Part II Identity, method of manufacture, specifications, and physical or technical effect (170.230)

A) Common name:

calcium acid dihydrogendiphosphate

B) Trade names:

calcium acid diphosphate; calcium acid pyrophosphate diphosphoric acid, calcium salt (1:1); calcium dihydrogenpyrophosphate; INS 450(vii); E450(vii)

C) Chemical name:

calcium dihydrogen diphosphate

D) CAS Registry#:

14866-19-4 (anhydrous form)

E) Empirical formula:

$CaH_2P_2O_7$

F) Structural formula:

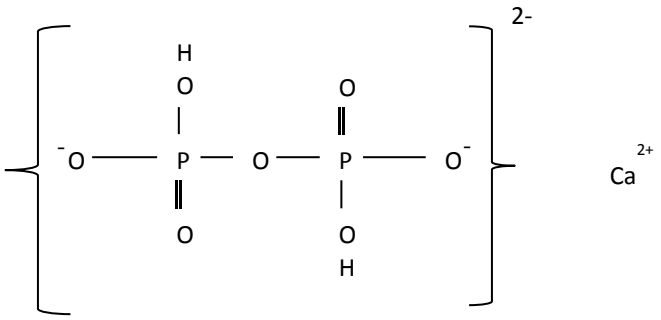

Figure 1 - structural formula of calcium acid pyrophosphate

Calcium and magnesium salts always occur naturally besides each other, at least at low quantities. Calcium hydroxide or calcium carbonate (potential raw materials) in the production process) have magnesium contents of less than 2 % in the raw material.

Considering the available purities of raw materials, it is possible without any significant limitation of raw material sources to limit the levels of Pb, As, Cd and Hg to 1 ppm (on an as is basis).
Aluminium is a naturally occurring contaminant of calcium and magnesium salts, contents varying from continent to continent, even within one country significantly from source to source. Substance analysis of 13 commercial batches (from 2014- 2016) gave the following results:

Aluminum: 105.3 ppm (average) ; 85 ppm (minimum); 130 ppm (maximum)
Lead: 0.9 ppm (average) ; 0.5 ppm (minimum); 1.0 ppm (maximum)
Arsenic: 1.0 ppm (average) ; 1.0 ppm (minimum); 1.0 ppm (maximum)
Cadmium: 0.7 ppm (average) ; 0.5 ppm (minimum); 1.0 ppm (maximum)
Mercury: 0.5 ppm (average) ; 0.5 ppm (minimum); 1.0 ppm (maximum)
Fluoride: 1.3 ppm (average) ; 1 ppm (minimum); 2 ppm (maximum)

A microbiological contamination is very unlikely due to the extreme conditions of production with product temperatures above 200°C and the absence of suitable growth media.

G) Method of manufacture

Calcium acid pyrophosphate is produced from two main raw materials, either calcium hydroxide (lime, $Ca(OH)_2$)or calcium oxide (burned lime, CaO) or calcium carbonate ($CaCO_3$) or a combination thereof and phosphoric acid (H_3PO_4). The raw materials need to be of an adequate quality to assure food safety requirements.

The process is as follows:

a. *The calcium source is being dispersed into an aqueous dispersion*
b. *The calcium dispersion is then slowly added to the phosphoric acid until a molar ratio between Ca:P of about 1:2 is reached, holding the temperature below 70°C during the reaction. In case Calcium carbonate was used, a release of carbon dioxide occurs.*
c. *About 0.1% hydrogen peroxide is added as processing aid in order to oxidize all potential ingredients (equipment protection).*
d. *The slurry is then processed in a drum-dryer between 200 – 230°C (product temperature), water and remaining hydrogen peroxide evaporate. Alternatively, other suitable heating processes could be used.*
e. *The resulting granules are milled to a powder, suitable for blending with other food ingredients.*
f. *The product is being filled into the necessary packaging materials (e.g. super bags, paper bags, bulk transport).*

Reduced to the chemical equation, the production is as follows:
If burned lime was used as a calcium source, the reaction is as follows:

1. $CaO + H_2O \rightarrow Ca(OH)_2$
2. $Ca(OH)_2 + 2\ H_3PO_4 \rightarrow Ca(H_2PO_4)_2 + 2\ H_2O$
3. $Ca(H_2PO_4)_2 \rightarrow CaH_2P_2O_7 + H_2O \uparrow$

If lime was used as a calcium source, the reaction is as follows:

1. $Ca(OH)_2 + 2\ H_3PO_4 \rightarrow Ca(H_2PO_4)_2 + 2\ H_2O$
2. $Ca(H_2PO_4)_2 \rightarrow CaH_2P_2O_7 + H_2O \uparrow$

If calcium carbonate was used as a calcium source, the reaction is as follows:

1. $CaCO_3 + 2\ H_3PO_4 \rightarrow Ca(H_2PO_4)_2 + H_2O + CO_2 \uparrow$
2. $Ca(H_2PO_4)_2 \rightarrow CaH_2P_2O_7 + H_2O \uparrow$

The resulting product has a shelf life is about 3 years from production date (using standard conditions of 60 %RH at 25°C), if the specified limits are matched. The shelf life can differ, under hot and humid conditions.

H) Characteristic properties

Calcium acid pyrophosphate appears as a fine white powder which reacts acidic in principle. The substance is soluble as per OECD 105 guideline test with >25 g/L with a final sample solution of pH of about 2.7. However, solubility is indicated to be low in the current FCC monograph (FCC X) for calcium acid pyrophosphate, probably due to different methodology and different chemistry of the products which were tested (current FCC: 75/25 blend of calcium phosphate, monobasic and calcium acid pyrophosphate; here: pure calcium acid pyrophosphate with residues <5% calcium phosphate, monobasic).
Melting and boiling points cannot be determined since the substance is going to condensate to higher polyphosphates if heated to temperatures higher than the processing conditions.

I) Content of potential human toxicants

The quantitative composition under G) shows that amounts of trace impurities like lead, cadmium, arsenic, aluminium and mercury are far below levels of comparable standards for other food grade phosphates. They are of no health concern. Phosphorous (phosphate) and breakdown constituent from the pyrophosphate anion, and calcium as main constituents are being evaluated in the toxicological assessment.

J) Specification for calcium acid pyrophosphate

There is an existing monograph for calcium acid pyrophosphate in the Food Chemicals Codex Version X. That specification is massively deviating from international standards which were established earlier, deviating from Codex Alimentarius (JECFA) specification for calcium dihydrogen diphosphate (INS450(vii)) and the European Union's specification for E450(vii) in EU regulation 231/2012. This is probably due to issue that the FCC monograph is covering a blend of 75% calcium acid pyrophosphate with 25 % calcium phosphate (monobasic) which is covered by GRAS notice 420 instead of the pure substance itself. It is recommended to align with international standards for harmonization (and reduction of analytical variety) instead of deviating from existing standards.

