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FOOD ADDITIVE SAFETY

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May 29, 2018

Paulette M. Gaynor,
Office of Food and Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

re: GRAS Notification for the Use of Calcium Chloride on Processed (Sliced/Cut) Fruits and Vegetables

Dear Dr. Gaynor:

Pursuant to 21 CFR Part 170, Wonderful Citrus, LLC, hereby provides notice of a claim that the food ingredient described in the enclosed notification document is exempt from the premarket approval requirement of the Federal, Food and Drug and Cosmetic Act because it has been determined to be generally recognized as safe (GRAS), based on scientific procedures, for use on processed fruits and vegetables.

As specified in 21CFR §170.210, we are providing a copy of the notification on the enclosed CD-ROM. If you have any questions about this submission or require additional information, please contact me at (202) 393-3903, ext. 114 or eharrison@lewisharrison.com

Sincerely,

(b) (6) [redacted]

Eliot Harrison,
Agent for Wonderful Citrus, LLC

Generally Recognized as Safe (GRAS) Notice for the Use of Calcium Chloride as an Antibrowning Agent in Processed Fruits and Vegetables

Submitted on Behalf of Wonderful Citrus, LLC

Prepared by:
Lewis & Harrison, LLC
122 C Street, NW
Suite 505
Washington, DC 20001
Tel: 202-393-3903

May 29, 2018

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Part 1. Signed Statements and Certification

Pursuant to 21CFR, Part 170, subpart E, Wonderful Citrus, LLC (“Wonderful”) is submitting this Generally Recognized as Safe (“GRAS”) Notice for the use of calcium chloride as an antibrowning agent on processed (e.g., cut/sliced) fruits and vegetables. As described in Parts 2 through 7 of this GRAS Notice, Wonderful is claiming that calcium chloride is not subject to the premarket approval requirements of the Federal Food, Drug and Cosmetic Act (“FFDCA”) based on its conclusion that calcium chloride is GRAS under the proposed conditions of use.

1.1 Name and Address of Notifier

Contact Person: Dr. Ram Uckoo
Company Name: Wonderful Citrus, LLC
Address: Delano, 1901 S. Lexington Street, Delano, CA 93215
Telephone Number: (661) 720-2400
E-mail Address: ram.uckoo@wonderful.com

1.2 Common Name of Notified Substance

The common name for the notified substance is calcium chloride. It is a component in an aqueous formulation that also contains calcium ascorbate and calcium propionate. As applied to processed fruits and vegetables, the formulation contains approximately 5% calcium ascorbate, 1% calcium propionate and 0.2% calcium chloride. The remaining constituent is water.

1.3 Conditions of Use of the Notified Substance

Calcium chloride will be part of a formulation that is used to treat processed fruits and vegetables in order to control enzymatic browning in these foods. The application procedure for calcium chloride involves dipping, spraying, or immersing fruits and vegetables into a container holding the aqueous formulation of calcium chloride, calcium ascorbate and calcium propionate. Any remaining liquid on the treated fruits and vegetables is then removed by centrifuging or similar removal processes.

1.4 Purpose for Which the Substance is Used

The combination of calcium chloride, calcium propionate and calcium ascorbate is highly effective in inhibiting enzymatic browning in processed fruits and vegetables. Enzymatic browning primarily affects the aesthetic quality of fruits and vegetables and, to a lesser extent, can also adversely affect their flavor and nutritional value.

1.5 Description of the Population Expected to Consume the Substance

Since calcium chloride will be used to treat fruits and vegetables, without geographical or other restrictions, dietary exposure will occur throughout the general population.

1.6 Basis for GRAS Determination

The basis for the GRAS determination regarding the use of calcium chloride as an antibrowning agent in processed fruits and vegetables are scientific procedures.

1.7 Availability of Information

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request, or are available for FDA's review and copying at reasonable times at the office of Lewis & Harrison, LLC, at the following address:

122 C Street, N.W.
Suite 505
Washington, D.C. 20001

In addition, should the FDA have any questions or additional information requests concerning this notification during or after the Agency's review of the notice, Lewis & Harrison will supply these data and information as requested.

1.8 Freedom of Information Act, 5 U.S.C. Section 552

None of the data presented in parts 2 through 7 of this notice contain any trade secret, commercial, or financial information that is privileged or confidential; therefore, all data and information presented herein are not exempt from the Freedom of Information Act, 5 U.S.C. Section 552.

1.9 Certification

We certify that, to the best of our knowledge, our GRAS notice is complete, representative, and a balanced submission that includes unfavorable information, as well as favorable information, available and pertinent to the evaluation of the safety and GRAS status of the use of calcium chloride as an antibrowning agent for use on processed fruits and vegetables.

(b) (6)

(Eliot Harrison for Ram Uckoo)

5/29/2018

Name: Ram Uckoo, Ph.D. Date
Title: Research and Development Manager

Part 2. The Identity, Method of Manufacture, Specifications and Physical and Technical Effect of the Notified Substance

Chemical and regulatory information regarding calcium chloride is presented below.

2.1 Identity

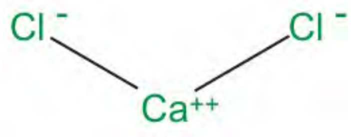
Common or Usual Name: Calcium chloride[1]

Chemical Name: Calcium chloride

Chemical Abstracts Service (CAS) Number: 10043-52-4

Empirical Formula and Formula Weight: $CaCl_2$

Chemical Structure:



Current Regulated Food Uses:

Calcium chloride is affirmed as Generally Recognized as Safe (GRAS), under 21 CFR §184.1193, for use in several types of food as an anticaking, antimicrobial, curing or pickling, firming, pH control, or surface active agent as well as a flavor enhancer, humectant, processing aid, stabilizer and thickener, synergist and texturizer. In addition, several calcium salts (calcium phosphate, calcium citrate, calcium hydroxide) and chloride salts of alkali metals (potassium chloride, sodium chloride, magnesium chloride) have been affirmed as GRAS under 21 CFR Part 184.

2.2 Manufacturing Information and Specifications

The notifier will purchase calcium chloride from suppliers that meet the manufacturing requirements in 21 CFR §184.1193 for calcium chloride.

[1] Calcium Chloride http://www.chemspider.com/Chemical-Structure.23237.html

Specifically, hydrated calcium chloride ($CaCl_2 \cdot 2H_2O$) or anhydrous calcium chloride ($CaCl_2$) may be commercially obtained as a byproduct in the ammonia-soda (Solvay) process and as joint product from natural salt brines, or it may be prepared by substitution reactions with other calcium and chloride salts.

The specifications for calcium chloride will meet the provisions established in the most recent Food Chemicals Codex (FCC) for this substance. Specifically, the assay for anhydrous calcium chloride requires that the substance contains not less than 93% and not more than 100.5% by weight of $CaCl_2$. In addition, the level of heavy metals (as Pb) cannot exceed 0.002%; the lead level cannot exceed 5 mg/kg; the fluoride level cannot exceed 0.004%; the acid insoluble matter cannot excced 0.02% and no particles per kg of sample can be greater than 2 mm in any dimension. For the dihydrate, the assay requirement is not less than 99% and not more than 107% of $CaCl_2 \cdot 2H_2O$.

