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Original Submission

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FOOD ADDITIVE SAFETY

August 11, 2004

Via Facsimile and Federal Express

Laura Tarantino, Ph.D.
Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety, HFS-200
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: GRAS Notification for Calcium Propionate; Our File No. BF4159

Dear Dr. Tarantino:

Pursuant to proposed 21 C.F.R. § 170.36(c) and on behalf of our client, Solutia, Inc., we hereby notify the Agency of our determination on the basis of scientific procedures that Solutia's calcium propionate manufactured from propionitrile and calcium hydroxide is generally recognized as safe (GRAS) for the uses and use levels identified in 21 C.F.R. § 184.1221, the GRAS affirmation regulation for calcium propionate. Three copies of Solutia's GRAS notification for its calcium propionate are enclosed.

We trust you will find the enclosed notification acceptable. Should any questions arise during the review process, please do not hesitate to contact us, preferably by telephone, so that we may respond as quickly as possible.

Very truly yours,

Melvin S. Drozen

Enclosures

cc: Don Lederer, Solutia

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OFFICE OF
FOOD ADDITIVE SAFETY

Before the
FOOD AND DRUG ADMINISTRATION
Department of Health and Human Services
Washington, D.C.

GRAS NOTIFICATION

Name of Notifier:	Solutia
Post Office Address:	All communications on this matter are to be sent in care of Counsel for the Notifier, Melvin S. Drozen, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001 Telephone: (202) 434-4222
Name of Substance and Intended Use:	Calcium propionate manufactured from propionitrile and calcium hydroxide for use as an antimicrobial agent
Dated:	August 11, 2004

Melvin S. Drozen
Counsel for Solutia

1. Claim of GRAS Exemption

(i) Name and Address of Notifier:

Solutia Inc.
575 Maryville Centre Drive
St. Louis
Missouri, 63141

All communications on this matter are to be sent in care of Counsel for the Notifier, Melvin S. Drozen, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001.
Telephone: (202) 434-4222

(ii) Common or usual name of the notified substance:

The common or usual name of the notified substance is calcium propionate (CaP). This substance is virtually identical to the CaP affirmed as generally recognized as safe (GRAS) under 21 C.F.R. § 184.1221. The only difference between the listed substance and the subject of this Notification is the method of preparation. Solutia's CaP is prepared by hydrolyzing propionitrile with aqueous calcium hydroxide, a process that deviates from the method described in 21 C.F.R. § 184.1221, in which propionic acid is directly neutralized with calcium hydroxide to form CaP.

(iii) Applicable conditions of use:

Calcium propionate produced as described herein is intended for use in food in a manner consistent with the scope of the GRAS affirmation regulation for calcium propionate, 21 C.F.R. § 184.1221. More specifically, calcium propionate will be used: (1) as an antimicrobial agent; (2) at levels not exceeding current good manufacturing practice in baked goods, cheeses, confections and frostings, gelatins, puddings and fillings, and jams and jellies.

(iv) Basis for GRAS determination

The described use of Solutia's CaP has been shown to be GRAS on the basis of scientific procedures, in accordance with 21 C.F.R. § 170.30, as discussed more fully in the accompanying summary of the basis for the GRAS determination.

(v) Statement of availability of data

The data and information that are the basis for the GRAS determination are available for the Food and Drug Administration's review and copying or will be sent to FDA upon request.

* * *

The foregoing and attached information considered, it is respectfully submitted that the use of CaP prepared as described is generally recognized as safe for use in various foods as an antimicrobial agent and is therefore exempt from the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act.

Respectfully submitted,

Solutia

By:_____

Melvin S. Drozen
Keller and Heckman LLP

COUNSEL FOR THE NOTIFIER

2. Identity of the Notified Substance

The notified substance is calcium propionate (CaP) prepared by the hydrolysis of propionitrile with aqueous calcium hydroxide (or its equivalent, slaked calcium oxide). This process yields calcium propionate and involves two distinct reactions: First, the alkaline hydrolysis of propionitrile to give propionamide (PAM), and then the reaction of PAM with calcium hydroxide to give CaP and ammonia.

$$CH_3CH_2CN + H_2O \xrightarrow{[OH^-]} CH_3CH_2CONH_2$$

$$2\ CH_3CH_2CONH_2 + Ca(OH)_2 \leftrightarrows Ca(CH_3CH_2CO_2)_2 + 2\ NH_3$$

Since the reaction of PAM to give CaP is reversible, ammonia must be stripped from the liquid phase to achieve complete conversion of the PAM. Following this, the mixture is neutralized with propionic acid, which reacts with excess calcium hydroxide to form additional CaP. This process differs from the conventional manufacturing process for CaP in which propionic acid is directly neutralized with calcium hydroxide.

