try and address FDA's concerns within the allotted time frame. FDA also indicated that if any questions were not fully addressed or if Niacet's responses raised new questions, then FDA would issue a No Basis letter for this notice, as the review process is not meant to be iterative. Responses may be provided via email or in a separate document. Please do not send a revised notice.

Sincerely,

**Rachel Morissette, Ph.D.**
*Consumer Safety Officer*

**Center for Food Safety and Applied Nutrition**
**Office of Food Additive Safety**
**U.S. Food and Drug Administration**
rachel.morissette@fda.hhs.gov


Dear Dr. Morissette,

Listed below are our responses to the questions/issues that were raised in emails dated November 28, 2017, December 1, 2017, and December 5, 2017 related to GRN 712. We are providing a point-by-point response to your queries along with some relevant discussion. We have highlighted our responses/comments in red for ease of review. The questions from your email are copied below and our responses are inserted below each question.

**General**

1. On page 26 of the notice, it is stated that calcium acetate is affirmed as GRAS under 21 CFR 184.1155. This is incorrect. The regulation for calcium acetate is 21 CFR 184.1185.

   Thank you for pointing this error out to us. Sorry for the oversight, the correct regulation is 21 CFR 184.1185.

2. Table 1 shows the use levels for calcium acetate in select foods according to 21 CFR 184.1185. In the last row of Table 1 "All other food categories", it lists a maximum level of 0.001%. This number is incorrect. According to the regulation the maximum allowed use level is 0.0001% for "All other food categories."

   Thank you for pointing this error out to us. According to the regulation 21 CFR 184.1185, the maximum allowed use level for calcium acetate is 0.0001%.

3. On page 25 in Section 6.1, Niacet cites the NIH Office of Dietary Supplements (ODS) Fact Sheet on calcium and indicates that this publication is available in Appendix VI of the notice. However, this fact sheet was not found in the notice provided to FDA. Rather the labeled Appendix VI is an FCC and JECFA specifications document.

   Thank you for pointing this omission out to us and sorry for the oversight. It was our intent to cite the web address for this document which is available at: https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/. In addition, we are attaching a copy of this Fact Sheet to this response (please see Tab A).

4. The in-text citations were difficult to follow as their formatting changed part way through the document and did not line up with the bibliography at the end.

   This question was clarified in an email dated December 5, 2017. With respect to the confusion related to the different reference formats, please note that it was our oversight. The different format refers to the citation given in the NIH: Dietary Supplement Fact Sheet. This in-text citation is for IOM (2010). It is our oversight and we should have changed [1] to IOM (2010) and the citation is as follows:

IOM (2010). Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

Additionally, please note that inadvertently we omitted the EFSA (2009) citation from the list of references. The reference is as follows:

EFSA (2009). 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. [Available at: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1088/epdf].

**Chemistry**

5. Niacet states that calcium acetate is prepared by reacting food grade calcium hydroxide with acetic acid. Niacet offered no additional information regarding its manufacturing process for calcium acetate. Though this chemical reaction is a common way of producing calcium acetate, the potential exists for the method of manufacture to allow contaminants to be introduced. Therefore, we request that Niacet provides more information on its production process for calcium acetate. Specific details, such as exact temperatures, are not necessary.

   Niacet prepares its calcium acetate as follows: It is produced entirely in fully enclosed equipment suitable for the preparation of food chemicals of this type. The facilities and process are all controlled using an approved HACCP plan. Production is accomplished according to detailed operating instructions. Testing is conducted in accordance with Food Chemicals Codex (FCC) test methods.

   Calcium acetate and water are the reaction products of a neutralization of acetic acid ($CH_3COOH$) and calcium hydroxide $Ca(OH)_2$. The reaction is exothermic and is carried out in a cooled vessel using metered amounts of reactants. The resulting solution of calcium acetate is filtered through a filter to a feed tank. The filtered solution is fed to a drying unit to remove moisture. The dried material is fed to a storage bin, and packaged for distribution.
   All ingredients are food grade meeting the specifications listed in the FCC. The water used meets potable water requirements and is obtained from municipal suppliers.

   The specifications for the finished calcium acetate are as follows:

| Parameters | Specifications |
|---|---|
| Purity (Dry Basis): | NLT 99% and NMT 100.5% (as Calcium Acetate) |
| Water (wt %) | ≤ 7.0% |
| pH of a 10% Aqueous Solution | 6.3 - 9.0 |
| Insolubles | ≤ 0.1% |
| Halides as Cl | ≤ 0.05% |
| Sulfate as SO4 | ≤ 0.1% |
| Fluoride | ≤ 50 ppm |
| Iron | ≤ 10 ppm |
| Arsenic (As) | ≤ 3 ppm |
| Lead | ≤ 2 ppm |
| Mercury | ≤ 1 ppm |
| Heavy metals as Pb | ≤5 ppm |
| Oxidizable impurities (as formic acid) | ≤ 0.1% |
| Appearance | White Powder (granules) |

All production batches are tested according to the specifications using approved FCC methods. Specifications for six non-consecutive batch lots are listed in Tab B.

The finished calcium acetate is packaged in 50 lb, or 20 kg kraft paper bags containing an integral poly liner. Product labels are numbered consecutively by pallet with a record kept with the production manager.

The shelf life of calcium acetate is generally considered to be indefinite; however, any remaining product is retested after two years to ensure conformance to specifications. This information is based on past experience including historical data.

6. The notice states that Appendix I contains Certificates of Analyses for five non-consecutive production lots of manufactured calcium acetate. We note that only three lot analyses are included in Appendix I. Further, the notice states that because calcium hydroxide and acetic acid are food grade, the potential for the formation of contaminants or impurities in the final product is low. Niacet has also established internal specifications for heavy metals (As, Hg, Pb, Cd).

While the results listed in the Certificate of Analyses for Niacet's calcium acetate are within FCC specifications, Niacet did not determine the amount of heavy metals in their analyses. We request that Niacet provide at least 3 non-consecutive batch analyses of all specifications listed in the Certificate of Analyses, including heavy metals.

Sorry for our oversight, we intended to mention from three lots. As indicated earlier, we are including CoAs for six non-consecutive lots in Tab B.

7. Niacet states that the intended use of the calcium acetate is substitutional for other calcium-containing substances, and that no increase in exposure to calcium in the diet is anticipated from the intended use in this notice.

However, we note that Niacet intends to use calcium acetate with no limitations other than good manufacturing practices (GMP) on the basis that calcium acetate use is self-limiting. In addition, Niacet has requested two additional uses of calcium acetate than are listed in the regulations (i.e., flavor enhancer and nutrient supplement).

Because Niacet intends to use calcium acetate with no limitations (other than GMP) and has requested two new uses not currently listed in the regulation, this raises the question whether the intended use of calcium acetate in this notice is actually substitutional.

We note that calcium is a recognized essential nutrient that is provided in the diet by many different calcium sources. In order to facilitate the review of this GRAS Notice, we are removing one of the additional uses of calcium as a flavoring agent and request that this use be removed from consideration in this document. Our premise for no increase in exposure to calcium acetate in the diet was based on the following two considerations:

First, the listing under 21 CFR 184.1185 regulation that allows use of calcium acetate as firming agent; pH control agent; processing aid; sequestrant; stabilizer and thickener; and texturizer, and Niacet is proposing for same technical effects. This regulation has recognized that the current good manufacturing practices that results 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. Given this the intended use by Niacet of calcium acetate will be substitutional.

Second, there are several calcium salts that are listed or affirmed as GRAS in Part 182 and 184, respectively, for uses that also use as a nutrient. In addition to its multipurpose uses as a GRAS ingredient, calcium phosphate is GRAS as a nutrient (21 CFR 182.8217). Similarly, calcium pyrophosphate is GRAS as a nutrient (21 CFR 182.8223). Additionally, calcium glycerophosphate (21 CFR 184.1201), calcium lactate (21 CFR 184.1207) and calcium pentothenate (21 CFR 184.1202) have been affirmed as GRAS as nutrient supplements. The intended use of calcium acetate by Niacet as a nutrient supplement will be substitutional to these existing uses.

In a recent GRAS notice (GRN 634)[1], PepsiCo has undertaken a cumulative dietary exposure to calcium from background sources of calcium (food and supplemental intake) and the intended use of their food ingredient, calcium chloride, in potato snacks. In this GRAS notice the estimates were generated using the 2007 - 2010 National Health and Nutrition Examination Survey two day average food consumption data.

This report suggest that mean and 90$^{th}$ percentile estimated daily intake of calcium from all background (total diet + supplement) sources will be 1,138 and 1,926 mg/person/day, respectively, for the entire population (1+ years). As compared to the Institute of Medicine (IOM) tolerable upper intake of calcium that ranges from 2000 to 3000 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 background intake is lower. This background intake considers all sources of calcium exposure such as food and supplement. Given the proposed substitutional uses by Niacet, it is unlikely that the proposed use of calcium acetate will add significantly to this background intake.

Furthermore, the performing of a cumulative intake analysis is very expensive and one needs to depend on the specialized programs that take into account several considerations. In our opinion, this will be an additional expense and will not provide any substantial insight as the proposed uses will be primarily substitutional.

8. Niacet references GRN 000634 to support dietary exposure to its calcium acetate. In its exposure assessment, the notifier of GRN 000634 considered, along with calcium exposure from its calcium-based substance, exposure to calcium from food and supplemental intake to determine a U.S. estimate of cumulative dietary exposure to calcium. Niacet should provide typical use levels for the intended uses for its calcium acetate product so that cumulative dietary calcium exposure can be estimated. In addition, if Niacet intends to use dietary exposures to calcium from GRN 000634, a narrative should be provided explaining how the dietary exposures in GRN 000634 relate to exposures from its intended uses of calcium acetate.

As indicated above, Niacet intends to market its calcium acetate as a substitute for other calcium salts in a direct 1:1 replacement. As a result, we do not anticipate a significant

[1] Complete GRAS notice available at:
https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf

change in the consumer exposure to calcium. We note that there could be minor changes in the exposure to the accompanying anions of the calcium salts. However, given that all of the accompanying anions, e.g., propionate, chloride, etc., are already present in foods and biological systems, these minor changes should not reflect a safety concern. Please also see above response to query number 7.

It should be noted that calcium acetate is not likely to be chosen to replace all other calcium salts on an equal basis. For example, we consider that calcium acetate will be used as a substitute for calcium propionate to a much greater extent than calcium chloride because of similar structures with the anion, etc.

**Toxicology**

*Overall Conclusion:* The safety narrative as written does not provide a basis for general recognition and does not adequately support Niacet's independent GRAS conclusion.

*Specific Comments:*

9. Prior GRAS notices for substances that contain calcium are mentioned in Niacet's GRAS notice, but the safety information contained in these prior notices was not incorporated into the current notice. Niacet does not adequately discuss or tie-in the safety data, information, and conclusions from these notices into GRN 000712 that would support the safety of its calcium acetate product. In addition, Niacet does not state whether it concurs with the safety findings and conclusions from prior notices in support of its independent GRAS conclusion. If Niacet instead has its own conclusions that differ from previous GRAS notices or that are based on updated information, this should be included.

Further, some limited general sources are provided (e.g., CFR, 1975 SCOGS, Expert Panel Report) with limited discussion to support the publicly available literature related to the safety of calcium acetate. However, very few actual references are noted or described in the safety narrative to support the general recognition status of Niacet's reasoning and conclusions.

A revised safety narrative including the points described above should be provided.

Please note that Niacet is proposing to use calcium acetate as some of its intended uses do not meet the existing regulation for other calcium salts, particularly the uses of calcium propionate. Given the current safe and approved uses of calcium salts, and, as calcium acetate is proposed to be used as a substitute for other approved calcium salts for existing uses, we limited the safety related description to calcium acetate. As per your suggestion, we are attempting to further elaborate on the safety related information.

As mentioned in GRN 712, several calcium salts have been extensively evaluated by national and international agencies. In 1973, JECFA has considered calcium acetate to have low toxicity and an Acceptable Daily Intake (ADI) was not established. In 1975, the SCOGS considered several uses of calcium acetate as GRAS. Furthermore, the IOM (2010) and EFSA (2012) also considered and reviewed the exposure to calcium from its

several salts used in food and considered it to be safe. An updated literature search revealed no new information that contradicts the safety of exposure to calcium from food.

It is commonly accepted that the toxicity of calcium compounds depends upon their bioavailability and the resultant release of calcium. The absorption of calcium depends upon several factors such as dietary components, the source of the dietary calcium, total calcium content of the diet and the body's need for calcium.

In 2011 and 2012, IOM and EFSA, respectively, extensively reviewed the biological and toxicological effects of calcium deficiency and excessive exposure to calcium. Based on its assessment, IOM established upper limits (ULs) for calcium that are lowest among infants (1000 and 1500 mg/day for infants 0-6 months and 6-12 months, respectively), while for older adults (51+ years) the UL ranges from 2000 mg/day based on the IOM evaluation to 2500 mg/day based on EFSA's evaluation. The ULs for the remaining life stages are 2500 mg/day for children 1– 8 years (IOM) and adults 19 – 50 years (IOM; EFSA) and 3000 mg/day for adolescents 9-18 years (IOM). The calcium ULs, established by the IOM, was based on calcium excretion in young children and formation of kidney stones among older children and adults.

The IOM 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 its evaluation, EFSA also reached similar conclusions on the lack of increase of CVD and other health endpoints but did not believe the available evidence required a revision of the UL established among adults of 2,500 mg/day. In their assessment, the expert panels in both the IOM and EFSA evaluations noted that it is difficult to measure the precise amount of daily calcium intake from both diet and supplements among the study subjects in the Women's Health Initiative (WHI) and can result in considerable uncertainty in the upper intake level associated with any adverse effects. A search and review of the recent publications that appeared subsequent to the IOM assessment on the end points considered by IOM as well as other health outcomes did not offer any conclusive evidence of cause and effects and do not appear to impact the IOM and EFSA conclusions on the safety of dietary calcium and the UL. Some of this recent data is summarized in response to the below query.

In summary, Niacet has based its determination of the GRAS status for its calcium acetate based on the following: The safety of calcium acetate has been reviewed and there is general concurrence that calcium acetate is safe for use in food; FDA has acknowledged that calcium acetate is GRAS in accordance with 21 CFR 184.1(b)(1); Niacet's calcium acetate meets the specifications listed in the Food Chemicals Codex; and, there is no evidence of adverse effects related to calcium acetate when used as intended in food. Also, please note that we concurs with the safety findings and conclusions from previous GRAS notices mentioned in GRN 712, in support of our independent GRAS conclusion for the intended uses of calcium acetate.

10. Niacet notes the tolerable upper intake levels (UL) for calcium determined by the Institute of Medicine (IOM) across various ages and the European Food Safety Authority (EFSA) in adults, and indicates that there is no evidence showing health effects of calcium since these determinations were made in 2011 and 2012, respectively.

Similarly, Niacet states in its GRAS notice that an updated comprehensive literature search was conducted for publicly available information since 2010 on the safety of calcium or calcium acetate and that no relevant animal or human safety studies were located. Further, the Expert Panel Report states that a comprehensive search of scientific literature through September 2016 was performed and also states that no new safety information was uncovered that would point to a safety concern for use of calcium acetate. However, several recently published epidemiology and meta-analysis studies on the relationship between calcium intake levels and aspects of cardiovascular disease (CVD) are available and were not acknowledged or discussed by Niacet.

This new information in the literature on calcium and CVD addresses the gap in information between calcium exposure and CVD noted by recognized sources (e.g., IOM, EFSA) that were cited by Niacet.

An updated literature search should be conducted and any new findings related to calcium and CVD or any other adverse events should be discussed and added to the safety narrative. If any data and information is found that is contrary to Niacet's safety conclusion, it should also be discussed and a reason why that information does not pose a safety concern should be included. Relevant references should also be cited and discussed.