As noted above, calcium chloride is a component of an antibrowing formulation that also contains calcium ascorbate and calcium propionate. For a 500-gallon batch of the formulation, the following amounts of each substance will be added:

- 94.63 kg (calcium ascorbate)
- 18.92 kg (calcium propionate)
- 3.785 kg (calcium chloride)

The batch is then made up to volume with potable water. The manufacturing process is a simple mixing procedure. No purification procedures or processing aids are used during the process.

2.3 <u>Intended Technical Effect</u>

In several efficacy trials, it has been demonstrated that the antibrowning formulation containing calcium chloride significantly inhibits enzymatic browning in processed fruits and vegetables. The antibrowning activity was effective for up to three weeks when compared to untreated controls.

Part 3. Dietary Exposure

3.1 Dietary Exposure from the Proposed Use

Dietary exposure to calcium chloride can result from the consumption of processed fruits and vegetables that are treated with the antibrowning formulation containing calcium chloride. Since calcium chloride readily dissociates when diluted in water, dietary exposure will occur to calcium and chloride ions.

In a residue study conducted at California Polytechnic State University, residue levels of ascorbate, propionate and chloride were measured after treatment of pre-cut apples. The apples were submerged in the formulation containing these components (5% calcium ascorbate, 1% calcium propionate and 0.2% calcium chloride and then centrifuged and dried. The results are shown in Table 1 below.

Table 1
Average Residue Levels of Ascorbate, Propionate and Chloride
After Treatment with Antibrowning Formulation

Ingredient	Residue Level (mg/kg apple)
Ascorbate	736.18 Standard Deviation: 137.22
Propionate	147.22 Standard Deviation: 27.44
Chloride	29.44 Standard Deviation: 5.49

Although the residue levels of calcium were not assayed, the calcium level can be calculated by assuming that calcium and chloride ions are similarly retained on treated apples. Based on this assumption, the calcium residue is then derived by multiplying the percent calcium in calcium chloride by the residue level of chloride, as follows:

Calcium Residue = Chloride Residue on Fruit (29.44 mg/kg fruit) × Percent Calcium in Calcium Chloride (36.3%)

Calcium Residue = 10.68 mg/kg fruit

The estimated daily intake (EDI) of calcium and chloride can then be quantified by multiplying the anticipated residue levels of calcium and chloride in treated fruits and vegetables by the dietary consumption of these food commodities.

The notifier expects that the antibrowning formulation will be used predominantly on processed apples and lemons and that almost all dietary exposure to calcium and chloride ions are expected to result from use on these foods. The estimated daily intake (EDI) for apples and lemons can be derived from the *Food Commodity Intake Database (FCID) Consumption Calculator*, which uses the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) food intake and recipe data to estimate food commodity consumption (http://fcid.foodrisk.org).

The daily intakes of apples and lemons for both young children and adults are shown in Table 2 below. For the child and adult exposures, body weights of 10 kg and 80 kg, respectively, were used. Dietary intakes are calculated on both an mg/kg and g/day basis.

Table 2

Daily Intake Values for Apples and Lemons

Population Group	Apple, fruit with peel/Apple Peeled Fruit	Lemon, /Lemon Juice/Lemon Peel
Child (10 kg)	4.8 g/kg-bw/day (90th percentile)*, or 48 g/day for an 10 kg child	0.3 g/kg-bw/day (90th percentile) ** or 3 g/day for an 10 kg child
Adult (80 kg)	1.4 g/kg-bw/day (90th percentile)*, or 112 g/day for an 80 kg adult	0.1 g/kg-bw/day (90th percentile)**, or 8 g/day for an 80 kg adult

*Results from FCID Consumption Calculator, page 10 of this notice
**Results from FCID Consumption Calculator, page11 of this notice

FCID Consumption Calculator Reports [Per Capita, Two-Day Average Consumption Commodity Mass (g) per Body Mass (kg) per Day (d)]

			N	Percent Consuming	Mean	SE	1%	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%	97.5%	99%	Max
Apple, fruit with peel | Apple, peeled fruit																													
Age Range	**Gender**	**Race**																											
All ages	All	All	24,673	24	0.37	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3	0.8	1.3	2.1	3.1	4.8	26.9†
Birth to < 12 months	All	All	1,190	7	0.22	0.06	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.7	2.3	8.6†	17.3†
1 to < 3 years	All	All	1,479	34	1.37	0.11	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	0.7	1.6	2.5	3.8	4.8	7.5	10.1	12.5†	26.9†
3 to < 6 years	All	All	1,418	31	1.18	0.12	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	1.3	2.3	3.3	4.5	6.0	8.4	11.4†	24.3†
6 to < 13 years	All	All	3,316	28	0.65	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.4	1.2	1.8	2.5	3.7	4.8	7.0	22.8†
13 to < 20 years	All	All	3,486	21	0.32	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	1.0	1.4	1.9	2.7	3.7	7.4†
20 to < 50 years	All	All	6,974	20	0.23	0.01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	0.4	1.0	1.5	2.2	2.9	14.1†
50 years and older	All	All	6,810	27	0.28	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0.4	0.8	1.1	1.7	2.2	3.0	9.4†
13 to < 50 years	Female	All	5,543	20	0.25	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	0.4	1.1	1.7	2.3	3.1	9.0†

Notes: '†' indicates estimates are less statistically reliable based on np < 8 * 'Design Effect' guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII
The **"Two-day average"** results are based on the average of the two days of food consumption reported in the NHANES/WWEIA survey for those "both day" respondents. If the respondent reports zero consumption on one of the two days and non-zero consumption on the other day, his/her average consumption would be the average of zero and nonzero consumption. Calculation performed on 12/6/2017 using FCID-WWEIA data for years 2005-2010 from http://fcid.foodrisk.org/percentiles

FCID Consumption Calculator Reports [Per Capita, Two-Day Average Consumption Commodity Mass (g) per Body Mass (kg) per Day (d)]

			N	Percent Consuming	Mean	SE	1%	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%	97.5%	99%	Max
Lemon | Lemon, juice | Lemon, peel																													
Age Range	**Gender**	**Race**																											
All ages	All	All	24,673	66	0.05	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.3	0.5	0.9	7.2†
Birth to < 12 months	All	All	1,190	8	0.03	0.02	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	0.1	0.5†	6.0†
1 to < 3 years	All	All	1,479	53	0.11	0.01	0†	0	0	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.2	0.3	0.6	0.9	1.9†	4.3†
3 to < 6 years	All	All	1,418	66	0.12	0.01	0†	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.2	0.3	0.7	1.0	1.4†	5.5†
6 to < 13 years	All	All	3,316	65	0.09	0.01	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.2	0.5	0.8	1.4	7.2†
13 to < 20 years	All	All	3,486	62	0.05	<0.005	0	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.2	0.5	0.9	5.3†
20 to < 50 years	All	All	6,974	68	0.05	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.3	0.5	0.7	5.9†
50 years and older	All	All	6,810	68	0.03	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.3	0.6	2.9†
13 to < 50 years	Female	All	5,543	68	0.05	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.3	0.5	0.8	2.7†

Notes: '†' indicates estimates are less statistically reliable based on np < 8 * 'Design Effect' guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII
The **"Two-day average"** results are based on the average of the two days of food consumption reported in the NHANES/WWEIA survey for those "both day" respondents. If the respondent reports zero consumption on one of the two days and non-zero consumption on the other day, his/her average consumption would be the average of zero and nonzero consumption. Calculation performed on 12/6/2017 using FCID-WWEIA data for years 2005-2010 from http://fcid.foodrisk.org/percentiles

Based on the residue levels for chloride and calcium (page 8 of this Notice) and the daily intakes for apples and lemons, the EDI for chloride and calcium from the use of the antibrowning formulation is shown below. It is assumed that the residue levels in lemons for chloride and calcium will be the same as those measured and calculated for apples.