Differences in Food Chemicals Codex, Codex Alimentarius and EU specification

Parameter (excerpt)	*FCC X*	*Codex Alimentarius INS 450(vii)*	*EU regulation 231/2012 (E 450(vii)*
Assay	*95.0 – 100.5 % Titrimetric (KMnO4)*	*NMT 64 % as P2O5 on a dried basis Titrimetric (NaOH)*	*61 – 66 % as P2O5 Titrimetric (NaOH)*
Acid insoluble matter	*Not specified*	*NMT 0.4 %*	*NMT 0.4 %*
Fluoride	*NMT 50 ppm*	*NMT 30 ppm*	*NMT 30 ppm*
Lead	*NMT 2 ppm*	*NMT 4 ppm*	*NMT 1 ppm*
Arsenic	*NMT 3 ppm*	*NMT 3 ppm*	*NMT 1 ppm*
Cadmium	*Not specified*	*Not specified*	*NMT 1 ppm*
Mercury	*Not specified*	*Not specified*	*NMT 1 ppm*
Aluminum	*Not specified*	*Not specified*	*NMT 200 ppm*
Loss on ignition	*NMT 10 % (0.5h@800°C)*	*Loss on Drying only NMT 1 % (4h@105°C)*	*Not specified*

Table 1 - differences in specifications

There are nominal differences in the specification limits for P2O5 in INS 450(vii), where Codex Alimentarius states that the Assay should not be more than 64%, expressed as P2O5 on a dried basis, and whereas the European Union requires a defined range of 61 – 66% P2O5 (as is).It is recommended to adopt the European approach to have lower and upper limits and to recommend changes to the Codex Alimentarius specification to align with the EU specification in order to harmonize them.

Further difference between Food Chemicals Codex, Codex Alimentarius and EU regulation 231/2012 for INS 450(vii) / E 450(vii) is the maximum limit for (naturally occurring) aluminium in calcium based phosphates. If aluminium was added together with potassium hydroxide during the production process on the surface, potassium aluminum phosphates/diphosphates would be formed and would lead to an improvement of the baking properties by creating another food additive in addition. However, it is possible to achieve very good baking properties without the addition of aluminium or potassium hydroxide to the additive without stability or caking problems. From a consumers point of view it should be highlighted that two additives were present if aluminium was added to perform a technological function and if two additives were formed. The 200 ppm aluminum from the European Union's specification can be considered as a threshold value for naturally occurring variances of aluminium in natural calcium sources used for the manufacturing of calcium dihydrogen pyrophosphate.

Added aluminium contributes to the acid insoluble matter which was skipped as a parameter in the FCC monograph and which would not be fulfilled by materials manufactured with added aluminum. Unfortunately GRAS notice 420 lacks information on maximum levels on added aluminium in the substance which could have been specified in the monograph.

In practice, the implementation of an aluminum limit did not lead to a supply chain interruption in Europe. The EU introduced (lower) impurity limits for lead, arsenic, cadmium and mercury

which are deviating from the current Codex Alimentarius specification which requires adaption to the current state of play as highlighted by JECFA for many never revised specifications. Reasonable behind were earlier performed updates of risk assessments for those impurities.

The EU specification of E450(vii) is used in practice/business and has proven to be workable except for the 2nd assay parameter for which no method was provided neither by the EU nor by JECFA. The theoretical P2O5 content of pure CAPP is about 65.7 %. With up to 5 % residues of calcium phosphate (monobasic) it changes to 65.5 %. In order to reflect production variability, the P2O5 limits should be set to 64-66 %. The current limit in JECFA is not workable.

All three existing specifications lack certain data to sufficiently characterize the substance itself and need revision with respect to current methodology and knowledge.

Basically, the substance could be preferably characterized by its content and ratio of calcium and phosphorous (1:2), a loss on dyring which indicates that there is no calcium phosphate (monobasic) in excess. Impurities should be included based on current standards. Likewise in magnesium acid pyrophosphate, we propose (besides the impurities from JECFA for harmonization purposes) to include a maximum limit for natural occurring aluminium to be able to differentiate from added aluminium which has the goal to enhance the baking properties and to form different substances which exert a technological function in food. From a toxicological point of view, aluminium is a well-known concern to neurological development and if technically possible, the addition should be reduced as much as possible simply to avoid potential exposure to the consumer.

Based on the above, we propose a specification as follows:

Table 2 - proposed specification of calcium acid pyrophosphate

Parameter (excerpt)	*Limits*	*Proposed method*
Test for calcium	*Passes test*	*JECFA (vol 4)*
Test for phosphate	*Passes test*	*JECFA (vol 4)*
Assay (after dryring)	*64 – 66 % as P2O5* *12.5 – 13.5 % as CaO*	*JECFA (assay method from calcium dihydrogen diphosphate), Titrimetric NaOH* *JECFA (assay method from INS 341(i)), Titrimetric KMnO4*
Acid insoluble matter	*NMT 0.4 %*	*JECFA (vol 4)*
Fluoride	*NMT 30 ppm*	*JECFA (vol 4)*
Lead	*NMT 1 ppm*	*FCC*
Arsenic	*NMT 1 ppm*	*FCC*
Cadmium	*NMT 1 ppm*	*JECFA (vol 4)*

Mercury	*NMT 1 ppm*	*JECFA (vol 4)*
Aluminum	*NMT 200 ppm*	*JECFA (vol 4)*
Loss on ignition	*Loss on Drying only NMT 1 % (4h@105°C)*	*JECFA (from calcium dihydrogen diphosphate)*

K) Purposes for which the substance is used:

Primary functional classes: raising agent, stabilizer, dough strengthener, texturizer, Flour treating agent and acidifier.

Chemical leavening is a traditional way of bringing volume into baked goods. This is commonly done by raising agents. Baking powders are produced for more than 100 years now. Natural leavening (yeast) causes a strong flavour which is undesirably in certain baked goods where other tastes should be perceived. The only known alternative to natural leavening is chemical leavening (raising).

Calcium acid pyrophosphate provides excellent properties as a raising agent, especially for industrial applications, optional in combination with other raising agents, such as monocalcium phosphate (MCP) or magnesium acid pyrophosphate (MgPP). The substance is used throughout the world for this purpose.

At the same time, the substance may serve complimentary as a nutrient source for calcium and potentially improve nutrient profile of processed foodstuffs.

Calcium acid pyrophosphate has become an important alternative due its nutritional value to commonly used sodium acid pyrophosphate (INS450i).

Crucial for baking performance of raising agents are two main parameters:

The NV (neutralisation value) is one of two important properties for a raising agent (acid). The value describes the amount which is necessary to neutralize 100g of sodium bicarbonate. It is a reference value, specific for each leavening agent (acid). The higher the NV is, the less leavening acid (raising agent) is needed. It is therefore desirably to have a rather high NV in order to reduce the amount of leavening acid (and costs, since additives are commonly the more expensive ingredients besides flavours in a formulation). Unfortunately, a higher NV usually comes along with a quicker reaction. An exception is sodium aluminium phosphate (INS541), which provides both properties, a high NV and a considerably slow reaction. The NV is described as the amount of sodium bicarbonate [g] divided by the amount of raising agent needed for neutralisation [g] times 100.

The other important property of a leavening acid is the "Rate of Reaction" (ROR), or

DRR (dough rate of reaction).

It is an efficiency test concerning a desired baking property in industrial use of raising agents: The value describes the speed of the release of carbon dioxide (providing volume) during the leavening reaction under defined conditions.
The speed or dynamic of a reaction is important in industrial preparation of baked goods, since benching time, preparation time and baking conditions have to be very strictly within certain limits, and otherwise the output may vary from a defined standard in colour, volume or texture and may differ from final customer expectations in a certain product.