In response to this concern, Niacet has conducted an updated literature search for information related to the safety of calcium acetate and other salts (databases searched December 7, 2017). Using search terms such as "calcium acetate", "calcium acetate food use", "calcium acetate safety", and "calcium acetate food safety" from 2015 - 2017 did not uncover any publications that were considered to be pertinent to the use/safety of calcium acetate in food. By contrast and as expected, a search using the search term "calcium", "calcium safety", "calcium toxicity", "calcium adverse effects" uncovered a large number of publications. The safety related relevant findings (summary) from these searches are described below, while details of the relevant recent publications are provided in a tabulated form and is included in Tab C. From the recently published articles, it appears that there are no new or ongoing calcium clinical trials being conducted. Thus, the majority of recent published studies on calcium and cardiovascular risk and any other adverse event is mainly secondary analyses of existing trials and observational studies where cardiovascular events were not the primary outcome. Information relevant to the safety of calcium from these meta-analyses, analyses/re-analyses of individual clinical studies, and observational studies are summarized herein.

In recent years, there has been considerable efforts to study the effects of supplemental calcium intake on nonskeletal outcomes, specifically cardiovascular health and its association with mortality and morbidity (Tankeu et al., 2017; Grey et al., 2015; Chung et al., 2016; Asemi et al., 2016) [2,3,4,5]. Most of these studies support the conclusion that adequate calcium intake is important for bone health and several major physiological functions. However, the effects of calcium supplementation on other health outcomes are still controversial. At the root of controversy is the meaning of the term "adequate" since the problem is not only the quantity but also the quality and source of calcium intake. Additionally, the controversy stems from the current view that more calcium is better as it is increasingly added to food and calcium supplement use, especially among older adults.

The available information from several cohort studies have shown an increase in cardiovascular risk and mortality associated with calcium supplementation but not dietary calcium intake. Hence,

it is commonly agreed upon that dietary calcium intake is safe compared with calcium supplementation. For example, in a prospective cohort study involving 388,229 male and female subjects (50 to 71 years), Xiao et al. (2013)[2] reported that men with >1000 mg/day intake of supplemental calcium had significantly higher risk of total CVD death after an average follow-up of 12 years.

Asemi et al. (2015) reported a significant relationship between the total calcium intake and an increased risk of CVD mortality for studies with a long follow-up time and a significant protective association between dietary calcium intake and all-cause and CVD mortality for studies with a mean follow-up of ≤10 years. Supplemental calcium intake was associated with a decreased risk of all-cause mortality. In another study, Anderson et al. (2016)[3] assessing the association between the risk of coronary artery calcification (CAC) and calcium intake, showed that, after 10 years of follow-up, calcium supplement use was associated with increased risk for incident CAC.

In a prospective study in which 132823 participants were followed during a period of 17.5 years, Yang et al. (2016)[4] reported that dietary calcium was not associated with all-cause mortality in either sex. However, in this study, men taking ≥1000 mg/day supplemental calcium had a higher risk of all-cause mortality and cardiovascular disease–specific mortality. For women, they found that supplemental calcium was inversely associated with mortality from all causes for intakes of 0.1 to <500, 500 to <1000, and ≥1000 mg/day, respectively. Overall, total calcium intake was inversely associated with mortality in women but not in men. In a Swedish AMORIS cohort study, Rohrmann et al. (2016)[5] examined the association of circulating calcium with incident and fatal CVD, myocardial infarction (MI), and stroke. The results support a modest positive association between serum calcium and risk of CVD, but the underlying mineral metabolism and the exact mechanisms are currently unclear.

In a robust meta-analysis, Chung et al. (2016) found no association between calcium intake and cardiovascular risk. These investigators reported that the strength of the evidence linking calcium supplementation with cardiovascular endpoints is weak, and a plausible biological mechanism has not been identified. The available evidence based on population data, supports the findings of Chung et al. (2016), and suggest that calcium supplementation within recommended intake levels does not increase cardiovascular risk. In a review article, Chin et al. (2017)[6] reported that calcium supplementation, which is often prescribed concurrently with vitamin D, has been associated with increased CVD risk in some (but not all) studies. In another recent review publication, Abrahamsen (2017)[7] noted that though large clinical RCTs currently evaluate the effects of higher vitamin D doses there is no current research effort regarding the calcium controversy. In the absence of such studies it is not possible to provide clinicians with evidence-based recommendations regarding the best use of CaD supplementation.

Considering the widespread use of calcium supplements, association between calcium supplementation and cardiovascular risk have received significant attention. This potential causal association has not yet been very carefully studied. However, as pointed out by many

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[2] Xiao et al. (2013). JAMA Intern Med. 173:639-646.

[3] Anderson et al. (2016). J Am Heart Assoc 5: e003815.

[4] Yang et al. (2016). Am J Clin Nutr. 2016;103:886-894.

[5] Rohrmann et al. (2016). Atherosclerosis 251: 85-93, 2016

[6] Chin et al. (2017). Curr Atheroscler Rep. 19(1):5. d.

[7] Abrahamsen (2017). Ther. Adv. Musculoskel. Dis. 9(5): 107-114.

researchers in the field, the methods used and results of these studies do not stand up to the standards of assigning causality on their own or in combination. In recent meta-analyses of experimental randomized controlled trials (RCTs) that investigated the use of calcium supplements on health outcomes, Lewis et al. (2015)[8] reported no significant association between the use of calcium supplements and CHD events, all-cause mortality, myocardial infarction (MI), angina pectoris and acute coronary syndrome, and chronic CHD. In prior reviews, Heaney et al. (2012)[9] and Wang et al. (2010)[10] also made similar observations. These investigators noted the inconsistencies in the direction of the effect as well as the strength of any association between calcium intake and/or supplementation and noted that CVD risk varies greatly among the studies. Heaney et al. (2012) outlined the lack of evidence for causality which is also repeated by many researchers and echoes the statements made by the IOM in 2011. In yet another systematic review, Fortmann et al. (2013)[11] concluded that there was no evidence of an effect of calcium supplements on CVD.

In addition to the cardiovascular risk, there are limited data available on other adverse outcomes related to calcium supplementation. In a re-analysis of the Woman's Health Initiative (WHI) dataset, Bolland et al. (2011)[12] reported that among women not taking calcium supplements at randomization, calcium and vitamin D supplementation significantly decreased the risk of total, breast, and invasive breast cancer (by 1420%) and showed a non-significant decrease in colorectal cancers (by 17%). The post-intervention analysis conducted by Cauley et al. (2013)[13] using 11.1 years of follow-up reported no significant difference between the CaD supplement and placebo group in incidence of colorectal cancer, invasive breast cancer, and all-cause mortality. Another group of researchers used the same WHI dataset to investigate the occurrence of kidney stones and found that neither total calcium intake nor the use of calcium supplements at baseline was associated with an increased risk of stone formation (Wallace et al., 2011)[14].

In summary, the current debate about the potential association between calcium supplementation and cardiovascular disease needs to be critically studied in controlled trials with a specific focus on those outcomes, with controls in place for known and potential cardiovascular risk factors, and accurate measurements of total calcium intake (diet and supplements) included. It is also possible that supplements taken as a large dose all at once that the body is unable to process and may cause some adverse effects. Given the inconsistent and inconclusive findings from recent meta-analyses, systematic reviews, and recent clinical and observational studies for cardiovascular outcomes as well as any other potential adverse outcomes, there is no new conclusive evidence of a cause and effect that would alter the significant scientific consensus presented by the IOM (2011) or the EFSA (2012) expert reviews.

11. Niacet did not provide a quantitative evaluation or comparison in the notice between its estimates of U.S. exposure to calcium from its intended use of calcium acetate along with background dietary and supplemental total calcium exposures (mean and upper percentile

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[8] Lewis et al. (2015). J Bone Min. Res. 30(1):165-175.
[9] Heaney et al. (2012). Adv Nutr. 2012;3(6):763-77.
[10] Wang et al. (2010). Ann Intern Med. 152(5):315-323.
[11] Fortmann et al. (2013). Ann Int Med. 159(12): 824-834.
[12] Bolland et al. (2011). Am J Clin Nutr. 94(4):1144-9.
[13] Cauley et al. (2013). J Women's Health. 22(11): 915-29.
[14] Wallace et al. (2011). Am J Clin Nutr. 2011;94(1):270-7.

intakes) to a hazard value or dietary reference value (DRV) across different age groups (in other words, a safety assessment evaluation). Such an analysis should be provided in GRN 000712. Please consider GRN 000634 as a model example for how to present this analysis.

We have attempted to address this question in response to earlier question 7, where the exposure to calcium has been summarized along with tolerable upper intake.

We hope the above information and clarification addresses your queries. If you have any questions or need additional explanation, please let me know.

Thank you for the opportunity to provide this explanation.

Best regards

Salvatore D'Angelo

Niacet

Email dated December 1, 2017

"Dear Mr. D'Angelo,

Attached is a document containing example references that are relevant to the issues described in our question. This should not be interpreted as an exhaustive list and Niacet is still responsible for conducting its own literature search on this topic to identify information that should be included in a revised safety narrative."

Best regards,

**Rachel Morissette, Ph.D.**
*Consumer Safety Officer*

In response to the above email exchange, we were provided with eight references that FDA describe as being relevant to question 10. In our revised safety assessment narrative provided earlier in response to question 10, these references are covered. We are attempting to provide additional information for each of these publications. We have copied the abstract of each of these references along with the conclusion reached by the authors. For ease of review, we have highlighted the findings/conclusion of the authors. Additionally, we note that the issue of calcium supplementation and CVD is not a settled issue. In fact, several references available in the published literature refute the findings in some of your references. We are also providing some additional references as well as summary below and details of relevant references in Tab C.

**Suggested Sampling of Calcium References**

1. Tankeu AT, Agbor VN, Noubiap JJ. Calcium supplementation and cardiovascular risk: A rising

Concern. J Clin Hypertens 19: 640–646, 2017

"Abstract

Over the past decade, the number of individuals taking calcium supplementation worldwide has been on the rise, especially with the emergence of new pharmaceutical companies specialized in the marketing of dietary supplements; with calcium supplementation being their main business axis. This is mostly because of the established role of calcium in the prevention and treatment of osteoporosis and, to a lesser extent, its role in the prevention of fractures. Recently, a rising body of evidence on the adverse effect of calcium supplementation on nonskeletal, especially cardiovascular, health has been a cause for concern. In fact, a significant number of studies have reported an association between calcium supplementation and adverse cardiovascular events, even though high dietary calcium intake was shown to have a protective effect. The mechanism by which calcium supplementation could cause a cardiovascular event was still unclear until a recent study published in the *Journal of the American Heart Association*. Combining this recent finding with available data associating calcium supplementation with cardiovascular mortality and all-cause mortality, we call on the need for an evidence-based approach to calcium supplementation, while stressing on the safety of dietary calcium intake over the former on cardiovascular health."

**CONCLUSIONS**

Recently published data suggest a significant increase in incident CAC with calcium supplementation. Along with previous data associating calcium supplementation with cardiovascular mortality and all-cause

mortality, this new evidence stresses the need for an evidence-based approach to calcium supplementation. Moreover, it is urgent to educate health care providers on the possible risk of excessive and unnecessary calcium supplementation. From a cardiovascular perspective, dietary calcium intake by eating foods high in calcium appears safer than calcium loading with supplements."

2. Anderson JJB, Kruszka B, Delaney JAC, He K, Burke GL, Alonso A, Bild DE, Budoff M, Michos ED. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the multi-ethnic study of atherosclerosis (MESA). J Am Heart Assoc 5: e003815, 2016

"Using a longitudinal cohort study, we assessed the association between calcium intake, from both foods and supplements, and atherosclerosis, as measured by coronary artery calcification (CAC). In summary, results from this long-term study of 10 years showed a protective relationship between total calcium intake and incident coronary atherosclerosis, particularly among nonsupplement users. Even though mean total calcium intake in quintile 5 was greater than the upper limits of current recommendations, no increased risk of CAC progression was found, and the highest quintile of calcium intake actually had decreased risk of incident CAC among those without prevalent CAC at baseline. However, we found evidence that calcium supplement use was independently associated with incident CAC, whether or not we adjusted for total calcium intake. This finding suggests that calcium loading with supplements may not be entirely free of undesirable side effects, especially considering evidence for events in randomized trials of calcium supplementation like the Women's Health Initiative. Finally, our findings should reassure individuals who are following dietary calcium recommendations by eating high-calcium foods that consuming calcium from diet alone at these levels or higher is not associated with incident CAC."

3. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium intake and cardiovascular disease risk: An updated systematic review and meta-analysis. Ann Intern Med 165: 856-866, 2016

"Abstract

Background:

Conflicting evidence exists regarding potential cardiovascular risks associated with high levels of calcium intake.

Purpose:

To update and reanalyze 2 systematic reviews to examine the effects of calcium intake on cardiovascular disease (CVD) among generally healthy adults."

Conclusion" "Calcium intake within tolerable upper intake levels (2000 to 2500 mg/d) is not associated with CVD risk in generally healthy adults."

## *Comments*

**Elizabeth (Lisa) Samelson**

Harvard Medical School, Beth Israel Deaconess Medical Center, Hebrew Senior Life

October 26, 2016

**Population-based data shows no adverse effect of calcium intake on increased risk of calcification of vascular tissues**

Chung and colleagues conducted a robust meta-analysis and found no association between calcium intake and cardiovascular risk. As the authors pointed out, the strength of the evidence linking calcium supplementation with cardiovascular endpoints is weak, and a plausible biological mechanism has not been identified.

However, we disagree with the authors that data on the calcification of vascular tissues associated with calcium supplementation for the general population does not exist. We assessed the association between calcium intake and the coronary artery calcification Agatston score, evaluated from CTs, in 1200 women and men the community-based Framingham Heart Study (Am J Clin Nutr 2012;96:1274–80). We found no association between increasing Agatston scores and calcium intake from supplements and/or diet. Our prospective study, conducted in a large, community-based population of women and men, used state-of-the-art CT measures of coronary artery calcification and was able to account for important potential confounders including vitamin D intake, prevalent coronary artery disease, and kidney function.

Thus, our study, based on population data, supports the findings of Chung and co-authors, and concludes that calcium supplementation within recommended intake levels does not increase cardiovascular risk."

4. Chin K, Appel LJ, Michos ED. Vitamin D, calcium, and cardiovascular disease: A"D"vantageous or "D"etrimental? An era of uncertainty. Curr Atheroscler Rep 19: 5, 2017

"Abstract

While the function of vitamin D in regulating calcium homeostasis is well established, there has been growing interest in its role in the prevention of numerous chronic diseases, including cardiovascular disease (CVD). There is mounting epidemiological evidence suggesting that vitamin D deficiency is linked to increased CVD risk. However, the results of previous vitamin D supplementation trials have yielded mixed results in regards to cardiovascular health, and the results of ongoing large-scale randomized controlled trials are not yet available. Further complicating the issue, calcium supplementation, which is often prescribed concurrently with vitamin D, has been associated with increased CVD risk in some (but not all) studies. Thus, it is currently unclear whether vitamin D supplements, particularly for those that are deficient, can help prevent the development of CVD. In addition, there has not been uniform consensus regarding the threshold of 25-hydroxyvitamin D levels that constitutes "sufficiency" across organizational guidelines. This review will provide an

update on the most recent evidence regarding the effects of vitamin D and calcium supplements on CVD clinical outcomes, summarize ongoing vitamin D trials, and discuss the current but remarkably disparate recommendations regarding vitamin D deficiency screening and supplementation."

5. Abrahamsen B. The calcium and vitamin D controversy. Ther Adv Musculoskel Dis 9(5): 107-114, 2017

"Abstract

Areas of the world where vitamin D levels are low for months of the year and intakes of calcium are high have a high prevalence of osteoporosis and cardiovascular disease. This suggests a public health message of avoiding calcium supplements and increasing vitamin D intake. No message could be more welcome as vitamin D can be given as a bolus while calcium must be taken daily and may be poorly tolerated. This approach is based on no evidence from intervention studies. Randomized controlled trials (RCTs) suggest that vitamin D given with calcium elicits a small reduction in fracture risk and deaths. This has not been demonstrated for D given alone. The cardiovascular safety of calcium and vitamin D (CaD) supplements is difficult to ascertain due to weaknesses in RCT designs and adjudication that cannot be remedied by subanalysis. Moreover, no major new RCTs are in process to provide better evidence. It remains unclear that calcium from dietary sources has health advantages over supplements. Benefits may be confined to patients with poor nutritional intake and the small effects at societal levels may be derived from large effects in a small number of patients. This has been impossible to confirm given the limited information about baseline vitamin D and calcium status at entry into trials. Future intervention studies should carefully capture baseline characteristics as these may determine the strength of the response, and make more efficient use of randomization strategies allowing subsequent disassembly or subanalyses while maintaining balancing. Though large clinical RCTs currently evaluate the effects of higher vitamin D doses (equivalent to 50–83 µg/d) there is no current research effort regarding the calcium controversy. In the absence of such studies it is not possible to provide clinicians with evidence-based recommendations regarding the best use of CaD supplementation."