Chloride

Child

- Apples:

(48 g/day) (0.029 g/1000 g of apples) = 1.3×10^{-3} g/day or 1.3 mg/day

- Lemons

(3 g/day) (0.029 g/1000 g of lemons) = 8.7×10^{-5} g/day or 0.087 mg/day

Accordingly, the total intake of chloride for children, at the 90th percentile, is 1.4 mg/day.

Adults

- Apples:

(112 g/day) (0.029 g/1000 g of apples) = 3.2×10^{-3} g/day or 3.2 mg/day

- Lemons

(8 g/day) (0.029 g/1000 g of lemons) = 2×10^{-4} g/day or 0.2 mg/day

Accordingly, the total intake of chloride for an adult, at the 90th percentile, is 3.4 mg/day.

Calcium

Child

- Apples:

(48 g/day) (0.010 g/1000 g of apples) = 4.8×10^{-4} g/day or 0.48 mg/day

- Lemons

(3 g/day) (0.010 g/1000 g of lemons) = 3×10^{-5} g/day or 0.03 mg/day

Accordingly, the total intake of calcium for children, at the 90th percentile, is 0.51 mg/day.

Adults

- Apples:

  (112 g/day) (0.010 g/1000 g of apples) = 1.1×10^{-3} g/day or 1.1 mg/day

- Lemons

  (8 g/day) (0.010 g/1000 g of lemons) = 8×10^{-5} g/day or 0.08 mg/day

Accordingly, the total intake of calcium for adults, at the 90^{th} percentile, is 1.18 mg/calcium/day.

3.2 Dietary Exposure from Existing Uses

Dietary intake values for calcium and chloride have been reported in previously submitted GRAS Notices and are summarized below.

Calcium

The dietary intake of calcium was presented in GRAS Notice No. 634, https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf. The notice reported that for the U.S. population age, 1 year and older, the *per user* intake of calcium at the 90^{th} percentile is 1,936 mg/day (see page 26 of the Notice). The EDI for calcium, from the use of calcium chloride as an antibrowning agent for processed fruits and vegetables, at the 90^{th} percentile, is 0.51 mg/day (child) and 1.18 mg/day (adult). Consequently, the antibrowning use results in a daily intake that is < 0.1% of the total daily intake of calcium at the 90^{th} percentile.

Chloride

According to GRAS Notice No. 634, the total amount of chloride in the adult human body is approximately 70-95 grams (see page 20 of the Notice). The chloride intake at the 90^{th} percentile for antibrowning use of calcium chloride is 0.2 mg/day (child) and 3.2 mg/day (adult). These levels are an exceedingly small fraction of the total chloride level in the human body.

Part 4. Self-Limiting Levels of Use

Calcium chloride will only be added to processed fruits and vegetables at levels to achieve its technological function. The notifier is unaware of any self-limiting levels of use associated with calcium chloride.

Part 5. Experience Based on Common Use in Food Before 1958

Although calcium chloride has a long history in food prior to 1958, the notifier is unaware if this ingredient has ever been used as an antibrowning agent in processed fruits and vegetables, including prior to 1958.

Part 6. Safety Evaluation and Basis for Our Conclusion of GRAS Status

As noted above, calcium chloride will dissociate into calcium and chloride ions. Accordingly, the safety assessment focuses on these ions as well as calcium chloride.

Calcium

The Health and Medicine Division (HMD, formerly the Institute of Medicine) of the National Academy of Sciences established an Upper Limit (UL) for calcium of 2,500 mg/person/day from all sources (e.g., food and supplements) for all age groups, including pregnant or lactating women, based on the risk for hypercalcemia and renal insufficiency at intakes ranging from 4,000 to 5,000 mg of calcium/person/day and greater (IOM, 1997)[2]. A UL for infants aged 0 to 12 months could not be established due to insufficient data. The IOM was subsequently asked to review the current data and in 2011 published updated ULs (IOM, 2011)[3].

For infants, new data were available regarding calcium excretion that suggested that infants can tolerate intakes of up to approximately 1,750 mg/day. Thus, a no-observed-adverse-effect level (NOAEL) of 1,750 mg/day was established. For infants 0 to 6 months of age, an uncertainty factor of 2 was applied to account for body weight differences and the UL was set at 1,000 mg/day. The UL for infants aged 7 to 12 months was set at 1,500 mg/day since an increased capacity to handle calcium will accompany increased body size.

The UL for children aged 1 through 8 years was not changed and remains at 2,500 mg/day, whereas the UL for children aged 9 to 13 years and adolescents aged 14 to 18 years, including pregnant and lactating adolescents, was raised by 500 mg/day to 3,000 mg/day to account for the increase in bone accretion and likely accompanying increases in tolerated intakes. For adults, although the IOM recognized that hypercalcemia was an adverse outcome, they noted that it was a disease state and they did not consider it appropriate for the derivation of ULs for the normal, healthy population. Kidney stone formation was selected as the indicator, and an UL of 2,000 mg/day was set for adults aged 51 to 70 and greater than 70 years based on increased risk of kidney stone formation at higher intakes.

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[2] IOM (1997). Calcium. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (I0M). Washington (DC): National Academy Press (NAP), pp. 71-145. Available from: http://books.nap.edu/openbook.php?isbn=0309063507&paqe=71.

[3] IOM (2011). *Dietary Reference Intakes for Calcium and Vitamin D.* Washington (DC): National Academy of Science (NAS), Institute of Medicine (I0M), Food and Nutrition Board. Available at: http://www.nap.edu/cataloq.php?record id=13050.

It was noted by the IOM committee that "intakes of calcium from food do not readily result in excess intakes and are not associated with adverse effects; rather, the adverse effects appear to be a function of calcium supplementation added to baseline intake" (IOM, 2011)[3]. Although kidney stone formation does occur in younger adults, the IOM committee noted that it does not appear to be correlated with calcium supplement use, and thus established an UL of 2,500 mg/day for adults, including pregnant and lactating women, aged 19 to 30 and 31 to 50 years using an interpolation approach based on the mid-point between the UL for adolescents and persons greater than 50 years of age.

The European Commission's Scientific Committee on Food (SCF) established a UL of 2,500 mg/person/day from all sources for all age groups, including pregnant or lactating women, based on no adverse effects observed at this intake level in human studies (SCF, 2003)[4].

Calcium Chloride

Calcium chloride is chemically and toxicologically similar to sodium chloride (table salt) and potassium chloride. It readily dissociated into calcium and chloride ions in water. Both calcium and chloride ions are considered essential to human health[5]. Calcium chloride is considered as generally recognized as safe (GRAS) by the U.S. Food and Drug Administration as a direct food substance for anticaking, curing, flavor enhancing, as a nutrient supplement, pH control agent, stabilizer and other food uses[6].

Calcium chloride was considered to have low toxicity and an Acceptable Daily Intake (ADI) was not specified by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA).[7] An updated literature search revealed no new information that contradicts JECFA's earlier conclusion on calcium chloride or that of the GRAS status of calcium chloride.

