Niacet Corporation
400 47th Street,
Niagara Falls, NY
14304 USA

Niacet
A KERRY COMPANY

10 January, 2023

Paulette Gaynor, Ph.D.
Supervisory Consumer Safety Officer
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration
5001 Campus Drive
College Park, MD
20740 USA

Dr. Paulette Gaynor:

Re: 21 CFR § 170 Subpart E consisting of § 170.203 through § 170.285 (U.S. FDA, 2020), GRAS Notice for Use of Calcium Acetate as a Multipurpose Food Ingredient

In accordance with 21 CFR §170 Subpart E consisting of §§ 170.203 through 170.285, Niacet Corp., as the notifier, is submitting one hard copy and one electronic copy (on CD), of all data and information supporting the company's conclusion that Calcium Acetate, is GRAS on the basis of scientific procedures, for specified uses as a multipurpose food ingredient; these food uses of calcium acetate are therefore not subject to the premarket approval requirements of the *Federal Food, Drug and Cosmetic Act*.

I certify that the enclosed electronic files were scanned for viruses prior to submission and are thus certified as being virus-free using Symantec Endpoint Protection 12.1.5.

Should you have any questions or concerns regarding this GRAS notice, please do not hesitate to contact me at any point during the review process so that we may provide a response in a timely manner.

Yours sincerely

Salvatore J. D'Angelo
Consulting Manager- Quality Assurance & Regulatory Affairs
Niacet Corporation
Tel: 716-285-1474 | Fax: 716-285-1497
Email: sdangelo@niacet.com; sjdangelo400@yahoo.com

Secondary contact:
Ian J. Horner, PhD
Manager, Quality Assurance & Regulatory Affairs
Niacet Corporation
Email: ian.horner2@kerry.com
Tel: 716 285 1474 | Mobile: 716 804 4151

GRAS NOTICE FOR USE OF CALCIUM ACETATE AS A MULTIPURPOSE FOOD INGREDIENT

SUBMITTED TO:
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration
5001 Campus Drive
College Park, MD
20740 USA

SUBMITTED BY:
Salvatore J. D'Angelo
Consulting Manager- Quality Assurance & Regulatory Affairs
Niacet Corporation
400 47th Street
Niagara Falls, NY
14304 USA

DATE:
10 January 2023

GRAS Notice for Use of Calcium Acetate as a Multipurpose Food Ingredient

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GRAS Notice for Calcium Acetate for Use as a Multipurpose Food Ingredient

Part 1. § 170.225 Signed Statements and Certification

In accordance with 21 CFR § 170 Subpart E consisting of § 170.203 through § 170.285 (U.S. FDA, 2021), Niacet Corporation (Niacet) hereby informs the United States (U.S.) Food and Drug Administration (FDA) that the intended food uses of calcium acetate as a multipurpose food ingredient, as described in Section 1.3, are not subject to the premarket approval requirements of the *Federal Food, Drug, and Cosmetic Act* based on Niacet's view that calcium acetate is Generally Recognized as Safe (GRAS). In addition, as a responsible official of Niacet, the undersigned hereby certifies that all data and information presented in this Notice represent a complete and balanced submission that is representative of the generally available literature. Niacet considered all unfavorable, as well as favorable, information that is publicly available and/or known to Niacet and that is pertinent to the evaluation of the safety and GRAS status of calcium acetate.

Signed,

[redacted]

10 January 2023

Salvatore J. D'Angelo
Consulting Manager- Quality Assurance & Regulatory Affairs
Niacet Corporation
400 47th Street
Niagara Falls, NY
14304 USA
Tel: 716-285-1474 | Fax: 716-285-1497
Email: sdangelo@niacet.com

Date

1.1 Name and Address of Notifier

Niacet Corporation
400 47th Street
Niagara Falls, NY
14304 USA
Tel: 716-285-1474 | Fax: 716-285-1497
www.niacet.com

1.2 Common Name of Notified Substance

Calcium acetate; acetic acid, calcium salt

1.3 Conditions of Use

Calcium acetate is used in the following foods as an anti-microbial agent at levels not to exceed current good manufacturing practices (cGMP): baked goods; cheeses; confections and frostings; gelatins, puddings, and fillings; and jams and jellies. These food uses are fully substitutional to the current GRAS uses of calcium propionate under 21 CFR § 184.1221 (U.S. FDA, 2021).

Calcium acetate also is intended for use as a firming agent, flavor enhancer, flavoring agent or adjuvant, nutrient supplement, and stabilizer and thickener in food (except infant foods and formulas) at levels not to exceed cGMP. These food uses are fully substitutional to the current GRAS uses of calcium lactate under 21 CFR § 184.1207 (U.S. FDA, 2021), except as a leavening agent.[1]

1.4 Basis for GRAS

Pursuant to 21 CFR § 170.30(a),(b), Niacet has concluded that the intended uses of calcium acetate, as described herein, are GRAS on the basis of scientific procedures (U.S. FDA, 2021).

1.5 Availability of Information

The data and information that serve as the basis for this GRAS Notice will be sent to the U.S. FDA upon request, or will be available for review and copying at reasonable times at the offices of:

Niacet Corporation
400 47th Street
Niagara Falls, NY
14304 USA
Tel: 716-285-1474 | Fax: 716-285-1497

Should the U.S. FDA have any questions or additional information requests regarding this Notice, Niacet will supply these data and information upon request.

1.6 Freedom of Information Act, 5 U.S.C. 552

It is Niacet's view that all data and information presented in Parts 2 through 7 of this Notice do not contain any trade secret, commercial, or financial information that is privileged or confidential, and therefore, all data and information presented herein are not exempted from the *Freedom of Information Act*, 5 U.S.C. 552.

[1] Calcium lactate is not intended for use as a leaving agent, as it is not suitable for this purpose.

Part 2. § 170.230 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1 Common or Usual Name

Calcium acetate; acetic acid, calcium salt

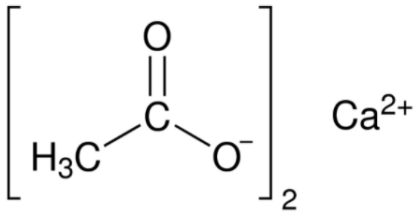
2.2 Chemical Name

Calcium acetate; acetic acid, calcium salt

2.3 Chemical Abstract Service (CAS) Number

62-54-4

2.4 Chemical and Physical Characteristics



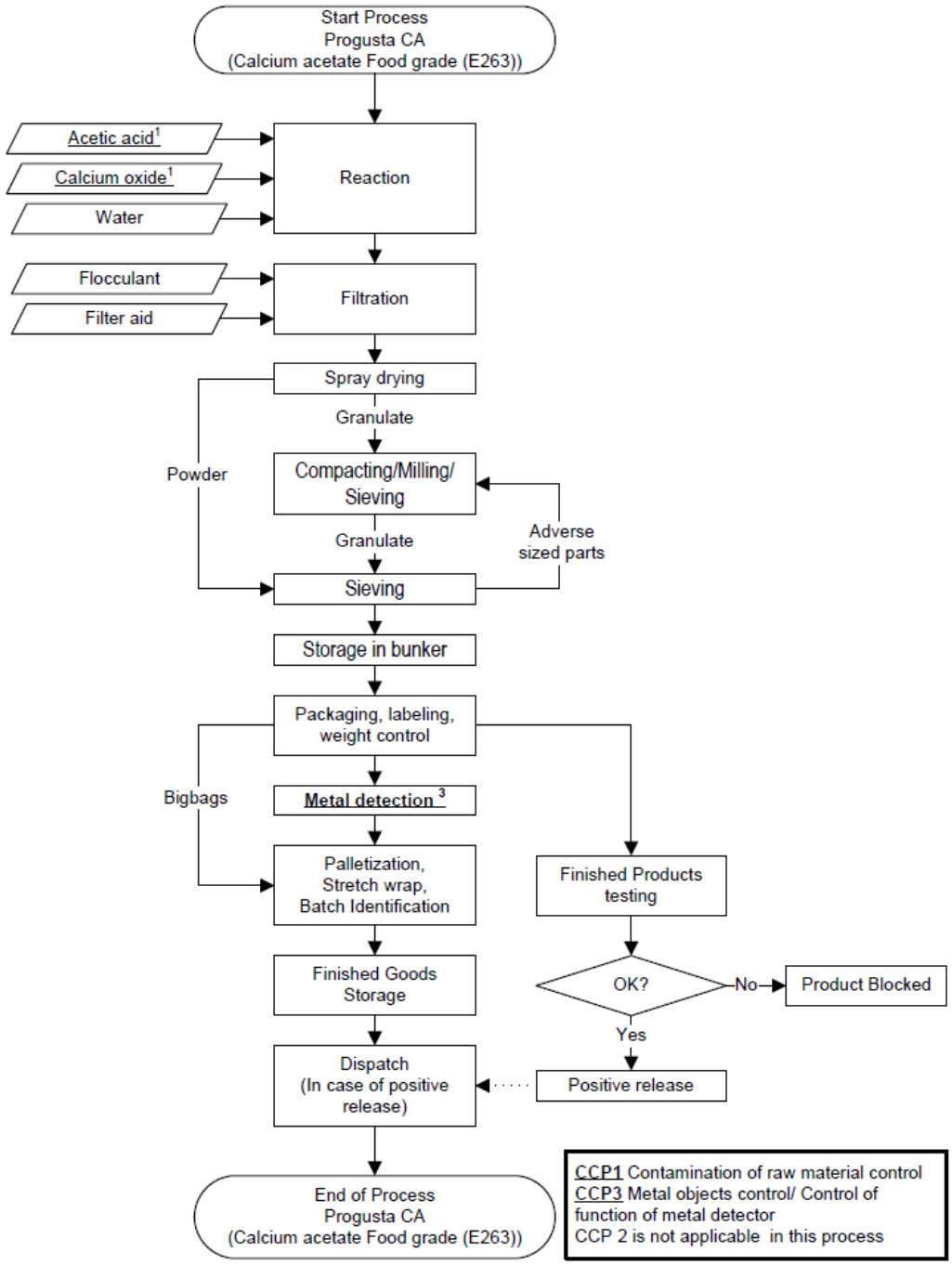
Synonym:	Acetate of lime, brown acetate, brown acetate of lime, calcium diacetate
Molecular Formula:	$C_4H_6CaO_4$
Molecular Weight:	158.17 g/mol
Appearance:	White powder
Solubility:	Freely soluble in water

2.5 Method of Manufacture

Niacet's calcium acetate is manufactured in accordance with cGMP and the principles of Hazard Analysis and Risk-Based Preventive Controls (HARPC) in a production facility certified under Food Safety System Certification (FSSC) 22000. The manufacturing process uses food-grade materials.

Calcium acetate is produced from the simple reaction of acetic acid and calcium hydroxide, as follows: $C_2H_4O_2 + Ca(OH)_2 \rightarrow C_4H_6CaO_4 + H_2O$. The manufacturing process for calcium acetate is illustrated in Figure 2.5-1. All raw materials and processing aids used in the manufacturing process are food-grade or equivalent (*e.g.*, *Food Chemicals Codex* [FCC]) and are used in accordance with the applicable federal regulations pertaining to their use in food production or have been concluded to be GRAS for their respective food uses. Any and all food contact articles used are permitted for use by federal regulation or have been the subject of an effective food contact notification.

Figure 2.5-1 Manufacturing Process for Calcium Acetate



CCP = Critical Control Point.