6. Rohrmann S, Garmo H, Malmstrom H, Hammar N, Jungner I, Walldius G, Van Hemelrijck M. Association between serum calcium concentration and risk of incident and fatal cardiovascular disease in the prospective AMORIS study. Atherosclerosis 251: 85-93, 2016

Abstract

"Background and aims

Previous epidemiological studies have shown positive associations between serum calcium concentration and risk of cardiovascular disease (CVD), but results differ by

definition of CVD. We examined the association of circulating calcium with incident and fatal CVD, myocardial infarction (MI), and stroke in the Swedish AMORIS cohort.

Methods

We included 441,738 participants of the AMORIS database linked for follow-up information on morbidity and mortality. Concentrations of total calcium were fully automated measured using a colorimetric method; concentrations of albumin were measured with a bromocresol green method between 1985 and 1995. The association of albumin-corrected calcium concentration and risk of incident and fatal CVD, MI, and stroke, respectively, was assessed with multivariable adjusted Cox proportional hazards models.

Results

Until December 31, 2011, during a median follow-up time of 21 years, 90,866 incident cases of CVD, 21,271 of MI, and 25,810 of stroke were identified. High serum calcium concentrations were associated with increased risk of non-fatal CVD (Hazard ratio [HR] = 1.12, 95% CI 1.10–1.14, top [≥2.40 nmol/L] vs. bottom [≤2–25 nmol/L] quintile), MI (1.19, 1.14–1.25), and stroke (1.11, 1.06–1.15) and fatal disease (CVD: 1.41, 1.35–1.47; MI: 1.41, 1.31–1.51; stroke: 1.30, 1.20–1.41). Effect modification by sex was observed for incident disease such that associations were stronger among women than men. Serum calcium was positively associated with both incident and fatal ischemic stroke and with fatal hemorrhagic stroke, but not with incident hemorrhagic stroke. In a sub-groups analysis, the results remained significant after adjustment for smoking.

Conclusions

The results support a modest positive association between serum calcium and risk of CVD, but the underlying mineral metabolism and the exact mechanisms are currently unclear."

7. Yang B, Campbell PT, Gapstur SM, Jacobs EJ, Bostick RM, Fedirko V, Flanders WD, McCullough ML. Calcium intake and mortality from all causes, cancer, and cardiovascular disease: the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr 103:886–94, 2016

"ABSTRACT
Background: Calcium intake may be important for bone health, but its effects on other outcomes, including cardiovascular disease (CVD) and cancer, remain unclear. Recent reports of adverse cardiovascular effects of supplemental calcium have raised concerns. Objective: We investigated associations of supplemental, dietary, and total calcium intakes with all-cause, CVD-specific, and cancer specific mortality in a large, prospective cohort. Design: A total of 132,823 participants in the Cancer Prevention Study II Nutrition Cohort, who were followed from baseline (1992 or 1993) through 2012 for mortality outcomes, were included in the analysis. Dietary and supplemental calcium information was first collected at baseline and updated in 1999 and 2003. Multivariable-adjusted Cox

proportional hazards models with cumulative updating of exposures were used to calculate RRs and 95% CIs for associations between calcium intake and mortality. Results: During a mean follow-up of 17.5 y, 43,186 deaths occurred. For men, supplemental calcium intake was overall not associated with mortality outcomes (P-trend . 0.05 for all), but men who were taking $1000 mg supplemental calcium/d had a higher risk of all-cause mortality (RR: 1.17; 95% CI: 1.03, 1.33), which was primarily attributed to borderline statistically significant higher risk of CVD-specific mortality (RR: 1.22; 95% CI: 0.99, 1.51). For women, supplemental calcium was inversely associated with mortality from all causes [RR (95% CI): 0.90 (0.87, 0.94), 0.84 (0.80, 0.88), and 0.93 (0.87, 0.99) for intakes of 0.1 to ,500, 500 to ,1000, and $1000 mg/d, respectively; P-trend , 0.01]. Total calcium intake was inversely associated with mortality in women (P-trend , 0.01) but not in men; dietary calcium was not associated with all-cause mortality in either sex. Conclusions: In this cohort, associations of calcium intake and mortality varied by sex. For women, total and supplemental calcium intakes are associated with lower mortality, whereas for men, supplemental calcium intake $1000 mg/d may be associated with higher all-cause and CVD-specific mortality. Am J Clin Nutr 2016;103:886–94.”"

8. Asemi Z, Saneei P, Sabihi SS, Feizi A, Esmaillzadeh A. Total, dietary, and supplemental calcium intake and mortality from all-causes, cardiovascular disease, and cancer: A meta-analysis of observational studies. Nutr Metab Cardiovasc Dis 25, 623-634, 2015

“Abstract

Aims

This systematic review and meta-analysis of observational studies was conducted to summarize the evidence on the association between calcium intake and mortality.

Methods and results

PubMed, Institute for Scientific Information (ISI) (Web of Science), SCOPUS, SciRUS, Google Scholar, and Excerpta Medica dataBASE (EMBASE) were searched to identify related articles published through May 2014. We found 22 articles that assessed the association between total, dietary, and supplementary intake with mortality from all-causes, cardiovascular disease (CVD), and cancer. Findings from this meta-analysis revealed no significant association between total and dietary calcium intake and mortality from all-causes, CVD, and cancer. Subgroup analysis by the duration of follow-up revealed a significant positive association between total calcium intake and CVD mortality for cohort studies with a mean follow-up duration of >10 years (relative risk (RR): 1.35; 95% confidence interval (CI): 1.09–1.68). A significant inverse association was seen between dietary calcium intake and all-cause (RR: 0.84; 95% CI: 0.70–1.00) and CVD mortality (RR: 0.88; 95% CI: 0.78–0.99) for studies with a mean follow-up duration of ≤10 years. Although supplemental calcium intake was not associated with CVD (RR: 0.95; 95% CI: 0.82–1.10) and cancer mortality (RR: 1.22; 95% CI: 0.81–1.84), it was inversely associated with the risk of all-cause mortality (RR: 0.91; 95% CI: 0.88–0.94).

Conclusions

We found a significant relationship between the total calcium intake and an increased risk of CVD mortality for studies with a long follow-up time and a significant protective association between dietary calcium intake and all-cause and CVD mortality for studies with a mean follow-up of ≤10 years. Supplemental calcium intake was associated with a decreased risk of all-cause mortality."

In summary, the above references, considered in totality, suggest that the evidence does not support a concern between calcium supplements and CVD.

## Additional Supporting evidence for safety of calcium acetate and some recent References

### Calcium acetate – Use in Dietary Supplements

We note that calcium acetate is not a major source of calcium in dietary supplements. In fact, a search of the Dietary Supplements Labeling Database (DSLB) (searched Dec. 2, 2017) did not find a single label that listed calcium acetate in a dietary supplement amongst products marketed in the U.S. (the results of these searches are listed below). Likewise, calcium propionate is seldom used in dietary supplements as a source of calcium. By contrast, calcium carbonate is listed in a large number of dietary supplement products as is calcium citrate. The NIH Fact Sheet on calcium states that: "The two major forms of calcium in supplements are carbonate and citrate." Based on these findings, we respectively suggest that calcium acetate in dietary supplements does not impact the safety of calcium acetate for other food uses. This indicates that exposure to calcium acetate will be primarily from its addition to food and unlike dietary supplement uses of other calcium products, it will not be exposed in bolus dose.

**Your search for "calcium acetate" was found in the following Label elements:**

1. Product Name: 0 products found containing "calcium acetate" in the product name
2. Dietary Ingredient Name: 0 dietary ingredients found containing "calcium acetate" as the dietary ingredient name
3. Brand Name: 0 brands found containing "calcium acetate" in the product brand name
4. Contacts Name: 0 contact found containing "calcium acetate" in the product contact name
5. Anywhere: 0 products found containing "calcium acetate" anywhere on the label

**Your search for "calcium propionate" was found in the following Label elements:**

1. Product Name: 0 products found containing "calcium propionate" in the product name
2. Dietary Ingredient Name: 0 dietary ingredients found containing "calcium propionate" as the dietary ingredient name

3. Brand Name: 0 brands found containing "calcium propionate" in the product brand name
4. Contacts Name: 0 contact found containing "calcium propionate" in the product contact name
5. Anywhere: 2 products found containing "calcium propionate" anywhere on the label

**Your search for "calcium carbonate" was found in the following Label elements:**

1. Product Name: 4 products found containing "calcium carbonate" in the product name
2. Dietary Ingredient Name: 3 dietary ingredients found containing "calcium carbonate" as the dietary ingredient name
3. Brand Name: 0 brands found containing "calcium carbonate" in the product brand name
4. Contacts Name: 0 contact found containing "calcium carbonate" in the product contact name
5. Anywhere: 3470 products found containing "calcium carbonate" anywhere on the label

**Your search for "calcium citrate" was found in the following Label elements:**

1. Product Name: 122 products found containing "calcium citrate" in the product name
2. Dietary Ingredient Name: 5 dietary ingredients found containing "calcium citrate" as the dietary ingredient name
3. Brand Name: 0 brands found containing "calcium citrate" in the product brand name
4. Contacts Name: 0 contact found containing "calcium citrate" in the product contact name
5. Anywhere: 1774 products found containing "calcium citrate" anywhere on the label

## Additional References

### 1. The Association of Calcium Supplementation and Incident Cardiovascular Events in the Multi-Ethnic Study of Atherosclerosis (MESA)

L.M. Raffield,[#†,a] S. Agarwal,[#b] F.C. Hsu,[c] I.H. de Boer,[d] J.H. Ix,[e] D. Siscovick,[f] M. Szklo,[g] G.L. Burke,[h] A.C. Frazier-Wood,[i] and D.M. Herrington[j]

Nutr Metab Cardiovasc Dis. 2016 October; 26(10): 899–907.
Published online 2016 July 16. doi: 10.1016/j.numecd.2016.07.007

## Abstract

### Background and Aims

Many US adults use calcium supplements to address inadequate dietary intake and improve bone health. However, recent reports have suggested that use of calcium supplements may elevate cardiovascular disease (CVD) risk. In this study, we examined associations between baseline calcium supplement use and incident myocardial infarction (MI) (n=208 events) and CVD events (n=641 events) over 10.3 years in men and women from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (n=6,236), with dietary calcium intake at baseline also examined as a supplementary objective.

Methods and Results

Using Cox proportional hazards models, no compelling associations between calcium intake from supplements or diet and incident CVD events were observed upon multivariate adjustment for potential confounders. An association with lower MI risk was observed comparing those with low levels of calcium supplement use (1-499 mg) to those using no calcium supplements (hazard ratio 0.69, 95% CI 0.48, 0.98, p=0.039). Relationships were homogeneous by gender, race/ethnicity, or chronic kidney disease. Results were also similar when the analysis was limited to postmenopausal women only.

Conclusion

Analysis of incident MI and CVD events in the MESA cohort does not support a substantial association of calcium supplement use with negative cardiovascular outcomes.

2. Lewis, J. R., Radavelli-Bagatini, S., Rejnmark, L., Chen, J. S., Simpson, J. M., Lappe, J. M., Mosekilde, L., Prentice, R. L. and Prince, R. L. (2015), The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials. J Bone Miner Res, 30: 165–175. doi:10.1002/jbmr.2311

ABSTRACT

Calcium supplementation, particularly with vitamin D, has been an approved public health intervention to reduce fracture risk. Enthusiasm for this intervention has been mitigated by meta-analyses suggesting that calcium supplementation with or without vitamin D increases myocardial infarction (MI) risk; however, concern has been raised over the design of these meta-analyses. We, therefore, undertook a meta-analysis of randomized controlled trials with placebo or no-treatment control groups to determine if these supplements increase all-cause mortality and coronary heart disease (CHD) risk including MI, angina pectoris and acute coronary syndrome, and chronic CHD verified by clinical review, hospital record, or death certificate in elderly women. The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases were searched from January 1, 1966, to May 24, 2013, for potentially eligible studies, reference lists were checked, and trial investigators were contacted where additional unpublished data were required. The search yielded 661 potentially eligible reports of which 18 met the inclusion criteria and contributed information on 63,563 participants with 3390 CHD events and 4157 deaths. Two authors extracted the data independently with trial data combined using random-effects meta-analysis to calculate the relative risk (RR). Five trials contributed CHD events with pooled relative RR of 1.02 (95% confidence interval [CI], 0.96–1.09; $p = 0.51$). Seventeen trials contributed all-cause mortality data with pooled RR of 0.96 (95% CI, 0.91–1.02; $p = 0.18$). Heterogeneity among the trials was low for both primary outcomes ($I^2 = 0\%$). For secondary outcomes, the RR for MI was 1.08 (95% CI, 0.92–1.26; $p = 0.32$), angina pectoris and acute coronary syndrome 1.09 (95% CI, 0.95–1.24; $p = 0.22$) and chronic CHD 0.92 (95% CI, 0.73–1.15; $p = 0.46$). In conclusion, current evidence does not support the hypothesis that calcium supplementation with or

without vitamin D increases coronary heart disease or all-cause mortality risk in elderly women. © 2014 American Society for Bone and Mineral Research.

3. Stephen L. Kopecky, Douglas C. Bauer, Martha Gulati, Jeri W. Nieves, Andrea J. Singer, Peter P. Toth, et al. Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology. Ann Intern Med. 2016;165:867–868. doi: 10.7326/M16-1743

# Abstract

**Description:**
Calcium is the dominant mineral present in bone and a shortfall nutrient in the American diet. Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. Whether calcium with or without vitamin D supplementation is beneficial or detrimental to vascular health is not known.

**Methods:**
The National Osteoporosis Foundation and American Society for Preventive Cardiology convened an expert panel to evaluate the effects of dietary and supplemental calcium on cardiovascular disease based on the existing peer-reviewed scientific literature. The panel considered the findings of the accompanying updated evidence report provided by an independent evidence review team at Tufts University.

**Recommendation:**
The National Osteoporosis Foundation and American Society for Preventive Cardiology adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. In light of the evidence available to date, calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d) should be considered safe from a cardiovascular standpoint.

4. Karen L. Margolis, JoAnn E. Manson. Calcium Supplements and Cardiovascular Disease Risk: What Do Clinicians and Patients Need to Know?. Ann Intern Med. 2016;165:884–885. doi: 10.7326/M16-2193

Calcium is the most abundant mineral in the body. Although 99% of total body calcium is found in the bones and teeth, it also plays an essential role in vascular contraction and dilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion (1). A recent comprehensive

review convened by the Institute of Medicine (IOM) to establish population needs for calcium and vitamin D intake concluded that the scientific evidence was strong enough to support recommendations for intakes of these nutrients for bone health (1) but that the evidence related to extraskeletal outcomes was "inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements" (2). Thus, the IOM recommended that men and women aged 19 to 50 years consume a total of 1000 mg/d of calcium, and that women older than 50 and men older than 70 years consume a total of 1200 mg/d, emphasizing that there is no evidence that consuming higher amounts results in greater health benefits (1).

5. Latest Data: Calcium Supplements Not Associated With CVD

Pam Harrison

April 22, 2016

Calcium supplements with and without vitamin D have again been shown not to adversely affect cardiovascular disease (CVD) outcomes in men or women between 40 and 69 years of age. The latest analysis to examine this issue includes data from more than half a million individuals.

"Historically, the only side effects of calcium supplementation were an increased risk of indigestion and a very small increased risk of kidney stones, but in recent years, there has been a suggestion from a small number of researchers that calcium supplementation might lead to an increased risk of heart attacks," lead author Nicholas Harvey, MD, University of Southampton, United Kingdom, told *Medscape Medical News* in an email.

"Using the UK Biobank cohort, we had the opportunity to examine this issue in 500,000 UK men and women in middle to older age, and our results suggest that calcium supplementation — with or without vitamin D supplementation — does not increase the risk of cardiovascular events."