Here is an overview about the performance of existing leavening acids with regard to their Neutralisation Value and Rate of Reaction:

Leavening acid	*NV*	*ROR (DRR)*
INS541 - A	*100*	*22*
INS541- B	*100*	*10*
INS450i	*71-73*	*10-40*
INS341i	*83*	*60*
INS334	*112*	*70*
INS575	*45*	*30*
INS336i	*45*	*66*

Table 3 - overview of existing leavening acids

Calcium acid pyrophosphate has the following performance properties:

Leavening acid	*NV*	*ROR*
Calcium acid pyrophosphate	*55-70*	*8-20*

Table 4 - overview calcium acid pyrophosphate

As obvious from the comparison to the substances above, there is a possibility to reduce the Rate of Reaction compared to e.g. organic acids /their salts and this indicates its suitability for technological uses.

The substance, depending on the exact production conditions may be produced as strongly retarded or less retarded leavening acid.

Customizing is important, which means adapting to given conditions and finding the perfect customer solution which enables him to run his production process as efficient as possible.

Since it is possible to produce ROR-related products for each customer individually, we believe this provides a big gain for industrial baking production.

In addition to existing (known) uses, calcium acid pyrophosphate is able to enhance the properties of microwavable foods by improving the absorption of microwaves to get a better heating and texture. From several trials it can be concluded that calcium acid pyrophosphate improves the crust of microwaved products and leads to a better temperature profile within the foodstuff. Here some examples using a branded calcium acid pyrophosphate (BUDAL MW 500):

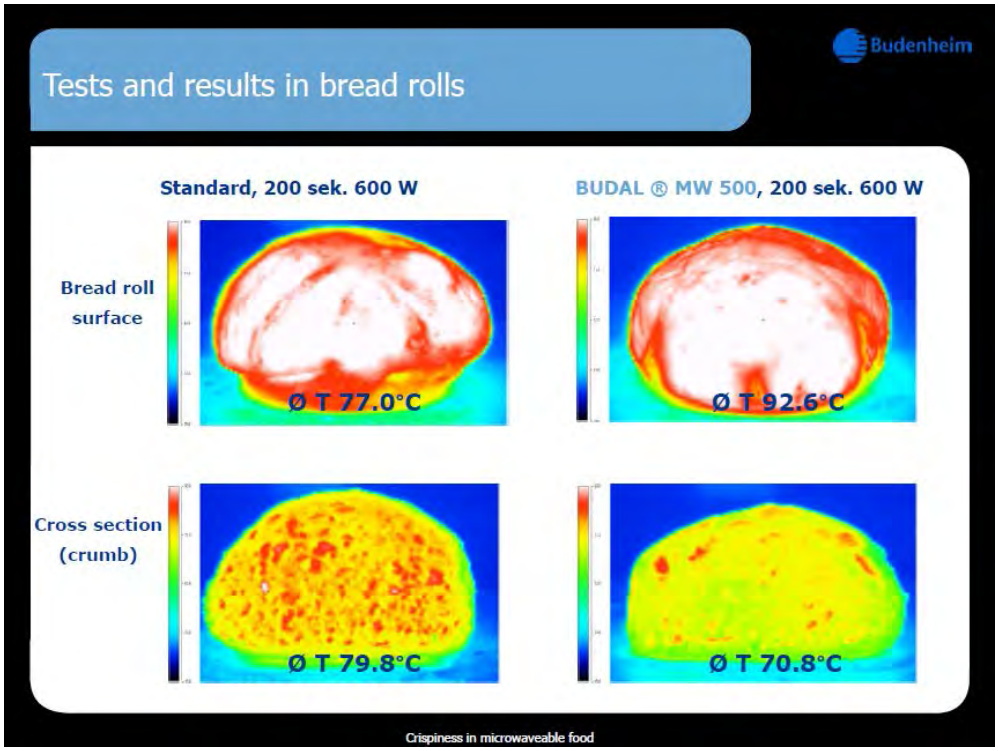

Figure 2 - test results of CAPP in bread rolls

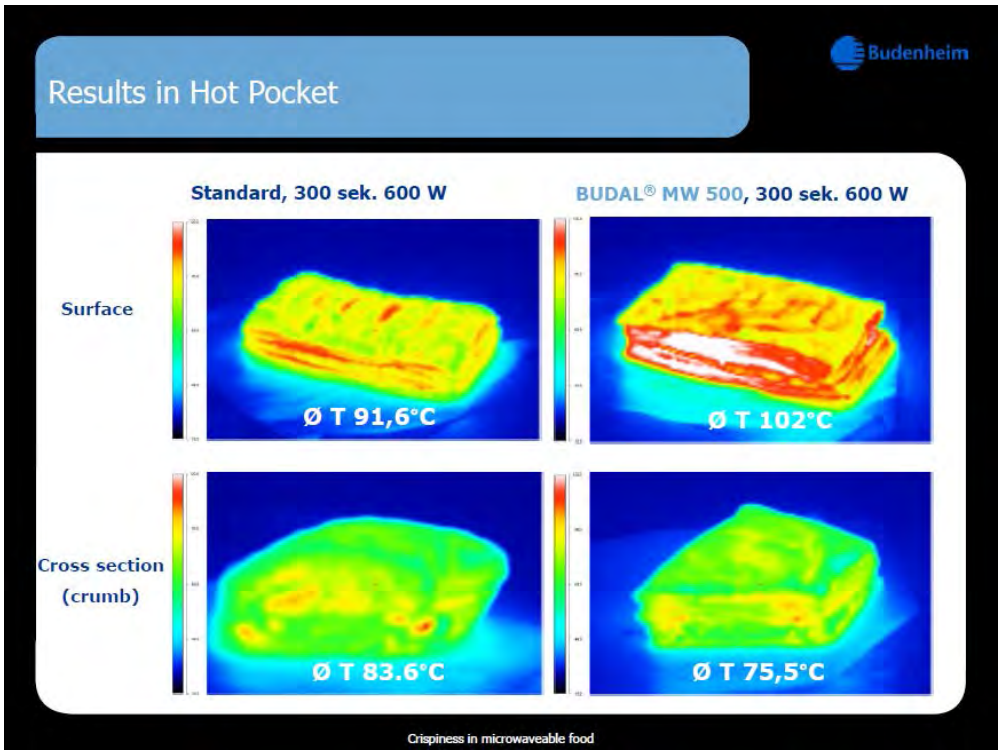

Figure 3 - test results of CAPP in Hot Pocket

The substance may be used likewise sodium acid pyrophosphate in batters and breadings which are used on breaded/battered meats or fish fillets.

Summary:

The use of calcium acid pyrophosphate is favourable over sodium acid pyrophosphate to improve covering the "pyro-taste", improve the nutritional profile by sodium reduction which is an opportunity to improve the healthiness of processed foodstuffs. Furthermore, new uses to improve microwaved foods lead to much better products, finally with a crumb from the microwave. The use in batter and breadings as a leavening agent could help to substitute sodium by calcium from processed foods.

Part III Dietary exposure (170.235)

Description of the population expected to consume the substance (exposure):

The normal consumer will come into contact with the new substance from the proposed uses.