2.6 Product Specifications

The product specifications for calcium acetate are presented in Table 2.6-1 and include physical and chemical specifications. All methods of analysis are internationally recognized (*e.g.,* Association of Official Analytical Chemists) or have been developed internally by Niacet. Calcium acetate is produced by the reaction of acetic acid and calcium hydroxide. The total calcium content of the ingredient is 25.3% (based on theoretical calculations). Niacet's specification is compliant with the specifications listed for calcium acetate in the *FCC* (11th Edition).

Table 2.6-1 Product Specifications for Calcium Acetate

Parameter	Niacet's Specification	Method[b]	*Food Chemicals Codex* Specification
Appearance	White agglomerate	Visual	Fine, white, bulky powder
Proximate Parameters			
Water	Not more than 6.0%	Karl Fischer Titration	Not more than 7.0%
pH (10% solution)	6.0 to 9.0	Potentiometric	Not specified
Purity			
Assay value	99.0 to 100.5% of calcium acetate (anhydrous basis)	Complexometric/ Potentiometric Titration	99.0 to 100.5% of calcium acetate (anhydrous basis)
Heavy Metals			
Lead	Not more than 2 ppm	Atomic Absorption Spectroscopy	Not specified
Mercury	Not more than 1 ppm	Mass Spectroscopy	Not specified
Arsenic	Not more than 3 ppm	Complexometric/Visual Inspection	Not specified
Cadmium	Not applicable	Complexometric/Visual Inspection	Not specified
Chemical Parameters			
Chloride	Not more than 500 ppm	Potentiometric Titration	Not more than 500 ppm
Fluoride	Not more than 50 ppm	Ion Selective Electrode	Not more than 50 ppm
Sulfate	Not more than 0.1%	Turbidity/Visual Inspection	Not more than 0.1%
Iron	Not more than 10 ppm	Complexometric/Visual Inspection	–
Other Parameters[a]			
Insoluble in water	Not more than 0.1%	Gravimetric	Not specified
Oxidizable impurities as formic acid	Not more than 0.1%	Permanganate Time Test/ Visual Inspection	Not specified

ppm = parts per million.
[a] Given that acetate is produced *via* a simple chemical reaction between food-grade calcium hydroxide and food-grade acetic acid, microbial contamination is not expected; therefore, specifications for microbial contamination were not established.
[b] Specification methods are as per the *Food Chemicals Codex* (11th Edition) for calcium acetate.

2.7 Product Analysis

Three non-consecutive lots of the calcium acetate were analyzed to verify that the manufacturing process results in an ingredient that consistently meets specifications. Niacet's calcium acetate meets the specifications established in the *FCC* (11th Edition) and the company's internal specifications. A summary of the chemical product analysis for 3 batches of calcium acetate is presented in Table 2.7-1.

Table 2.7-1 Batch Analyses of 3 Non-consecutive Lots of Calcium Acetate

Parameter	Niacet's Specification	Manufacturing Batch No.		
		2000066579	**2000068020**	**2000074491**
Appearance	White agglomerate	Conforms	Conforms	Conforms
Proximate Parameters				
Water	Not more than 6.0%	5.4%	5.1%	5.2%
pH (10% solution)	6.0 to 9.0	7.3	7.2	7.2
Purity				
Assay value	99.0 to 100.5% of calcium acetate (anhydrous basis)	100.1%	99.7%	100.0%
Heavy Metals				
Lead	Not more than 2 ppm	<2 ppm	<2 ppm	<2 ppm
Mercury	Not more than 1 ppm	<0.1 ppm	<0.1 ppm	<0.1 ppm
Arsenic	Not more than 3 ppm	<1 ppm	<1 ppm	<1 ppm
Cadmium	Not applicable	<0.1 ppm	<0.1 ppm	<0.1 ppm
Chemical Parameters				
Chloride	Not more than 500 ppm	222 ppm	250 ppm	283 ppm
Fluoride	Not more than 50 ppm	7 ppm	<5 ppm	<50 ppm
Sulfate	Not more than 0.1%	<0.1%	<0.1%	<0.1%
Iron	Not more than 10 ppm	<2.0 ppm	<2.0 ppm	<2.0 ppm
Other Parameters[a]				
Insoluble in water	Not more than 0.1%	<0.1%	<0.1%	<0.1%
Oxidizable impurities as formic acid	Not more than 0.1%	<0.1%	<0.1%	<0.1%

ppm = parts per million.

[a] Given that calcium acetate is produced *via* a simple chemical reaction between food-grade calcium hydroxide and food-grade acetic acid, microbial contamination is not expected; therefore, specifications for microbial contamination were not established.

2.8 Antimicrobial Functionality

Calcium acetate is intended for use as an alternative to calcium propionate as an antimicrobial at levels not to exceed cGMP in the following foods: baked goods; cheeses; confections and frostings; gelatins, puddings, and fillings; and jams and jellies. These food uses are fully substitutional to the current GRAS uses of calcium propionate as an antimicrobial under 21 CFR § 184.1221 (U.S. FDA, 2021). Organic acids have a long history of use as preservatives for preventing food spoilage and extending the shelf-life of readily perishable foods (*e.g.*, use of acetic acid as a pickling agent). Calcium acetate is listed under the *Codex Alimentarius* for use as an acidity regulator, preservative, and stabilizer in a large variety of foods across multiple food categories at use levels limited to cGMP (FAO/WHO, 2019). Organic acids and their salts display biocidal activity by disruption of cell wall and cytoplasmic membranes of microorganisms, as well as through disruption of intracellular metabolic processes and cellular transport mechanisms; the specific mechanisms by which organic acids exert these effects are not well characterized (Ricke, 2003). It is generally recognized that as weak acids, compounds like acetic acid are neutral at pH values below 5 and therefore are transported across the bacteria cell membrane where dissociation of the acid results in pH imbalances that disrupt cellular function; however, external disruption of metal transport processes also can have bactericidal anti-fungal properties and may be an important mechanism for acetate salts such as calcium acetate. Calcium acetate is an effective antifungal agent and has been reported to inhibit the growth of several spoilage fungi (Kaiser *et al.*, 2011). The antifungal property of calcium acetate is conducive to uses in bread making to prevent mold growth. Typical recommended use levels of calcium acetate for antimicrobial food uses on products such as bread and cut produce range between 0.2 to 0.5%[2].

Niacet has conducted investigations comparing the antimicrobial effects of calcium acetate with calcium propionate and has demonstrated inhibition of mold growth without negatively impacting bread productivity (see Appendix A). Effective antimicrobial activity against various spoilage organisms and microbial pathogens also have been demonstrated experimentally with highly comparable antimicrobial activity observed between calcium acetate and calcium propionate (see Appendix A). These studies demonstrate that in the U.S., calcium acetate would be suitable for use in foods as a substitute for calcium propionate.

[2] Niacet, Progusta Calcium Acetate, https://www.niacet.com/product/calcium-acetate-food/.

Part 3. § 170.235 Dietary Exposure

Since food uses of calcium acetate are fully substitutional to calcium propionate and calcium lactate, except as a leavening agent, the introduction of calcium acetate to the U.S. food supply as an alternative to the regulated uses of calcium propionate under 21 CFR § 184.1221 and calcium lactate under 21 CFR § 184.1207 would not result in changes to the dietary intake of calcium in the food supply (U.S. FDA, 2021). Similarly, dietary intakes of acetate from food uses of calcium acetate in the diet are toxicologically insignificant relative to current consumption patterns for acetic acid as food from permitted food uses, which are GRAS (*e.g.*, 21 CFR § 184.1005 – U.S. FDA, 2021). Furthermore, acetate (and acetic acid) is synthesized by the body and is present in a variety of foods (*e.g.*, plants, animals, processed foods), making the intakes of acetic acid in the general population notably difficult to assess (EFSA, 2009). Despite this, estimation of dietary intakes of calcium acetate (and equivalent calcium and acetate) using statistical modeling approaches with survey data from the National Health and Nutrition Examination Surveys (NHANES) has been conducted and summarized below.

3.1 Methodology

As discussed in Section 1.3 above, calcium acetate will be used as an alternative to the current regulated food uses of calcium propionate under 21 CFR § 184.1221 and calcium lactate under 21 CFR § 184.1207 (U.S. FDA, 2021). In addition to the proposed uses, calcium acetate is permitted for use as a direct food substance in the U.S. under specific conditions of use which must also be considered in the assessment (U.S. FDA, 2021). Furthermore, since calcium is a nutrient that is naturally present in the diet, added to a variety of foods in accordance with approved food additive regulations, and added to dietary supplements for fortification purposes, calcium intakes from all dietary sources were also estimated. However, as noted above, no increase in the overall exposure to calcium in the diet is anticipated from the fully substitutional proposed uses of calcium acetate; therefore, estimates for current intake of calcium from the background diet is provided for comparison and transparency only. Three intake assessments were conducted:

1. Estimated current daily intake of calcium from the background diet;

2. Estimated daily intake of calcium acetate from the permitted and proposed uses based on calcium acetate as the sole source of calcium in the diet; and

3. Refined estimated daily intakes of calcium acetate from the permitted and proposed uses (*i.e.,* calcium acetate as the sole source of calcium in the diet, limited by cGMP).

Estimates for the intake of calcium acetate were based on the permitted and proposed uses and use levels for calcium acetate in conjunction with food consumption data included in the U.S. National Center for Health Statistics' NHANES 2017-2018 (CDC, 2022a,b; USDA, 2022a,b). A detailed description of the survey and methodology employed in the intake assessment of calcium acetate is provided in Appendix B, while an abbreviated summary along with the pertinent results is presented herein.

The NHANES data are collected and released in 2-year cycles with the most recent cycle containing data collected in 2017-2018. Information on food consumption was collected from individuals *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2). Sample weights were incorporated with NHANES data to compensate for the potential under-representation of intakes from specific populations and allow the data to be considered nationally representative (CDC, 2022a,b; USDA, 2022a,b). The NHANES data were employed to assess the mean and 90th percentile intake for the following population groups in accordance with the age groupings established by the Institutes of Medicine (IOM) and U.S. FDA for dietary reference intake (DRI) values of calcium (IOM, 2011; U.S. FDA, 2021):

- Infants, 0 to 5 months (both gender groups combined);
- Infants, 6 to 11 months (both gender groups combined);
- Children, 1 to 3 years (both gender groups combined);
- Children, 4 to 8 years (both gender groups combined);
- Females or males, 9 to 13 years (gender groups assessed separately);
- Females or males, 14 to 18 years (gender groups assessed separately);
- Females or males, 19 to 30 years (gender groups assessed separately);
- Females or males, 31 to 50 years (gender groups assessed separately);
- Females or males, 51 to 70 years (gender groups assessed separately);
- Females or males, 71 years and older (gender groups assessed separately); and
- Total population (ages 1 year and older, and both gender groups combined).

For the 3 intake assessments, consumption data from individual dietary records, detailing food items ingested by each survey participant, were collated by computer and used to generate estimates for the intake of calcium acetate by the U.S. population.[3] Estimates for the daily intake of calcium acetate represent projected 2-day averages for each individual from Day 1 and Day 2 of NHANES 2017-2018 (*i.e.*, a value was established for each person). From these average amounts, a distribution was established from which the mean and percentile intake estimates for the cohort of interest were determined, which incorporated survey weights in order to provide representative intakes for the entire U.S. population. "Consumer-only" intake refers to the estimated intake of calcium acetate by only those individuals who reported consuming food products of interest on either Day 1 or Day 2 of the survey. The consumer-only estimates are more relevant to risk assessments as they represent exposures in the target population; consequently, only consumer-only intake results are presented herein.