The study was presented at the World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases, held in Malaga, Spain, April 14–17, 2016.

Reassurance That Calcium/Vitamin D Supplementation Safe

The UK Biobank is a large, prospective cohort involving 502,664 men and women from the United Kingdom. At baseline, the median age of participants was 58 years.

Investigators recorded baseline intake of calcium and vitamin D supplements and linked this to hospital admissions for ischemic heart disease, any CV event, and death through 7 years of follow-up.

They found that 34,890 participants reported taking calcium supplements and that 20,004 were taking vitamin D supplements. Only 2.1% of the group overall were taking both.

In both crude and adjusted analyses for all possible confounders, "There were no associations between use of calcium supplements and risk of incident hospital admission with ischemic heart disease, any cardiovascular event, or death following either admission category," Dr Harvey reported.

**Hazard Ratios in the Adjusted Model for Study End Points**

| Group | Ischemic heart disease admission: HR (95% CI) | Death from ischemic heart disease: HR |
|---|---|---|
| Women taking calcium vs no calcium intake | 1.06 (0.32–1.61; *P* = .62) | 0.71 (0.32–1.61; *P* = .42) |
| Men taking calcium vs no calcium intake | 1.02 (0.80–1.30; *P* = .87) | 0.92 (0.52–1.62; *P* = .76) |

HR=hazard ratio
95% CI=95% confidence interval

"Results were similar for vitamin D and combination supplementation," he and his colleagues add. Further adjustment for the use of hormone-replacement therapy in women also did not alter the association between calcium supplementation and CVD end points.

Investigators also pointed out that the findings remained robust when corrected for possible confounders, including age, body mass index, and medication use, and they remained the same whether participants had a history of CVD or not at baseline.

"Calcium supplementation is widely used, including as an adjunct to therapy for osteoporosis," Dr Harvey said in a statement. "Our results, using the largest single study to date, provide reassurance that such supplementation appears safe."

**No Evidence for Causal Relationship**

There has long been debate about the relative safety of calcium supplements, with physicians recommending that individuals try to obtain the calcium they need from food sources rather than pills.

But because calcium and vitamin D are essential for bone health and the elderly often cannot meet the recommended daily requirements for either nutrient through diet alone, supplements are widely used.

Asked by *Medscape Medical News* to comment, Bess Dawson-Hughes, MD, director of the bone metabolism laboratory at the United States Department of Agriculture nutrition center on aging and professor of medicine, Tufts University School of Medicine, Boston, Massachusetts, said that there is a lot of material out there right now on the possible causal relationship between calcium supplementation and CVD end points.

The weight of evidence is that there is not an identifiable risk from calcium supplementation in the CV arena, she asserted.

This is particularly important for the elderly, for whom supplementation may be critical for bone health, she added.

"The elderly are not only at risk for osteoporosis but they are also at risk for CVD, so you don't want to have an intervention that prevents one but aggravates the other," Dr Dawson-Hughes said.

"So this is a very important issue, and I'm relieved that the evidence does not support a causal relationship."

*Dr Harvey has received personal fees, consultancy fees, lecture fees, and honoraria from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Servicer, Shire, Consoling Healthcare, and Internis Pharmaceuticals outside the current work. Dr Dawson-Hughes has received an investigator-initiated research grant from Pfizer and DSM to study the effects of vitamin D on muscle.*

World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; April 16, 2016; Malaga, Spain. Abstract P311.

[Available at: https://www.medscape.com/viewarticle/862345].

6. Calcium Supplement Intake and Risk of Cardiovascular Disease in Women

Paik, J.M., Curhan, G.C., Sun, Q. et al. Osteoporos Int (2014) 25: 2047. https://doi.org/10.1007/s00198-014-2732-3

## Abstract

### Background

Some recent reports suggest that calcium supplements may increase cardiovascular disease (CVD) risk.

### Purpose

The objective was to examine the independent associations between calcium supplement use and risk of CVD.

### Methods

We conducted a prospective cohort study of supplemental calcium use and incident CVD in 74,245 women in the Nurses' Health Study (1984–2008) free of CVD and cancer at baseline. Calcium supplement intake was assessed every four years. Outcomes were incident coronary heart disease (CHD) (nonfatal or fatal MI) and stroke (ischemic or hemorrhagic), confirmed by medical record review.

### Results

During 24 years of follow-up, 4,565 cardiovascular events occurred (2,709 CHD and 1,856 strokes). At baseline, women who took calcium supplements had higher levels of physical activity, smoked less, and had lower trans fat intake compared with those who did not take calcium supplements. After multivariable adjustment for age, body mass index, dietary calcium, vitamin D intake, and other CVD risk factors, the relative risk of CVD for women taking >1,000mg/day of calcium supplements compared with none was 0.82 (95% CI 0.74 to 0.92; p for trend <0.001). For women taking >1,000mg/day of calcium supplements compared with none, the multivariable-adjusted relative risk for CHD was 0.71 (0.61 to 0.83; p for trend<0.001) and for

stroke was 1.03 (0.87 to 1.21; p for trend=0.61). The relative risks were similar in analyses limited to non-smokers, women without hypertension, and women who had regular physical exams.

## Conclusions

The available evidence, when considered in its totality, does not support the hypothesis that calcium supplement intake increases CVD risk in women. Also, the available evidence does not indicate that calcium acetate is used in dietary supplements. Additional research is needed in this area to further understand the role, if any, that calcium supplementation, through the use of dietary supplements may play in these etiologies.

# Tab A. Calcium Fact Sheet for Professionals

## (attached separately)

**[Also available at:** https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/.]

**Tab B. Specifications for Six Non-consecutive Lots of Niacet's Calcium acetate**

**(attached separately)**

# Tab C. Details of the relevant recent publications

**(attached separately)**

# Tab A

**CERTIFICATE OF ANALYSIS** **80020744** 1 (2)
80020744

23.10.2017
Customer's reference
4500028714
Order no. / date
1000018610
15.09.2017

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

---

**Description**
PROGUSTA CA GRANULAR 20KG

**Cust. No.:**
52489

**Code**
50276

**Gross Weight**
18.486,000 KG

**Net Weight**
18.000,000 KG

**Batch**
2000043473

**Manufacturing date**
16.10.2017

**Expiration date**
16.10.2019

| Characteristic | Result | Specification | Unit |
|---|---|---|---|
| Assay on dried material | 99,2 | 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 | 232 | < = 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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www.niacet.com

IBAN NL61BOFA0266533965
Trade register Tiel
Registration no. 11044303
VAT NL807461817B01

Niacet

**CERTIFICATE OF ANALYSIS** **80018486** 1 (2)
80018486

12.10.2017
Customer's reference
4500024803
Order no. / date
1000016366
28.04.2017

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

---

**Description**
PROGUSTA CA GRANULAR 20KG

**Cust. No.:**
52489

**Code**
50276

**Gross Weight**
18.465,460 KG

**Net Weight**
17.980,000 KG

**Batch**
2000041879

**Manufacturing date**
09.09.2017

**Expiration date**
09.09.2019

| Characteristic | Result | Specification | Unit |
|---|---|---|---|
| Assay on dried material | 99,4 | 99,0 - 100,5 | %(m) |
| Mercury (Hg)* | | < = 1 | ppm |
| Oxidisable Impurities as Formic Acid | < 0,1 | < = 0,1 | %(m) |
| pH of 10% solution | 7,4 | 6,0 - 9,0 | |
| Water | 5,8 | < = 6,0 | %(m) |
| Chloride | 267 | < = 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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Trade register Tiel
Registration no. 11044303
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Niacet

**CERTIFICATE OF ANALYSIS** **80018983** 1 (2)
80018983

14.06.2017
Customer's reference
4500025678
Order no. / date
1000016972
31.05.2017

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

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**Description**
PROGUSTA CA POWDER 20KG

**Cust. No.:**
52487

**Code**
52025

**Gross Weight**
9.175,680 KG

**Net Weight**
8.640,000 KG

**Batch**
2000040253

**Manufacturing date**
13.06.2017

**Expiration date**
13.06.2019

| Characteristic | Result | Specification | Unit |
|---|---|---|---|
| Assay on dried material | 100,2 | 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 | 6,0 | < = 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).

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Registration no. 11044303
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Niacet

**CERTIFICATE OF ANALYSIS** **80010066** 1 (2)
80010066

16.12.2015
Customer's reference
4500011139
Order no. / date
1000008779
08.12.2015

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

---

**Description**
PROGUSTA CA POWDER 20KG

| **Code** | **Gross Weight** | **Net Weight** |
|---|---|---|
| 52025 | 764,640 KG | 720,000 KG |
| **Batch** | **Manufacturing date** | **Expiration date** |
| 2000023850 | 22.11.2015 | 21.11.2017 |

| Characteristic | Result | Specification | Unit |
|---|---|---|---|
| Assay on dried matter | 99,3 | 99,0 - 100,5 | %(m) |
| Mercury (Hg)* | | < = 1 | ppm |
| Insoluble in water | < 1000 | < = 1000 | ppm |
| pH of 10% solution | 7,1 | 6,0 - 9,0 | |
| Sulphate | < 600 | < = 1000 | ppm |
| Water | 5,2 | < = 6,0 | %(m) |
| Chloride | < 400 | < = 500 | ppm |
| Iron | < 2,0 | < = 10,0 | ppm |
| Appearance | White powder | White powder | |
| 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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IBAN NL61BOFA0266533965
Trade register Tiel
Registration no. 11044303
VAT NL807461817B01

Niacet

**CERTIFICATE OF ANALYSIS** **80006988** 
80006988

03/24/2015
Customer's reference
233507
Order no. / date
1000005946
03/04/2015

Niacet Corporation
400 47th street
Niagara Falls, NY NY 14304
US

**Description**
PROGUSTA CA POWDER 20KG

| **Code** | **Gross Weight** | **Net Weight** |
|---|---|---|
| 52026 | 4,818.660 KG | 4,620.000 KG |
| **Batch** | **Manufacturing date** | **Expiration date** |
| 2000016672 | 03/10/2015 | 03/09/2017 |

| Characteristic | Result | Specification | Unit |
|---|---|---|---|
| Assay on dried matter | 99.5 | 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 | < 500 | <= 1000 | ppm |
| Water | 5.4 | <= 6.0 | %(m) |
| Chloride | < 400 | <= 500 | ppm |
| Iron | < 5.0 | <= 10.0 | ppm |
| Appearance | White powder | White powder | |
| 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).

This CoA is only valid when the product is in its original undamaged packaging and when stored

**CERTIFICATE OF ANALYSIS** **80005523** 
80005523

10/27/2014
Customer's reference
231532
Order no. / date
1000004780
10/20/2014

Niacet Corporation
400 47th street
Niagara Falls, NY NY 14304
US

**Description**
PROGUSTA CA POWDER 20KG

| **Code** | **Gross Weight** | **Net Weight** |
|---|---|---|
| 52025 | 382.320 KG | 360.000 KG |
| **Container no.** | | |
| APHU6744876/TSI3063620 | | |
| **Batch** | **Manufacturing date** | **Expiration date** |
| 2000010903 | 07/05/2014 | 07/04/2016 |

| Characteristic | Result | Specification | Unit |
|---|---|---|---|
| Assay on dried matter | 99.0 | 99.0 - 100.5 | %(m) |
| Mercury (Hg)* | | <= 1 | ppm |
| Insoluble in water | < 1000 | <= 1000 | ppm |
| pH of 10% solution | 7.3 | 6.0 - 9.0 | |
| Sulphate | < 1000 | <= 1000 | ppm |
| Water | 5.8 | <= 6.0 | %(m) |
| Chloride | < 100 | <= 500 | ppm |
| Appearance | White powder | White powder | |
| Oxidisable impurities as H. Form | < 1000 | <= 1000 | ppm |
| Lead* | | <= 2 | ppm |
| Iron* | | <= 10 | 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).

Tab B



# Calcium

Fact Sheet for Health Professionals

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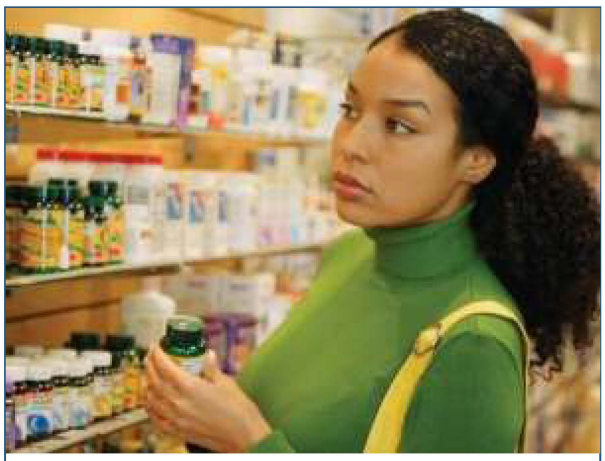
## Introduction





Calcium, the most abundant mineral in the body, is found in some foods, added to others, available as a dietary supplement, and 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 [1].

## Recommended Intakes

Intake recommendations for calcium and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences) [1]. DRI is the general term for a set of reference values used for planning and assessing the nutrient intakes of healthy people. These values, which vary by age and gender, include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals.
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.
- Estimated Average Requirement (EAR): average daily level of intake estimated to meet the requirements of 50% of healthy individuals. It is usually used to assess the adequacy of nutrient intakes in populations but not individuals.
- Tolerable Upper Intake Level (UL): maximum daily intake unlikely to cause adverse health effects [1].

The FNB established RDAs for the amounts of calcium required for bone health and to maintain adequate rates of calcium retention in healthy people. They are listed in Table 1 in milligrams (mg) per day.

**Table 1: Recommended Dietary Allowances (RDAs) for Calcium [1]**

| Age | Male | Female | Pregnant | Lactating |
|---|---|---|---|---|
| 0–6 months* | 200 mg | 200 mg | | |
| 7–12 months* | 260 mg | 260 mg | | |
| 1–3 years | 700 mg | 700 mg | | |
| 4–8 years | 1,000 mg | 1,000 mg | | |
| 9–13 years | 1,300 mg | 1,300 mg | | |
| 14–18 years | 1,300 mg | 1,300 mg | 1,300 mg | 1,300 mg |
| 19–50 years | 1,000 mg | 1,000 mg | 1,000 mg | 1,000 mg |
| 51–70 years | 1,000 mg | 1,200 mg | | |
| 71+ years | 1,200 mg | 1,200 mg | | |

* Adequate Intake (AI)

## Sources of Calcium

### *Food*

Milk, yogurt, and cheese are rich natural sources of calcium and are the major food contributors of this nutrient to people in the United States [1]. Nondairy sources include vegetables, such as Chinese cabbage, kale, and broccoli. Spinach provides calcium, but its bioavailability is poor. Most grains do not have high amounts of calcium unless they are fortified; however, they contribute calcium to the diet because they contain small amounts of calcium and people consume them frequently. Foods fortified with calcium include many fruit juices and drinks, tofu, and cereals. Selected food sources of calcium are listed in Table 2.