The proposed use is widely a substitutional use (instead of INS 450i, sodium acid pyrophosphate) not an add-on use to other phosphates or other additives – it is an alternative to existing additives. The maximum intake of phosphates (as P2O5 or P) will not be affected since the proposed maximum and use levels are comparable to current uses of other phosphates. However, in specific products such as popcorn, vegetable masses (spring rolls) and meat masses (emulsion type products; sausages; Hamburger; minced meat) might contain the substance as well. USDA products may be affected as well in case the substance is used as a substitute for sodium acid pyrophosphate in batters and breadings of meat products.

This means from a risk management perspective, there is no or little additional exposure to phosphorous, because it is already covered by existing exposure assumptions made for other phosphates used in the same foods, having a similar phosphorous content.

There is an additional exposure of calcium to consumers if for example sodium acid pyrophosphate is replaced by calcium acid pyrophosphate. To draw analogue conclusions, one might use the Crème study report on probalistic modelling[1] of magnesium acid pyrophosphate and convert the results from Phosphorous intake for the difference in P content of the substances by applying a factor of 0.93 (P content calcium acid pyrophosphate/ P content magnesium acid pyrophosphate).

Tables 4, 5 of the report (attachment 7) still apply.

Mean intake results for phosphorous in bakery wares from table 6 would change as follows: 92.1 (O); 87.0 (10 % (I); 87.1 (10 % (P);99.4 (100 %) [mg/ day].

97.5th percentile results for phosphorous intake in bakery wares in table 7 would change as follows: 403.5 (O); 382.4 (10 % (I); 385.8 (10 % (P); 424.5 (100 %) [mg/ day].

Tables 10 and 11 of that report would be still applicable.

Mean intake results for phosphorous in bakery wares from table 12 would change as follows: 92.1 (O); 87.2 (10% (I); 87.2 (10% (P);100.8 (100 %) [mg/ day].

97.5th percentile results for phosphorous intake in bakery wares in table 13 would change as follows: 403.5 (O); 381.8 (10 % (I); 382.1 (10 % (P); 426.3 (100 %) [mg/ day].

P-content in $CaH_2P_2O_7$:28.7%

P-content in $MgH_2P_2O_7$:30.8 %

[1] Creme Global Study 2010 - Replacing sodium acid pyrophosphate with magnesium acid pyrophosphate in bakery wares

Part IV Self-limiting levels of use (170.240)

Information on any self-limiting levels of use

Technically, the use of any raising agent or acidifier is limited due their effects on the food (e.g. denaturation of proteins; interaction with other ingredients) to the necessary effect. This includes ratio (neutralisation value) between the raising agent and the carbon dioxide source. If one of the two ingredients is significantly overdosed, the resulting baked good will have off-flavor and discolorations compared to the standard product. Accordingly, nobody wants to use more than necessary and nobody wants to deviate from the optimum dosage.

Part V Experience based on common use in foods before 1958 (170.245)

Uses before 1958

The GRN 420 was submitted in 2012, therefore we assume no use could be reported for 1958 and before.

Part VI Safety Narrative (170.250)

Safety Narrative

The basis for the notifier's determination that a particular use of the notified substance is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act is, because such use is GRAS through scientific procedures, since it has a significant equivalence to existing GRAS substances (e.g. GRN 420) and its suggested additional uses are a pure substitutional uses.

Similar existing substances, such as mono-, di-, and tri- calcium phosphate (21 CFR §182.1217) have obtained GRAS status as multipurpose GRAS Food substances.

The most similar substance is calcium pyrophosphate (21 CFR §182.8223) which is a GRAS nutrient and GRN 420 which is the same substance.

Calcium acid pyrophosphate has been evaluated and was found to be GRAS (GRN 420) and can be described as an ignited form of calcium phosphate, monobasic.

If the ignited form is being put into water for hydrolysis and heated, again calcium-ions and orthophosphate-anions are formed due to natural hydrolysis of the pyrophosphate-anion.

The substance is a salt of phosphoric acid (orthophosphate) and calcium, both occurring naturally and being already constituents of foods, whether intentionally added or naturally occurring. A MTDI of 70 mg P/kg BW has been established in 29182 by JECFA and was confirmed several times by independent risk assessment bodies, such as the FDA and EFSA. This value applies to all phosphorous from food sources, including calcium acid pyrophosphate.

The requested uses of calcium acid pyrophosphate are not additional uses which would lead to additional exposure, but the requested uses are substitutional uses for sodium acid pyrophosphate, leading to a reduction of sodium and an increase of calcium levels in foods simultaneously, both could be considered as positive health effects. The intake of phosphorous as a whole is not affected. Phosphorous and calcium are ubiquitously present in foods.

The difference in production of calcium acid pyrophosphates compared to the notified way of manufacturing in GRN 420 improves safety since it reduces the amount of aluminium added to foods. Additionally, transparency for the consumer increases since the omission of aluminium in the production does not form aluminium phosphates likewise in the manufacturing described in GRN 420.

Safety assessment of calcium acid pyrophosphate

Introduction

Since the calcium acid pyrophosphate is a soluble salt of calcium and pyrophosphate, chemically very similar to calcium pyrophosphate existing risk assessments and the established by MTDI from JECFA (phosphorous from all food sources of 70mg/kg BW/day,) in 1982, is applicable. The substance's toxicity can be considered as the toxicity of its ions. This MTDI was confirmed by the other competent bodies, such as the SCF in 2001 and EFSA in 2009 and 2005, taking into consideration latest developments (if any) until their publications. The FDA evaluated the safe use of this substance in GRAS notice 420 already in 2015.

All existing phosphate-related safety evaluations refer to the phosphate-part of the substances, since it is a soluble salt, splitting into its ions under aqueous conditions, allowing evaluating phosphates by their most relevant toxic effects which are mostly dependent from the phosphate part of phosphate containing additives. In case of calcium acid pyrophosphate, the relevant ions are calcium (essential nutrient), hydrogen (a non-toxic ion) and the pyrophosphate anion.

Since pyrophosphates hydrolyse under stomach conditions to orthophosphates, the oral toxicology is accordingly the same as for orthophosphates.

Since the phosphate part of the substance is the toxicologically relevant compound, we restrict the assessment to this potion, but for completeness information on calcium is included.

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Toxicological data

a) Calcium

Exposure

The occurrence of calcium in and from foods is ubiquitous. Foods vary widely in calcium content. The best sources are milk and milk products, which provide about 45 to 70 % of the dietary calcium in European diets. Some plants, drinking and mineral water, and food supplements are also good sources of well absorbable calcium[1].