Chemical Name:	Calcium propionate (CaP)
CAS Registry:	4075-81-4
Molecular and structural formula:	$Ca(CH_3CH_2CO_2)_2$ (Mol wt = 186.22)
Quantitative composition:	Complies with purity specifications set forth below.
Method of Manufacture:	The manufacturing process is summarized in Appendix 1.

Characteristic properties – The Solutia CaP produced from propionitrile described in this notification is highly purified calcium propionate. The CaP consists of white crystals, possessing not more than a faint odor of propionic acid. The pH of a 10% solution is 8.5. The

characterization of the major components in Solutia CaP is listed in Table 1, where Solutia CaP is compared with CaP manufactured by the conventional procedure.

Table 1

Calcium Propionate Characteristics – Major Components

Analyte	Solutia CaP Powder	Conventional CaP Powder
CaP (total basis)	97.70%	92.40%
CaP (dry basis)	98.73%	98.65%
Water	1.04%	6.34%
Magnesium	0.00%	0.19%
Chloride	0.12%	0.11%
Propionic acid	0.06%	0.19%
Free hydroxide	0.00%	0.03%
Insolubles	0.03%	0.40%
Trace impurities	0.11%	0.08%

Table 1 shows that the Solutia CaP from propionitrile is virtually identical to the conventional CaP and that no difference in functional effectiveness is expected or conceivable.

Content of potential human toxicants –

Known Impurities: Table 2 lists average concentrations of the identified trace impurities in both Solutia CaP from propionitrile and commercial CaP prepared by the conventional process. The trace organic impurities in Solutia CaP were identified and quantified by GC-FID, GC-MS, headspace GC-MS, electrospray LC-MS/MS, atmospheric pressure chemical ionization (APCI) LC-MS/MS or direct probe MS procedures down to low ppm levels. During the hydrolysis of propionitrile to CaP, the intermediate propionamide is formed. If the reaction does not proceed to completion some amide will remain in the final product. Another source of impurities arises from the hydrolysis of nitrile impurities in the

propionitrile. The major nitrile impurities in propionitrile are acrylonitrile and methacrylonitrile. These nitrile impurities hydrolyze to their corresponding acids; acrylic and methacrylic acids. Although the various carboxylic acids were analyzed and reported as the free acids, they are presumably present in the CaP as their calcium salts. Unconverted nitriles such as propionitrile, acrylonitrile, or methacrylonitrile are volatilized and removed in the ammonia removal step of the process. All other impurities are in the low ppm range and represent no conceivable toxicological concern because of the dilution of CaP in food. CaP is used in food at an average concentration of 73 ppm (see Section 4.ii. "Safety of Impurities in Solutia CaP") and any impurity present in CaP at 5 ppm or below would be consumed at a level below FDA's 0.5 part per billion threshold of regulation.

Differences in impurity levels from pilot plant to production lots: Solutia CaP from propionitrile has been scaled up from a 300 milliliter autoclave to a 300 gallon pilot plant. Further scale up to commercial reactors is expected to raise the level of propionamide in the Solutia CaP powder to as much as 100 ppm, predominately due to faster production rates reducing the time available for the propionamide to convert to CaP and differences in mass transfer. The variation in the propionitrile quality and scale-up issues similar to those cited for propionamide may also increase the levels of acrylic acid and methacrylic acid. The other impurities in Table 2 are not expected to change significantly. To provide a reliable specification we have assumed that acrylic acid and methacrylic acid may be produced at their stoichiometric maximums. If, therefore, the starting propionitrile contains 1000 ppm of acrylonitrile and 1000 ppm of methacrylonitrile (the anticipated maximum specification) the acrylic acid level may increase to a maximum of 804 ppm and methacrylic acid may increase to a maximum of 759 ppm. We show below that even these higher levels are safe. (*See* Section 4.ii. "Safety of Impurities in Solutia CaP".)