**Table 2: Selected Food Sources of Calcium [2]**

| Food | Milligrams (mg) per serving | Percent DV* |
|---|---|---|
| Yogurt, plain, low fat, 8 ounces | 415 | 42 |
| Mozzarella, part skim, 1.5 ounces | 333 | 33 |
| Sardines, canned in oil, with bones, 3 ounces | 325 | 33 |
| Yogurt, fruit, low fat, 8 ounces | 313–384 | 31–38 |
| Cheddar cheese, 1.5 ounces | 307 | 31 |
| Milk, nonfat, 8 ounces** | 299 | 30 |
| Soymilk, calcium-fortified, 8 ounces | 299 | 30 |
| Milk, reduced-fat (2% milk fat), 8 ounces | 293 | 29 |
| Milk, buttermilk, lowfat, 8 ounces | 284 | 28 |
| Milk, whole (3.25% milk fat), 8 ounces | 276 | 28 |
| Orange juice, calcium-fortified, 6 ounces | 261 | 26 |
| Tofu, firm, made with calcium sulfate, ½ cup*** | 253 | 25 |
| Salmon, pink, canned, solids with bone, 3 ounces | 181 | 18 |
| Cottage cheese, 1% milk fat, 1 cup | 138 | 14 |
| Tofu, soft, made with calcium sulfate, ½ cup*** | 138 | 14 |
| Ready-to-eat cereal, calcium-fortified, 1 cup | 100–1,000 | 10–100 |
| Frozen yogurt, vanilla, soft serve, ½ cup | 103 | 10 |
| Turnip greens, fresh, boiled, ½ cup | 99 | 10 |
| Kale, fresh, cooked, 1 cup | 94 | 9 |
| Ice cream, vanilla, ½ cup | 84 | 8 |
| Chinese cabbage, bok choi, raw, shredded, 1 cup | 74 | 7 |
| Bread, white, 1 slice | 73 | 7 |
| Pudding, chocolate, ready to eat, refrigerated, 4 ounces | 55 | 6 |
| Tortilla, corn, ready-to-bake/fry, one 6” diameter | 46 | 5 |
| Tortilla, flour, ready-to-bake/fry, one 6” diameter | 32 | 3 |
| Sour cream, reduced fat, cultured, 2 tablespoons | 31 | 3 |
| Bread, whole-wheat, 1 slice | 30 | 3 |
| Kale, raw, chopped, 1 cup | 24 | 2 |
| Broccoli, raw, ½ cup | 21 | 2 |
| Cheese, cream, regular, 1 tablespoon | 14 | 1 |

* DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for calcium is 1,000 mg for adults and children aged 4 years and older. Foods providing 20% of more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet. The U.S. Department of Agriculture’s (USDA’s) Nutrient Database Web site lists the nutrient content of many foods and provides comprehensive list of foods containing calcium arranged by nutrient content and by food name.

** Calcium content varies slightly by fat content; the more fat, the less calcium the food contains.

*** Calcium content is for tofu processed with a calcium salt. Tofu processed with other salts does not provide significant amounts of calcium.

In its food guidance system, *MyPlate*, the U.S. Department of Agriculture recommends that persons aged 9 years and older eat 3 cups of foods from the milk group per day [3]. A cup is equal to 1 cup (8 ounces) of milk, 1 cup of yogurt, 1.5 ounces of natural cheese (such as Cheddar), or 2 ounces of processed cheese (such as American).

#### *Dietary supplements*

The two main forms of calcium in supplements are carbonate and citrate. Calcium carbonate is more commonly available and is both inexpensive and convenient. Due to its dependence on stomach acid for absorption, calcium carbonate is absorbed most efficiently when taken with food, whereas calcium citrate is absorbed equally well when taken with or without food [4]. Calcium citrate is also useful for people with achlorhydria, inflammatory bowel disease, or absorption disorders [1]. Other calcium forms in supplements or fortified foods include gluconate, lactate, and phosphate. Calcium citrate malate is a well-absorbed form of calcium found in some fortified juices [5].

Calcium supplements contain varying amounts of elemental calcium. For example, calcium carbonate is 40% calcium by weight, whereas calcium citrate is 21% calcium. Fortunately, elemental calcium is listed in the Supplement Facts panel, so consumers do not need to calculate the amount of calcium supplied by various forms of calcium supplements.

The percentage of calcium absorbed depends on the total amount of elemental calcium consumed at one time; as the amount increases, the percentage absorption decreases. Absorption is highest in doses ≤500 mg [1]. So, for example, one who takes 1,000 mg/day of calcium from supplements might split the dose and take 500 mg at two separate times during the day.

Some individuals who take calcium supplements might experience gastrointestinal side effects including gas, bloating, constipation, or a combination of these symptoms. Calcium carbonate appears to cause more of these side effects than calcium citrate [1], so consideration of the form of calcium supplement is warranted if these side effects are reported. Other strategies to alleviate symptoms include spreading out the calcium dose throughout the day and/or taking the supplement with meals.

#### *Medicines*

Because of its ability to neutralize stomach acid, calcium carbonate is found in some over-the-counter antacid products, such as Tums® and Rolaids®. Depending on its strength, each chewable pill or softchew provides 200 to 400 mg of elemental calcium. As noted above, calcium carbonate is an acceptable form of supplemental calcium, especially for individuals who have normal levels of stomach acid.

## Calcium Intakes and Status

In the United States, estimated calcium intakes from both food and dietary supplements are provided by the National Health and Nutrition Examination Survey (NHANES), 2003–2006 [6]. Mean dietary calcium intakes for males aged 1 year and older ranged from 871 to 1,266 mg/day depending on life stage group; for females the range was 748 to 968 mg/day. Groups with mean intakes falling below their respective EAR—and thus with a prevalence of inadequacy in excess of 50%—include boys and girls aged 9–13 years, girls aged 14–18 years, women aged 51–70 years, and both men and women older than 70 years [1,6]. Overall, females are less likely than males to get adequate amounts of calcium from food [7].

About 43% of the U.S. population (including almost 70% of older women) uses dietary supplements containing calcium, increasing calcium intakes by about 330 mg/day among supplement users [1,6].

According to NHANES 2003–2006 data, mean total calcium intakes from foods and supplements ranged from 918 to 1,296 mg/day for people aged 1 year and older [6]. When considering total calcium intakes, calcium inadequacy remains a concern for several age groups. These include females aged 4 years and older—particularly adolescent girls—and males aged 9 to 18 years and older than 51 years [1,8]. At the other end of the spectrum, some older women likely exceed the UL when calcium intakes from both food and supplements are included [1].

Not all calcium consumed is actually absorbed in the gut. Humans absorb about 30% of the calcium in foods, but this varies depending upon the type of food consumed [1]. Other factors also affect calcium absorption including the following:

- Amount consumed: the efficiency of absorption decreases as calcium intake increases [1].
- Age and life stage: net calcium absorption is as high as 60% in infants and young children, who need substantial amounts of the mineral to build bone [1,9]. Absorption decreases to 15%–20% in adulthood (though it is increased during pregnancy) and continues to decrease as people age; compared with younger adults, recommended calcium intakes are higher for females older than 50 years and for both males and females older than 70 years [1,9,10].
- Vitamin D intake: this nutrient, obtained from food and produced by skin when exposed to sunlight of sufficient intensity, improves calcium absorption [1].
- Other components in food: phytic acid and oxalic acid, found naturally in some plants, bind to calcium and can inhibit its absorption. Foods with high levels of oxalic acid include spinach, collard greens, sweet potatoes, rhubarb, and beans. Among the foods high in phytic acid are fiber-containing whole-grain products and wheat bran, beans, seeds, nuts, and soy isolates [1]. The extent to which these compounds affect calcium absorption varies. Research shows, for example, that eating spinach and milk at the same time reduces absorption of the calcium in milk [11]. In contrast, wheat products (with the exception of wheat bran) do not appear to lower calcium absorption [12]. For people who eat a variety of foods, these interactions probably have little or no nutritional consequence and, furthermore, are accounted for in the overall calcium DRIs, which factor in differences in absorption of calcium in mixed diets.

Some absorbed calcium is eliminated from the body in urine, feces, and sweat. This amount is affected by such factors as the following:

- Sodium and protein intakes: high sodium intake increases urinary calcium excretion [13,14]. High protein intake also increases calcium excretion and was therefore thought to negatively affect calcium status [13,14]. However, more recent research suggests that high protein intake also increases intestinal calcium absorption, effectively offsetting its effect on calcium excretion, so whole body calcium retention remains unchanged [15].
- Caffeine intake: this stimulant in coffee and tea can modestly increase calcium excretion and reduce absorption [16]. One cup of regular brewed coffee, for example, causes a loss of only 2–3 mg of calcium [14]. Moderate caffeine consumption (1 cup of coffee or 2 cups of tea per day) in young women has no negative effects on bone [17].
- Alcohol intake: alcohol intake can affect calcium status by reducing its absorption [18] and by inhibiting enzymes in the liver that help convert vitamin D to its active form [19]. However, the amount of alcohol required to affect calcium status and whether moderate alcohol consumption is helpful or harmful to bone is unknown.
- Phosphorus intake: the effect of this mineral on calcium excretion is minimal. Several observational

studies suggest that consumption of carbonated soft drinks with high levels of phosphate is associated with reduced bone mass and increased fracture risk. However, the effect is probably due to replacing milk with soda rather than the phosphorus itself [20,21].

- Fruit and vegetable intakes: metabolic acids produced by diets high in protein and cereal grains increase calcium excretion [22]. Fruits and vegetables, when metabolized, shift the acid/base balance of the body towards the alkaline by producing bicarbonate, which reduces calcium excretion. However, it is unclear if consuming more fruits and vegetables affects bone mineral density. These foods, in addition to reducing calcium excretion, could possibly reduce calcium absorption from the gut and therefore have no net effect on calcium balance.

## Calcium Deficiency

Inadequate intakes of dietary calcium from food and supplements produce no obvious symptoms in the short term. Circulating blood levels of calcium are tightly regulated. Hypocalcemia results primarily from medical problems or treatments, including renal failure, surgical removal of the stomach, and use of certain medications (such as diuretics). Symptoms of hypocalcemia include numbness and tingling in the fingers, muscle cramps, convulsions, lethargy, poor appetite, and abnormal heart rhythms [23]. If left untreated, calcium deficiency leads to death.

Over the long term, inadequate calcium intake causes osteopenia which if untreated can lead to osteoporosis. The risk of bone fractures also increases, especially in older individuals [1]. Calcium deficiency can also cause rickets, though it is more commonly associated with vitamin D deficiency [1].

## Groups at Risk of Calcium Inadequacy

Although frank calcium deficiency is uncommon, dietary intakes of the nutrient below recommended levels might have negative health consequences over the long term. The following groups are among those most likely to need extra calcium.

### *Postmenopausal women*

Menopause leads to bone loss because decreases in estrogen production both increase bone resorption and decrease calcium absorption [10,24,25]. Annual decreases in bone mass of 3%–5% per year frequently occur in the first years of menopause, but the decreases are typically less than 1% per year after age 65 [26]. Increased calcium intakes during menopause do not completely offset this bone loss [27,28]. Hormone replacement therapy (HRT) with estrogen and progesterone helps increase calcium levels and prevent osteoporosis and fractures. Estrogen therapy restores postmenopausal bone remodeling to the same levels as at premenopause, leading to lower rates of bone loss [24], perhaps in part by increasing calcium absorption in the gut. Several medical groups and professional societies support the use of HRT as an option for women who are at increased risk of osteoporosis or fractures [29-31]. Such women should discuss this matter with their health care providers. In addition, consuming adequate amounts of calcium in the diet might help slow the rate of bone loss in all women.

### *Amenorrheic women and the female athlete triad*

Amenorrhea, the condition in which menstrual periods stop or fail to initiate in women of childbearing age, results from reduced circulating estrogen levels that, in turn, have a negative effect on calcium balance. Amenorrheic women with anorexia nervosa have decreased calcium absorption and higher urinary calcium excretion rates, as well as a lower rate of bone formation than healthy women [32]. The “female athlete triad”

refers to the combination of disordered eating, amenorrhea, and osteoporosis. Exercise-induced amenorrhea generally results in decreased bone mass [33,34]. In female athletes and active women in the military, low bone-mineral density, menstrual irregularities, certain dietary patterns, and a history of prior stress fractures are associated with an increased risk of future stress fractures [35]. Such women should be advised to consume adequate amounts of calcium and vitamin D. Supplements of these nutrients have been shown to reduce the risk of stress fractures in female Navy recruits during basic training [36].

#### *Individuals with lactose intolerance or cow's milk allergy*

Lactose intolerance refers to symptoms (such as bloating, flatulence, and diarrhea) that occur when one consumes more lactose, the naturally occurring sugar in milk, than the enzyme lactase produced by the small intestine can hydrolyze into its component monosaccharides, glucose and galactose [37]. The symptoms vary, depending on the amount of lactose consumed, history of consumption of lactose-containing foods, and type of meal. Although the prevalence of lactose intolerance is difficult to discern [38], some reports suggest that approximately 25% of U.S. adults have a limited ability to digest lactose, including 85% of Asians, 50% of African Americans, and 10% of Caucasians [39,40,41].

Lactose-intolerant individuals are at risk of calcium inadequacy if they avoid dairy products [1,38,39]. Research suggests that most people with lactose intolerance can consume up to 12 grams of lactose, such as that present in 8 ounces of milk, with minimal or no symptoms, especially if consumed with other foods; larger amounts can frequently be consumed if spread over the day and eaten with other foods [1,38,39]. Other options to reduce symptoms include eating low-lactose dairy products including aged cheeses (such as Cheddar and Swiss), yogurt, or lactose-reduced or lactose-free milk [1,38,39]. Some studies have examined whether it is possible to induce adaptation by consuming incremental lactose loads over a period of time [42,43], but the evidence in support of this strategy is inconsistent [38].

Cow's milk allergy is less common than lactose intolerance, affecting 0.6% to 0.9% of the population [44]. People with this condition are unable to consume any products containing cow's milk proteins and are therefore at higher risk of obtaining insufficient calcium.

To ensure adequate calcium intakes, lactose-intolerant individuals and those with cow's milk allergy can choose nondairy food sources of the nutrient (such as kale, bok choy, Chinese cabbage, broccoli, collards and fortified foods) or take a calcium supplement.

#### *Vegetarians*

Vegetarians might absorb less calcium than omnivores because they consume more plant products containing oxalic and phytic acids [1]. Lacto-ovo vegetarians (who consume eggs and dairy) and nonvegetarians have similar calcium intakes [45,46]. However, vegans, who eat no animal products and ovo-vegetarians (who eat eggs but no dairy products), might not obtain sufficient calcium because of their avoidance of dairy foods [47,48]. In the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition, bone fracture risk was similar in meat eaters, fish eaters and vegetarians, but higher in vegans, likely due to their lower mean calcium intake [49]. It is difficult to assess the impact of vegetarian diets on calcium status because of the wide variety of eating practices and thus should be considered on a case by case basis.

## Calcium and Health

Many claims are made about calcium's potential benefits in health promotion and disease prevention and

treatment. This section focuses on several areas in which calcium is or might be involved: bone health and osteoporosis; cardiovascular disease; blood pressure regulation and hypertension; cancers of the colon, rectum, and prostate; kidney stones; and weight management.

***Bone health and osteoporosis***

Bones increase in size and mass during periods of growth in childhood and adolescence, reaching peak bone mass around age 30. The greater the peak bone mass, the longer one can delay serious bone loss with increasing age. Everyone should therefore consume adequate amounts of calcium and vitamin D throughout childhood, adolescence, and early adulthood. Osteoporosis, a disorder characterized by porous and fragile bones, is a serious public health problem for more than 10 million U.S. adults, 80% of whom are women. (Another 34 million have osteopenia, or low bone mass, which precedes osteoporosis.) Osteoporosis is most associated with fractures of the hip, vertebrae, wrist, pelvis, ribs, and other bones [50]. An estimated 1.5 million fractures occur each year in the United States due to osteoporosis [51].

When calcium intake is low or ingested calcium is poorly absorbed, bone breakdown occurs as the body uses its stored calcium to maintain normal biological functions. Bone loss also occurs as part of the normal aging process, particularly in postmenopausal women due to decreased amounts of estrogen. Many factors increase the risk of developing osteoporosis, including being female, thin, inactive, or of advanced age; smoking cigarettes; drinking excessive amounts of alcohol; and having a family history of osteoporosis [52].

Various bone mineral density (BMD) tests are available. The T-score from these tests compares an individual's BMD to an optimal BMD (that of a healthy 30-year old adult). A T-score of -1.0 or above indicates normal bone density, -1.0 to -2.5 indicates low bone mass (osteopenia), and lower than -2.5 indicates osteoporosis [53]. Although osteoporosis affects individuals of all races, ethnicities, and both genders, women are at highest risk because their skeletons are smaller than those of men and because of the accelerated bone loss that accompanies menopause. Regular exercise and adequate intakes of calcium and vitamin D are critical to the development and maintenance of healthy bones throughout the life cycle. Both weight-bearing exercises (such as walking, running, and activities where one's feet leave and hit the ground and work against gravity) and resistance exercises (such as calisthenics and that involve weights) support bone health.