Adsorption, Desorption, Metabolism, Excretion

Calcium homeostasis is under endocrine and genetic control. Systemic and local factors regulate intestinal absorption, influx and efflux from bone, and calcium excretion and re-absorption by the kidney. Calcium must be in a soluble form or bound to soluble organic molecules to be absorbable. Depending on solubility, chemical form and other factors of the food, the fractional absorption of dietary calcium in adults is around 25 % (range 10 to 40 %). Fractional absorption decreases with high calcium content of diets and increases with low-calcium diets. This adaptation is modulated by PTH and 1,25-(OH)2-D in response to lower or higher serum calcium concentrations. Ionised calcium in serum following the ingestion of 1,000 mg of calcium as a supplement just before a meal by healthy subjects rose in 20 of 40 trials above the upper limit of normal (specified as 1.28 mmol/L) within two to four hours, and was accompanied by a significant increase in calcium excretion in the urine and by an increase of the calcium/creatinine ratio by up to 0.13[2]*. Passive para-cellular diffusion through the tight junctions of the intestinal epithelium, particularly of the jejunum and ileum, follows down an electrochemical gradient together with water, sodium and glucose, which is determined by the concentration of soluble calcium in the gut lumen. Passive para-cellular diffusion becomes important when dietary calcium is high and the trans-cellular pathway is down-regulated.*[3] *The majority of calcium absorbed is stored in the skeleton. Excess of absorbed calcium is excreted in urine, faeces and sweat. Calcium balance is positive in healthy children, adolescents and young adults before bone growth and bone modelling cease. Renal calcium excretion is the net result of glomerular filtration and tubular passive (collecting duct) or active (proximal tubule, loop of Henle, distal tubule) reabsorption (normal over 98 % of the filtered load). Active transport is under the control of PTH, calcitonin and 1,25-(OH)2-D, the levels of which are set via the CaSR by the calcium concentrations in extracellular fluid.*[4]

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[1] EFSA Journal 2012;10(7):2814

[2] Reid IR, Schooler BA, Hannan SF and Ibbertson HK, 1986. The acute biochemical effects of four proprietary calcium preparations. Australian and New Zealand Journal of Medicine, 16, 193-197

[3] Bronner F, 1992. Current concepts of calcium absorption: an overview. Journal of Nutrition, 122, 641-643.

[4] Hoenderop JG, Nilius B and Bindels RJ, 2002. Molecular mechanism of active Ca2+ reabsorption in the distal nephron. Annual Review of Physiology, 64, 529-549.

Acute Toxicity

An acute oral toxicity (limit) test (OECD 420, GLP) was performed on calcium acid pyrophosphate with the result LD_{50} >2000 mg/kg BW (rat).[5]

Genotoxicity

Calcium is an essential body constituent and has not shown genotoxic potential in literature[6]*. Genotoxic in vitro tests (OECD 487, 471, both GLP)of e.g. tricalcium phosphate (pentacalcium hydroxy tris(orthophosphate)), a chemically similar substance, did not show any effects.*[7][8]

Chronic Toxicity and Carcinogenicity

Milk-alkali syndrome(MAS) or calcium-alkali-syndrom (CAS) is characterised by metabolic alkalosis and hypercalcaemia with dehydration, renal failure, nephrocalcinosis and nephrolithiasis in variable combinations and severity. On the basis of 14 cases (2004-2010) reporting elevated serum calcium (2.64-6.43 mmol/L) and creatinine concentrations in males and females (35-81 years) consuming calcium carbonate at doses >1,000-44,000 mg/day, the IoM concluded that supplemental intakes of calcium carbonate 3,000 mg/day were hazardous. Duration of supplementation was only reported in seven cases (from weeks to 19 years). It can be noted that high calcium intakes at doses >1000 mg/day may increase the risk of CAS, but available data does not allow a clear dose-response relationship.

Supplementation of about 5000 subjects with calcium doses between 500 and 2000 mg/day for a duration between three months and four years did not increase the risk of kidney stone formation.[9]

Many epidemiological studies indicating an associated risk between high calcium intake and prostate cancer are lacking information and have uncontrolled factors. There is no evidence for an increased risk of prostate cancer from high calcium intake of about 2000 mg/day.[10]

Developmental and Reproductive Toxicity

No negative effects of calcium salts on reproductive or developmental toxicity were reported[11]*.*

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[5] Bradshaw, J. 2014, IP 25: Calcium dihydrogenpyrophosphate: ACUTE ORAL TOXICITY IN THE RAT - FIXED DOSE METHOD, PROJECT NUMBER: 41205112

[6] EGVM (Expert Group on Vitamins and Minerals) (2003). Report on safe upper levels for vitamins and minerals. London. May 2003, pp264-273

[7] Kolp, N. 2014:Study report 61948-20-132-2014030824 (OECD 471)

[8] Prietzsch, H. 2015: Study report 61948-20-164-2014030824 (OECD 487)

[9] SCF (Scientific Committee on Food), 2003. Opinion on the Tolerable Upper Intake Level of Calcium. SCF/CS/NUT/UPPLEV/64 Final, 39 pp.

[10] Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, Mandel JS, Heber D and Greenberg ER, 2005. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiology, Biomarkers and Prevention, 14, 586-589

[11] EGVM (Expert Group on Vitamins and Minerals) (2003). Report on safe upper levels for vitamins and minerals. London. May 2003, pp287-290

b) Phosphate

Exposure

Phosphorus is widely found in foods as phosphates; especially foods rich in protein are usually high in phosphorus, such as dairy products (100-900 mg/100 g), meats (200 mg/100g), fish (200 mg/100 g) and grain products (100-300 mg/100 g). The average intake from foods in adults is usually between 1000-2000 mg/day. In the US the contribution from phosphorus-containing food additives is estimated at 320mg/day, i.e. 20-30% of the adult phosphorus intake[12]*.*

Adsorption, Desorption, Metabolism, Excretion

During normal digestion, phosphate is released from phosphate-containing biochemicals in food and actively absorbed in the upper small intestine, and somewhat less in the more basic environment of the lower small intestine. Absorption has been reported to be about 70% in adults and between 60% - 90% in infants and children.

Absorption takes place by a satiable, active transport mechanism, facilitated by vitamin D, as well as by passive diffusion. Intestinal absorption of phosphate normally fluctuates widely. It is decreased by high intake of calcium, magnesium, or iron, forming insoluble phosphates in the gut, by unusually high intestinal alkalinity, and by low vitamin D intake. Phosphate absorption is significantly higher in acid pH environments than in alkaline environments.

Approximately 80% of phosphorus in the human body is bound with calcium in the bones and teeth. Phosphorus-containing organic compounds in the blood and muscle such as proteins, lipids, and carbohydrates constitute another 10% of body phosphorus. Nearly all organic forms of phosphorus in blood, such as 2,3-diphosphoglyceric acid, adenosine triphosphate (ATP), and fructose-1,6-di-phosphate, occur in erythrocytes[13]*. The remaining 10% has an extensive distribution in the fluids of the body*[14]*.*

Excretion takes place mainly in the faeces, but in excessive amounts of phosphate versus calcium, magnesium or iron, the urinary excretion becomes a significant route.

Acute Toxicity

There is an OECD 420 GLP-compliant study on oral toxicity for the substance itself available..

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[12] Calvo MS and Park YK (1996). Changing phosphorus content of the U.S. diet: potential for adverse effects on bone. J Nutr 126:pp1168-1180

[13] Henry RJ. 1967. Clinical chemistry: Principles and techniques. New York: Harper and Row, Publ.,409-416

[14] Tietz NW. 1970. Electrolytes. In: Tietz NW ed. Fundamentals of clinical chemistry. Philadelphia: W.B. Saunders Co., 636-639

Genotoxicity

No genotoxic effects of inorganic salts of phosphorus have been reported[15]. A set of three genotoxic tests (OECD 471, 476 and 487, all GLP) have been carried out in 2015 on an analogue substance (calcium phosphate, tribasic (pentacalcium hydroxide tris orthophosphate) with negative results.

Chronic Toxicity and Carcinogenicity

Trautvetter et al. (2016) reported that there is no influence from additional high phosphorous intake (1000 mg P/day) on calcium, magnesium and iron metabolism in healthy adults in a randomized placebo-controlled human intervention study. They found that initially elevated levels of FGF23 returned to normal levels within eigth weeks[16].It is noteworthy that this was added P and background P consumption was presumably another 800 - 1000 mg P per day.