3.2 Food Usage Data

3.2.1 Background Diet

All food codes and supplement codes identified as containing calcium based on the United States Department of Agriculture's Food and Nutrient Database for Dietary Studies (FNDDS) or Dietary Supplement Ingredient Information (DSII) dataset from the NHANES Dietary Supplement Database (NHANES-DSD) (*i.e.*, associated nutrient value >0 µg) were selected from the NHANES 2017-2018 dataset (CDC, 2022c; USDA ARS, 2022). Associated calcium values were applied to food codes and supplements codes identified as containing calcium. Results for this assessment are presented in Section 3.3.1.

[3] Statistical analysis and data management were conducted in DaDiet Software (Dazult Ltd., 2018). DaDiet Software is a web-based software tool that allows accurate estimate of exposure to nutrients and to substances added to foods, including contaminants, food additives and novel ingredients. The main input components are concentration (use level) data and food consumption data. Data sets are combined in the software to provide accurate and efficient exposure assessments.

3.2.2 Proposed Food Uses

Calcium acetate is affirmed as GRAS for use as a direct food substance at levels not to exceed cGMP, in accordance with 21 CFR § 184.1185 (U.S. FDA, 2021). Hence, the following use levels have been reported for calcium acetate:

- 0.2% in baked goods;
- 0.02% in cheese;
- 0.2% in gelatins, puddings, and fillings;
- 0.15% in sweet sauces, toppings and syrups; and
- 0.0001% for "all other food categories."

In addition to these permitted uses, calcium acetate is proposed for use as a substitute for other sources of calcium such as calcium propionate and calcium lactate. As such, calcium acetate is intended for use under the same conditions as those affirmed to be GRAS in 21 CFR § 184.1221 (calcium propionate) and 21 CFR § 184.1207 (calcium lactate) (U.S. FDA, 2021). However, the aforementioned includes use in all food with no limitation other than cGMP; no levels of use have been specified. On this basis, 2 conservative models were used to determine the intake of calcium acetate, described below in Section 3.2.2.1 and 3.2.2.2.

3.2.2.1 Total Calcium Substitution Model

In addition to the permitted food uses and use levels for calcium acetate specified above, the background diet assessment of calcium was incorporated such that food codes identified as containing calcium based on the FNDDS (*i.e.*, associated nutrient value >0 µg) were selected from the NHANES 2017-2018 dataset and use levels were replaced with equivalent use levels of calcium acetate (assuming calcium acetate is the sole source of calcium from calcium-containing substances). Food codes for fluid milks and food codes indicated as "raw" were excluded from this model, as it is reasonably expected that the calcium value does not originate from the addition of direct food substances.

3.2.2.2 cGMP-Refined Substitution Model

The total calcium substitution model crudely assumes that nearly all calcium in the background diet originates from calcium acetate. However, this assumption yields use levels of up to 6%; in reality, it is expected that the maximum levels to achieve the various technical functions would be lower than the levels of background calcium, much of which likely consists of calcium naturally in the diet as opposed to calcium-containing substances added to food. Furthermore, the use of calcium acetate is self-limiting, as use in excess will produce adverse organoleptic effects on foods. On this basis, the total calcium substitution model was refined by applying the highest cGMP maximum use level observed among the existing calcium acetate cGMP uses denoted in 21 CFR § 184.1185 (*i.e.*, 0.2% in "baked goods" and "gelatins, puddings, and fillings") to all food codes that would otherwise exceed 0.2% as the maximum use level.

3.3 Estimated Dietary Consumption of Calcium Acetate

3.3.1 Estimated Daily Intake of Calcium from Background Diet in the U.S.

Table 3.3.1-1 summarizes the estimated total intake of calcium from the background diet (foods and dietary supplements) in the U.S. population group. All individuals surveyed in the NHANES were consumers of calcium; thus, the resulting *per capita* and the consumer-only intakes are identical.

Among the total population (≥1 year of age), mean and 90th percentile intakes of calcium from the background diet were determined to be 1,046 and 1,711 mg/person/day, respectively. Of the individual population groups, male adults 31 to 50 years of age were determined to have the greatest mean and 90th percentile intakes of calcium from the background diet, at 1,181 and 1,980 mg/person/day, respectively. Infants 0 to 5 months of age had the lowest mean and 90th percentile intake of calcium, at 335 and 784 mg/person/day, respectively (Table 3.3.1-1).

Table 3.3.1-1 Summary of the Estimated Daily Intake of Calcium from the Background Diet (Food and Dietary Supplements) in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	*Per Capita* Intake (mg/day)		Consumer-only Intake (mg/day)				Tolerable Upper Intake Level[a] (mg/day)
	Mean	90th Percentile	% Consumers	n	Mean	90th Percentile	
Infants							
0 to 5 months	335	784	100	162	335	784	1,000
6 to 11 months	655	1,143	100	139	655	1,143	1,500
Children							
1 to 3 years	939	1,417	100	415	939	1,417	2,500
4 to 8 years	963	1,494	100	530	963	1,494	2,500
Females							
9 to 13 years	968	1,574	100	307	968	1,574	3,000
14 to 18 years	808	1,436	100	283	808	1,436	3,000
19 to 30 years	956	1,581	100	390	956	1,581	2,500
31 to 50 years	985	1,692	100	689	985	1,692	2,500
51 to 70 years	1,033	1,644	100	812	1,033	1,644	2,000
≥71 years	1,137	1,921	100	324	1,137	1,921	2,000
Males							
9 to 13 years	1,014	1,592	100	282	1,014	1,592	3,000
14 to 18 years	1,063	1,741	100	281	1,063	1,741	3,000
19 to 30 years	1,118	1,882	100	357	1,118	1,882	2,500
31 to 50 years	1,181	1,980	100	573	1,181	1,980	2,500
51 to 70 years	1,114	1,795	100	769	1,114	1,795	2,000
≥71 years	1,089	1,766	100	326	1,089	1,766	2,000
Total Population							
All ages (≥1 year)	1,046	1,711	100	6,338	1,046	1,711	na

n = sample size; na = not available; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
[a] Calcium tolerable upper intake level reported in IOM (2011).

3.3.2 Estimated Daily Intake of Calcium Acetate from Proposed Uses in the U.S.

Tables 3.3.2.1-1 and 3.3.2.2-1 summarize the estimated daily intake of calcium acetate, as well as the corresponding theoretical intake calcium and acetate intake, from the proposed uses in the U.S. population groups. The percentage of consumers is high (≥99.8%), rendering almost identical *per capita* and consumer-only intakes with the exception of infants aged 0 to 5 months which had a slightly lower percentage of consumers (75.1%). As consumer-only estimates represent exposures in the target population and are more relevant to risk assessment, only these results are discussed in detail herein.

3.3.2.1 Total Calcium Substitution Model

Among the total population (≥1 year of age), the mean and 90th percentile consumer-only intakes of calcium acetate from permitted and proposed uses were determined to be 2,538 and 4,255 mg/person/day, respectively. Of the individual population groups, male adults 19 to 30 years of age were determined to have the greatest mean intake of calcium acetate, at 3,233 mg/person/day, while male adults 31 to 50 years of age were determined to have the greatest 90th percentile intake of calcium acetate, at 5,954 mg/person/day. Infants 0 to 5 months of age had the lowest mean intake of calcium acetate, at 1,753 mg/person/day, while female adults 71 years of age and older had the lowest 90th percentile intake of calcium acetate, at 3,163 mg/person/day (Table 3.3.2.1-1).

Table 3.3.2.1-1 Summary of the Estimated Daily Intake of Calcium Acetate, Calcium, and Acetate from Proposed Food uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	n	Consumer-only Intake (mg/day)					
		Calcium Acetate		Calcium[a]		Acetate[a]	
		Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Infants							
0 to 5 months	125	1,753	3,213	444	813	1,310	2,400
6 to 11 months	138	1,968	3,849	498	974	1,470	2,875
Children							
1 to 3 years	415	1,891	3,572	478	904	1,412	2,669
4 to 8 years	530	2,283	3,651	578	924	1,705	2,727
Females							
9 to 13 years	307	2,401	4,069	608	1,029	1,794	3,039
14 to 18 years	283	2,236	3,764	566	952	1,670	2,812
19 to 30 years	390	2,548	4,341	645	1,098	1,903	3,243
31 to 50 years	689	2,429	4,003	614	1,013	1,814	2,990
51 to 70 years	812	2,136	3,435	540	869	1,595	2,566
≥71 years	324	1,916	3,163	485	800	1,431	2,363
Males							
9 to 13 years	282	2,573	4,272	651	1,081	1,922	3,191
14 to 18 years	281	2,747	4,610	695	1,166	2,052	3,444
19 to 30 years	357	3,233	5,954	818	1,506	2,415	4,447
31 to 50 years	573	3,211	5,006	812	1,267	2,399	3,740
51 to 70 years	769	2,703	4,393	684	1,111	2,019	3,282
≥71 years	326	2,269	3,613	574	914	1,695	2,699

Table 3.3.2.1-1 Summary of the Estimated Daily Intake of Calcium Acetate, Calcium, and Acetate from Proposed Food uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	n	Consumer-only Intake (mg/day)					
		Calcium Acetate		Calcium[a]		Acetate[a]	
		Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Total Population							
All ages (≥1 year)	6,338	2,538	4,255	642	1,076	1,896	3,178

n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
[a] Results were calculated based on the molar weight of calcium acetate (158.16 g/mol) and calcium (40.08 g/mol), yielding a theoretical calcium content of approximately 25.3%.

3.3.2.2 cGMP-Refined Substitution Model

Among the total population (≥1 year of age), the mean and 90th percentile consumer-only intakes of calcium acetate from permitted and proposed uses were determined to be 1,527 and 2,390 mg/person/day, respectively. Of the individual population groups, male adults 31 to 50 years of age were determined to have the greatest mean and 90th percentile intakes of calcium acetate, at 1,889 and 2,935 mg/person/day, respectively. Children 1 to 3 years of age had the lowest mean and 90th percentile intakes of calcium acetate, at 987 and 1,672 mg/person/day, respectively (Table 3.3.2.2-1).

Table 3.3.2.2-1 Summary of the Estimated Daily Intake of Calcium Acetate, Calcium, and Acetate from Proposed Food uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	n	Consumer-only Intake (mg/day)					
		Calcium Acetate		Calcium[a]		Acetate[a]	
		Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Infants							
0 to 5 months	125	1,429	2,432	362	615	1,068	1,817
6 to 11 months	138	1,274	2,297	322	581	951	1,716
Children							
1 to 3 years	415	987	1,672	250	423	737	1,249
4 to 8 years	530	1,199	1,817	303	460	896	1,358
Females							
9 to 13 years	307	1,332	2,011	337	509	995	1,502
14 to 18 years	283	1,319	2,087	334	528	985	1,559
19 to 30 years	390	1,505	2,243	381	567	1,124	1,675
31 to 50 years	689	1,524	2,449	386	620	1,138	1,829
51 to 70 years	812	1,410	2,133	357	540	1,053	1,594
≥71 years	324	1,249	1,949	316	493	933	1,456
Males							
9 to 13 years	282	1,320	2,035	334	515	986	1,520
14 to 18 years	281	1,521	2,344	385	593	1,136	1,751
19 to 30 years	357	1,844	2,880	467	729	1,378	2,152
31 to 50 years	573	1,889	2,935	478	743	1,411	2,193
51 to 70 years	769	1,735	2,604	439	659	1,296	1,945
≥71 years	326	1,490	2,170	377	549	1,113	1,621

Table 3.3.2.2-1 Summary of the Estimated Daily Intake of Calcium Acetate, Calcium, and Acetate from Proposed Food uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	n	Consumer-only Intake (mg/day)					
		Calcium Acetate		Calcium[a]		Acetate[a]	
		Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Total Population							
All ages (≥1 year)	6,338	1,527	2,390	386	605	1,141	1,786

n = sample size; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
[a] Results were calculated based on the molar weight of calcium acetate (158.16 g/mol) and calcium (40.08 g/mol), yielding a theoretical calcium content of approximately 25.3%.