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[4] SCF (2003). *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium* (expressed 4 April 2003). (SCF/CS/NUT/UPPLEV/64 Final). European Commission, Scientific Committee on Food (SCF). Available at:https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out194_en.pdf

[5] US EPA Office of Chemical Safety. Memorandum: Human Health and Environmental Risk Assessment for the New Active Ingredient, Calcium Chloride, for Use in a Moisture Absorber. Office of Chemical Safety and Pollution Prevention. July 1, 2016.

[6] Title 21—Food and Drugs, Chapter 1—Food and Drug Administration Department of Health and Human Services, Subchapter B—Food for Human Consumption. 21CFR184.1193., Revised as of April 1, 2013.

[7] Joint FAO/WHO Expert Committee on Food Additives. Toxicological Evaluation of Certain Food Additives with a Review of General Principles and of Speciation's. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 25 June – 4 July 1973.

As noted above, calcium chloride dissociates to calcium and chloride ions. Chloride is the most abundant anion in all animal species and the total chloride level in the adult human body is approximately 70-95 g. The biological and toxicological effects related to calcium intake have been extensively reviewed by both the Institute of Medicine (IOM, 2011) and the European Food Safety Authority (EFSA, 2012)[8]. As discussed above, based on calcium excretion in young children and formation of kidney stones in older children and adults, the IOM established tolerable upper limits (ULs) for infants 0-6 months (1,000 mg/day), infants 6-12 months (1,500 mg/day), children 1– 8 years (2,500 mg/day), adolescents 9-18 years (3,000 mg/day), adults 19 – 50 years (2,500 mg/day), and older adults 51+ years (2,000 mg/day). The IOM concluded that there were insufficient data to determine a UL based on other effects, including increased risk of cardiovascular disease (CVD) among post-menopausal women and older men. EFSA's most recent evaluation (2012) reached similar conclusions on the lack of adverse associations between calcium intake and CVD as well as other health endpoints but did not believe the available evidence required a revision of the UL of 2,500 mg/day for adults as previously established by the Scientific Committee on Food (SCF) in 2003. The literature published since the IOM review in 2011 did not indicate any new new data or assessments that would alter the significant scientific consensus presented in the IOM (2011) or the EFSA (2012) reviews.

Toxicological Studies

The published literature includes several animal toxicology studies and mutagenicity studies conducted with calcium chloride. The pertinent studies are summarized below.

- **Acute Toxicity**

The acute oral toxicity for calcium chloride ranges from1000 to 4179 mg/kg in rats and up to around 2000 mg/kg in mice. The acute dermal toxicity was reported to be >2000 mg/kg. Calcium chloride is non-irritating to slightly irritating to skin[9].

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[8] European Food Safety Authority (EFSA). Scientific opinion on tolerable upper intake level of calcium. EFSA Journal. 2012; 10(7):2814.
[9] IUCLID Dataset. Calcium Chloride. European Commission – European Chemicals Bureau. February 18, 2000.

- **Genotoxicity**[10]

In the reverse mutation assay conducted with *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537, with and without the S9 fraction, calcium chloride was found not to be mutagenic under the conditions of the test.

In an *in vitro* chromosomal aberration assay in Chinese Hamster Lung Cells (CHL), no significant increase in polyploid formation or structural chromosome aberrations were observed.

- **Short-Term/Subchronic Toxicity Studies**

Calcium chloride was administered at a level of 1% in the drinking water (10,000 ppm or 1 g/kg bw; n=24) or 2% in a goitrogenic basal diet (20,000 ppm or 2 g/kg bw; n = 71) over a period of 12 weeks to male and female rats that were 4 to 5 weeks old. Growth and survival of the animals were unaffected. Calcium chloride caused no thyroid enlargement when compared to that produced by the basal diet except for a slight increase in thyroid weight when vitamin D was present. No microscopic alterations were observed[11].

- **Chronic Toxicity**

A group of twenty 40-day old rats were administered 20 mg calcium chloride/g diet for 12 months. Based on the food consumption (22 g diet/day), the daily intake of calcium chloride was estimated to be 440 mg. Given that 1 mg/g diet is equivalent to 100 and 50 mg/kg bw/day for young and old rats, respectively, the dose used in this study (20 mg/g diet) corresponded to 1,000 to 2,000 mg/kg- bw/day. No difference in mortality, weight gain, or daily food consumption was observed between the test and the control groups. In addition, no neoplastic lesions were observed in gastrointestinal tract, urinary tract, liver, heart, brain or spleen of the animals. These results indicate that oral chronic administration of calcium chloride to rats at 1000 – 2000 mg/kg bw/day does not induce any adverse effects to rats[11].

[10] Hazardous Substances Data Bank (HSDB). Calcium Chloride HSDB No. 923. Reviewed on January 19, 2012.
[11] OECD SIDS. Calcium Chloride SIDS Initial Assessment Report for SIAM 15. Boston, USA October 22-25, 2002.

- **Developmental Toxicity**

A developmental toxicity study equivalent to OECD Test Guideline 414 examined the effect of calcium chloride on embryo lethality and teratogenicity in mice, rats and rabbits[12]. All animals were observed daily for appearance, body weight and behavior with particular attention to food consumption. The numbers of implantation sites, resorption sites, and live and dead fetuses were recorded when all dams were subjected to Caesarean section. All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations. The remaining two-thirds were examined for skeletal defects. The administration of calcium chloride had no clearly discernible effect on implantation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. These data show no toxic effects on dams or fetuses at doses up to 189 mg/kg bw/day (mouse), 176 mg/kg bw/day (rat) and 169 mg/kg bw/day (rabbit).

Overall Summary of Human and Animal Data

Calcium and chloride are both essential nutrients for humans as well as other animal species and daily human intake of more than 1000 mg of each is recommended. Calcium is essential for the formation and maintenance of bones and teeth, and for the regulation of various physiological functions such as neural transmission and muscle contraction. Chloride is also essential for the regulation of acid-base balance of the body and intracellular osmotic pressure and acid-base buffering.

For healthy humans, the Upper Limit (UL) for calcium is set at 2500 mg per day (equivalent to 6.9 g $CaCl_2$ per day) and the reference nutrient intake for chloride at 2500 mg/day (equivalent to 3.9 g $CaCl_2$ per day). Consistent with this, the establishment of the ADI for calcium chloride has not been deemed necessary by JECFA. When orally absorbed, the plasma concentrations of calcium and chloride ions are efficiently regulated by the hormonal systems and excess ions are rapidly excreted in the urine via glomerular filtration.

[12] OECD SIDS. Calcium Chloride SIDS Initial Assessment Report for SIAM 15. Boston, USA October 22-25, 2002.

Calcium chloride has low acute toxicity via oral or the dermal routes of exposure, it has been shown not to be genotoxic in a bacterial reverse mutation assay and an *in vitro* chromosomal aberration assay in CHL; and the oral repeat exposure studies show an oral no-observable effect-level comparable to 1000 to 2000 mg/kg- bw for 12 months.

Conclusion

A safety assessment regarding the use of calcium chloride as a component of an antibrowning formulation applied to processed fruits and vegetables was conducted by Dr. Nicholas Skoulis. Dr. Skoulis is an expert in assessing the safety of food ingredients and is highly qualfied to issue a determination regarding the GRAS status of calcium chloride. Dr. Skoulis's assessment is based on publically available safety data for calcium chloride and safety evaluations from other qualified scientific groups.