In 2009, a 90-day feeding study of Sprague-Dawley rats with ß-calcium-pyrophosphate showed no significant effects at a level of 30mg/kg BW[17].

A report from Whybro et al[18] about two studies showed on one hand an increase in the urinary excretion of phosphate, but showed one the other hand no changes in serum phosphate. Reversible diarrhoea was reported in one subject in the one of the studies when receiving phosphorus at 2000 mg/day.

Pathological effects in the parathyroid, kidneys and bones were observed in mature male rats fed a diet containing very high levels of sodium orthophosphate (8% in the diet, corresponding to about 4 g/kg body weight/day) for 7 months or until death respectively[19]. Microscopic examinations of the tissues at the time of death revealed hypertrophy and hyperplasia of parathyroid cells. Haut et al. investigated renal toxicity of phosphates in rats. Phosphorus was fed in the diet at different levels of 0.5, 1.0 and 2% for 18 weeks. None of the animals on a normal phosphorus intake (250 mg/kg body weight/day) showed any abnormalities[20].

The finding of Dymsza et al.[21] using rats was that adequate absorption and utilisation of calcium, phosphorus and iron were observed, feeding a control, a normal orthophosphate, and a high orthophosphate diet.

Observations were made after 50, 60 and 150 days and no adverse physiological effects were reported. The authors concluded that at both high and normal levels of dietary phosphorus the

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[15] Joint FAO-WHO Expert Committee on Food Additives 542., food additives series 17, Phosphoric acid and phosphate salts

[16] Trautvetter et al. Nutrition Journal (2016) 15:7; Consequences of a high phosphorus intake on mineral metabolism and bone remodeling in dependence of calcium intake in healthy subjects – a randomized placebo-controlled human intervention study

[17] Lee JH et al 2009; A 90-day subchronic toxicity study of beta-calcium pyrophosphate in rat, Drug Chem Toxicol. 2009;32(3):277-82

[18] Whybro, A., Jagger, H., Barker, M., Eastell, R. (1998) Phosphate supplementation in young men: lack of effect on calcium homeostasis and bone turnover. European Journal of Clinical Nutrition 52, 29-33

[19] Saxton, J. A., Jr & Ellis, G. H. (1941) Effects of long-continued ingestion of sodium phosphate, Amer. J. Path., 17 : 590

[20] Haut LL, Alfrey AC, Guggenheim S, Buddington B, Schrier N (1980). Renal toxicity of phosphate in rats. Kidney International 17: 722-731

[21] Dymsza HA, Reussner G Jr, Thiessen R Jr (1959). Effect of normal and high intakes of orthophosphate and metaphosphate in rats. J Nutr 69: 419-428

calcium, phosphorus and iron absorption and utilisation were adequate.
High phosphate intakes can affect calcium distribution in the body and may in some cases produce soft tissue calcification and affect bone formation.

Kidney damage, soft tissue calcification and bone effects were the main findings in laboratory animals fed phosphates[22] [23] [24]. However, such effects were not observed in studies in humans, except in patients with end stage renal disease. In ill individuals, hypophosphatemia is caused by vomiting and severe diarrhoea, and is associated with various liver diseases[25].

Developmental and Reproductive Toxicity

No conclusive evidence of reproductive effects have been demonstrated in feeding studies with phosphate salts in various species of laboratory animal although limited studies have suggested testicular effects and reduced fertility in rats. No carcinogenic potential was demonstrated in limited feeding studies in rats treated with phosphates; however, in rodents treated orally, several phosphates have been shown to promote the effects of known carcinogens. A wide range of genotoxicity assays have yielded essentially negative results with phosphate salts[26].

Long-term effects of dietary phosphoric acid in three generations of rats have been investigated[27]. The animals received diets containing 1.4% and 0.75% phosphoric acid (equivalent to approximately 200 and 375 mg phosphorus/kg body weight/day) for 90 weeks. No harmful effects on growth or reproduction were observed, and also no significant differences were noted in haematological parameters in comparison with control animals. There was no acidosis, nor any change in calcium metabolism. The quality of these older studies would be considered limited by current standards. JECFA reviewed the available data from studies in mice and rats and concluded that dosing with phosphoric acid and inorganic phosphate salts does not induce maternal toxicity or teratogenic effects. Maximum dose levels tested for the various inorganic phosphate salts varied between 130 and 410 mg phosphorus/kg bodyweight[28].

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[22] MacKay EM and Oliver J (1935). Renal damage following the ingestion of a diet containing an excess of inorganic phosphate. J exp Med 61: 319
[23] McFarlane, D. (1941) Experimental phosphate nephritis in the rat, J. Path. Bact., 52,17-24
[24] Sanderson, P. H. (1959) Functional aspects of renal calcification in rats, Clin. Sei., 18,67-79
[25] Latner AL. 1975. Clinical biochemistry. Philadelphia: W.B. Saunders Co., 47-49, 279-315, 479, 842
[26] Sanderson, P. H. (1959) Functional aspects of renal calcification in rats, Clin. Sei., 18,67-79
[27] Bonting SL and Jansen B C (1956). The effect of a prolonged intake of phosphoric acid and citric acid in rats. Voeding 17: 137
[28] Joint FAO-WHO Expert Committee on Food Additives 542., food additives series 17, Phosphoric acid and phosphate salts

Summary of the safety assessment

The prediction of the toxicological behaviour of calcium acid pyrophosphate bases on the evaluation of its compounds, calcium and diphosphate. The salt dissociates into its ions under aqueous conditions and the diphosphates hydrolysis into orthophosphate under stomach conditions.

In the case of ionisable salts, like in this case, it is scientifically justifiable to assess the anions and cations individually and to make separate predictions accordingly for calcium and orthophosphate.

The safety of calcium acid pyrophosphate is assessed by the consideration of the safety of the particular ions.

Calcium has not shown any significant toxicological effect from intakes from food up to 2500 mg/day. Due to the lack of chronic toxicological effects, the limiting factor for use in foodstuffs is not calcium.

Phosphorus is a likewise essential body constituent. Generally, phosphates show a low acute oral toxicity in laboratory animals. Ingestion of excess amounts of phosphates by man may result in electrolyte imbalances in the body which can disrupt the function of a variety of organ systems. Kidney damage, soft tissue calcification and bone effects were the main findings in laboratory animals fed phosphates. However, such effects were not observed in studies in healthy individuals, only in patients with end stage renal disease. No conclusive evidence of reproductive effects has been demonstrated in feeding studies with phosphate salts in animals. No carcinogenic potential was demonstrated in feeding studies in rats treated with phosphates; however several phosphates have been shown to promote the effects of known carcinogens in rodents. Genotoxicity assays have yielded essentially negative results with phosphate salts.

A comprehensive peer review of existing data was performed by Weiner et al (2001)[29].

The European Food Safety Authority (EFSA) took a look into existing data during the evaluation of ferrous phosphate and ferrous ammonium phosphate as iron sources for food supplements in 2009/2010, but no new data on phosphates had been reported[30] [31].

US FDA cleared GRAS notice 420 on calcium acid pyrophosphate in 2015 based on given information, no new toxicity data was provided.