Table 2

Calcium Propionate Characteristics – Trace Impurities

Impurity	Solutia CaP Powder	Conventional CaP Powder
Ammonia	nd	nd

Propionamide	nd	na
Propionitrile	nd	na
Acetic Acid	32 ppm	481 ppm
Butyric Acid	10 ppm	nd
Isobutyric Acid	10 ppm	nd
Acrylic Acid	292 ppm	5 ppm
Methacrylic Acid	280 ppm	nd
Valeric Acid	10 ppm	nd
Isovaleric Acid	10 ppm	nd
Caproic Acid	18 ppm	10 ppm
Isocaproic Acid	10 ppm	nd
Fluoride	nd	nd
Sodium	124 ppm	131 ppm
Arsenic	nd	nd
Sulfur	142 ppm	119 ppm
Potassium	115 ppm	56 ppm
Phosphorous	nd	11 ppm
Iron	2 ppm	nd
Lead	nd	nd
Cadmium	nd	nd
Nickel	nd	nd
Total	0.11%	0.08%

Other Impurities – In addition to the impurities listed and characterized in Table 4, several trace impurities were detected in Solutia CaP at levels in the 1-15 ppm range.[1] Five independent mass spectroscopic techniques were employed to identify them: GC-MS,

[1] These analyses are based on five batches of Solutia CaP from the pilot plant that are as representative as possible of the process that will be used to produce the marketed product. The analysis of an earlier sample, which was produced on a smaller scale than the pilot plant, using different conditions and different feedstock qualities, may have contained as many as 10 unidentified impurities. Only four unknowns were found in the later pilot plant batches using the conditions and feedstocks intended for the commercial process.

headspace GC-MS, electrospray LC-MS, atmospheric pressure chemical ionization (APCI) LC-MS and direct probe MS. A total of four unknown peaks were detected, all by APCI LC-MS analyses. The chemical structures of these trace impurities were not immediately apparent but an effort, using LC-MS/MS, was made to identify them and to rule out structures that were possibly potent carcinogens and therefore a potential risk at these low levels. None of the impurities found contained chlorine or bromine. Acrylamide and acrylonitrile were also specifically searched for and were not detected.

Further research on the identity of the four unknown impurities revealed likely structures for three of these impurities. These are 5-methyl-2-furamide (Mol wt = 125), 2-methyl-4,6-diethyltriazine (Mol wt =151) and, 2,4,6-triethyltriazine (Mol wt = 165). The fourth impurity (Mol wt = 221) had too many possible empirical formulas and isomers to be extrapolated with any reliability.

Food-Grade Specifications – Using *Food Chemicals Codex* specifications, analysis of Solutia CaP powder produced by the proposed process is compared with the analysis of CaP powder produced by the conventional process in Table 3.

Table 3
Food Chemicals Codex Analysis of Calcium Propionate

Analysis: Specification	Solutia CaP Powder	Conventional CaP Powder
Calcium: Positive Test	Positive Test	Positive Test
Assay: 98% -100.5% (anhydrous basis)	99.73%	98.65%
Fluoride: ≤0.003%	<0.0001%	nd
Insoluble Substances: ≤0.2%	0.03%	0.4%
Magnesium: Pass Test (about 0.4% as MgO)	Pass Test	Pass Test
Lead: ≤2 mg/kg	<2 mg/kg	< 2 mg/kg
Water: ≤5.0%	1.04%	6.34%

Appearance: White Crystals or Crystalline Solid	White Crystalline Solid	White Crystalline Solid
pH of 10% soln: 7.5 – 10.5	8.5	8.5
Water Solubility: 1 gram in about 3 mL of water	Pass Test	Pass Test

Solutia's assay of CaP produced by the conventional process did not meet the *FCC* requirements for insoluble substances and water content. The high value of the water content may be due to absorption of water from the atmosphere. The specifications for the Solutia CaP from propionitrile meet or exceed the requirements for food-grade CaP listed in the *Food Chemicals Codex* (5th Edition, 2003).

3. Self-Limiting Levels of Use

Calcium propionate is affirmed as GRAS for use as an antimicrobial under 21 C.F.R. § 184.1221 with no limitation on the level of use other than current good manufacturing practice (gmp). There is no obvious self-limit on the level of use. In commercial practice the amount of calcium propionate used will be limited by cost and the possibility of imparting off-tastes or textures to food when gmp concentrations are exceeded.

4. Summary of Basis for GRAS Determination

(i) Safety of CaP

Solutia's CaP from propionitrile is substantially equivalent to the CaP prepared by the conventional neutralization of propionic acid with calcium hydroxide, which is affirmed as GRAS in 21 C.F.R. § 184.1221. This is substantiated by the discussion above on manufacture of CaP and its chemical characteristics. The composition of the impurities produced by the new manufacturing process is slightly different from that produced by the conventional manufacturing process; although the overall assay of 98.73% on an anhydrous basis is virtually the same as the 98.65% for CaP produced by the conventional process. To assure that the

impurities in Solutia's CaP do not represent any concern, they have been identified, quantitated and determined to be safe.