For the following reasons, Dr. Skoulis has concluded that calcium choride is GRAS when used as an antibrowing agent on processed fruits and vegetables.

- Calcium chloride is widely used in food and, pursuant to 21CFR §184.1193, calcium chloride has been affirmed as GRAS for several uses as a food ingredient.
- The Estimated Daily Intake (EDI) of calcium chloride from the antibrowing use is significantly lower than EDIs that have previously been considered GRAS by the scientific community (refer to GRAS Notice No. 634).
- The publically available safety studies for calcium and calcium chloride support the GRAS determination for the antibrowning use since no adverse effects of concern were observed at exposure levels that significantly exceed the EDI values for these substances.

It is the opinion of Dr. Skoulis and Wonderful Citrus that other qualified experts would concur with these conclusions.

(b) (6)

Nicholas P. Skoulis, Ph.D.
Senior Consulting Toxicologist

Part 7. References

Calcium Chloride http://www.chemspider.com/Chemical-Structure.23237.html

IOM (1997). Calcium. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (I0M). Washington (DC): National Academy Press (NAP), pp. 71-145. Available from: http://books.nap.edu/openbook.php?isbn=0309063507&paqe=71.

IOM (2011). *Dietary Reference Intakes for Calcium and Vitamin D.* Washington (DC): National Academy of Science (NAS), Institute of Medicine (I0M), Food and Nutrition Board. Available at: http://www.nap.edu/cataloq.php?record id=13050.

SCF (2003). *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium* (expressed 4 April 2003). (SCF/CS/NUT/UPPLEV/64 Final). European Commission, Scientific Committee on Food (SCF). Available at:https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out194_en.pdf

US EPA Office of Chemical Safety. Memorandum: Human Health and Environmental Risk Assessment for the New Active Ingredient, Calcium Chloride, for Use in a Moisture Absorber. Office of Chemical Safety and Pollution Prevention. July 1, 2016.

Title 21—Food and Drugs, Chapter 1—Food and Drug Administration Department of Health and Human Services, Subchapter B—Food for Human Consumption. 21CFR184.1193., Revised as of April 1, 2013.

Joint FAO/WHO Expert Committee on Food Additives. Toxicological Evaluation of Certain Food Additives with a Review of General Principles and of Speciation's. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 25 June – 4 July 1973.

European Food Safety Authority (EFSA). Scientific opinion on tolerable upper intake level of calcium. EFSA Journal. 2012; 10(7):2814.

IUCLID Dataset. Calcium Chloride. European Commission – European Chemicals Bureau. February 18, 2000.

Hazardous Substances Data Bank (HSDB). Calcium Chloride HSDB No. 923. Reviewed on January 19, 2012.

OECD SIDS. Calcium Chloride SIDS Initial Assessment Report for SIAM 15. Boston, USA October 22-25, 2002.

Thomas, Joseph

From: Eliot Harrison <eharrison@lewisharrison.com>
Sent: Monday, August 20, 2018 7:49 PM
To: Thomas, Joseph
Subject: RE: Questions for GRAS Notice GRN 000785
Attachments: GRASN 000785_20180820193758.pdf

Hi Dr. Thomas,
Response to questions for GRAS Notice 000785 are attached.
Best regards,
Eliot

From: Thomas, Joseph [mailto:Joseph.Thomas@fda.hhs.gov]
Sent: Monday, July 30, 2018 10:46 AM
To: Eliot Harrison
Subject: Questions for GRAS Notice GRN 000785

Dear Mr. Harrison,

Please find attached a letter requesting clarification of several issues with regard to GRN 000785.

Sincerely,

Joseph M. Thomas, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 301-796-9465
joseph.thomas@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

LEWIS &
HARRISON
Consultants in Government Affairs

2461 South Clark Street
Suite 710
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telephone 202.393.3903
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August 20, 2018

Joseph M. Thomas, Ph.D.
Consumer Safety Officer
Division of Petition Review (HFS-265)
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

re: GRAS Notice Number 000785
Calcium Chloride as a Component of an Anti-Browning Formulation Applied to Processed Fruits
Notifier: Wonderful Citrus, LLC
Your Letter Dated July 30, 2018

Dear Dr. Thomas:

On behalf of Wonderful Citrus, LLC ("WC"), I am responding to the questions and issues from your letter dated July 30, 2018 concerning the above referenced GRAS Notice. Each question/issue and our response is presented below. In addition, revised pages for the GRAS Notice are attached.

Question/Issue No. 1a: Please confirm that magnesium is an alkaline earth metal.

Response: WC concurs that magnesium is an alkaline earth metal. However, please note that the reference to magnesium chloride has been deleted from the revised page 6 of the GRAS Notice (attached).

Question/Issue 1b: Please confirm that sodium chloride is listed in 21 CFR §182.1(a).

Response: WC concurs that sodium chloride is listed in 21 CFR §182.1(a). The appropriate CFR section is included on the revised page 6 of the GRAS Notice.

Questions/Issues 2a and 2b: Please clarify whether the intended use for calcium chloride is on "vegetables" or "processed vegetables" and please comment on the rationale behind extrapolating dietary exposure from this use on vegetables using only data on processed apples.

Response: Wonderful is requesting that the GRAS Notice be modified to only include use of calcium chloride on processed fruits.

Question/Issue No. 3: Please correct the dietary calculations on page 8 and any sections in the submission relying on the resulting value for calcium residue levels.

Response: The correct calculations are on revised pages 6, 8, 12 and 13 of the GRAS Notice.

Question/Issue No. 4: Please summarize the conclusions of SCOGS Report #45 and discuss the published safety study by Smith (1940) that was mentioned in the SCOGS report.

Response: The subject SCOGS report and the Smith (1940) are discussed in the updated Part 6 (Safety Evaluation) for the GRAS Notice.

Question/Issue No. 5: Please clarify the acute oral toxicity references and values for calcium chloride.

Response: The appropriate reference and values for the acute oral toxicity values for calcium chloride are presented in the attached updated Safety Evaluation (Part 6 of the GRAS Notice).

Question/Issue No. 6: Please clarify the reference, species and value for the acute dermal toxicity study.

Response: The appropriate reference, value and species for the acute dermal toxicity study is presented in the attached updated Safety Evaluation. The >2000 mg/kg value reported in the original submission was a typographical error.

Question/Issue No. 7: Please provide the month and year of Wonderful Citrus' updated scientific literature search for calcium chloride and its ionic components.

Response: Information regarding the literature search is included in the updated Safety Evaluation.

If you have any questions about this response, please contact me at (202) 393-3903, ext. 114 or by e-mail at eharrison@lewisharrison.com.

Sincerely,

(b) (6)

Eliot Harrison
Agent for Wonderful Citrus

Part 2. The Identity, Method of Manufacture, Specifications and Physical and Technical Effect of the Notified Substance

Chemical and regulatory information regarding calcium chloride is presented below.