No new relevant studies could be identified to question the safety assessment for phosphates from all food sources from JECFA(1982). The currently assigned MTWI of 70 mg P/kg BW/week is still valid.

[29] Weiner ML et al (2001) Toxic review of inorganic phosphates, food and chemical tox,30 2001 pp759-786
[30] EFSA Scientific Opinion - Ferrous phosphate added for nutritional purposes to food Supplements, The EFSA Journal (2009) 951, 1-13
[31] EFSA - Scientific Opinion on the safety of ferrous ammonium phosphate as a source of iron added for nutritional purposes to foods for the general population (including food supplements) and to foods for particular nutritional uses, EFSA Journal 2010;8(5):1584

Conclusions

Because of the lack of new relevant data, we still consider the MTDI of 70mg Phosphorous /kg BW/day as appropriate and see no obstacles to formally assign the same MTDI to calcium acid pyrophosphate, since phosphorous (here: pyrophosphate) is the limiting factor from a toxicological point of view and the MTDI is expressed as phosphorous from all food sources.

Chemically similar substances such as calcium pyrophosphate (21 CFR 182.8223 calcium pyrophosphate) and mono-, di-, and tri- calcium phosphate (21 CFR 182.1217) have obtained GRAS status, so there is no reason to assume this substance should not be safe if used in accordance with GMP.

On the exposure side, the use of calcium acid pyrophosphate is a substitutional use for sodium acid pyrophosphate and does not lead to a different exposure scenario for phosphorous.

There is additional intake of calcium and less intake of sodium by consumers if sodium acid pyrophosphate is replaced by calcium acid pyrophosphate.

There is no doubt that the intended uses of calcium acid pyrophosphate is not harmful and can be considered to be safe for human consumption.

Part VII List of supporting data and information in your GRAS notice (170.255)

The complete references are enclosed as appendix 7 “references.zip”.
The complete references as redacted versions (indicated in red below) are enclosed as appendix 8 “references_red.zip”.

EFSA - Scientific Opinion on the Tolerable Upper Intake Level of calcium, The EFSA Journal 2012;10(7):2814

Reid IR, Schooler BA, Hannan SF and Ibbertson HK, 1986. The acute biochemical effects of four proprietary calcium preparations. Australian and New Zealand Journal of Medicine, 16, 193-197

Bronner F, 1992. Current concepts of calcium absorption: an overview. Journal of Nutrition, 122, 641-643.

Hoenderop JG, Nilius B and Bindels RJ, 2002. Molecular mechanism of active Ca2+ reabsorption in the distal nephron. Annual Review of Physiology, 64, 529-549.

Bradshaw, J. 2014, IP 25: Calcium dihydrogenpyrophosphate: ACUTE ORAL TOXICITY IN THE RAT - FIXED DOSE METHOD, PROJECT NUMBER: 41205112 – this data is not generally available, but attached to the GRAS notice for FDA evaluation purposes only

EGVM (Expert Group on Vitamins and Minerals) (2003). Report on safe upper levels for vitamins and minerals. London. May 2003, pp264-273

Kolp, N. 2014:Study report 61948-20-132-2014030824 (OECD 471) – this data is not generally available, but attached to the GRAS notice for FDA evaluation purposes only

Prietzsch, H. 2015: Study report 61948-20-164-2014030824 (OECD 487) – this data is not generally available, but attached to the GRAS notice for FDA evaluation purposes only

SCF (Scientific Committee on Food), 2003. Opinion on the Tolerable Upper Intake Level of Calcium. SCF/CS/NUT/UPPLEV/64 Final, 39 pp.

Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, Mandel JS, Heber D and Greenberg ER, 2005. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiology, Biomarkers and Prevention, 14, 586-589

EGVM (Expert Group on Vitamins and Minerals) (2003). Report on safe upper levels for vitamins and minerals. London. May 2003, pp287-290

Calvo MS and Park YK (1996). Changing phosphorus content of the U.S. diet: potential for adverse effects on bone. J Nutr 126:pp1168-1180

Henry RJ. 1967. Clinical chemistry: Principles and techniques. New York: Harper and Row, Publ.,409-416

Tietz NW. 1970. Electrolytes. In: Tietz NW ed. Fundamentals of clinical chemistry. Philadelphia: W.B. Saunders Co., 636-639

Joint FAO-WHO Expert Committee on Food Additives 542., food additives series 17, Phosphoric acid and phosphate salts

Trautvetter et al. Nutrition Journal (2016) 15:7; Consequences of a high phosphorus intake on mineral metabolism and bone remodeling in dependence of calcium intake in healthy subjects – a randomized placebo-controlled human intervention study

Lee JH et al 2009; A 90-day subchronic toxicity study of beta-calcium pyrophosphate in rat, Drug Chem Toxicol. 2009;32(3):277-82

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Haut LL, Alfrey AC, Guggenheim S, Buddington B, Schrier N (1980). Renal toxicity of phosphate in rats. Kidney International 17: 722-731

Dymsza HA, Reussner G Jr, Thiessen R Jr (1959). Effect of normal and high intakes of orthophosphate and metaphosphate in rats. J Nutr 69: 419-428

MacKay EM and Oliver J (1935). Renal damage following the ingestion of a diet containing an excess of inorganic phosphate. J exp Med 61: 319

McFarlane, D. (1941) Experimental phosphate nephritis in the rat, J. Path. Bact., 52,17-24

Sanderson, P. H. (1959) Functional aspects of renal calcification in rats, Clin. Sei., 18,67-79

Latner AL. 1975. Clinical biochemistry. Philadelphia: W.B. Saunders Co., 47-49, 279-315, 479, 842

Bonting SL and Jansen B C (1956). The effect of a prolonged intake of phosphoric acid and citric acid in rats. Voeding 17: 137

Weiner ML et al (2001) Toxic review of inorganic phosphates, food and chemical tox,30 2001 pp759-786

EFSA Scientific Opinion - Ferrous phosphate added for nutritional purposes to food Supplements, The EFSA Journal (2009) 951, 1-13

EFSA - Scientific Opinion on the safety of ferrous ammonium phosphate as a source of iron added for nutritional purposes to foods for the general population (including food supplements) and to foods for particular nutritional uses, EFSA Journal 2010;8(5):1584

#718

Bonnette, Richard

From: Dammeier, Jana <Jana.Dammeier@budenheim.com>
Sent: Monday, July 24, 2017 5:22 AM
To: Bonnette, Richard
Subject: AW: Your submission (calcium acid pyrophosphate) to US FDA GRAS notification program
Attachments: GRAS CAP meat and poultry uses 240717.pdf

Dear Mr Bonnette,

Thank you for your advice. I have attached a letter requesting the exclusion of those uses.