3.3.3 Summary and Conclusions

Consumption data and information pertaining to the individual proposed food uses of calcium acetate were used to estimate the consumer-only intakes of calcium acetate for specific demographic groups and for the total U.S. population. There were a number of assumptions included in the assessments which render exposure estimates that may be considered suitably conservative. For example, in both models, the basis of the approach is substitution of all calcium content with equivalent levels of calcium acetate when in reality it is likely that a significant proportion of the calcium content consists of calcium naturally in the diet as opposed to calcium-containing ingredient added to food. Furthermore, it has been assumed in both exposure assessments that all food products within a food category contain calcium acetate at the maximum specified level of use. In reality, the levels added to specific foods will vary depending on the nature of the food product and it is unlikely that calcium acetate will have 100% market penetration in all identified food categories. According to an evaluation by the Select Committee on GRAS Substances (SCOGS) of the Life Science Research Organization (LSRO) in 1975, the practices of manufacturers is evidently quite variable with regard to use of calcium salts in foods (FASEB, 1975). For calcium acetate specifically, the SCOGS Panel reported that calcium acetate is not added to “baking mixes” or “gelatins, puddings, and fillings” by most manufacturers, despite these having the highest indicated cGMP maximum use levels among the GRAS affirmed uses. Therefore, based on the market-based use levels reported during the SCOGS evaluation, the exposure estimates resulting from the cGMP-refined model should be considered suitably conservative.

In summary, on a consumer-only basis, the resulting mean and 90th percentile intakes of calcium acetate by the total U.S. population (ages 1 year and older), based on the cGMP-refined model, were estimated to be 1,527 and 2,390 mg/person/day, respectively. Among the individual population groups, the highest mean and 90th percentile consumer-only intakes of calcium acetate were determined to be 1,889 and 2,935 mg/person/day, respectively, as identified among male adults 31 to 50 years of age. Children 1 to 3 years of age had the lowest mean and 90th percentile intakes of calcium acetate, at 987 and 1,672 mg/person/day, respectively. Since food the proposed food uses are intended to be fully substitutional, dietary intake of calcium within the U.S. population is not expected to change. Despite this, in all population groups, 90th percentile consumer-only estimated daily intakes of calcium from current sources and proposed food uses are below tolerable upper intakes values established by the IOM for calcium.

Part 4. § 170.245 Self-limiting Levels of Use

Food uses of calcium acetate are self-limiting and will produce adverse organoleptic effects on foods when used in excess. The concentration threshold for these self-limiting levels is not known. Other self-limiting properties include adverse technical effects on dough proof times when incorporated into baked goods at concentrations >2%.

Part 5. § 170.250 Experience Based On Common Use in Food Before 1958

Not applicable.

Part 6. § 170.250 Information to Establish the Safety of Calcium Acetate

6.1 Introduction

The safety of calcium acetate as a multipurpose food ingredient for various specified food uses and use levels (*i.e.*, as a firming agent, pH control agent, processing aid, sequestrant, stabilizer and thickener, texturizing agent, flavor enhancer) has been previously evaluated by the U.S. FDA and was affirmed as GRAS under 21 CFR § 184.1185 and 21 CFR § 182.6197 (U.S. FDA, 2021). In addition, the safety of calcium acetate has been evaluated by several scientific bodies and regulatory agencies, including the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) (JECFA, 2006; EFSA, 2009). Calcium acetate is freely soluble in water and readily dissociates into calcium ion and acetate; calcium is an essential nutrient, while acetate is a normal constituent of the body with important biochemical functions (*e.g.,* its role in the Krebs cycle and the glycolytic pathway).

The safety of calcium and calcium salts has been assessed extensively; UL values for calcium have been derived by the IOM and EFSA (EFSA, 2009; IOM, 2011). In addition, 11 calcium-containing substances or compounds have been concluded to be GRAS for various food uses and notified to the U.S. FDA without objection.[4] One of the most recent and comprehensive GRAS safety evaluations of dietary calcium was reported in GRN 634 by PepsiCo., Inc. to support the use of calcium chloride in the manufacturing of potato snacks to reduce the formation of acrylamide (PepsiCo, Inc., 2016). PepsiCo, Inc. notified the U.S. FDA of its GRAS conclusion, and the U.S. FDA did not object (date of closure was 08 August 2016). A comprehensive search of the public domain was conducted to identify new data and information relevant to the safety of calcium acetate using the following literature search strategy:

- **Update of the literature search conducted for <u>calcium</u> in GRN 634[5]:** GRN 634 included studies relevant to the safety of calcium that were identified *via* literature searches on PubMed in October 2013 and updated in June 2014, October 2015, and February 2016. A literature search strategy similar to the strategy used by PepsiCo, Inc. was used to identify new studies published since 2016.[6]

- **Literature search on <u>calcium acetate</u>**: A literature search was conducted on PubMed,[7] without date restriction, to identify studies relevant to the safety of **<u>calcium acetate</u>**.

[4] Bonlac Foods Limited, 1998 – GRN 11 (Calcium casein peptone-calcium phosphate), U.S. FDA, 1999; Marigot Ltd./Celtic Sea Minerals, 1999 – GRN 28 (Seaweed-derived calcium), U.S. FDA, 2000; Purac Biochem, 2003 – GRN 136 (Calcium gluconate), U.S. FDA, 2004a; Solutia Inc., 2004 – GRN 157 (Calcium propionate [alternative method of manufacture]), U.S. FDA, 2004b; Del Monte Foods, 2010 – GRN 363 (Calcium disodium ethylenediaminetetraacetic acid [EDTA] and disodium EDTA), U.S. FDA, 2011; Innophos, Inc., 2012 – GRN 420 (Calcium acid pyrophosphate), U.S. FDA, 2012; The Ester C Company, 2012 – GRN 451 (Calcium ascorbate with added threonate), U.S. FDA, 2013; Exponent Inc., 2015 – GRN 573 (Calcium disodium ethylenediaminetetraacetate [EDTA]), U.S. FDA, 2015; PepsiCo, Inc., 2016 – GRN 634 (Calcium chloride), U.S. FDA, 2016; PepsiCo, Inc., 2017 – GRN 747 (Calcium lactate), U.S. FDA, 2018a; Wonderful Citrus, LLC, 2018 – GRN 786 (Calcium propionate), U.S. FDA, 2018b.

[5] Niacet notes that a subsequent GRAS Notice for calcium lactate (GRN 747) was filed by PepsiCo. in 2018 and included updated comprehensive literature searches; however, for conservative reasons, Niacet's literature review was conducted from the date of the original safety evaluation in 2016.

[6] The search was conducted on 17 November, 2022.

[7] The search was conducted on 17 November, 2022.

- **Literature search for meta-analyses and/or systematic reviews on calcium**: Given that there are many human studies on the health benefits of calcium, a literature search for meta-analyses or systematic reviews of these human studies was conducted. Meta-analyses or systematic reviews published since 2016 were searched for on PubMed[8].

- **Literature search for meta-analyses and/or systematic reviews on acetate**: A literature search was conducted on PubMed[9], without date restriction, to identify meta-analyses or systematic reviews of human studies on acetate (or "acetic acid" or "vinegar").

A summary of the strategies and results of the 4 literature searches is provided in Appendix C. Based on the literature searches, 2 human study on calcium, 6 studies (5 in animals and 1 in humans) related to the safety of calcium acetate, and 33 systematic reviews and meta-analyses were identified. This information is summarized below and its relevance to safety is discussed where applicable.

6.2 Safety Information on Calcium Acetate

6.2.1 Metabolic Fate of Calcium Acetate

Calcium acetate is highly soluble and readily dissociates into its component ions, calcium and acetate, under aqueous conditions and in the gut. Dietary calcium is absorbed in the small intestine by active transport and also by passive diffusion. Based on information reported by Sheikh *et al*. (1987), approximately 32% of the calcium in calcium acetate will be absorbed in humans. Absorbed calcium is distributed throughout the body and bioaccumulation occurs in the skeleton and teeth. Excess calcium is excreted in urine, feces, and sweat. The acetate ion is expected to be readily absorbed and is rapidly converted to bicarbonate (Richards *et al*., 1982).

Studies conducted in mice (Ueda and Taira, 2013), rats (Cai *et al*., 2004), and humans (Sheikh *et al*., 1987) evaluating the pharmacokinetics of oral calcium acetate identified during the literature search are summarized below.

6.2.1.1 Mice

In 7-week-old male ddY mice (weighing 20 to 30 g), oral administration of 150 mg/kg body weight of calcium acetate resulted in a maximum plasma concentration (C_{max}) of 103.6 µg/mL, a time to reach the maximum plasma concentration (T_{max}) of 45 minutes, an area under the curve (AUC) of 1,137.4 ± 225.1 µg/mL·minute. The absolute bioavailability of calcium from calcium acetate (8.6 ± 1.7%) was similar to calcium lactate (8.9 ± 1.7%), higher than calcium chloride (5.7 ± 1.7%), but lower than calcium ascorbate (14.8 ± 1.2%). The mean residence time of calcium from calcium acetate was similar to calcium chloride and calcium lactate (*i.e.,* approximately 40 to 45 minutes). A tabular summary of the pharmacokinetic parameters of calcium following administration of calcium salts is provided in Table 6.2.1.1-1.

[8] The search was conducted on 17 November, 2022
[9] The search was conducted on 17 November, 2022

Table 6.2.1.1-1 Pharmacokinetic Parameters of Calcium Following Administration of Calcium Salts (Ueda and Taira, 2013)

Subjects/Animals	Calcium Salt	AUC (µg/mL·minute)	T_{max} (minutes)	C_{max} (µg/mL)	MRT (minutes)	F_{abs} (%)
7-week-old male ddY mice (20 to 30 g)	Calcium chloride: 150 mg/kg	813.0 ± 187.6	30	94.5	46.6 ± 1.8	5.7 ±1.3
	Calcium lactate: 150 mg/kg	1,394.6 ± 225.3	30	98.2	41.4 ± 2.8	8.9 ± 1.4
	Calcium ascorbate: 150 mg/kg	2,007.6 ± 159.9	15	100.8	64.7 ± 3.8	14.8 ± 1.2
	Calcium acetate: 150 mg/kg	1,137.4 ± 225.1	45	103.6	45.0 ± 2.6	8.6 ± 1.7

AUC = area under the curve; C_{max} = maximum plasma concentration; F_{abs} = absolute bioavailability; MRT = mean residence time; T_{max} = time to reach the maximum plasma concentration.

6.2.1.2 Rats

In 3-month-old male Sprague-Dawley rats (weighing 250 to 275 g), 18% of the 25 mg dose of calcium provided as calcium acetate was absorbed, while 82.0% and 0.1% were excreted *via* feces and urine, respectively (Cai *et al.*, 2004).

6.2.1.3 Humans

In the Sheikh *et al.* (1987) study, 8 healthy men (aged 25 to 30 years) were administered a 500 mg dose of elemental calcium provided by various calcium salts or whole milk. Approximately 32% (163 mg) of the 500 mg elemental calcium available in the calcium acetate capsule was absorbed. The net calcium absorption was determined to be similar across the calcium salts that were tested (including calcium carbonate, calcium lactate, calcium gluconate, and calcium citrate), as 27 to 39% of the elemental calcium was absorbed. The difference in calcium absorption between the calcium salts and whole milk (31%) was not statistically significant.