2.1 Identity

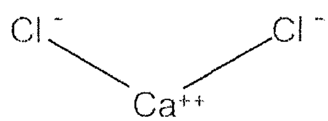
Common or Usual Name: Calcium chloride[1]

Chemical Name: Calcium chloride

Chemical Abstracts Service (CAS) Number: 10043-52-4

Empirical Formula and Formula Weight: $CaCl_2$

Chemical Structure:



Current Regulated Food Uses:

Calcium chloride is affirmed as Generally Recognized as Safe (GRAS), under 21 CFR §184.1193, for use in several types of food as an anticaking, antimicrobial, curing or pickling, firming, pH control, or surface active agent as well as a flavor enhancer, humectant, processing aid, stabilizer and thickener, synergist and texturizer. In addition, several calcium salts (calcium phosphate, calcium citrate, calcium hydroxide) and chloride salts of alkali metals (potassium chloride, and sodium chloride) have been affirmed as GRAS under either 21 CFR Part 182 or 184.

2.2 Manufacturing Information and Specifications

The notifier will purchase calcium chloride from suppliers that meet the manufacturing requirements in 21 CFR §184.1193 for calcium chloride.

[1] Calcium Chloride http://www.chemspider.com/Chemical-Structure.23237.html

Part 3. Dietary Exposure

3.1 Dietary Exposure from the Proposed Use

Dietary exposure to calcium chloride can result from the consumption of processed fruits that are treated with the antibrowning formulation containing calcium chloride. Since calcium chloride readily dissociates when diluted in water, dietary exposure will occur to calcium and chloride ions.

In a residue study conducted at California Polytechnic State University, residue levels of ascorbate, propionate and chloride were measured after treatment of pre-cut apples. The apples were submerged in the formulation containing these components (5% calcium ascorbate, 1% calcium propionate and 0.2% calcium chloride and then centrifuged and dried. The results are shown in Table 1 below.

Table 1
Average Residue Levels of Ascorbate, Propionate and Chloride
After Treatment with Antibrowning Formulation

Ingredient	Residue Level (mg/kg apple)
Ascorbate	736.18 Standard Deviation: 137.22
Propionate	147.22 Standard Deviation: 27.44
Chloride	29.44 Standard Deviation: 5.49

Although the residue levels of calcium were not assayed, the calcium level can be calculated by assuming that calcium and chloride ions are similarly retained on treated apples. Based on this assumption, the calcium residue is then derived by multiplying the chloride residue levels by the ratio of calcium to chloride in calcium chloride. Since the molar weight of calcium and chloride are 40 g/mol and 35.45 g/mol, respectively, and there are two moles of chloride per mole of calcium, the weight ratio is 40 ÷ (2 x 35.45) or 0.564. Therefore, the calcium residue is as follows:

Calcium Residue = Chloride Residue on Fruit (29.44 mg/kg fruit) × Ratio of Calcium to Chloride in Calcium Chloride (0.564)

Calcium Residue = 16.6 mg/kg fruit

Based on the residue levels for chloride and calcium (page 8 of this Notice) and the daily intakes for apples and lemons, the EDI for chloride and calcium from the use of the antibrowning formulation is shown below. It is assumed that the residue levels in lemons for chloride and calcium will be the same as those measured and calculated for apples.

Chloride

Child

- Apples:

  (48 g/day) (0.0294 g/1000 g of apples) = 1.41 x 10^{-3} g/day or 1.41 mg/day

- Lemons

  (3 g/day) (0.0294 g/1000 g of lemons) = 8.9 x 10^{-5} g/day or 0.08 mg/day

Accordingly, the total intake of chloride for children, at the 90th percentile, is 1.41 mg/day + 0.08 mg/day = 1.49 mg/day.

Adults

- Apples:

  (112 g/day) (0.0294 g/1000 g of apples) = 3.29 x 10^{-3} g/day or 3.29 mg/day

- Lemons

  (8 g/day) (0.0294 g/1000 g of lemons) = 2.3 x 10^{-4} g/day or 0.23 mg/day

Accordingly, the total intake of chloride for an adult, at the 90th percentile, 3.29 mg/day + 0.23 mg/day = 3.52 mg/day.

Calcium

Child

- Apples:

  (48 g/day) (0.0166 g/1000 g of apples) = 7.9 x 10^{-4} g/day or 0.79 mg/day

- Lemons

  (3 g/day) (0.0166 g/1000 g of lemons) = 4.9 x 10^{-5} g/day or 0.05 mg/day

Accordingly, the total intake of calcium for children, at the 90th percentile, is 0.79 mg/day + 0.05 mg/day =0.84 mg/day.

Adults

- Apples:

  (112 g/day) (0.0166 g/1000 g of apples) = 1.85×10^{-3} g/day or 1.85 mg/day

- Lemons

  (8 g/day) (0.0166 g/1000 g of lemons) = 1.3×10^{-4} g/day or 0.13 mg/day

Accordingly, the total intake of calcium for adults, at the 90th percentile, is 1.85 mg/day + 0.13 mg/day = 1.98 mg/day.

3.2 Dietary Exposure from Existing Uses

Dietary intake values for calcium and chloride have been reported in previously submitted GRAS Notices and are summarized below.

Calcium

The dietary intake of calcium was presented in GRAS Notice No. 634, https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf. The notice reported that for the U.S. population age, 1 year and older, the *per user* intake of calcium at the 90th percentile is 1,936 mg/day (see page 26 of the Notice). The EDI for calcium, from the use of calcium chloride as an antibrowning agent for processed fruits and vegetables, at the 90th percentile, is 0.84 mg/day (child) and 1.98 mg/day (adult). Consequently, the antibrowning use results in a daily intake that is < 1.0% of the total daily intake of calcium at the 90th percentile.

Chloride

According to GRAS Notice No. 634, the total amount of chloride in the adult human body is approximately 70-95 grams (see page 20 of the Notice). The chloride intake at the 90th percentile for antibrowning use of calcium chloride is 1.49 mg/day (child) and 3.29 mg/day (adult). These levels are an exceedingly small fraction of the total chloride level in the human body.

Part 6. Safety Evaluation and Basis for Our Conclusion of GRAS Status

It is well established that calcium chloride, when diluted in water will dissociate into calcium and chloride ions. Accordingly, the safety assessment focuses on these ions as well as calcium chloride.

Assessments from Authoritative Bodies

Calcium

In 1997, the Health and Medicine Division (HMD, formerly the Institute of Medicine) of the National Academy of Sciences established an Upper Limit (UL) for calcium of 2,500 mg/person/day from all sources (e.g., food and supplements) for all age groups, including pregnant or lactating women, based on the risk for hypercalcemia and renal insufficiency at intakes ranging from 4,000 to 5,000 mg of calcium/person/day and greater (IOM, 1997)[1]. A UL for infants, aged 0 to 12 months, could not be established due to insufficient data. Subsequently, the IOM/HMD was asked to review new data and, in 2011, published updated ULs (IOM, 2011)[2].

For infants, new data were available regarding calcium excretion that suggested that infants can tolerate intakes of up to approximately 1,750 mg/day. Thus, a no-observed-adverse-effect level (NOAEL) of 1,750 mg/day was established. For infants 0 to 6 months of age, an uncertainty factor of 2 was applied to account for body weight differences and the UL was set at 1,000 mg/day. The UL for infants aged 7 to 12 months was set at 1,500 mg/day since an increased capacity to handle calcium will accompany increased body size.

The UL for children aged 1 through 8 years was not changed and remains at 2,500 mg/day, whereas the UL for children aged 9 to 13 years and adolescents aged 14 to 18 years, including pregnant and lactating adolescents, was raised by 500 mg/day to 3,000 mg/day to account for the increase in bone accretion and likely accompanying increases in tolerated intakes. For adults, although the IOM/HMD recognized that hypercalcemia was an adverse

[1] IOM (1997). Calcium. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (IOM). Washington (DC): National Academy Press (NAP), pp. 71-145. Available from: http://books.nap.edu/openbook.php?isbn=0309063507&paqe=71.