Mit freundlichen Grüßen / Best regards / Atentamente,

Jana Dammeier
Product Stewardship

Chemische Fabrik Budenheim KG
Rheinstr. 27
55257 Budenheim
Germany

[T] +49 (6139) 89631

http://www.budenheim.com
Jana.Dammeier@budenheim.com

Von: Bonnette, Richard [mailto:Richard.Bonnette@fda.hhs.gov]
Gesendet: Freitag, 14. Juli 2017 17:15
An: Productstewardship <Productstewardship@budenheim.com>
Betreff: Your submission (calcium acid pyrophosphate) to US FDA GRAS notification program

Dear Dr. Dammeier,
We received your most recent submission for calcium acid pyrophosphate (CAP) and have completed a preliminary evaluation to determine if it is suitable for filing as a GRAS notice. There is one issue that will need to be resolved before filing the submission as a GRAS notice and fully evaluating it. The issue relates to the meat and poultry intended uses of CAP. As I mention in my previous email below to Dr. Janssen, we work with the U.S Department of Agriculture (USDA) jointly on submissions where there are intended uses of a substance in foods under their regulatory authority (primarily meat and poultry products). The submission currently lacks information regarding safety and suitability that USDA would require to evaluate the submission, and thus the submission is not complete.

One simply remedy at this stage would be to request, by email or by letter, that we exclude those meat and poultry uses from the scope of this submission. We would then be able to move forward with the submission. Otherwise, I would (as I did in the email below) recommend contacting USDA regarding the type of information you will need to include and then provide that.

Regards,
Richard

From: Bonnette, Richard
Sent: Thursday, March 16, 2017 7:13 AM
To: thomas.janssen@budenheim.com
Subject: Letter attached regarding your submission (calcium acid pyrophosphate) to US FDA GRAS notification program

Dr. Janssen,
I've attached a letter explaining that FDA has not filed your GRAS submission for calcium acid pyrophosphate for use in food. The primary reason is simply formatting, and I think it will be a simple matter to revise the submission and resubmit it. We have relatively new regulations (effective in October 2016) that describe the format and content of a GRAS notice that aren't reflected in your submission from January. Another potential issue, though not mentioned in the official letter, is the presence of meat products as an intended use category and the absence of any information about the ingredient's use in meat products. In the US, ingredients used in meat products are regulated jointly by FDA and the U.S. Department of Agriculture (USDA), and the submission is reviewed by both agencies. USDA has specific requirements for demonstrating the technical effectiveness of an additive in addition to safety. I suggest that you consider contacting the USDA office that handles ingredients to insure that your next submission contains the appropriate information for their review. You can contact Val Green at valeria.green@fsis.usda.gov or (301) 504-0846.

I'll include some links below that will be helpful.

21 CFR 170 Subpart E – GRAS notice regulations
http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=1b05ef79b886b0588278eca7b2fcfbea&ty=HTML&h=L&mc=true&n=sp21.3.170.e&r=SUBPART

GRAS main page (links to guidance, publications, etc.)
https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm

GRAS notice inventory (an inventory of our responses to submissions, and electronic versions of the submissions themselves)
http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices

I'll hold onto the stack of references you've included pending receipt of your revised submission. Let me know if you have any questions.

Regards,
Richard Bonnette

Richard E. Bonnette, M.S.
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 240-402-1235
richard.bonnette@fda.hhs.gov

#718

Budenheim

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Product Stewardship
Jana Dammeier
+49 6139 89 631
jana.dammeier@budenheim.com

July 24th, 2017

Submission (calcium acid pyrophosphate) to US FDA GRAS notification program

Dear Mr Bonnette,

In response to your e-mail from July 14th, 2017, we would like to request to exclude the meat and poultry uses from the scope of our submission of calcium acid pyrophosphate to the US FDA GRAS notification program.

Sincerely,

(b) (6)

Jana Dammeier
Product Stewardship
Chemische Fabrik Budenheim KG

From:	Morissette, Rachel
To:	Dammeier, Jana
Subject:	RE: GRN 000718 (calcium acid pyrophosphate) - response requested
Date:	Friday, September 22, 2017 7:52:00 AM
Attachments:	image001.png image002.png

Thank you for your response. We will prepare your cease to evaluate letter. Please let me know if you have further questions or wish to schedule a pre-submission meeting with FDA at any point in the future.

Best regards,

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

From: Dammeier, Jana [mailto:Jana.Dammeier@budenheim.com]
Sent: Friday, September 22, 2017 6:57 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: AW: GRN 000718 (calcium acid pyrophosphate) - response requested

Dear Ms. Morissette,

Thank you for your advice. We will follow your recommendation and work with an agent towards a new submission on that substance. Therefore I would like to request, that FDA cease to evaluate the GRAS notice GRN 000718.

Mit freundlichen Grüßen / Best regards / Atentamente,

Jana Dammeier
Product Stewardship

Chemische Fabrik Budenheim KG
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http://www.budenheim.com
Jana.Dammeier@budenheim.com

Von: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Gesendet: Donnerstag, 14. September 2017 18:31

An: Dammeier, Jana <Jana.Dammeier@budenheim.com>
Betreff: GRN 000718 (calcium acid pyrophosphate) - response requested

Dear Dr. Dammeier,

This email is regarding your GRAS notice submission for calcium acid pyrophosphate, designated GRN 000718. Our review team has identified significant issues related to the information provided and the quality of the submission. At this time, we are recommending that Chemische Fabrik Budenheim KG request that we cease our evaluation of this notice. Our recommendation is based on issues raised by our review team, and the main points are highlighted below. However, there were numerous other issues that were identified as well and not mentioned in this email.

1. There is no discussion of the chemical composition of your calcium pyrophosphate product, preventing the reviewers from deciphering how your substance differs from or is similar to the subject of GRN 000420.
2. There are several specifications listed, but no corresponding batch analyses provided to show conformance with these specifications.
3. The section on estimation of dietary exposure is confusing, disjointed, and inaccurate, as there is no mention of calcium intake and no survey-based calculations.
4. Without an exposure estimation, it is impossible to evaluate the safety of the proposed uses. For example, exposures to calcium and phosphorus, along with the nature of the relationship between these exposures, is known to be a factor in the development of kidney stones and cardiovascular disease, and in calcium metabolism and homeostasis. However, information on the levels of intake of these mineral compounds and a discussion of potential related adverse effects was not provided.
5. Data from GRN 000420 was alluded to but not incorporated into and properly discussed in your notice.
6. Many of the referenced tables or attachments were not provided to FDA with the submission. Additionally, it was very difficult to locate the appropriate references, as they were not numbered in the notice or in the list of supporting information, which did not match the references that were physically provided to FDA on CD.
7. A discussion on the general recognition of safety component of your GRAS conclusion was not provided, which is particularly important in light of the references provided that were listed as “not generally available” to the public.
8. A statement that Chemische Fabrik Budenheim KG concludes that the intended use of calcium acid pyrophosphate is GRAS was not provided in the notice.
9. Part V of the notice “Experience based on common use in foods before 1958” was not properly stated.

If you decide to request that FDA cease to evaluate your notice, please provide a statement in writing via email within 10 business days. You also have the choice to not request that FDA cease to evaluate your notice, at which time FDA will issue a no basis letter for this GRAS notice. Should you decide to resubmit your GRAS notice to FDA, we strongly encourage that you request a pre-submission meeting with FDA to discuss the notice and your potential revisions. This would give you an opportunity to meet with our review team

and ask any questions you may have, as well as receive feedback from the review team prior to submitting the notice. This meeting can be held in person or via teleconference. Additionally, many of our notifiers choose to use an agent familiar with the GRAS process to represent their company. While this is not a requirement, it may be helpful to companies new to our GRAS Notification Program or who are new to the changes brought about by the GRAS Final Rule. Please let me know if you have any questions at this time.

Sincerely,

Rachel Morissette, Ph.D.
Consumer Safety Officer

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