(ii) Safety of Impurities in Solutia CaP

Estimate of dietary exposure. The exposure estimate for CaP that forms the basis for the impurity intake estimates in Table 4 is based on known CaP production volume data. Approximately 50 million pounds of CaP is currently produced in the United States each year. Solutia will produce approximately one half of this amount.[2] For intake estimate purposes, we assume that all individuals in the U.S. population of 290 million consume CaP. This is a reasonable assumption because of CaP's varied use in widely consumed foods. From its affirmed uses in baked goods, cheeses, confections, frostings, gelatins, jams and jellies as an antimicrobial agent it can be inferred that CaP is widely distributed in the food supply and it is unlikely that special population groups will consume CaP at substantially higher levels than the average. We also assume (in keeping with FDA practice in estimating exposure) that the Solutia CaP product may eventually achieve 100% market penetration. The calculated average intake of CaP per day is then [(50,000,000 pounds/year) × (454 grams /pound)] ÷ [(290,000,000 persons) × (365 days/year)] = 0. 22 g/person/day or 3.7 mg/kg.bw/day. Using FDA's default assumption that an individual consumes 3,000 grams of food each day, the average intake is equivalent to (0.22 g/p/d) ÷ (3,000 g food/p/d) = 73 ppm. Multiplying 73 ppm by the concentration of various impurities in the CaP gives the maximum potential dietary exposure to the impurities. For example, for an impurity present at 5 ppm in CaP, the dietary exposure is 0.37 ppb: (5 ppm × 73 ppm = $365 \times 10^{-12} = 0.37 \times 10^{-9}$ = 0.37 ppb). Thus, any impurity present at less than 5 ppm in the product would be diluted in the diet to less than 0.5 ppb, below the Threshold of Regulation. While the Threshold of Regulation, *per se,* applies to food contact substances, rather than to direct additives, the toxicological principles and analysis on which it is based are valid for all types of added chemical substances present at low concentration in foods regardless of the source of the substance.

[2] See memo from Don Lederer, Product Steward, Solutia Inc., regarding information on current annual CaP production volume, July 8, 2004. Attached as Appendix 2.

The identity, concentration, and estimated dietary exposure of the major impurities in Solutia CaP are provided below in Table 4.

Discussion of Safety - Table 4 divides the known impurities into two groups. The first group contains substances cleared for use in food as direct additives or flavors: acetic acid, butyric acid, isobutyric acid, caproic acid, isocaproic acid, valeric acid and isovaleric acid. These substances all occur naturally in food or are cleared for food use at levels higher than or similar to those anticipated from Solutia CaP.[3] The second group contains three chemicals, acrylic acid, methacrylic acid and propionamide, which, to our knowledge, have no clearances for use in food either as direct additives or flavoring substances. Their safety is discussed below.

Table 4

Identity and Maximum* Concentrations of Known Organic Impurities in Solutia CaP Not Found in GRAS Affirmed CaP

Known Organic Impurities	Maximum Concentration in CaP	Maximum Concentration in Diet
Substances cleared by FDA for use in food at similar or higher levels:		
acetic acid	32 ppm	**2.3 ppb** [32 ppm x 73 ppm = 2.3 ppb]
butyric acid, isobutyric acid	10 ppm, 10 ppm	**0.7 ppb, 0.7 ppb** [10 ppm x 73 ppm = 0.7 ppb] [10 ppm x 73 ppm = 0.7 ppb]
caproic acid, isocaproic acid	18 ppm, 10 ppm	**1.3 ppb, 0.7 ppb** [18 ppm x 73 ppm = 1.3 ppb] [10 ppm x 73 ppm = 0.7 ppb]
valeric acid, isovaleric acid	10ppm, 10 ppm	**0.7 ppb, 0.7 ppb** [10 ppm x 73 ppm = 0.7 ppb] [10 ppm x 73 ppm = 0.7 ppb]
Substances not cleared for use in food, but present in Solutia CaP:		

[3] The fatty acids listed occur naturally in foods (caproic, isocaproic, butyric, isobutyric) and/or are cleared, GRAS listed or GRAS affirmed for direct use in foods (acetic, 21 C.F.R. § 184.1005; butryric, § 182.60; valeric and isovaleric, § 172.15).

acrylic acid	804 ppm*	**59 ppb** [804 ppm x 73 ppm = 59 ppb]
methacrylic acid	760 ppm*	**55 ppb** [760 ppm x 73 ppm = 55 ppb]
propionamide	100 ppm*	**7.3 ppb** [100 ppm x 73 ppm= 7.3 ppb]
*These levels are upper limits. The acrylic and methacrylic acid levels represent theoretical maximum levels based on an assumed stoichiometric conversion of 1000 ppm of acrylonitrile and methacrylonitrile impurities in the starting propionitrile. The 100 ppm propionamide figure represents the level to which propionamide will be limited via the controlled removal of ammonia during production.		