6.2.1.4 Other Information

Studies on the metabolic fate of the acetate dissociated from calcium acetate were not identified; however, acetate from calcium acetate is expected be cleared from the body rapidly. In 10 healthy volunteers, 4 mM/kg body weight of sodium acetate infusion caused the plasma acetate concentrations to rise from 0.04 ± 0.01 mM to 2.12 ± 0.29 mM; however, the acetate concentrations diminished rapidly when the infusion was terminated (Richards *et al*., 1982). The mean fractional generation of bicarbonate was calculated to be 100 ± 21%, suggesting that acetate is rapidly metabolized and converted to bicarbonate.

6.2.2 Animal Studies on Calcium Acetate

No toxicology studies conducted using the U.S. FDA's Redbook 2000: *Guidance for Industry and Other Stakeholders, Toxicological Principles for the Safety Assessment of Food Ingredients* (July 2000; revised July 2007) or Organisation for Economic Co-operation and Development Guidelines for the Testing of Chemicals were identified in the literature; however, 3 studies administering calcium acetate salts to animals with endpoints/outcomes relevant to safety were identified. The designs of these studies were not conducted in accordance with validated internationally recognized animal toxicity study designs and therefore are of limited relevance to the GRAS evaluation; however, general overviews of the authors' findings are summarized below for completeness.

In Poirier *et al*. (1983), the anti-carcinogenic potential of calcium acetate on cadmium chloride ($CdCL_2$)-induced carcinogenicity was assessed in 400 male Wistar rats (weighing 120 to 150 g). The male rats were divided into 18 groups (25 rats per group) and calcium acetate was administered to groups of 6 animals at concentrations of 3% in the diet for 2 weeks prior to and 2 weeks after the $CdCl_2$ injection, or as 3 daily subcutaneous injections of 0.16 mmol calcium acetate per kg body weight at the same site as $CdCl_2$ on the day before, the day of, and the day after $CdCl_2$ dosing. Control groups were given 0.9% sodium chloride (NaCl) solution instead of $CdCl_2$ plus subcutaneous injection or dietary calcium acetate.

Calcium acetate did not significantly affect growth rate relative to the control (0.9% NaCl solution), and acute toxic effects of calcium acetate were not observed. After 110 weeks, tumor yields and latent periods were not significantly affected by dietary calcium acetate or subcutaneous injections of calcium acetate, relative to control. Also, calcium acetate did not significantly impact the carcinogenicity of cadmium chloride injections.

In Kasprzak *et al*. (1985a), the effect of divalent cations from calcium acetate to displace lead and reduce the toxicity of lead acetate was assessed in 210 male Sprague-Dawley rats (weighing 80 to 100 g). The male rats were divided into 7 groups (30 rats per group), and calcium acetate was administered in 5 of the groups over 79 weeks: (i) 3% calcium acetate in chow diet; (ii) 0.3% calcium acetate with 1% lead acetate; (iii) 1.0% calcium acetate with 1% lead acetate; (iv) 3.0% calcium acetate with 1% lead acetate; and (v) 6.0% calcium acetate with 1% lead acetate. Compared to the control mice (that were fed a basal diet), there was a statistically significant reduction in mean body weight of 7% (723.3 ± 13.1 g in control mice *versus* 671.1 ± 21.4 g in mice fed 3% calcium acetate diet). The reduction in mean body weight was even greater in mice that were administered lead acetate; food and water intake were not measured. There were no significant differences in mortality, number of adenocarcinomas, number of adenomas, yield of renal tumors, kidney to body weight ratio, and liver to body weight ratio between the control mice *versus* mice fed the 3% calcium acetate diet. In mice that were administered lead acetate with calcium acetate, there were statistically significant increases in yield of renal tumors compared to mice that were administered lead acetate only.

Kasprzak *et al*. (1985b) conducted a similar study of calcium acetate with nickel subsulfide using 220 male Fischer F344 rats (weighing 50 to 80 g). The male rats were divided into 11 groups (20 rats per group), and calcium acetate was administered in 4 of the groups: (i) 3% calcium acetate in chow diet for 3 months; (ii) 3% calcium acetate for 6 months; (iii) 0.16 mmol/kg subcutaneous injections (3 times weekly) for 1 month; and (iv) 0.16 mmol/kg subcutaneous injections (3 times weekly) for 4 months. It should be noted that all 4 of these groups were also administered nickel subsulfide (*i.e.*, no mice were administered calcium acetate only). Relative to the mice administered nickel subsulfide without calcium acetate, the consumption of dietary calcium acetate did not significantly affect yield of muscle tumors (at 79 Weeks) and the latency period. Tumor yields were higher (statistical significance was not reported) in mice injected with calcium acetate and nickel subsulfide, suggesting that calcium acetate does not attenuate the toxic effects of nickel.

Across the 3 carcinogenicity studies, consumption of dietary calcium acetate alone was not associated with acute toxic effects and increased carcinogenicity. Although the body weight was significantly reduced by 7% in mice that consumed chow diet containing 3% calcium acetate relative to the control rats, food intake was not measured in the study (Kasprzak *et al*., 1985a). Given that the chow diet contained 3% calcium acetate and given that calcium acetate has a bitter taste, it is not clear whether the decreased body weight was due to the consumption of calcium acetate *versus* decrease in chow consumption. Overall, there were no findings in the above-referenced animal studies to suggest that current and proposed food uses of calcium acetate would be unsafe.

6.2.3 Authoritative Safety Evaluations on Calcium Acetate

6.2.3.1 European Food Safety Authority

EFSA evaluated the safety of adding calcium acetate (and other calcium or magnesium salts) in food supplements and issued a Scientific Opinion on May 13, 2009 (EFSA, 2009). EFSA concluded that the use of calcium acetate in food supplements is not a safety concern provided that the calcium UL as established by the Scientific Committee on Food (SCF) in 2003 (SCF, 2003) is not exceeded. The following pivotal points formed the basis of the agency's conclusion:

- Calcium is readily absorbed when soluble organic salts containing calcium are orally ingested.
- The safety of calcium has been evaluated previously and the intake of calcium is not a safety concern, provided that the UL established by the SCF for calcium is not exceeded. EFSA acknowledged that at the maximum proposed use level of 800 mg calcium per day, and accounting for calcium intake from the diet, the UL would be exceeded in a small population of heavy consumers (at the 97.5th percentile) of potential calcium-containing foods within the European adult population.[10]
- Acetate is a normal constituent of the body and its biochemical fate in the Krebs cycle or glycolytic pathway is well documented. At the maximum proposed use level of 800 mg calcium/day, the exposure to acetate would be 2.4 g/day; these dietary quantities would be rapidly metabolized to water and carbon dioxide and that no adverse effects have been reported at these levels.

6.2.3.2 Joint FAO/WHO Expert Committee on Food Additives

In JECFA's evaluation of acceptable daily intake (ADI) for calcium acetate, short- and long-term studies specifically on the toxicity of calcium acetate were not identified at the time of their literature evaluation (JECFA, 1974). JECFA noted that humans have consumed 400 mg to 3 g of calcium and 1 g of acetic acid/day without apparent side effects. Given that substantial increases in calcium and acetate intakes are unlikely when calcium acetate is used as a food additive, a numerical ADI value was not established for calcium acetate when used in food as a preservative, stabilizer, or acidity regulator.

[10] Although the significance of this was not further discussed it should be recognized that the consumption patterns of heavy consumer of potential foods containing calcium in combination with daily use of calcium supplemented foods is unlikely to represent a situation of chronic dietary intakes due to overestimations that are inherent with dietary intake assessments.

6.3 Safety of Dietary Calcium

Calcium acetate is highly soluble in aqueous solutions and will readily dissociate to its constituent counter ions, calcium and acetate, following consumption of foods to which calcium acetate is added. In addition to the safety information about calcium acetate presented in Section 6.2 above, Niacet's GRAS evaluation reviewed available safety data for the constituent ions. A focus was placed on calcium, as this compound is a micronutrient with potential safety concerns when consumed in excess. The safety of dietary calcium has been the subject of several comprehensive evaluations by qualified experts, most notably, the evaluations conducted by the Food and Nutrition Board of the Institute of Medicine (FNB-IOM) at the National Academy of Sciences (NAS) in 2011 and the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) in 2012 (IOM, 2011; EFSA, 2012), discussed in Section 6.3.1 below. The results of Niacet's literature search for new information relevant to the safety of excess intakes of dietary calcium published since 2016 is provided in Section 6.3.2 below.

6.3.1 Authoritative Safety Evaluations and Tolerable Upper Limits

The maximum safe level of intake of a nutrient is referred to as a tolerable upper limit (*i.e.*, UL). It should be noted that a UL value is not a recommended intake, but a level above which the risk for harm begins to increase, and is defined as:

> "*The highest average daily intake of a nutrient that is likely to pose no risk of adverse health effects for nearly all persons in the general population. As intake increases above the UL, the potential risk for adverse effects increases*" (IOM, 2011).

In determining the UL, IOM considered hypercalcemia, hypercalciuria, vascular and soft tissue calcification, nephrolithiasis (kidney stones), prostate cancer, interactions with iron and zinc, and constipation as potential indicators of adverse outcomes (IOM, 2011). The IOM established the UL for calcium in older adults and the elderly based on the relationship between calcium intakes of 2,000 mg/day and nephrolithiasis (kidney stones) as the critical endpoint in older adults as reported by Jackson *et al*. (2006). No uncertainty factor was applied to this value due to the robustness of the dataset. A UL of 3,000 mg for age groups 9 to 13 and 14 to 18 years was derived by interpolation taking into account a presumed increased need for and corresponding higher tolerance for calcium during the pubertal growth spurt in this population group. A UL for calcium in infants aged 0 to 6 months and 6 to 12 months was derived from a randomized controlled trial reported by Dalton *et al*. (1997) and Sargent *et al*. (1999) where a no-observed-adverse-effect level value of 1,750 mg/day and critical endpoint of hypercalcemia was determined. Uncertainty factors of 2 and 1.2 were applied to adjust for the weight increments during the trial to derive UL values of 1,000 mg/day for infants aged 0 to 6 months and of 1,500 mg/day for infants aged 6 to 12 months. The IOM noted that there was emerging evidence that excess intakes of calcium (of approximately 2,000 mg/day or higher) were associated with higher risk of prostate cancer and myocardial infarction in older adults and the elderly (*i.e.*, 50 years of age or older); however, the data are associated with limitations and the relationships are not conclusive. It is worth noting that the increased risk of prostate cancer and myocardial infarction occurred at intakes of 2,000 mg/day or higher in older adults and the elderly; therefore, the UL would have likely stayed the same even if prostate cancer and myocardial infarction were the basis for the UL.

The ULs for calcium were determined separately for the DRI life stage groups, a summary of which is provided in Table 6.3.1-1.

Table 6.3.1-1 Summary of Calcium Tolerable Upper Limit and the Basis for the UL Determination

Life Stage Group	Tolerable Upper Limit (mg/day)	Basis for the Tolerable Upper Limit
0 to 6 months of age	1,000	• Calcium excretion measures and no AE on iron status in a RCT on infants that consumed calcium-supplemented infant formula.
6 to 12 months of age	1,500	
1 to 3 years of age 4 to 8 years of age	2,500	• No safety data specific to children and adolescents; therefore, the UL established for adults was used. • To account for increased metabolic demand and pubertal growth spurt, 500 mg/day was added for older children.
9 to 13 years of age 14 to 18 years of age	3,000	
19 to 30 years of age 31 to 50 years of age	2,500	• Interpolating the UL for children of 3,000 mg/day and UL of older adults of 2,000 mg/day, 2,500 mg/day was determined to be the UL for adults (19 to 50 years of age). • Hypercalcemia was not selected as the basis for determining the UL because it is an outcome that reflects an extreme pathological condition (*e.g.*, compromised kidney function) or currently available data on outcomes associated with hypercalcemia (*e.g.*, vascular calcification in post-menopausal women) are conflicting. • Prostate cancer was not selected as the basis for determining the UL because the data on prostate cancer are too confounded. • Currently available data on nutrient interaction and constipation were determined to be inadequate to serve as the basis for the UL. • Incidence of kidney stones were selected as the basis for the UL; intakes of approximately 2,000 mg/day were associated with increased risk of kidney stones in women between the ages of 50 and 70 years.
51 to 70 years of age >70 years of age	2,000	

AE = adverse effect; RCT = randomized controlled trial; UL = tolerable upper limit.