[2] IOM (2011). *Dietary Reference Intakes for Calcium and Vitamin D.* Washington (DC): National Academy of Science (NAS), Institute of Medicine (IOM), Food and Nutrition Board. Available at: http://www.nap.edu/cataloq.php?record id=13050.

outcome, they noted it was a disease state and was not considered appropriate for the derivation of ULs of the normal, healthy population. Kidney stone formation was selected as the indicator, and an UL of 2,000 mg/day was set for adults aged 51 to 70 and greater than 70 years based on increased risk of kidney stone formation at higher intakes.

It was noted by the IOM/HMD committee that "intakes of calcium from food do not readily result in excess intakes and are not associated with adverse effects; rather, the adverse effects appear to be a function of calcium supplementation added to baseline intake" (IOM, 2011)[2]. Although kidney stone formation does occur in younger adults, the IOM/HMD committee noted that it does not appear to be correlated with calcium supplement use, and thus established an UL of 2,500 mg/day for adults, including pregnant and lactating women, aged 19 to 30 and 31 to 50 years using an interpolation approach based on the mid-point between the UL for adolescents and persons greater than 50 years of age.

The European Commission's Scientific Committee on Food (SCF) established a UL of 2,500 mg/person/day from all sources for all age groups, including pregnant or lactating women, based on no adverse effects observed at this intake level in human studies (SCF, 2003)[3].

Calcium Chloride

Calcium chloride is chemically and toxicologically similar to sodium chloride (table salt) and potassium chloride. As noted above, calcium chloride readily dissociates into calcium and chloride ions in water. Both calcium and chloride ions are considered essential to human health[4]. Moreover, chloride is the most abundant anion in all animal species and the total chloride level in the adult human body is approximately 70-95 g. Calcium chloride is considered as generally recognized as safe (GRAS) by FDA, as a direct food substance. for several types of food uses[5].

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[3] SCF (2003). *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium* (expressed 4 April 2003). (SCF/CS/NUT/UPPLEV/64 Final). European Commission, Scientific Committee on Food (SCF). Available at:https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out194_en.pdf

[4] US EPA Office of Chemical Safety. Memorandum: Human Health and Environmental Risk Assessment for the New Active Ingredient, Calcium Chloride, for Use in a Moisture Absorber. Office of Chemical Safety and Pollution Prevention. July 1, 2016.

[5] Title 21—Food and Drugs, Chapter 1—Food and Drug Administration Department of Health and Human Services, Subchapter B—Food for Human Consumption. 21CFR184.1193., Revised as of April 1, 2013.

Calcium chloride was considered to be a substance of low toxicity and an Acceptable Daily Intake (ADI) was not specified by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA).[6]

For FDA, the safety of calcium chloride was evaluated by the Select Committee on GRAS Substances (SCOGS). The SCOGS report[7] concluded that:

> "There is no evidence in the available information on calcium acetate, calcium chloride, calcium gluconate, and calcium phytate that demonstrates or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future".

An updated literature search revealed no new information that contradicts JECFA's earlier conclusion on calcium chloride or that of the GRAS status of calcium chloride.

In summary, the biological and toxicological effects related to calcium intake have been extensively evaluated in contemporary reviews conducted by the above referenced National Academy of Sciences (IOM, 2011) study and a recent study conducted by the European Food Safety Authority (EFSA, 2012)[8]. As discussed above, based on calcium excretion in young children and formation of kidney stones in older children and adults, the IOM/HMD established tolerable upper limits (ULs) for infants 0-6 months (1,000 mg/day), infants 6-12 months (1,500 mg/day), children 1– 8 years (2,500 mg/day), adolescents 9-18 years (3,000 mg/day), adults 19 – 50 years (2,500 mg/day), and older adults 51+ years (2,000 mg/day). The IOM/HMD concluded that there were insufficient data to determine a UL based on other effects, including increased risk of cardiovascular disease (CVD) among post-menopausal women and older men. EFSA's most recent evaluation (2012) reached similar conclusions on the lack of adverse associations between calcium intake and CVD, as well as other health endpoints, but did not believe the available evidence required a revision

[6] Joint FAO/WHO Expert Committee on Food Additives. Toxicological Evaluation of Certain Food Additives with a Review of General Principles and of Speciation's. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 25 June – 4 July 1973.

[7] Select Committee on Gras Substances (SCOGS). Evaluation of the Health Aspects of Certain Calcium Salts as Food Ingredients. Life Sciences Research Office Federation of American Societies for Experiential Biology. Contract No. FDA 223-75-2004. PB254539 (SCOGS-45), (1975).

[8] European Food Safety Authority (EFSA). Scientific opinion on tolerable upper intake level of calcium. EFSA Journal. 2012; 10(7):2814.

of the UL of 2,500 mg/day for adults as previously established by the Scientific Committee on Food (SCF) in 2003.

The literature published since the IOM/HMD review in 2011 did not indicate any new new data or assessments that would alter the significant scientific consensus presented in the IOM (2011) or the EFSA (2012) reviews.

Toxicological Studies

The published literature includes several animal toxicology studies and mutagenicity studies conducted with calcium chloride. The pertinent studies are summarized below.

- **Acute Toxicity**

The acute oral toxicity of calcium chloride has been reported to have an oral LD_{50} in rats of 3798 mg/kg (males) and 4179 mg/kg (females); the oral LD_{50} in mice was reported to be 2045 mg/kg (males) and 1940 mg/kg (females); and in rabbits the oral LD_{50} has been reported to be 500-1000 mg/kg[9]. The dermal toxicity was reported to be >5000 mg/kg (rabbit) and was sight to non-irritating to the skin and considered an irritant to the eyes[9].

- **Absorption, Metabolism and Distribution**

Calcium chloride readily dissociates to its respective ions, calcium ion and chloride counter-ion when placed in water. Chloride is absorbed from the intestines via co-transporters, which transports both sodium and chloride ions via active transport[10]. Calcium absorption across the intestinal wall is facilitated by vitamin D via active transport.

- **Genotoxicity**

In the reverse mutation assay conducted with *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537, with and without the S9 fraction, calcium chloride was found not to be mutagenic under the conditions of the test[11,12].

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[9] OECD SIDS Calcium Chloride, CAS# 10043-52-4. SIDS Initial Assessment for SIAM 15. Boston, MA USA 22-25th October 2002.

[10] Fordtran, J.S., Rector, F.C., and Carter, N.W. The Mechanisms of Sodium Absorption n the Human Small Intestine. The Journal of Clinical Investigation 47:884-900, (1968).

[11] Hazardous Substances Data Bank (HSDB). Calcium Chloride HSDB No. 923. Reviewed on January 19, 2012.

In an *in vitro* chromosomal aberration assay in Chinese Hamster Lung Cells (CHL), no significant increase in polyploid formation or structural chromosome aberrations were observed[12].