Acrylic acid

Acrylic acid (propenoic acid) migrates into food from several cleared food packaging sources. FDA has calculated the total dietary exposure (EDI) from all the cleared uses at 33.5 ppb. The FDA acceptable daily intake (ADI) for acrylic acid is 8.1 mg/p/d (0.1 mg/kg.bw/day) or 8.1 mg/p/d/3kg/p/d = 2.7 ppm in the diet. (*See* FDA Interoffice Memo from Allan B. Bailey, Division of Product Safety, Scientific Support Branch (HFS-207), to Vivian Gilliam, Petition Control Branch. *See also* FDA Website CEDI (cumulative estimated daily intake) list for Indirects.) The exposure estimate of 59 ppb for acrylic acid in food from the use of Solutia's CaP from propionitrile (Table 4) is comparable to that from individual food packaging uses and much less than the FDA ADI. Acrylic acid represents no safety risk at this level.

Methacrylic acid

Methacrylic acid (MAA) is methyl substituted acrylic acid. The methyl ester of MAA is methyl methacrylate. Studies on both acrylic acid and methyl methacrylate are far more extensive than those on MAA itself, and, to a large extent, past reviews of MAA toxicity have relied on its similarity to these compounds. The toxicity of methacrylic acid was most recently assessed by the European Chemicals Bureau.[4] Methyl methacrylate in fact is readily metabolized to MAA in mammals and administering it is a recognized technique of achieving exposure to MAA.[5]

[4] European Union, Existing Substances, 1st Priority List, Vol 25. EU Risk Assessment Report, Methacrylic Acid, EUR 19837 N, 2002.

Acute toxicity, oral - The acute data that exist for both acrylic and methacrylic are very limited and variable, but the two chemicals appear to be of broadly equivalent toxicity with LD_{50} in the range of 2,000-10,000 mg/kg (RTECS database).[6] The oral LD_{50} values for methyl methacrylate have been reported in the range of 7,550- 9,440 mg/kg (EU, 2002).[7]

Subchronic toxicity - There are no repeated dose data on MAA; but there are data on methyl methacrylate. Methyl methacrylate, the most widely tested member of the methacrylate esters, rapidly hydrolyzes into methacrylic acid (Bereznowski, 1995). It is considered a worst case surrogate for methacrylic acid because of its lipophilicity and greater absorption.

An early 2-year oral chronic study in dogs and rats treated with methyl methacrylate revealed no adverse effects other than decreased weight gain in the high-dose dogs and elevated kidney weights in the high-dose rats.[8] The no observed adverse effect level (NOAEL) for methyl methacrylate was established at 200 mg/kg bw from the two-year drinking water study in rats by Borzelleca *et al.* All three substances, acrylic acid, methyl methacrylate and methacrylic acid, are negative in the usual *Salmonella typhimurium* tester strains.[5, 9] Based on these comparisons, it is reasonable to assume that the toxicities of methacrylic acid, acrylic acid and methyl methacrylate are approximately the same. This is also obviously supported by their close structural similarity. The EU Scientific Committee for Food recommended a group total daily intake of 0.1 mg/kg bw/day (temporary TDI) for all methacrylates (including both methacrylic acid and acrylic acid) based on a two-year oral

[5] Bereznowski Z (1995) In vivo assessment of methyl methacrylate metabolism and toxicity. Int J. Biochem. Cell Biol. 27:1311-1316.
[6] Oral LD_{50} values reported for methacrylic acid range from 2,260- 9,400 mg/kg in rats and 1,600 mg/kg in mice. Corresponding LD_{50}s for acrylic acid are 340-2590 mg/kg in rats and 830 mg/kg in mice. RTECS On Line (STN) data base.
[7] European Union, Existing Substances, 1st Priority List, Vol 22. EU Risk Assessment Report, Methyl methacrylate, EUR-19832-N, 2002.
[8] Borzelleca JF, Larsen PS Hennigar GR, Huf EG, Crawford EM, Blackwell Smith R (1964) Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol. Appl. Pharmacol. 6:29-36.
[9] Waegemaekers, THJM and Bensink MPM (1984) Non-mutagenicity of 27 aliphatic acrylate esters in the Salmonella-microsome test. *Mutation Research,* 17, 95-102.

study in rats and several other studies with methyl methacrylate (EUR 19837 N, 2002).[10] This ADI is identical with FDA's value of 0.1 mg/kg bw/day for acrylic acid. The estimated maximum dietary concentration of methacrylic acid from Table 4 is 55 ppb, in the same range as acrylic acid. If the toxicological equivalence of the two substances is assumed, then the amount of methacrylic acid present is still far under the ADI for acrylic acid (2.7 ppm in the diet) (2,700/ 55 = 49). Accordingly, we believe that there are no safety concerns with the anticipated levels of methacrylic acid from consumption of CaP.