Following a request from the European Commission, the EFSA NDA Panel was asked to re-evaluate the safety of calcium intakes and, where applicable, provide revised ULs of calcium for all relevant population groups (EFSA, 2012). EFSA reached similar conclusions to the IOM, and the EFSA NDA Panel proposed a UL for calcium of 2,500 mg for adults, and for pregnant and lactating women, but concluded that the available data were insufficient to set a UL for infants, children, or adolescents. EFSA's evaluation considered potential associations between excess calcium intake and endpoints related to nephrolithiasis, cardiovascular disease (CVD), or prostate cancer, and in agreement with findings by the IOM concluded that no relationship has been established between long-term calcium intakes and increased risk of these conditions could be identified.

6.3.2 Literature Search for New Published Information Relevant to the Safety of Dietary Calcium

As discussed in Part 3 of this Notice, calcium acetate manufactured by Niacet is intended for use as an alternative to various existing food uses of calcium salts in the U.S. food supply. The introduction of calcium acetate to the U.S. food supply for such uses is therefore not expected to alter dietary intakes of calcium in the American population. Accordingly, the GRAS uses of calcium acetate will not result in dietary intakes of calcium that exceed the current UL values for calcium established by the IOM in 2011 and EFSA in 2012. As discussed by the IOM, "*Excess calcium intake from foods alone is difficult if not impossible to achieve. Rather, excess intakes are more likely to be associated with the use of calcium supplements*" (IOM, 2011). The IOM's views that current food uses and corresponding intakes of calcium in the diet are not of safety concern can be extended to the proposed GRAS uses of calcium acetate. Since the IOM's and EFSA's evaluations of the literature were completed in 2011 and 2012, respectively, updated searches of the literature have been conducted to determine whether new data or information relevant to the safety of calcium intake have been reported that would call into question the presumed safety of calcium at the

current dietary intakes. One of the most recent updated evaluations of the literature on calcium safety was conducted by PepsiCo., Inc. during the company's evaluation of the GRAS use of calcium chloride for use in the manufacturing of potato snacks (GRN 634 – PepsiCo, Inc. 2016). As discussed in pages 42 through 50 of the Notice, Pepsi Co., Inc. reviewed published literature on the same endpoints considered by the IOM in 2011 and performed a complete search for other potential health outcomes not considered by the IOM. Pepsi Co., Inc. concluded that while adding to the body of literature, this new information did not offer any conclusive evidence of cause-and-effect relationships between calcium intake and adverse health effects and did not appear to impact the IOM and EFSA conclusions on the safety of dietary calcium and the UL. For the sake of completeness, Niacet has conducted an updated search of the literature for new information relevant to the safety of excess intakes of dietary calcium. Although findings from new clinicals were reviewed (see Section 6.3.2.1), the findings from any individual study should consider the totality of evidence and therefore a focus was placed on identifying new meta-analyses and systematic reviews. Summaries of the findings from new meta-analyses and systematic reviews published since PepsiCo, Inc.'s GRAS evaluation in 2016 are presented in Section 6.3.2.2 below. For a discussion of the literature search strategy, see Section 6.1.

6.3.2.1 Human Studies

The results of Niacet's literature search identified 2 new human studies published since GRN 634. The first of these was one reported by Kaats *et al*., (2016), whose objective was to assess the effects of plant-derived calcium (AlgaeCal) on bone mineral density (BMD) and safety measures (*i.e.*, 45-measurement blood chemistry panel). Participants who had a record of previous dual-energy X-ray absorptiometry measurement and/or blood chemistry tests with the research facility and who had been consuming AlgaeCal were recruited (*i.e.*, the study was an observational study). Compared to age-matched individuals in the research facility's database with blood chemistry panels, no adverse effects or safety concerns, including adverse changes in blood lipids, glucose, or other blood chemistry measures, were reported.

The second study was published by Aloia *et al*., (2018). The primary objective of this study was to compare the episodes of hypercalciuria and hypercalcaemia from calcium supplements co-administered with high intake of vitamin D (10 000 IU or 600 IU vitamin D/day). In this randomized-controlled trial, 132 healthy participants (age 56 – 70 years) were randomized to receive 2000 mg calcium/day in combination with 10,000 IU vitamin D or 600 IU vitamin D per day for 12 months. Participants received 1200 mg/day of a calcium supplement and 800 mg calcium was assumed to come from diet. At baseline and at every 3-month interval, blood and urine calcium levels as well as serum parathyroid hormone (PTH), vitamin D metabolites and bone turnover marker [serum C-telopeptide (CTX)]. Also, participants were followed up every for development of adverse events. This study demonstrated that 23% of study participants in the high vitamin D group has hypercalcemia (defined as serum calcium >10.2 mg/dL) at least once during the study, while only 17% of those in the low vitamin D group experienced this. These effects were not statistically significant. On the other hand, there was significantly higher urinary calcium level in the high vitamin D group when compared to their counterparts in the low vitamin D group. The incident of adverse events was described to be similar between the two groups. Of note, the authors did not attribute these reports of adverse events to calcium alone, neither was there a description of these adverse effects in order to determine their severity.

6.3.2.2 Meta-analyses and Systematic Reviews

Based on the literature search to identify meta-analyses and systematic reviews on calcium that have been published after the literature search conducted in GRN 634, 32 meta-analyses and systematic reviews were

identified. Across the 32 meta-analyses and systematic reviews, effects of calcium (with or without vitamin D) on the following outcomes were assessed:

- Heart health, including blood lipids, blood pressure, risk of CVD, in 7 studies;
- Cancer in 8 studies;
- Bone health, including bone density and risk of falls and fractures, in 5 studies;
- Preeclampsia and other pregnancy-related outcomes in 4 studies;
- Metabolic syndrome in 2 studies
- Post-operative hypocalcemia in 2 studies;
- Other outcomes:
    - Weight loss in 1 study;
    - Glycemic control in 1 study;
    - Growth parameters in infants in 1 study;
    - Inflammatory markers in 1 study; and
    - Menstrual regularity in 1 study.

The systematic reviews and meta-analyses on cardiovascular parameters are addressed in Table 6.3.2.2-1 and the remaining topics (cancer, bone health preeclampsia or pregnancy, post-operative hypocalcemia, metabolic syndrome, and other outcomes) are addressed in Table 6.3.2.2-2.

Other than the meta-analyses and systematic reviews on heart health, the main objectives of these studies were to assess the efficacy of calcium on the measured outcomes. In the case of heart health, studies were conducted to assess the potential beneficial and harmful effects of calcium on CVD, given that calcium supplementation has been associated with increased risk of CVD. Only 4 studies were identified during the literature search where pooled findings related to adverse effects (*e.g.*, hypercalcemia, gastrointestinal tolerance) were reported [Cai *et al*. (2020)—bone mineral density; Veettil *et al.* (2017)—adenoma; Heshmati *et al.* (2019)—blood lipids; and Artenz *et al.* (2017)—menstrual regularity]. These studies are therefore presented separately in Table 6.3.2.2-3.

Of the 6 systematic reviews and meta-analyses that evaluated cardiovascular parameters, effects of calcium on blood lipids were assessed in 2 studies (Heshmati *et al*., 2019; Cheng *et al*., 2020). Calcium was associated with statistically significant improvements in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol in both studies. In the studies on the risk of hypertension or blood pressure, statistically significant reduction in the incidence of hypertension was observed in a meta-analysis of prospective cohort studies (Jayedi and Zargar, 2019) and no effects on blood pressure in a meta-analysis of randomized controlled trials (RCTs) were observed (Wu *et al*., 2017). In a sub-group analysis of gender effects, Wu *et al*. (2017) reported that systolic (but not diastolic) blood pressure was significantly increased in males. In Chung *et al*. (2016), calcium did not increase the risk of CVD. However, in the meta-analysis by Yang *et al*. (2020a), calcium intake, specifically calcium supplementation in 16 RCTs, was associated with statistically significant increases in coronary heart disease (CHD) and myocardial infarction. In contrast to findings on calcium supplementation, the authors (Yang *et al*., 2020a) reported that findings from meta-analyses of prospective cohort studies did not support an association between dietary calcium intake and CHD or myocardial infarction risk. Further, the meta-analysis of 9 double-blind, placebo-controlled RCTs conducted by Myung *et al.*, (2021) demonstrated that calcium, at a daily dose range of 700-1000 mg/day significantly increased the risk of CVD and CHD by about 15% in healthy postmenopausal women. The authors concluded that calcium supplementation may increase CHD risk, but dietary sources of calcium do not adequately increase risk of CVD or CHD (Yang *et al*., 2020a).

The IOM reviewed meta-analyses that had nearly identical evidence bases as the meta-analyses by Yang *et al*. (2020a) (*i.e.*, the meta-analysis that was identified *via* the literature search where a statistically significant relationship between calcium supplementation and CHD were observed) (IOM, 2011). In the IOM's review of the meta-analysis performed by Bolland *et al*. (2010), a study in which a statistically significant increased risk in myocardial infarction with calcium supplementation was observed,[11,12] it was noted that the studies included in the meta-analysis were small and the event frequency was low. Furthermore, the studies did not have cardiovascular events as the primary outcome, they may not have adequately adjudicated the outcomes, and they did not control for renal function. In addition, total calcium intakes would have exceeded 2,000 mg/day in many of the included studies because the subjects were supplemented with 1,000 to 1,200 mg of calcium per day.

The mechanism between calcium intake and CHD risk is based upon the hypothesis that chronic hypercalcemia from excess dietary intake of calcium can result in calcification of soft tissues; however, no relationship between calcium intake and nephrocalcinosis or vascular calcification has been established in healthy humans except where decreased kidney function is noted (EFSA, 2012). As reported by the EFSA NDA Panel, several limitations in the design of studies evaluating the association between excess calcium intake and adverse CHD risk are recognized. For example, in most cases cardiovascular events (*e.g*., myocardial infarction) were not endpoints evaluated in the trials but were events attributed on the basis of a self-reported health questionnaire and were not verified. In other studies, event frequency and differences in the number of events between the calcium and placebo groups were small, and, in addition, the frequent use of multiple endpoints without adjustment of the level of significance for multiple testing further increases the likelihood of chance findings (EFSA, 2012). Studies evaluated within meta-analyses published since the IOM and EFSA's reviews are subject to the same confounding circumstances. New studies published to date do not change the previous conclusions that current dietary intake patterns for calcium are not associated with increased risk of CHD.

Table 6.3.2.2-1 Summary of Systematic Reviews and Meta-analyses on Cardiovascular Parameters

Reference	Number of Studies Included (Number of Subjects)	Dose Range (for RCTs[a])	Study Duration or Follow-up Period	Outcome Assessed	Effects of Calcium on the Outcome Assessed
Cheng *et al*. (2020)	22 RCTs (n=4,071)	NR	2 weeks to 5 years	Blood lipids	• SS beneficial effects on LDL- and HDL-cholesterol • No effect on triglycerides and total cholesterol
Chung *et al*. (2016)	4 RCTs; 1 CC; 26 Cohort (n=NR)	1,000 to 1,200 mg/day	2 to 7 years (for RCTs); 4.5 to 24 years (for observational studies)	Risk of CVD	• No effect on risk of CVD or mortality

[11] It should be noted that the effects of calcium supplementation on incidence of stroke, the composite endpoint of myocardial infarction, stroke, sudden death, or death were not statistically significant.