- **Short-Term/Subchronic Toxicity Studies**

Calcium chloride was administered at a level of 1% in the drinking water (10,000 ppm or 1 g/kg bw; n=24) or 2% in a goitrogenic basal diet (20,000 ppm or 2 g/kg bw; n = 71) over a period of 12 weeks to male and female rats that were 4 to 5 weeks old. Growth and survival of the animals were unaffected. Calcium chloride caused no thyroid enlargement when compared to that produced by the basal diet except for a slight increase in thyroid weight when vitamin D was present. No microscopic alterations were observed[9].

In a study conducted by Smith (1940)[13], calcium gluconate and calcium chloride were administered by gavage to two groups of ten rats, with calcium gluconate administered as a suspension and calcium chloride in a water solution. Each test animal received approximately 0.4 g of calcium per kg body-weight per day. Five of the animals receiving calcium chloride for 65 days and two receiving calcium gluconate for 70 days died prior to sacrifice. Microscopic examination of the heart, kidney and liver from animals given either calcium gluconate or calcium chloride did not shown any abnormalities. Smith (1940) concluded that calcium chloride was more toxic than calcium gluconate when given orally. Regarding the relative oral toxicity of calcium gluconate vs. calcium chloride, it was originally believed that calcium gluconate was metabolized by the liver to provide ionic calcium; however, Cote et al. (1987)[14] showed that calcium gluconate generated ionized calcium too rapidly when administered intravenously to be due to hepatic metabolism. Therefore, Smith's (1940)[13] conclusion that calcium chloride is more toxic than calcium gluconate, when adminstered orally at equal elemental calcium doses, must have been due to the fact that the calcium gluconate was administered as a dispersion and did not dissociate as rapidly in the gut as calcium chloride.

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[12] Ishidate, M., Jr., Sofumi, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matusuoka, A. Primary Mutagenicity Screening of Food Additives Currently Used in Japan. FD Chem. Toxic., 22:623-636, (1987)

[13] Smith. E. R. B. 1940. A comparison of the effects of large doses of calcium gluconate-idonate, calcium gluconate, and calcium chloride. J. Lab. Clin. Med. 25:1018-1021.

[14] Cote, CJ, Drop, LJ, Daniels, AL, and Hoaglin, DC. Calcium Chloride versus Calcium Gluconate: Comparison of Ionization and Cardiovascular Effects in Children and Dogs. Anesthesiology 66(4):465-470, April 1987.

- **Chronic Toxicity**

A group of twenty 40-day old rats were administered 20 mg calcium chloride/g diet for 12 months. Based on the food consumption (22 g diet/day), the daily intake of calcium chloride was estimated to be 440 mg. Given that 1 mg/g diet is equivalent to 100 and 50 mg/kg bw/day for young and old rats, respectively, the dose used in this study (20 mg/g diet) corresponded to 1,000 to 2,000 mg/kg- bw/day. No difference in mortality, weight gain, or daily food consumption was observed between the test and the control groups. In addition, no neoplastic lesions were observed in gastrointestinal tract, urinary tract, liver, heart, brain or spleen of the animals. These results indicate that oral chronic administration of calcium chloride to rats at 1000 – 2000 mg/kg bw/day does not induce any adverse effects to rats[9,15].

- **Developmental Toxicity**

A developmental toxicity study equivalent to OECD Test Guideline 414 examined the effect of calcium chloride on embryo lethality and teratogenicity in mice, rats and rabbits[9]. All animals were observed daily for appearance, body weight and behavior with particular attention to food consumption. The numbers of implantation sites, resorption sites, and live and dead fetuses were recorded when all dams were subjected to Caesarean section. All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations. The remaining two-thirds were examined for skeletal defects. The administration of calcium chloride had no clearly discernible effect on implantation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. These data show no toxic effects on dams or fetuses at doses up to 189 mg/kg bw/day (mouse), 176 mg/kg bw/day (rat) and 169 mg/kg bw/day (rabbit).

[15] World Health Organization (WHO) (1990). Environmental Health Criteria 104: Principles for the toxicological assessment of pesticide residues in food.

Overall Summary of Human and Animal Data

Calcium and chloride are both essential nutrients for humans as well as other animal species and daily human intake of more than 1000 mg of each is recommended. Calcium is essential for the formation and maintenance of bones and teeth, and for the regulation of various physiological functions such as neural transmission and muscle contraction. Chloride is also essential for the regulation of acid-base balance of the body and intracellular osmotic pressure and acid-base buffering.

For healthy humans, the Upper Limit (UL) for calcium is set at 2500 mg per day (equivalent to 6.9 g $CaCl_2$ per day) and the reference nutrient intake for chloride at 2500 mg/day (equivalent to 3.9 g $CaCl_2$ per day). Consistent with this, the establishment of the ADI for calcium chloride has not been deemed necessary by JECFA. When orally absorbed, the plasma concentrations of calcium and chloride ions are efficiently regulated by the hormonal systems and excess ions are rapidly excreted in the urine via glomerular filtration.

Calcium chloride has low acute toxicity via oral or the dermal routes of exposure, it has been shown not to be genotoxic in a bacterial reverse mutation assay and an *in vitro* chromosomal aberration assay in CHL; and the oral repeat exposure studies show an oral no-observable effect-level comparable to 1000 to 2000 mg/kg-bw for 12 months.

Multiple evaluations have been undertaken to demonstrate the nutritional significance of calcium as delivered as a consituent of food and has become very common. Previous assessments by the Joint FAO/WHO Expert Committee on Food Additives, concluded that the average daily intake of elemental calcium for man could extend to 2000 or even 3000 mg[16]. The current concentrations of calcium compounds commonly present in or as an additive to foods provides no information that even suggests possible adverse effects.

[16] Joint FAO/WHO Expert Committee on Food Additives. 1963. Calcium acetate and calcium chloride. Pages 49- 54 in Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers. stabilizers, bleaching and maturing agents. 7th rept. Food and Agriculture Organization of the United Nations, Rome, Italy.

Conclusion

A safety assessment regarding the use of calcium chloride as a component of an antibrowning formulation applied to processed fruits was conducted by Dr. Nicholas Skoulis. Dr. Skoulis is an expert in assessing the safety of food ingredients and is highly qualfied to issue a determination regarding the GRAS status of calcium chloride.

Dr. Skoulis's assessment is based on publically available safety data for calcium chloride and safety evaluations from other qualified scientific groups.

For the following reasons, Dr. Skoulis has concluded that calcium choride is GRAS when used as an antibrowing agent on processed fruits:

- Calcium chloride is widely used in food and, pursuant to 21CFR §184.1193, calcium chloride has been affirmed as GRAS for several uses as a food ingredient.
- The Estimated Daily Intake (EDI) of calcium chloride from the antibrowing use is significantly lower than EDIs that have previously been considered GRAS by the scientific community (refer to GRAS Notice No. 634).
- The publically available safety studies for calcium and calcium chloride support the GRAS determination for the antibrowning use since no adverse effects of concern were observed at exposure levels that significantly exceed the EDI values for these substances.

It is the opinion of Dr. Skoulis and Wonderful Citrus that other qualified experts would concur with these conclusions.

(b) (6) [redacted]

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Literature Search

An updated, comprehensive literature search and evaluation for use in the safety evaluation of calcium chloride and its ionic components was conducted on September 28, 2017. The following databases were searched.

- PubMed
- ToxPlanet (ChemExpert, ReproExpert, Toxline®Special, RTECS, HDSB®, ChemSpider, EFSA, IARC)
- GRAS Substance Database
- OECD Screening Information
- ECHA BPD/BPR/REACH Database