Supplementation with calcium plus vitamin D has been shown to be effective in reducing fractures and falls (which can cause fractures) in institutionalized older adults [54]. However, among community-dwelling older adults over age 50, the benefits of supplementation with these nutrients on fracture resistance are much less clear. A recent systematic review of 26 randomized controlled trials found that calcium supplements, with or without vitamin D, modestly but significantly reduced the risk of total and vertebral fractures, but not fractures of the hip or forearm [55]. But the four trials with the lowest risk of bias, involving a total of 44,505 individuals, showed no effect of supplementation on risk of fracture at any site. A related meta-analysis of calcium intake on bone mineral density found that calcium supplementation produced only a small, initial, and non-progressive increase in bone mineral density that was unlikely to result in a clinically significant reduction in the risk of bone fractures [56]. The U.S. Preventive Services Task Force (USPSTF) concluded that the current evidence is insufficient to assess the balance of benefits and harms of combined vitamin D and calcium supplementation to prevent bone fractures in premenopausal women or in men [57]. For non-institutionalized postmenopausal women, the USPSTF concluded that while current evidence was insufficient to assess the balance of benefits and harms of combined supplementation with vitamin D (at more than 400 IU/day) and calcium (at more than 1,000 mg/day) to prevent bone fractures, there was clearly no benefit in supplementing with smaller doses of these nutrients for this purpose.

In 1993, the U.S. Food and Drug Administration authorized a health claim related to calcium and osteoporosis for foods and supplements [58]. In January 2010, this health claim was expanded to include vitamin D. Model health claims include the following: "Adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis" and "Adequate calcium and vitamin D as part of a healthful diet, along with physical activity, may reduce the risk of osteoporosis in later life" [58].

#### *Cancer of the colon and rectum*

Data from observational and experimental studies on the potential role of calcium in preventing colorectal cancer, though somewhat inconsistent, are highly suggestive of a protective effect [1]. Several studies have found that higher intakes of calcium from foods (low-fat dairy sources) and/or supplements are associated with a decreased risk of colon cancer [59-62]. In a follow-up study to the Calcium Polyp Prevention Study, supplementation with calcium carbonate led to reductions in the risk of adenoma (a nonmalignant tumor) in the colon, a precursor to cancer [63,64], even as long as 5 years after the subjects stopped taking the supplement [65]. In two large prospective epidemiological trials, men and women who consumed 700–800 mg per day of calcium had a 40%–50% lower risk of developing left-side colon cancer [66]. But other observational studies have found the associations to be inconclusive [62,67,68].

In the Women's Health Initiative, a clinical trial involving 36,282 postmenopausal women, daily supplementation with 1,000 mg of calcium and 400 International Units (IU) of vitamin $D_3$ for 7 years produced no significant differences in the risk of invasive colorectal cancer compared to placebo [69]. The authors of a Cochrane systematic review concluded that calcium supplementation might moderately help prevent colorectal adenomas, but there is not enough evidence to recommend routine use of calcium supplements to prevent colorectal cancer [70]. Given the long latency period for colon cancer development, long-term studies are needed to fully understand whether calcium intakes affect colorectal cancer risk.

#### *Cancer of the prostate*

Several epidemiological studies have found an association between high intakes of calcium, dairy foods or both and an increased risk of developing prostate cancer [71-77]. However, others have found only a weak relationship, no relationship, or a negative association between calcium intake and prostate cancer risk [78-81]. The authors of a meta-analysis of prospective studies concluded that high intakes of dairy products and calcium might slightly increase prostate cancer risk [82].

Interpretation of the available evidence is complicated by the difficulty in separating the effects of dairy products from that of calcium. But overall, results from observational studies suggest that total calcium intakes >1,500 mg/day or >2,000 mg/day may be associated with increased prostate cancer risk (particularly advanced and metastatic cancer) compared with lower amounts of calcium (500–1,000 mg/day [1,83]. Additional research is needed to clarify the effects of calcium and/or dairy products on prostate cancer risk and elucidate potential biological mechanisms.

#### *Cardiovascular disease*

Calcium has been proposed to help reduce cardiovascular disease (CVD) risk by decreasing intestinal absorption of lipids, increasing lipid excretion, lowering cholesterol levels in the blood, and promoting calcium influx into cells [1]. However, data from prospective studies of calcium's effects on CVD risk are inconsistent, and whether dietary calcium has different effects on the cardiovascular system than supplemental calcium is not clear. In the Iowa Women's Health Study, higher calcium intake from diet and/or supplements was associated with reduced ischemic heart disease mortality in postmenopausal women [84]. Conversely, in a

cohort of older Swedish women, both total and dietary calcium intakes of 1,400 mg/day and higher were associated with higher rates of death from CVD and ischemic heart disease than intakes of 600–1,000 mg/day [85]. Other prospective studies have shown no significant associations between calcium intake and cardiac events or cardiovascular mortality [83]. Data for stroke are mixed, with some studies linking higher calcium intakes to lower risk of stroke, and others finding no associations or trends in the opposite direction [83,85].

Several studies have raised concerns that calcium from supplements might increase the risk of CVD, including myocardial infarction and coronary heart disease [86-89]. For example, Xiao and colleagues reported that men who took more than 1,000 mg/day supplemental calcium had a 20% higher risk of total CVD death than men who did not take supplemental calcium, but supplemental calcium intake in women was unrelated to CVD mortality [90]. A reanalysis of data from the Women's Health Initiative (WHI) found that calcium supplements (1,000 mg/day) taken with or without vitamin D (400 IU/day) increased the risk of cardiovascular events in women who were not taking calcium supplements when they entered the study [91]. While there is no established biological mechanism to support an association between calcium and CVD, some scientists hypothesize that excessively high calcium intakes from supplements might override normal homeostatic controls of serum calcium levels and produce a temporary hypercalcemia [85,91,92]. Hypercalcemia is associated with increased blood coagulation, vascular calcification, and arterial stiffness, all of which raise CVD risk [90,91,93,94].

Many scientists question the strength of the available evidence linking supplemental calcium intake with CVD risk, noting that no clinical trials were designed primarily to evaluate this potential relationship, so researchers have only considered CVD outcomes in secondary analyses of trial data [93,95,96]. Based on a 2016 systematic review and meta-analysis of 4 randomized trials and 27 observational studies [97], the American Society for Preventive Cardiology and the National Osteoporosis Foundation concluded that there is "moderate-quality evidence" that calcium with or without vitamin D (from supplements or foods) "has no relationship (beneficial or harmful) with the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults" [92]. They added that based on the evidence to date, "calcium intake from food and supplements that does not exceed the [UL] should be considered safe from a cardiovascular standpoint."

#### *Blood pressure and hypertension*

Several clinical trials have demonstrated a relationship between increased calcium intakes and both lower blood pressure and risk of hypertension [98-100], although the reductions are inconsistent. In the Women's Health Study, calcium intake was inversely associated with risk of hypertension in middle-aged and older women [101]. However, other studies have found no association between calcium intake and incidence of hypertension [83]. The authors of a systematic review of the effects of calcium supplements for hypertension found any link to be weak at best, largely due to the poor quality of most studies and differences in methodologies [102].

Calcium's effects on blood pressure might depend upon the population being studied. In hypertensive subjects, calcium supplementation appears to lower systolic blood pressure by 2–4 mmHg, whereas in normotensive subjects, calcium appears to have no significant effect on systolic or diastolic blood pressure [83].

Other observational and experimental studies suggest that individuals who eat a vegetarian diet high in minerals (such as calcium, magnesium, and potassium) and fiber and low in fat tend to have lower blood

pressure [48,103-106]. The Dietary Approaches to Stop Hypertension (DASH) study was conducted to test the effects of three different eating patterns on blood pressure: a control "typical" American diet; one high in fruits and vegetables; and a third diet high in fruits, vegetables, and low-fat dairy products. The diet containing dairy products resulted in the greatest decrease in blood pressure [107], although the contribution of calcium to this effect was not evaluated. Additional information and sample DASH menu plans are available on the National Heart, Lung, and Blood Institute Web site.

***Preeclampsia***

Preeclampsia is a serious medical condition in which a pregnant woman develops hypertension and proteinuria, usually after 20 weeks' gestation [108]. It is a leading cause of maternal and neonatal morbidity and mortality, affecting about 5–8% of pregnancies in the United States and up to 14% of pregnancies worldwide [108,109].

Studies suggest that calcium supplementation during pregnancy reduces the risk of preeclampsia, but the benefits may apply only to populations with inadequate calcium intakes [109,110]. For example, in a randomized clinical trial among 524 healthy women in India with mean baseline calcium intakes of only 314 mg/day, daily supplementation with 2,000 mg calcium starting between 12 and 25 weeks' gestation and continuing until delivery significantly reduced the risk of preeclampsia, as well as preterm birth, compared to placebo [111]. Conversely, in a randomized trial of 4,589 healthy women in the United States, daily supplementation with 2,000 mg calcium from 13–21 weeks' gestation through the remainder of pregnancy did not reduce the incidence of preeclampsia, pregnancy-induced hypertension, or other adverse perinatal outcomes compared to placebo [112]. The mean baseline calcium intake among these women, however, was about 1,100 mg/day. The authors of a 2014 Cochrane review of 13 clinical trials concluded that daily supplementation with 1,000 mg or more of calcium during pregnancy reduced the risk of preeclampsia by 55% [113]. The reduction in risk was greatest for women at high risk of preeclampsia and those with low baseline calcium intakes (less than about 900 mg/day). For women with higher dietary calcium intakes, however, the reduction in preeclampsia risk was not statistically significant.

Several professional organizations recommend calcium supplements during pregnancy for women with low calcium intakes to reduce the risk of preeclampsia. For example, the American College of Obstetrics and Gynecology (ACOG) states that daily supplementation with 1,500–2,000 mg calcium may reduce the severity of preeclampsia in pregnant women who have calcium intakes less than 600 mg/day [109]. Similarly, the World Health Organization (WHO) recommends 1,500–2,000 mg calcium for pregnant women with low dietary calcium intakes, particularly those at higher risk of gestational hypertension [110]. The WHO recommends dividing the total daily dose into three doses, preferably to be taken at mealtimes, and taking the supplements from 20 weeks' gestation until delivery. The WHO also recommends separating calcium and prenatal iron supplements by several hours to minimize the inhibitory effects of calcium on iron absorption. But some researchers argue that this interaction has minimal clinical significance and suggest that providers not counsel patients to separate the supplements to simplify the supplement regimen and facilitate adherence [114]. The Canadian Hypertensive Disorders of Pregnancy Working Group [115], the International Society for the Study of Hypertension in Pregnancy [116], and the Society of Obstetric Medicine of Australia and New Zealand [117] have all issued similar recommendations to ACOG and the WHO.

***Kidney stones***

Kidney stones in the urinary tract are most commonly composed of calcium oxalate. Some, but not all, studies suggest a positive association between supplemental calcium intake and the risk of kidney stones,

and these findings were used as the basis for setting the calcium UL in adults [1]. In the Women's Health Initiative, postmenopausal women who consumed 1,000 mg of supplemental calcium and 400 IU of vitamin D per day for 7 years had a 17% higher risk of kidney stones than subjects taking a placebo [118]. The Nurses' Health Study also showed a positive association between supplemental calcium intake and kidney stone formation [117]. High intakes of *dietary* calcium, on the other hand, do not appear to cause kidney stones and may actually protect against developing them [1,119-122]. For most individuals, other risk factors for kidney stones, such as high intakes of oxalates from food and low intakes of fluid, probably play a bigger role than calcium intake [123].

#### *Weight management*

Several studies have linked higher calcium intakes to lower body weight or less weight gain over time [124-127]. Two explanations have been proposed. First, high calcium intakes might reduce calcium concentrations in fat cells by decreasing the production of parathyroid hormone and the active form of vitamin D. Decreased intracellular calcium concentrations in turn increase fat breakdown and discourage fat accumulation in these cells [126]. Secondly, calcium from food or supplements might bind to small amounts of dietary fat in the digestive tract and prevent its absorption [126,128,129]. Dairy products, in particular, might contain additional components that have even greater effects on body weight than their calcium content alone would suggest [127,130-134].

Despite these findings, the results from clinical trials have been largely negative. For example, dietary supplementation with 1,500 mg/day of calcium (from calcium carbonate) for 2 years was found to have no clinically significant effects on weight in 340 overweight and obese adults as compared with placebo [133]. Three reviews of published studies on calcium from supplements or dairy products on weight management came to similar conclusions [83,136,137]. A meta-analysis of 13 randomized controlled trials published in 2006 concluded that neither calcium supplementation nor increased dairy product consumption had a statistically significant effect on weight reduction [136]. More recently, a 2009 evidence report from the Agency for Healthcare Research and Quality concluded that, overall, clinical trial results do not support an effect of calcium supplementation on weight loss [83]. Also, a 2012 meta-analysis of 29 randomized controlled trials found no benefit of an increased consumption of dairy products on body weight and fat loss in long-term studies [137]. Overall, the results from clinical trials do not support a link between higher calcium intakes and lower body weight or weight loss.

For additional information on calcium and weight management, see our health professional fact sheet on **Weight Loss**.

## Health Risks from Excessive Calcium

Excessively high levels of calcium in the blood known as hypercalcemia can cause renal insufficiency, vascular and soft tissue calcification, hypercalciuria (high levels of calcium in the urine) and kidney stones [1]. Although very high calcium intakes have the potential to cause hypercalcemia [85], it is most commonly associated with primary hyperparathyroidism or malignancy [1].

High calcium intake can cause constipation. It might also interfere with the absorption of iron and zinc, though this effect is not well established [1]. High intake of calcium from supplements, but not foods, has been associated with increased risk of kidney stones [1,116,117]. Some evidence links higher calcium intake with increased risk of prostate cancer, but this effect is not well understood, in part because it is challenging to separate the potential effect of dairy products from that of calcium [1]. Some studies also link high calcium

intake, particularly from supplements, with increased risk of cardiovascular disease [85-88,90,91].

The Tolerable Upper Intake Levels (ULs) for calcium established by the Food and Nutrition Board are listed in Table 3 in milligrams (mg) per day. Getting too much calcium from foods is rare; excess intakes are more likely to be caused by the use of calcium supplements. NHANES data from 2003–2006 indicate that approximately 5% of women older than 50 years have estimated total calcium intakes (from foods and supplements) that exceed the UL by about 300–365 mg [1,6].

**Table 3: Tolerable Upper Intake Levels (ULs) for Calcium [1]**

| Age | Male | Female | Pregnant | Lactating |
|---|---|---|---|---|
| 0–6 months | 1,000 mg | 1,000 mg | | |
| 7–12 months | 1,500 mg | 1,500 mg | | |
| 1–8 years | 2,500 mg | 2,500 mg | | |
| 9–18 years | 3,000 mg | 3,000 mg | 3,000 mg | 3,000 mg |
| 19–50 years | 2,500 mg | 2,500 mg | 2,500 mg | 2,500 mg |
| 51+ years | 2,000 mg | 2,000 mg | | |

## Interactions with Medications

Calcium supplements have the potential to interact with several types of medications. This section provides a few examples. Individuals taking these medications on a regular basis should discuss their calcium intake with their healthcare providers.

Calcium can decrease absorption of the following drugs when taken together: biphosphonates (to treat osteoporosis), the fluoroquinolone and tetracycline classes of antibiotics, levothyroxine, phenytoin (an anticonvulsant), and tiludronate disodium (to treat Paget's disease) [138-140].

Thiazide-type diuretics can interact with calcium carbonate and vitamin D supplements, increasing the risks of hypercalcemia and hypercalciuria [139].

Both aluminum- and magnesium-containing antacids increase urinary calcium excretion. Mineral oil and stimulant laxatives decrease calcium absorption. Glucocorticoids, such as prednisone, can cause calcium depletion and eventually osteoporosis when they are used for months [139].

## Calcium and Healthful Diets

The federal government's 2015-2020 *Dietary Guidelines for Americans* notes that "Nutritional needs should be met primarily from foods. … Foods in nutrient-dense forms contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive health effects. In some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less-than-recommended amounts."

For more information about building a healthy diet, refer to the *Dietary Guidelines for Americans* and the U.S. Department of Agriculture's MyPlate.

The *Dietary Guidelines for Americans* describes a healthy eating pattern as one that:

- Includes a variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils. Many dairy products, such as milk, cheese, and yogurt, are rich sources of calcium. Some

vegetables provide significant amounts of calcium, as do some fortified cereals and juices.

- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.

  Tofu made with calcium salts is a good source of calcium (check the label), as are canned sardines and canned salmon with edible bones.
- Limits saturated and *trans* fats, added sugars, and sodium.

  Low-fat and nonfat dairy products provide amounts of calcium that are roughly similar to the amounts in their full-fat versions.
- Stays within your daily calorie needs.

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## Disclaimer

This fact sheet by the Office of Dietary Supplements provides information that should not take the place of medical advice. We encourage you to talk to your healthcare providers (doctor, registered dietitian, pharmacist, etc.) about your interest in, questions about, or use of dietary supplements and what may be best for your overall health. Any mention in this publication of a specific brand name is not an endorsement of the product.

**Updated:** November 17, 2016 History of changes to this fact sheet

# Tab C

**Calcium and CVD – summary of clinical trials and meta-analysis published subsequent to the IOM 2011 report**

| Study Design | Population | Findings | Considerations | Citation |
|---|---|---|---|---|
| ***Meta-analyses*** | | | | |
| 18 randomized placebo-controlled trials (1966 – May 24, 2013, with study duration >1y and calcium dose >0.5g | 63,564 post-menopausal women, mean cohort age >50y<br>CHD: 48,460 participants (5 trials), 3390 CHD events<br>All-cause mortality: 62,383 participants (17 trials, 4157 deaths<br>MI: 51,111 participants (7 trials), 1123 events<br>Angina pectoris with acute coronary syndrome: 48,033 participants (4 trials), 876 events<br>Chronic CHD: 48,033 participants (4 trials), 1506 events | • No statistically significant increase in risk of CHD events (pooled RR = 1.02; 95% CI: 0.96-1.09) from 5 trials<br>• No statistically significant increase in risk of all-cause mortality (pooled RR = 0.96; 95% CI: 0.91-1.02) from 17 trials<br>• No statistically significant increase in risk of angina pectoris with acute coronary syndrome (RR = 1.09; 95% CI: 0.95 – 1.24) from 4 trials<br>• No statistically significant increase in risk of chronic CHD (RR = 0.92; 95% CI: 0.73 – 1.15) from 4 trials | • Heterogeneity among trials was low for CHD events and all-cause mortality (I2 = 0%)<br>• Total dietary intake of calcium was not measured<br>• WHI study heavily weighted in analyses<br>• Outcomes in the RCTs included in meta-analysis were not the primary outcomes<br>• Only outcomes verified by clinical review, discharge record, or death certificate included | Lewis et al., 2015 |
| Randomized, double-blind, placebo controlled trials (1966 March 2010) with a study duration > 1y | Studies with 100 or more male and female participants of mean age > 40y<br>Updated Bolland et al.,2010 meta-analysis with the restricted | • Increased risk of MI among calcium/vit D supplementation group (RR = 1.24; 95% CI: 1.07 – 1.45) and MI/stroke (RR = 1.15; 95% CI: 1.03 – 1.27) | • CVD outcomes in the RCTs included in meta-analysis were not the primary outcomes<br>• CVD outcomes are based on self-report | Bolland et al., 2011a |

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| | analysis of the WHI CaD study among women not reporting use of calcium supplements at randomization<br>28,072 participants from 8 trials of calcium supplements | | events and were not adjudicated<br>• Totally dietary intake of calcium is not measured<br>• WHI study heavily weighted in analyses<br>• Low CVD event frequency<br>• Lack of ability to control for important confounding factors including renal failure and several known CVD risk factors<br>• This analysis is an update of the 2010 meta-analysis (Bolland et al., 2010) and has the same limitations described in the IOM 2011 report | |
| Randomized, double-blind, placebo controlled trials (1966 March 2010) with a study duration > 1y | Studies with 100 or more male and female participants of mean age > 40y | • 15 trials included in analysis<br>  • 5 with patient level data<br>  • 11 with trial-level data<br>• Patient-level analysis: increased risk of MI in those allocated to calcium (HR = 1.31; 95% CI: 1.02 – 1.67); no increased risk of | • CVD outcomes in the RCTs included in meta-analysis were not the primary outcomes<br>• CVD outcomes are based on self-report events and were not adjudicated<br>• Totally dietary intake of calcium is not measured | Bolland et al., 2010 (Included in IOM review but summarized here) |

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| | | stroke, MI/stroke/sudden death or death<br>• Trial-level analysis: increased incidence of MI in those allocated to calcium (pooled relative risk = 1.27; 95% CI: 1.01 – 1.59) | • WHI study heavily weighted in analyses<br>• Low CVD event frequency<br>• Lack of ability to control for important confounding factors including renal failure and several known CVD risk factors<br>• Findings from this study provide no new information as this analysis was reviewed by the IOM as part of setting the current ULs | |
| ***Analysis of WHI*** | | | | |
| Randomized, double-blind placebo-controlled trial (secondary analysis of WHI randomized trial) | 25,983 women from WHI, age 50-79 y, with 744 adjudicated incident heart failure (HF) cases Supplemented with 1000 mg/day calcium with 400 IU/day vitamin D | • No increase in risk of HF with calcium supplementation (HR = 0.95; 95% CI: 0.82 – 1.09)<br>• Baseline risk factors affected HR risk; low risk (HR = 0.63; 95% CI: 0.46 – 0.87), high risk (HR = 1.06; 95% CI: 0.90 – 1.24) | | Donneyong et al., 2015 |
| Randomized, blinded, placebo-controlled trial – post intervention analysis (WHI: Women's Health Initiative) | 36,282 post-menopausal women ages 50-79 y; subjects consumed placebo or 400 IU vitamin $D_3$ with 1000 mg calcium carbonate daily for an | • The post-intervention period showed similar effects as the intervention period<br>• Overall HRs among | • No control group as all subjects took calcium supplement with vitamin D; can't isolate effects of supplemental calcium | Cauley et al., 2013 |

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| | average of 7 y; 29,868 (86%) women included in post-intervention follow-up (4.9 y) | women who received CaD supplements were not significantly increased for overall CHD (HR = 1.03; 95% CI: 0.94 – 1.13), CHD deaths (HR = 0.99; 95% CI: 0.84 – 1.18), clinical MI (HR = 1.03; 95% CI: 0.92 – 1.15), stroke (HR = 1.04; 95% CI: 0.93 – 1.16) and CVD deaths (HR = 1.03; 95% CI: 0.92 – 1.17)<br>• Findings similar among both women who reported taking supplements at baseline and those who did not | • Population of older women; findings may not be generalizable to the total population<br>• CVD outcomes were not the primary outcomes<br>• CVD outcomes are based on self-report events and were not adjudicated<br>• Total dietary intake of calcium is not measured<br>• Low CVD event frequency | |
| Randomized, blinded, placebo-controlled trial (WHI: Women's Health Initiative) | 36,282 post-menopausal women ages 50-79 y; subjects consumed placebo or 400 IU vitamin $D_3$ with 1000 mg calcium carbonate daily for an average of 7 y | • No association between calcium supplementation and CVD events among all study subjects or among study subjects with no reported personal use of supplements at randomization<br>• Hazard ratios ranged from 1.00 (95% CI: 0.86 – 1.18) for all heart disease to 1.18 | • No control group as all subjects took calcium supplement with vitamin D; can't isolate effects of supplemental calcium<br>• Population of older women; findings may not be generalizable to the total population<br>• CVD outcomes were not the primary outcomes | |

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| | | (95% CI: 0.88 – 1.59) for MIs among women with no reported use of supplements at randomization | • Analysis accounts for duration of supplement use<br>• Low CVD event frequency<br>• Lack of ability to control for important confounding factors including renal failure and several known CVD risk factors | |
| Randomized, blinded, placebo-controlled trial (WHI: Women's Health Initiative) | 36,282 post-menopausal women ages 50-79 y; subjects consumed placebo or 400 IU vitamin $D_3$ with 1000 mg calcium carbonate daily for an average of 7 y | • Interaction observed between personal supplement use at enrollment and allocated calcium and vitamin D for CVD events<br>• Among the 16,718 women (46%) not taking personal calcium supplements at randomization, borderline significant increase in risk for MI (HR = 1.22; 95% CI: 1.00 – 1.50)<br>• Among women taking personal calcium supplements, no increased risk observed | • No control group as all subjects took calcium supplement with vitamin D; can't isolate effects of supplemental calcium<br>• Population of older women; findings may not be generalizable to the total population<br>• CVD outcomes were not the primary outcomes<br>• CVD outcomes are based on self-report events and were not adjudicated<br>• Total dietary intake of calcium is not measured<br>• Low CVD event frequency | Bolland et al., 2011a |

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| ***Other Clinical Trials*** | | | | |
| Randomized, placebo-controlled trial | 100 post-menopausal New Zealand women with 1 g calcium/day (3 months) | • Systolic blood pressure (BP) significantly lower at 2, 4, 6, and 8 hours post initial treatment in all groups<br>• Smaller reduction in BP for Ca group compared to placebo (Systolic BP at 2, 4, and 6 hours; diastolic BP at 2 h)<br>• No significant difference in change in BP from baseline to 3 months<br>• No difference in BP between groups at 3 months | • BP was not the primary outcome<br>• Total dietary intake of calcium is not measured<br>• Type of calcium supplement varied among the treatment groups (citrate, carbonate, two preparations of microcrystalline hydroxyapatite<br>• Population of older women; findings may not be generalizable to the total population<br>• Small control group (N= 20) | Bristow et al., 2016 |
| Randomized, double-blind placebo-controlled trial (Calcium Intake Fracture Outcome Study (CAIFOS)) 5 y trial; 4.5 y follow-up | 1460 Australian women aged 75 ± 2.7 y at baseline (1998)<br>Supplemented with 1200 mg/day of calcium carbonate daily or placebo | • No increased risk of death or first-time hospitalization from atherosclerotic vascular disease (HR = 0.938; 95% CI: 0.690 – 1.275) during RCT<br>• Similar null findings during 9.5 y of observational study (HR = 0.919; 95% CI: 0.737 – 1.146) | • Adjustment for many CVD risk factors included in analysis<br>• Outcomes were based on verified hospitalization and death registries<br>• Potential lower bioavailability of calcium from calcium carbonate however this is not well-established | Lewis et al., 2011 |

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| Randomized, placebo-controlled trial | 1471 post-menopausal women supplemented with 1 g calcium/day (5 y)<br>323 men 40 y supplemented with calcium at 600 or 1200 mg/day (2 y) | • Dietary or supplemental calcium intake was not associated with abdominal aortic calcification (AAC) changes; calcium supplementation also was not related to coronary artery calcification (CAC) scores in men | | Wang et al., 2010 |

**Calcium and CVD – summary of observation studies and meta-analysis published subsequent to the IOM 2011 report**

| Study Design | Population | Findings | Considerations | Citation |
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| ***Meta-analysis*** | | | | |
| 11 prospective studies (12 independent cohorts) (1950 – Dec. 30, 2013) | 757,304 male and female participants, 4+ y<br>CVD mortality: 704,499 participants (9 studies), >21,457 deaths<br>All-cause mortality: 225,189 participants (6 studies), >21,055 deaths | • For risk of CVD mortality, pooled RR = 0.97 (95% CI: 0.89 – 1.07) when comparing "highest" and "lowest" dietary calcium intake<br>• For all-cause mortality, RR = 0.83 (95% CI: 0.70 – 1.00) when comparing "highest" and "lowest" dietary calcium intake<br>• In dose-response analysis, nonlinear association between dietary calcium intake and risk of CVD mortality observed ($p < 0.01$ for non-linearity); when compared to individuals with calcium intakes of 800 mg/d, significantly increased risk of | Study did not find statistically significant association between calcium intake and CVD mortality based on pooled RR across nine studies<br>The mathematically derived non-linear dose response model needs further explanation regarding the selection of the number of knots to determine the reference point. This coupling with the limitation of exposure information inherent with observational studies, as acknowledged by study authors, the dose response data from this analysis would need to be subject to further assessment and validation | Wang et al., 2014 |

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| | | CVD mortality with 1200 mg/day calcium intakes (RR = 1.05 (95% CI: 1.01 – 1.09) and calcium intakes of 1400 mg/day RR = 1.10 (95% CI: 1.02– 1.18)<br>• In a dose-response analysis, nonlinear association between dietary calcium intake and risk of mortality from all causes observed ($p<0.01$ for non-linearity) when compared with the reference intake of 900 mg/day, lower intake was associated with increased risk for all-cause mortality while there was no reduction in risk at intakes above 900 mg/day<br>• No statistically significant association between supplemental calcium and CVD mortality (6 studies; RR = 0.96; 95% CI: 0.82 – 1.13) | | |
| ***Cohort studies with findings of no or inverse association*** | | | | |
| Prospective cohort; 24 y follow-up | 74,245 female registered nurses (30-55 y) free of CVD and cancer at baseline | • Dietary and supplemental calcium intake measured through a semi-quantitative food frequency questionnaire<br>• Calcium intake not associated with increased incidence of fatal or non-fatal MI (RR $>_{1000 \text{ vs } 0 \text{ mg/day}}$ = 0.71; 95% CI: 0.61 – 0.83) or stoke (RR $>_{1000 \text{ vs } 0 \text{ mg/day}}$ = 1.03; 95% CI: 0.87 – 1.21) | • Multivariate models adjusted for dietary factors and known health behaviors that may confound this relationship<br>• Large number of events and long follow-up with repeated measure of Ca intake<br>• Study population is female and predominantly white – not generalizable to men and/or other races/ethnicities<br>Conclusion: this study provides no | Paik et al., 2014 |

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| | | | new adverse associations to call the current calcium UL into question | |
| Prospective cohort | 46.892 postmenopausal women in the same catchment area as the WHI clinical trial | • No association between calcium intake supplementation and CVD events | • CVD outcomes were not the primary outcomes<br>• Analysis accounts for duration of supplement use | Prentice et al., 2013 |
| Prospective (Framingham Offspring Study) | 669 women; 532 men (age = 60 y; range: 36-83 y); baseline clinic visit in 1998-2001; CT exam in 2002-2005 | • Total (diet + supplements) calcium intake:<br>○ 1185 ± 565 mg/day (women)<br>○ 891 ± 461 mg/day (men)<br>• Inverse association between mean age-adjusted coronary artery-calcification Agatston score and total calcium intake<br>• Results were similar for dietary calcium and calcium supplement use | • Measured total calcium intake<br>• Adjusted for several known CVD risk factors | Samelson et al., 2012 |
| Prospective (MIDSPAN Family Study); 14.4 y median follow-up | 1040 men and 1298 women from the West of Scotland recruited in 1996; age 45-64 y | • No association between albumin-corrected serum calcium levels and CVD events (ICD-10 100-199 coded on death certificate or discharge record) | | Welsh et al., 2012 |
| ***Cohort studies with some findings of an association*** | | | | |
| Prospective longitudinal cohort; 19 y median follow-up | Swedish mammography cohort, population-based (1987-90); 61,433 women (born 1914-1948) | • No association between calcium tablet use (500 mg calcium per tablet) and all cause or cause specific mortality<br>• Dietary calcium intake > 1400 mg/day among calcium tablet users was associated with increased risk of mortality (HR | • Dietary calcium intake based on food frequency questionnaires with standard portion sizes, not measured portion sizes, which tend to overestimate intake<br>• Results from this observational study are not consistent with other cohort analyses nor are they confirmed by clinical trials | Michaelsson et al., 2013 |