[12] It should be noted that the studies included in the pooled assessment included all but 1 study that was included in Yang *et al*. (2020a). Study results from the Women's Health Initiative were not included because studies were excluded if calcium and vitamin D were compared to a control group that did not also consume vitamin D. Effects of calcium on myocardial infarction or CHD were not associated with statistically significant increase in risk.

Table 6.3.2.2-1 Summary of Systematic Reviews and Meta-analyses on Cardiovascular Parameters

Reference	Number of Studies Included (Number of Subjects)	Dose Range (for RCTs[a])	Study Duration or Follow-up Period	Outcome Assessed	Effects of Calcium on the Outcome Assessed
Heshmati *et al*. (2019)	11 RCTs (n=1,257)	126 to 1,250 mg/day	8 weeks to 2 years	Blood lipids	• SS beneficial effects on LDL- and HDL-cholesterol • No effect on triglycerides and total cholesterol
Jayedi *and Zargar* (2019)	8 Prospective Cohort (n=248,398)	NA	2 to 10 years	Risk of hypertension	• SS beneficial effects on risk of hypertension
Myung *et al.*, (2021)	14 RCTs (n=14,243)	700 to 1000 mg/day	2 - 7 year duration (2-8 year follow up)	Risk of CVD and CHD	• 15% risk of CVD and CHD in postmenopausal women
Wu *et al*. (2017)	8 RCTs (n=36,806)	600 to 2,000 mg/day	8 months to 7 years	Blood pressure	• No effect on blood pressure • Based on sub-group analysis, systolic blood pressure was SS increased with calcium supplementation in males
Yang *et al*. (2020a)	16 RCTs (n=138,188); 26 Prospective Cohort (n=1,221,041)	1,000 to 1,500 mg/day	6 months to 7 years (for RCTs); 5.5 to 65 years (for cohort studies)	Risk of CVD	• Based on RCTs, SS increase in risk of CHD and myocardial infarction; NSS effect on risk of CVD • Based on cohort studies, no effect on risk of CVD

CC = case-control; CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; NR = not reported; NSS = not statistically significant; RCT = randomized control trials; SS = statistically significant

[a] For observational studies, the meta-analysis was primarily conducted on the highest *versus* lowest intake groups (*e.g.,* highest quartile *versus* lowest quartile); therefore, a specific dose could be derived.

Across the 26 studies on outcomes other than those related to cardiovascular health (Table 6.3.2.2-2), statistically significant beneficial associations were reported between calcium intake and various health outcomes in 19 studies, no statistically significant effects were reported in 6 studies, and a statistically significant association between higher calcium intake and increased risk of prostate cancer was reported in 1 study by Rahmati *et al*. (2018). All of the studies (n=12) that were included in the Rahmati *et al*. (2018) meta-analysis were observational studies. In 10 of the 11 studies included in the analyses, estimates of calcium intake were based upon food frequency questionnaires, which are subject to recall bias and are the least accurate measure of food and dietary intake. The findings reported by Rahmati *et al*. (2018) are consistent with weak associations between calcium intake and prostate cancer reported by the IOM during their safety evaluation where it was noted that a meta-analysis of 12 cohort studies (Chung *et al*., 2009) reported an association between calcium intake and risk of prostate cancer (IOM, 2011). The IOM noted that the data were at best emerging but not sufficiently robust (IOM, 2011). Similarly, EFSA also concluded that "l*ong-term calcium intakes from diet and supplements above 2,000 mg/day are not associated with an increased risk of prostate cancer*" (EFSA, 2012). The study by Rahmati *et al*. (2018) does not change these conclusions.

Other than an increase in the incidence of hypercalcemia reported by Veettil *et al*. (2017), no other adverse effects were reported or increased in the subjects that were in the calcium group. The increased incidence of hypercalcemia reported by Veettil *et al.* (2017) was based upon findings from 2 studies (Chu *et al*., 2011; Baron *et al*., 2015). Chu *et al.* (2011) reported 2 cases (grade 1) of hypercalcemia in the control group (n=99) and 2 cases of hypercalcemia in the treatment group (grade 1 and 4) provided 1,800 mg of calcium carbonate (n=95). The study by Baron *et al.* (2015) reported 17 cases of hypercalcemia in the treatment group (n=840) provided 1,200 mg of calcium carbonate *versus* 5 cases of hypercalcemia in the control group (n=835); however, the authors reported that "*medical symptoms and complications were not associated with treatment assignment,*" and therefore Veettil *et al*. (2017) excluded this study from the analyses.

Table 6.3.2.2-2 Summary of Systematic Reviews and Meta-analyses

Reference	Number of Studies Included (Number of Subjects)	Dose Range (for RCTs[a])	Study Duration or Follow-up Period	Outcome Assessed	Effects of Calcium on the Outcome Assessed
Studies on Cancer (n=8)					
Bonovas *et al*. (2016)	4 RCTs (n=2,984)	1,200 to 2,000 mg/day	3 to 5 years	Recurrence of adenomas and advanced adenomas	• SS beneficial effect
Hidaya *et al*. (2016)	11 prospective cohort (n=872,895)	NA	7 to 25 years	Risk of breast cancer	• SS beneficial effect
Huang *et al*. (2020)	11 RCTs; 77 observational (n=NR)	NR	NR	Risk of colorectal cancer	• SS beneficial effect
Li *et al*. (2017)	15 observational	NA	NR	Risk of esophageal cancer	• SS beneficial effect
Rahmati *et al*. (2018)	12 observational (n=905,046)	NA	6 to 17 years	Risk of prostate cancer	• **SS increased risk of prostate cancer**
Song *et al*. (2017)	13 observational (n=367,057)	NA	8 to 20 years	Risk of ovarian cancer	• SS beneficial effect
Veettil *et al*. (2017)	5 RCTs (n=2,234)	1,200 to 2,000 mg/day	3 to 5 years	Recurrence of adenomas and advanced adenomas	• SS beneficial effect
Yang *et al*. (2016)	32 observational (n=1,346,930)	NA	NR	Risk of lung cancer	• NSS effect
Studies on Bone Health (n=5)					
Cai *et al.* (2020)	5 RCTs (n=567)	600 to 1,000 mg/day	6 to 18 months	Bone mineral density	• NSS effect
Eleni and Panagiostis (2020)	NR	NR	NR	Risk of fracture	• SS beneficial effect on risk of total and hip fractures • NSS effect on wrist fractures
Weaver *et al*. (2016)	8 RCTs (n=970)	500 to 1,200 mg/day	NR	Risk of fracture	• SS beneficial effect on risk of total and hip fractures
Yang *et al*. (2020b)	9 RCTs (n=908)	NR	NR	Bone mineral content	• SS beneficial effect (increase in bone mineral content)
Zhao *et al*. (2017)	27 RCTs (n=51,145)	464 to 1,500 mg/day	4 months to 7 years	Risk of fracture	• NSS effect on hip, vertebral, non-vertebral, and total fractures with calcium alone • SS beneficial effect on hip fracture with co-administration of calcium and vitamin D

Table 6.3.2.2-2 Summary of Systematic Reviews and Meta-analyses

Reference	Number of Studies Included (Number of Subjects)	Dose Range (for RCTs[a])	Study Duration or Follow-up Period	Outcome Assessed	Effects of Calcium on the Outcome Assessed
Studies on Preeclampsia or Pregnancy (n=4)					
Hofmeyr *et al*. (2018)	4 to 13 RCTs (depending on outcome)	120 to 2,000 mg/day	NA (from pregnancy until birth)	High blood pressure; preeclampsia; pre-term birth; maternal death; serious morbidity	• SS beneficial effect on blood pressure, preeclampsia, pre-term birth, maternal death, and serious morbidity • NSS effect on other outcomes (*i.e.,* neonatal intensive care, still birth, or death)
Hofmeyr *et al*. (2019)	1 RCT (n=1,355)	Regimen of 500 mg/day until gestation age of 20 weeks + 1,500 mg/day thereafter	NA (from pregnancy until birth)	Preeclampsia risk, maternal morbidity, still birth risk, birth weight, pre-term birth	• NSS effect on all outcomes
Khaing *et al*. (2017)	27 RCTs (n=28,000)	NR	4 Mo. to 3 years	Risk of preeclampsia	• SS beneficial effect on risk of preeclampsia
Sun *et al*. (2019)	27 RCTs (n=28,492)	500 mg to 2,000 mg/day	NA (from pregnancy until birth)	Risk of preeclampsia; gestational hypertension	• SS beneficial effect on risk of preeclampsia and gestational hypertension
Studies on Post-operative Hypocalcemia (n=2)					
Sanabria *et al*. (2019)	15 RCTs (n=3,037)	150 to 3,000 mg/day	1 to 28 days	Risk of hypocalcemia	• SS beneficial effect
Xing *et al*. (2019)	10 RCTs (n=1,620)	1,500 to 3,000 mg/day	NR	Risk of hypocalcemia	• SS beneficial effect
Studies on Metabolic Syndrome (n=2)					
Cheng *et al*. (2019)	15 cross-sectional studies (n=56,291)	NA	NR	Risk of metabolic syndrome	• SS beneficial effect
Han *et al*. (2019)	10 observational studies (n=63,017)	NA	NR	Risk of metabolic syndrome	• SS beneficial effect
Studies on Other Outcomes (n=5)					
Asbaghi *et al*. (2019)	12 RCTs (n=4,395)	500 to 1,000 mg/day	6 weeks to 6 years	Glycemic parameters	• SS beneficial effect on fasting blood glucose, insulin, and HOMA-IR
Asbaghi *et al*. (2020)	8 RCTs (n=706)	500 to 2,000 mg/day	6 weeks to 3 years	Inflammatory markers	• SS beneficial effect in C-reactive protein • NSS effect on interleukin-6, and tumor necrosis factor-*alpha*
Artenz *et al*. (2017)	2 RCTs (n=78)	1,000 mg/day	12 to 16 weeks	Menstrual regularity	• NSS effect

Table 6.3.2.2-2 Summary of Systematic Reviews and Meta-analyses

Reference	Number of Studies Included (Number of Subjects)	Dose Range (for RCTs[a])	Study Duration or Follow-up Period	Outcome Assessed	Effects of Calcium on the Outcome Assessed
Harding *et al*. (2017)	1 RCT (n=40)	45 mg/kg body weight/day	6 weeks	Growth parameters (in infants)	• NSS effect
Li *et al*. (2016)	33 RCTs (n=NR)	800 to 2,100 mg/day	12 weeks to 4 years	Weight loss	• NSS effect

HOMA-IR = homeostatic model assessment of insulin resistance; NA = not applicable; NR = not reported; NSS = not statistically significant; RCT = randomized control trial; SS = statistically significant.
[a] For observational studies, the meta-analysis was primarily conducted on the highest *versus* lowest intake groups (*e.g.,* highest quartile *versus* lowest quartile); therefore, a specific dose could be derived.