Propionamide

The dietary level of propionamide from CaP is very small, < 7.3 ppb. Based on information about its physiological properties, there is, in fact, no reason to question the safety of this level of propionamide. Propionamide (CAS 79-05-0) is the third member of a class of simple carboxylic amides, distinguished (with the possible exception of formamide) by their lack of toxicity in virtually any animal. Regarding the reason the amides are not toxic, Patty's states, "the lack of cumulative or other toxic effect is probably explained by their relatively rapid hydrolysis to the corresponding acid or in some cases their excretion in the urine unchanged."[11]

Propionamide is used in modern neurotoxicology as a non-toxic control for acrylamide, its neurotoxic, unsaturated analogue. It can be injected intraperitoneally in rats at doses of 49 mg/kg without effect.[12] There are little specific toxicological data on propionamide, but RTECS gives a lowest intravenous effect-dose in the rabbit of 230 mg/kg bw. The site of propionamide metabolism appears to be the liver where there are nonspecific amidases, which would likely metabolize propionamide to propionic acid.[13] This is the generic metabolic reaction that applies to many amides (Casarett and Doull's Toxicology, 3rd Ed., p. 72 , 1986). It is not known whether this precise reaction occurs with propionamide in

[10] Directorate Generale III, EC Synoptic Document 7 Draft of provisional List of monomers and additives used in the manufacture of plastics and coatings intended to come in contact with foodstuffs, CS/PM2356, 15.05.1994.
[11] *Patty's Industrial Hygiene and Toxicology,* 2nd Revised Edition (1963).
[12] Reagan *et al., NeuroChem. Int'l* 25(2) 133-143 (1994).
[13] Bray *et al., Biochem. J.* 44:618 (1949); 45:467 (1949); 47:294 (1950).

humans, but, based solely on its structure, propionic acid is a likely metabolite. Propionic acid is, of course, the acid form of propionate salts.

We have not found a 90-day subchronic study on propionamide and there are very few acute studies. The absence of any repeated-dose studies in this case for such a well-known substance probably means that propionamide has not been of sufficient toxicological concern to warrant such testing. One would certainly expect that the corresponding acid, in this case propionic acid, to serve as a conservative toxicological surrogate for propionamide. Based on this, it is clear that the NOAEL for propionamide would be in the range of 1 g/kg/day, tens of thousands of times higher than the exposure level from its presence in CaP.

Propionic acid is GRAS affirmed under 21 C.F.R. § 184.180 for use in food with no limitation except gmp's. Propionic acid was reviewed as a food ingredient by JECFA in 1973.[14] There are long-term studies in rats fed diets containing 0.075% (750 ppm) and 3.75% (37.50 ppm) in baked bread for one year. There was no effect on growth, mortality, body weight or on any gross anatomical or histological observation. Based on their review of the toxicology data, JECFA did not limit the acceptable daily intake of propionic acid. We believe this conclusion also supports the safety of low doses of propionamide which in the stomach will metabolize to propionic acid. The anticipated exposure to propionamide from the proposed use is 73 ppm x 100 ppm or 7.3 ppb.

Other Impurities

As indicated in Section 2, four other trace impurities were detected at levels in the 1-15 ppm range. These are likely to be 5-methyl-2-furamide, 2-methyl-4,6-diethyltriazine, and 2,4,6-triethyltriazine. The fourth impurity had too many possible empirical formulas and isomers to be structurally characterized. Triazines are known to form from nitriles at high temperatures. The 2,4,6-triethyltriazine would be formed from the cyclization of three molecules of propionitrile while the 2-methyl-4,6-diethyltriazene would be formed from the cyclization of two molecules of propionitrile and one molecule of acetonitrile (an impurity in

propionitrile). At these concentrations in Solutia's CaP, these impurities would be present in food at levels near if not below 0.5 ppb.

Triazine is the nucleus of a major class of herbicides (e.g., atrazine and simazine). All of these triazine herbicides are various substituted derivatives of the triazine molecule, which gives them their different herbicidal activities. Because of their commercial importance, the toxicity of the triazine herbicides has been extensively studied and reviewed. Reviews by Hauswirth and Wetzel (1998)[15] and by Eldridge *et al.* (1999)[16] show that this class of compounds possesses a very low acute toxicity in animals, is not genotoxic or mutagenic, and does not possess estrogenic agonist activity. The lowest NOAELs for atrazine and simazine are in the range of 5 mg/kg bw/day (300 mg/p/d) for reproductive and developmental toxicity. These NOAELs imply ADIs of 3.0 mg/p/d or acceptable dietary levels of approximately 1.0 ppm. As indicated in Table 4, impurities in the range of 5-10 ppm in CaP translate to levels of 1 ppb in the food, approximately 1000 times below a reasonable ADI.