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| | | = 2.57; 95% CI: 1.19 – 5.55) | | |
| Prospective analysis using NHANES III mortality linkage follow-up | US population 17+ y eligible for mortality follow-up and free from history of heart disease (N = 18,714) | • ~10% of population died of cardiovascular disease (N = 1870); majority were ischemic heart disease (IHD;5.4%)<br>• Increased risk of IHD death among women with serum calcium levels in top 5% compared to those in the mid 90% (HR = 1.72; 95% CI: 1.13 – 2.61)<br>• Among men, low serum calcium was related to increased IHD mortality (HR = 2.32; 95% CI: 1.14 – 3.01)<br>• No associations observed with dietary or supplemental calcium intake | • Adjusted for many dietary and known risk factors for CVD<br>• Dietary calcium assessed using a 24-hour diary which may not reflect long-term intake<br>• Supplement intake is self-reported but NHANES records the supplement name directly from the label | Van Hemelrijk et al., 2013 |
| Prospective cohort (National Institutes of Health (NIH) – AARP Diet and Healthy Study); 12 y follow-up | 388,229 men and women in the US aged 50-71 y | • 7904 CVD deaths in men; 3874 CVD deaths in women<br>• Calcium-containing supplement use was 51% and 70% in men and women, respectively<br>• In men, supplemental calcium intake was associated with CVD mortality (RR $>_{1000 \text{ vs } 0 \text{ mg/day}}$ = 1.20; 95% CI: 1.05 – 1.36), heart disease mortality (RR = 1.19; 95% CI: 1.03 – 1.37), but not cerebrovascular disease mortality (RR = 1.14; 95% CI: 0.81 – 1.61)<br>• No association between calcium supplements and CVD events in women | • Adjusted for dietary variables<br>• No data on duration of supplement use<br>• Incomplete adjustment for other CVD risk factors including nutrients | Xiao et al., 2013 |

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| Prospective cohort (European Prospective Investigation into Cancer and Nutrition Study (EPIC) – Heidelberg); 11 y follow-up | 23,980 German participants in the EPIC study, aged 35-64 y CVD-free at recruitment | • 354 MIs; 260 stroke cases; 267 CVD deaths<br>• Significant reduction in MI risk among the third quartile of total dietary calcium intake compared to the lowest (HR = 0.69; 95% CI: 0.50 – 0.94)<br>• No association with stroke and CVD mortality<br>• Increased risk of MI in users of calcium supplements compared to non-users (HR = 1.86; 95% CI: 1.17 – 2.96)<br>• Larger risk observed among calcium supplement only users (HR = 2.39; 95% CI: 1.12 – 5.12) | • Dose of calcium supplements unknown<br>• Close to half of supplement users (44.5%) did not report name of supplement; prevalence of calcium supplement use is lower than observed in a German elderly population or that observed in the US | Li et al., 2012 |
| ***Cross-sectional studies with findings of no association*** | | | | |
| Cross-sectional | 23,652 Korean men and women, asymptomatic for CVD, without kidney disease, with mean age 40.8 y | • Comparing the highest (≥ 478.2 mg/day) and lowest (< 221.8 mg/day) quartiles of dietary calcium intake, tomographic score ratios of coronary artery calcification (CAC), a risk factor for CVD, were not associated with dietary calcium intake (0.84; 95% CI: 0.58 – 1.20)<br>• Comparing the highest (≥ 9.7 mg/dL) and lowest (< 9.3 mg/dL) quartiles of serum, serum calcium levels were positively associated with CAC score ratios; no association was described as to the relationship of serum calcium to estimated calcium intake | • Details of supplement use were not described<br>• Relationship of serum calcium to calcium intake not described<br>• Concurrent assessment of intake and risk | Kwak et al., 2014 |

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| Cross-sectional (Diabetes Heart Study) | 720 male and female type 2 diabetes (T2D) enrolled in Diabetes Heart Study | • No significant association of dietary calcium or supplements with measures of vascular plaques in men or women<br>• No significant association of dietary calcium intake with all-cause or CVD mortality risk in men and women; no significant association of supplemental calcium with CVD mortality risk in men and women or all-cause mortality in men<br>• For women, HR = 0.62 (95% CI: 0.42 – 0.92) for all-cause mortality associated with supplemental calcium use when comparing the highest and lowest intakes (> 500 mg/day compared to 0 mg/day) | • Quintiles of energy-adjusted total calcium intake (dietary and supplement) utilized for analysis<br>• Concurrent assessment of calcium intake and risk | Raffield et al., 2014 |
| ***Cross-sectional studies with findings of an association*** | | | | |
| Cross-sectional | 197 male and female type 2 diabetes (T2D), age > 65 y | • Patients whose dietary calcium intake was high (>600 mg/day) or low (<402 mg/day) had higher C-reactive protein (CRP) levels, an emerging biomarker for CVD risk, than those with moderate (402 – 600 mg/day) calcium intake (moderate vs high, $p<0.05$) | • CVD risk, CVD mortality, or all-cause mortality were not primary outcomes<br>• Publication does not mention supplement use of inclusion/exclusion of patients utilizing calcium supplements<br>• Concurrent assessment of intake and risk | Huang et al., 2014 |
| Cross-sectional analysis of a prospective cohort (J-MICC cohort) | 535 men with dietary calcium intake data, 35-69 y, in cohort from Tokushima Prefecture, Japan | • When comparing the highest (>497.3 mg/day) and lowest (≤ 351.8 mg/day) quartiles of dietary calcium intake, measurements of branchial-ankle pulse wave velocity, a | • Exclusion or inclusion of subjects based on supplement use was not described | Uemura et al., 2014 |

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| | | measure of arterial stiffness, were significantly inversely associated with dietary calcium intake (p for trend = 0.02) | | |

**Calcium and Other Outcomes – Summary of published subsequent to the IOM review of calcium**

| Study Design | Population | Findings | Considerations | Citation |
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| ***Clinical Trials*** | | | | |
| Randomized, blinded, placebo-controlled trial – Post intervention analysis (WHI: Women's Health Initiative) | 36,282 post-menopausal women ages 50-79 y; subjects consumed placebo or 400 IU vitamin $D_3$ with 1000 mg calcium carbonate daily for an average of 7 y; 29,868 (86%) women included in post-intervention follow-up (4.9 y) | • The post-intervention period showed similar effects as the intervention period<br>• No significant difference between the CaD supplement and placebo group in incidence of colorectal cancer (HR = 0.95; 95% CI: 0.80 – 1.13), invasive breast cancer (HR = 1.04; 95% CI: 0.94 – 1.14), and all-cause mortality (HR = 0.96; 95% CI: 0.90 – 1.03), | • No control group as all subjects took calcium supplement with vitamin D; can't isolate effects of supplemental calcium<br>• Population of older women; findings may not be generalizable to the total population<br>• Cancer/mortality outcomes were not the primary outcomes<br>• Outcomes are based on self-report events and were not adjudicated<br>• Total dietary intake of calcium is not measured | Cauley et al., 2013 |
| Randomized, blinded, placebo-controlled trial (WHI: Women's Health Initiative) | 36,282 post-menopausal women ages 50-79 y; subjects consumed placebo or 400 IU vitamin $D_3$ with 1000 mg calcium carbonate daily for an average of 7 y | • Among the 16,718 women (46%) not taking personal calcium supplements at randomization, significant reductions observed for total cancer, total breast cancer and invasive breast cancer (HRs ranging from 0.80 – 0.86)<br>• In women taking personal calcium or vitamin D supplements, trial | • No control group as all subjects took calcium supplement with vitamin D; can't isolate effects of supplemental calcium<br>• Population of older women; findings may not be generalizable to the total population<br>• Cancer outcomes were not the primary outcomes<br>• Cancer outcomes are based on self-report events and were not adjudicated | Bolland et al., 2011b |

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| | | supplementation did not alter cancer risk (HR = 1.06 – 1.26) | • Total dietary intake of calcium is not measured | |
| Randomized, blinded, placebo-controlled trial (WHI: Women's Health Initiative) | 36,282 post-menopausal women ages 50-79 y; subjects consumed placebo or 400 IU vitamin $D_3$ with 1000 mg calcium carbonate daily for an average of 7 y | • 449 women in the CaD group and 381 women in the placebo group reported a stone during the trial<br>• Increased incidence of self-reported clinically diagnosed urinary tract stones in women supplemented with CaD compared to placebo (HR = 1.17; 95% CI: 1.02 – 1.34)<br>• The rates of self-reported stones did not differ between various demographic, anthropomorphic, dietary, and other hypothesized risk factors<br>• Increased incidence (17%) of self-reported clinically diagnosed urinary tract stones in the vitamin D/calcium group relative to the placebo group<br>• Neither the total calcium intake nor the use of calcium supplements at baseline was associated with the risk of stones | • No control group as all subjects took calcium supplement with vitamin D; can't isolate effects of supplemental calcium<br>• Population of older women; findings may not be generalizable to the total population<br>• Small absolute difference in occurrence of urinary tract stones between groups: 0.35 vs 0.30%<br>• Findings from this study provide no new information relevant to determination of the UL, as the increased risk for kidney stones had been published (Jackson et al., 2006, as cited by IOM 2011) before the IOM set the present UL | Wallace et al., 2011 |
| ***Observational Studies and Meta-Analyses*** | | | | |
| Meta-analysis of prospective | Total calcium: 750,275 participants (9 cohorts), | • Total calcium intake associated with increased | • Studies included both the NIH-AARP cohort and the HPFS cohort | Aune et al., 2015 |

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| studies of dietary, supplemental, and total calcium | 33,127 cases<br>Dietary calcium: 800,879 participants (15 cohorts), 35,493 cases | prostate cancer risk per 400 mg calcium/day (RR = 1.02; 95% CI: 1.01 – 1.04) and when comparing the highest and lowest intake levels (RR = 1.10; 95% CI: 1.01 – 1.21) for prostate cancer risk<br>• Total dietary calcium associated with increased prostate cancer risk per 400 mg calcium/day (RR = 1.05; 95% CI: 1.02 – 1.09), and when comparing highest and lowest intake levels (RR = 1.18; 95% CI: 1.08 – 1.30) | • Exclusion of the NIH-AARP reduced the RR for total calcium and prostate cancer risk to 1.03 (95% CI: 1.02 – 1.05) and exclusion of the HPFS cohort reduced the RR to 1.02 (95% CI: 1.01 – 1.03)<br>• Published concurrently with Wilson et al., 2015<br>• Study by Wilson et al., 2015 suggests that correction for phosphorus intake may attenuate association between prostate cancer and total calcium found in this analysis | |
| Cross-sectional study of calcium supplementation and age-related macular degeneration (AMD) | 3191 male and female participants aged 40+ y, from NHANES; 248 (7.8%) diagnosed with AMD | • Comparing the highest and lowest quintiles of self-reported calcium supplementation, supplementation with greater than 800 mg/day calcium had higher odds of AMD diagnosis compared to those reporting no (≤ 100 mg/day) supplementation (OR = 1.85; 95% CI: 1.25 – 2.75); no association was observed when comparing the other quintiles of supplementation<br>• For older participants (> 67 y) the odds of AMD diagnosis were higher (OR = 2.63; 95% CI: 1.52 – 4.54) | • Supplement intake was self-reported<br>• Comorbidities (confounders) were not adjudicated, but self-reported<br>• No accounting for dietary or total calcium intake<br>• A clear dose-response was not established. Lack of dose response limits strength of findings | Kakigi et al., 2015 |
| Prospective study | 47,885 men from HPFS | • Comparing intake categories, | • Cancer diagnosis initially self- | Wilson et al., |

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| based on Health Professionals Follow-up Study (HPFS). Study collected data from 1986 – 2010, every 4 years | cohort aged 40-75 y; 5861 cases of prostate cancer including 789 lethal cancers (defined as fatal or metastatic) | calcium intake of ≥ 2000 mg/day (compared to 500 – 749 mg/day) associated with greater risk of total (RR = 1.24; 95% CI: 1.02 – 1.51), lethal (RR = 1.66; 95% CI: 1.09 – 2.53), and high-grade (RR = 1.88; 95% CI: 1.13 – 3.12) prostate cancer. All significance attenuated after adjustment for phosphorus intake | reported followed by confirmation by review of medical records and pathology reports<br>• No increased risk was found when correction for phosphorus intake was conducted | 2015 |
| Cross-sectional study of calcium supplementation and brain lesion volume | 227 male and female participants age > 60 y; 149 supplement users, and 78 non-users | • Users of calcium supplements (yes/no), after controlling for dietary calcium intake, had significantly greater lesion volumes than non-use of calcium supplements (p=0.0011)<br>• Among supplement users, the amount of supplement consumed was not associated with lesion volume (p=0.81), therefore no dose response<br>• For users with duration information (N = 106), there was no association between lesion volume and supplement use duration (p=0.35) | • No dose response established; daily supplement intake ranged from 37-1130 mg/day (mean 744.2 mg/day)<br>• Duration of supplementation only available for 106 or 149 participants<br>• Exposure assessment could not distinguish between calcium-only and calcium/vitamin D containing supplements<br>• Concurrent assessment of intake and risk<br>• Lack of dose response and duration response limit strength of findings | Payne et al., 2014 |

HR: Hazard ratio; For RCTs, RR refers to risk ratio, while for observational studies in this table, RR refers to relative risk

(Adapted from GRN 634)

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| **From:** | Salvatore DAngelo |
| **To:** | Morissette, Rachel |
| **Subject:** | RE: amendment to GRN 000712 |
| **Date:** | Thursday, January 11, 2018 1:49:50 PM |
| **Attachments:** | image013.png<br>image019.png |

Thank you.

**From:** Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
**Sent:** Thursday, January 11, 2018 1:42 PM
**To:** Salvatore DAngelo <SDAngelo@niacet.com>
**Subject:** RE: amendment to GRN 000712

Dear Mr. D'Angelo,
Thank you for your response. I confirm receipt of your request that we cease our evaluation of GRN 000712. A formal cease-to-evaluate letter will be forthcoming.

Best regards,

**Rachel Morissette, Ph.D.**
*Consumer Safety Officer*

**Center for Food Safety and Applied Nutrition**
**Office of Food Additive Safety**
**U.S. Food and Drug Administration**
rachel.morissette@fda.hhs.gov

**From:** Salvatore DAngelo [mailto:SDAngelo@niacet.com]
**Sent:** Thursday, January 11, 2018 1:38 PM
**To:** Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
**Cc:** Minsk, Alan G. <Alan.Minsk@AGG.com>
**Subject:** RE: amendment to GRN 000712

Dear Dr. Morissette,

Niacet is submitting a cease to evaluate request for the GRN 712 submission at this time. Please contact me if you require any additional information or action.

Sincerely,

Salvatore J. D'Angelo
Manager, Quality Assurance & Regulatory Affairs
**Niacet Corporation**
400 47th Street | Niagara Falls, NY 14304

P: 716-285-1474 | F: 716-285-1497
www.niacet.com

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**From:** Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
**Sent:** Wednesday, January 10, 2018 9:05 AM
**To:** Salvatore DAngelo <SDAngelo@niacet.com>
**Subject:** amendment to GRN 000712

Dear Mr. D'Angelo,

Thank you for sending your responses to our questions for GRN 000712. We reviewed the amendment and found that there are key points lacking in Niacet's response. The main issues are highlighted below:

- FDA requested that Niacet provide at least 3 non-consecutive batch analyses of all specifications listed in the Certificate of Analyses, including heavy metals. While Niacet provided additional Certificates of Analyses, none of them contained values for heavy metals as requested.
- Though FDA pointed out some errors in the original notice in Questions 1-4 that made the notice difficult to follow, the amendment still contains many similar typographical errors throughout, such as incorrect CFR references and inconsistent citation formatting that makes the information difficult to navigate.
- While more discussion and references to support Niacet's safety conclusion were provided as requested, the revised narrative is still disjointed and does not adequately tie in GRN 000712's safety conclusion with information contained in prior notices that Niacet is incorporating into this notice. Niacet makes the following blanket statement in the amendment "Also, please note that we concurs with the safety findings and conclusions from previous GRAS notices mentioned in GRN 712, in support of our independent GRAS conclusion for the intended uses of calcium acetate." However, Niacet does not explain what specific safety studies and findings from each notice they are referring to and how that relates to the safety of their ingredient's intended use.

We appreciate your effort in responding to our questions; however, as the responses did not adequately address our concerns, we will not be able to reach a No Questions opinion for this notice. As we stated previously, the review process is not designed to be iterative. As there are still questions that remain, we advise that you request that we cease-to-evaluate your notice. You have until close of business January 17, 2018 to make this request. Otherwise, we will issue a No Basis letter for this notice.

If you choose to withdraw this notice and resubmit a revised notice, we strongly encourage you to schedule a pre-submission meeting with our review team prior to resubmitting.

Sincerely,

**Rachel Morissette, Ph.D.**
*Consumer Safety Officer*

**Center for Food Safety and Applied Nutrition**
**Office of Food Additive Safety**
**U.S. Food and Drug Administration**
rachel.morissette@fda.hhs.gov