Table 6.3.2.2-3 Systematic Reviews and Meta-analyses on Calcium Intake where Adverse Effects and Safety Outcomes were Evaluated

Reference	Number of Studies Included (Number of Subjects)	Dose Range	Outcome Assessed	Discussion on Safety or Adverse Effects
Cai *et al*. (2020)	5 RCTs (567 subjects)	600 to 1,000 mg/day	Bone mineral density	• Adverse effects of calcium supplementation were not reported in any of the included studies.
Veettil *et al*. (2017)	5 RCTs (2,234 subjects)	1,200 to 2,000 mg/day	Adenoma	• Studies included data on constipation, diarrhea, cardiovascular adverse events, hypercreatininemia, and urolithiasis. • There was a statistically significant increase in the incidence of hypercalcemia in the calcium group compared to the control (p=0.0095). • There was a statistically significant decrease in the incidence of myocardial infarctions. • No statistically significant differences in other measures.
Heshmati *et al*. (2019)	11 RCTs (1,257 subjects)	126 to 1,250 mg/day	Blood lipids	• No studies reported adverse effects and no subjects withdrew from the study due to this reason.
Artenz *et al*. (2017)	2 RCTs (78 subjects)	1,000 mg/day	Menstrual regularity	• No adverse effects were reported.

RCT = randomized control trial.

6.4 Additional Safety Data on Acetate

6.4.1 Meta-analyses and Systematic Reviews

Based on the literature search of meta-analyses and systematic reviews on the health effects of consuming acetate (or vinegar or acetic acid), 3 systematic reviews were identified (Shishehbor *et al*., 2017; Cheng *et al.,* 2020; Launholt *et al*., 2020). A summary of the 3 systematic reviews is provided in Table 6.4.1-1.

Across the 3 identified systematic reviews, the effects of vinegar on measures of glycemic control were assessed in 3 reviews, blood lipids in 2 reviews, body composition in 1 review, and adverse events in 1 review. The number of human intervention studies included in each of the systematic reviews was 6, 11, and 13 with a range of study duration (post-prandial [after a meal], 2 days, and 3 months). The dose of vinegar ranged from 2 to 60 mL/day and the corresponding dose of acetic acid ranged from 0.1 to 2.8 g/day.

Table 6.4.1-1 Summary of Systematic Reviews on Acetate

Reference	Number of Studies Included (Number of Subjects)	Dose Range	Study Duration	Outcome Assessed	Notable Results
Shishehbor *et al*. (2017)	11 RCTs (204 subjects)	18 to 50 g/day of vinegar (AA NR)	Post-prandial studies	Glycemic control	Safety outcomes: • Results related to adverse effects or tolerance were not discussed. Efficacy outcomes: • SS reductions in post-prandial glucose and insulin responses were observed.
Cheng *et al*. (2020)	6 RCTs (317 subjects)	15 to 30 mL/day of vinegar (AA NR)	2 days to 3 months	Glycemic control; blood lipids	Safety outcomes: • Results related to adverse effects or tolerance were not discussed. Efficacy outcomes: • SS reduction in fasting blood glucose, hemoglobin A1c, total cholesterol, and LDL cholesterol was observed.
Launholt *et al*. (2020)	13 intervention studies (493 subjects)		2 days to 12 weeks	Glycemic control; blood lipids; body composition; adverse effects	Safety outcomes: • Adverse effects were reported in 3 of the 13 studies. ○ Three (of 35) subjects had vinegar intolerance and dropped out in 1 study that provided 20 mL/day of apple vinegar.

Table 6.4.1-1 Summary of Systematic Reviews on Acetate

Reference	Number of Studies Included (Number of Subjects)	Dose Range	Study Duration	Outcome Assessed	Notable Results
					○ One diabetic patient (of 10 with gastroparesis) showed a higher rate of hypoglycemia in 1 study that provided 30 mL/day (1.5 mg/day of AA) of apple vinegar. ○ NSS increased rate of adverse events related to bowel function (*e.g.*, more bowel movements and increased frequency of burping or flatulence) were reported (p=0.11) in 1 study that provided 60 mL/day (2.8 g/day of AA) of apple vinegar. Efficacy outcomes: • Various health effects were observed across the identified studies. ○ SS effects on blood lipids were observed in 2 studies. ○ SS effects on glycemic response were observed in 6 studies. ○ SS effects on body composition measures were observed in 1 study.

AA = acetic acid; LDL = low-density lipoprotein; NR = not reported; NSS = not statistically significant; RCT = randomized control trials; SS = statistically significant.

In the review by Launholt *et al*. (2020), adverse effects were reported in 3 of the 13 included studies. The adverse effects ranged from vinegar intolerance in 3 of 35 subjects that consumed 20 mL/day of vinegar (amount of acetic acid was not reported), hypoglycemia in 1 of 10 diabetic patients with gastroparesis that consumed 30 mL/day of vinegar (1.5 g/day of acetic acid), and a non-statistically significant (p=0.11) higher rate (*i.e.*, in 56% of the subjects) of frequent bowel movements and flatulence or burping in the group that consumed 60 mL/day of vinegar (2.8 g/day of acetic acid) *versus* the reference group (*i.e.*, in 11% of the subjects). Notwithstanding these observations, the authors of the review concluded that the daily consumption of vinegar at moderate levels (*e.g.,* 2 tablespoons daily) would be safe while higher doses (*e.g.*, 4 tablespoons daily) could induce a higher rate of gastrointestinal discomfort (*i.e.*, increased bowel movement, flatulence, or burping).

6.4.2 Reviews by Regulatory or Scientific Bodies

Acetic acid is affirmed as GRAS for use as a curing and picking agent, flavoring agent and adjuvant, pH control agent, solvent and vehicle, and boiler water additive (21 CFR § 184.1005 – U.S. FDA, 2021). The SCOGS of the LSRO evaluated the safety of acetic acid, sodium acetate, and sodium diacetate as food ingredients in 1977. The SCOGS Panel reported that acetate is a common constituent in plants and animal tissues and is produced in large quantities during food digestion and metabolism (FASEB, 1977). Given that adverse effects of acetates are observed in short-term studies[13] only when the consumption levels far exceed what would be consumed in the normal diet, SCOGS concluded that there were no reasonable grounds to suspect a hazard to the public in using acetic acid at levels that were being used or that might be used in the future. Similar conclusions were drawn by JECFA; an ADI was not derived by JECFA because the metabolic pathway is well-established, it is generally consumed in humans, and the acidic taste would limit its use in foods (JECFA, 1967).

6.5 Bioavailability

Calcium acetate is intended to be used as a nutrient supplement similar to some of the calcium salts that are affirmed to be GRAS (*i.e.*, calcium chloride, calcium glycerophosphate, calcium lactate, calcium oxalate, calcium pantothenate, and calcium sulfate). As discussed in Section 6.2.1, bioavailability of calcium from calcium acetate was similar to calcium lactate, higher than calcium chloride, but lower than calcium ascorbate in mice (Ueda and Taira, 2013). In humans, calcium absorption from calcium acetate (*i.e.*, 32% rate of absorption) was similar (*i.e.*, all ranging from 27 to 39% rate of absorption) to calcium carbonate, calcium lactate, calcium gluconate, and calcium citrate (Sheikh *et al*., 1987). In fact, the rate of calcium absorption was not significantly different from that of whole milk (*i.e.,* rate of absorption of 31%). Therefore, calcium from calcium acetate would be bioavailable and similar conclusions have been drawn by EFSA who reported that the calcium from calcium acetate would be bioavailable and that calcium acetate could be used as a nutritional substance in food supplements (EFSA, 2009).

6.6 Overall Conclusions Pertaining to Safety

Calcium acetate is intended to be used as an alternative to the current regulated food uses of calcium propionate under 21 CFR § 184.1221 and calcium lactate under 21 CFR § 184.1207 (except as a leavening agent) (U.S. FDA, 2021). Since food uses were fully substitutional, dietary intake of calcium within the U.S. population is not expected to change, and therefore estimation of dietary intakes of calcium acetate using statistical modeling approaches with NHANES survey data were not necessary.

Given that calcium is an essential nutrient and acetate is a normal constituent in the body that is also widely consumed in foods, JECFA did not establish a specific ADI in their safety evaluation on calcium acetate. Similar conclusions have been drawn by EFSA in that calcium acetate is safe for use as the UL for calcium is not exceeded. In the U.S., the UL established by the IOM ranges from 1,000 mg/day (in infants) to 3,000 mg/day (in children 9 to 18 years of age). Based on intake estimates of calcium in the U.S. population from all sources in the GRAS Notice for calcium chloride (GRN 634 – PepsiCo, Inc., 2016), the mean and 90th percentile intakes were 1,152 mg/day and 1,936 mg/day, respectively. Intakes at the 90th percentile exceeded the UL in male and female adults aged 51 to 70 years, and in female adults aged 71 years and over. The excess intakes in these population groups are primarily due to the use of dietary supplements; intake estimates based on dietary sources only were well below the UL in these population groups at the 90th percentile. Regardless, calcium acetate will replace other calcium salts when used as a nutrient

[13] Long-term feed studies were not identified in their evaluation.

supplement and flavor enhancer; therefore, calcium exposure is not expected to change in the U.S. population. Findings from updated literature searches did not identify studies to call into question findings by scientific bodies (IOM, 2011; EFSA, 2012) that current dietary intake patterns of calcium are safe.

Intake estimates of acetate or acetic acid have been noted by EFSA to be difficult. However, safety concerns related to acetate exposure in foods were not raised in the EFSA, SCOGS, or JECFA evaluations on calcium acetate or acetic acid given that acetate or acetic acid is a common constituent in foods; it is produced in large quantities in the body during food digestion and metabolism; the metabolic pathway is well-established; and its acidic taste would limit its use in foods. Due to potential health benefits of vinegar, various clinical studies have been conducted with the dose of acetic acid in vinegar reaching up to 2.8 g/day. Although adverse effects were noted (*i.e.,* vinegar intolerance, hypoglycemia, gastrointestinal discomfort), the occurrences were infrequent, in specific populations (*i.e.,* diabetic patients with gastroparesis), or only at very high doses (*i.e.,* 2.8 g/day of acetic acid). It is worth noting that in these vinegar studies, controlling for acetic acid consumption from the background diet would have been difficult, and the acetic acid consumed from vinegars would have been in addition to what is normally consumed from the diet.

6.7 Conclusion

Based on the above data and information presented herein, Niacet has concluded that the intended uses of calcium acetate as described in Section 1.3 are GRAS based on scientific procedures. Calcium acetate, as well as calcium and acetate (as acetic acid) have been the subject of multiple safety evaluations by various qualified expert bodies (*e.g*., JECFA, IOM, EFSA, SCOGS) and current food uses of calcium salts have been unanimously concluded to be safe, thereby supporting the general recognition (*i.e*., general consensus within the scientific community of qualified experts) standard under the GRAS rule [170.250(b)] (U.S. FDA, 2021). The dietary intake assessment conducted using the refined cGMP-refined substitution model demonstrated that the intake of calcium from calcium acetate in all the population groups were all within the upper tolerable levels defined by IOM (IOM, 2011). Since the food uses of calcium acetate as described herein will not increase dietary intake of calcium in the diet, conclusions from authoritative scientific bodies can be extended to the intended food uses of calcium acetate.

Calcium acetate therefore may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under 21 CFR § 170.3 (U.S. FDA, 2021).

Part 7. § 170.255 List of Supporting Data and Information

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Table of CFR Sections Referenced (Title 21—Food and Drugs)

Part	Section §	Section Title
170—Food additives	170.3	Definitions
	170.30	Eligibility for classification as generally recognized as safe (GRAS)
	Subpart E (170.203 through 170-285)	Generally recognized as safe (GRAS) notice
182—Substances generally recognized as safe	182.6197	Calcium diacetate
184—Direct food substances affirmed as generally recognized as safe	184.1005	Acetic acid
	184.1185	Calcium acetate
	184.1207	Calcium lactate
	184.1221	Calcium propionate

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