A search of the literature did not reveal any known carcinogenicity or mutagenicity of either 5-methyl-2-furamide or the alkylated triazines as a class. While more complex chlorinated, ammoniated, or methoxylated triazine derivatives constitute an important class of regulated herbicides, the simple alkylated triazines above would not be expected to possess any herbicidal activity.

(iii) Basis for Concluding that the Notified Use of CaP Is GRAS

General recognition of safety based on scientific procedures requires (1) that a substance (as a whole) is generally recognized as safe on the basis of a scientific evaluation of toxicity and level of use, and (2) that the scientific information on which this assessment is

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[14] Joint Expert Committee on Food Additives, 17th Meeting (June-July 1973, WHO/FAO).
[15] Hauswirth JW and Wetzel LT (1998) Toxicity characteristics of the 2-chlorotriazines: atrazine and simazine. In Ballantine IG, McFarland JE, Hackett DS editors, "Triazine Herbicides: Risk Assessment". Washington D.C. Oxford University Press, 1998 pp 370-83.
[16] Eldridge JC, Wetzel LT, Stevens JT, and Simpkins JW (1999) The mammary tumor response in triazine-treated female rats: A threshold-mediated interaction with strain and species-specific reproductive senescence. *Steroids* 64: 672-678.

based is generally available (21 C.F.R. § 170.30). This scientific information is ordinarily based on published studies, which may be corroborated by unpublished studies and other data. These two specified findings have already been established for CaP produced by the conventional process as evidenced by its GRAS affirmation at 21 C.F.R. § 184.1221. In the present Notification, because we are requesting only a new method of production for the same substance (CaP), the salient issue is whether the new process produces CaP that is substantially equivalent to that made by the conventional process. The safety of possible new impurities that may be introduced by this new method of production is the substantive new scientific question.

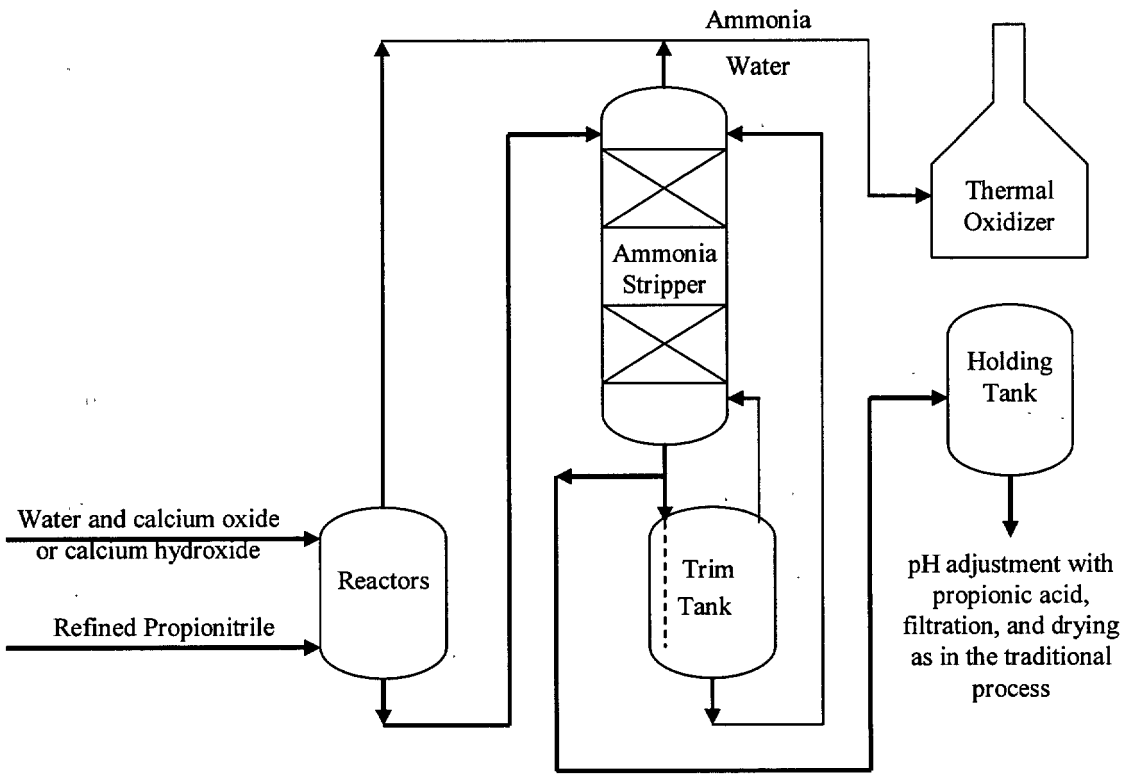
Analytical data presented above identify and quantitate the impurities present in Solutia CaP derived from propionitrile down to the low parts per million level. Unidentified impurities at this level or lower are quantitated above, and shown not to consist of specific, potentially harmful substances. The intake of the notified product will be less than 250 mg/p/d or 4.2 mg/kg bw /day for a 60 kg person (*see "Estimate of dietary exposure"* within Section (ii) Safety of Impurities in Solutia CaP). This intake estimate reduces the potential level of impurities in the diet to fractional ppb levels. Based on the known chemical structures of these substances, their established toxicities and their well-known physiological properties, we have shown that these substances, individually, are safe. In the case of propionamide we have relied upon the established relationship between propionamide and its more reactive, corresponding acid. Based on the totality of this information we believe that any differences between these impurities and those resulting from the conventional process of manufacturing CaP are insignificant.

The foregoing and attached information considered, it is respectfully submitted that, under the conditions of intended use, Solutia's CaP from propionitrile, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because it is generally recognized as safe.

Appendix 1

Simplified Process Flow Diagram

(major equipment only, no utilities)



Production Steps

1. Charge water and calcium oxide or calcium hydroxide to the reactor (the same raw material as is used in the traditional process)
2. Heat to nearly reaction temperature (approximately 200° C) under pressure (approximately 250 psig)
3. Add propionitrile slowly, heat of reaction raises reaction temperature to approximately 200° C
4. Hold at 200° C to complete the reaction
5. Vent reactor to remove most of the byproduct ammonia (with water)
6. Feed the product from the reactor to the ammonia stripper to remove the residual ammonia
7. Circulate the product from the trim tank to the ammonia stripper to remove the last traces of ammonia
8. Divert the product to the holding tank when the ammonia specification has been attained
9. Adjust the pH to the specification with propionic acid as in the traditional process
10. Filter and dry as in the traditional process

Appendix 2

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Solutia's estimate that the current annual production of calcium propionate in the United States is 50 million pounds is based on information found in the following:

- A July 2001 *Chemical Economics Handbook* (CEH) article published by SRI International on propionic acid which shows that 43 million pounds was used to produce calcium and sodium propionate in 2000. Based on historical data, this extrapolates to 45 million pounds of propionic acid produced in 2005 which, in turn, could produce 57 million pounds of calcium propionate assuming that no sodium propionate is produced.
- A chemical profile for propionic acid published by the Innovation Group (www.the-innovation-group.com) shows a production volume of 44 million pounds in 2002.
- Information published by the United States International Trade Commission in *Synthetic Organic Chemicals – United States Production and Sales 1994* puts calcium propionate production at 44 million pounds. This number is 93% of the number of the CEH production estimate for the same year. Therefore, it is assumed that 93% of the production numbers published by SRI in the CEH reference are calcium propionate and 7% are sodium propionate.
- A 1999 SRI International *Specialty Chemical* article on food additives lists the 1998 US consumption of calcium and sodium propionate at 34 million pounds. Comparing this to the 42 million pounds produced in 1998 that was reported in the CEH article referenced above suggests that 80% of the total production is consumed as a food additive.
- A 2002 Technical Advisory Panel (TAP) review published by the Center for Food and Nutritional Policy (CFNP) showed the following estimates of calcium and sodium propionate usage: Baked Goods, 80%; Feed Grain, 10%; and Miscellaneous, 10%.
  This suggests that no more than 90% of the calcium propionate will be used as a food additive. Assuming that only 80% (SRI International) to 90% (CFNP) of the calcium propionate produced is used as a food additive, the 2005 consumption is estimated to be from 38 to 48 million pounds.
- According to the public 2002 EPA Inventory Update Rule, Solutia Inc. is believed to be the only manufacturer of propionitrile in the US. The company's maximum annual capacity of propionitrile would be produce 42 million pounds of calcium propionate per year.

In summary, the annual consumption of calcium propionate has been reported to be from 38 to 48 million pounds per year which is supported by annual production numbers of 42 to 53 million pounds per year. Therefore, an estimate of 50 million pounds per year of calcium propionate production is considered reasonable.

Submission End