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GRAS Notice Review

February 3, 2012

Paulette Gaynor, Ph.D.
Supervisory Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review (HFS-255)
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Dear Paulette:

Pursuant to proposed 21 CFR 170.36 (62 FR 18960; April 17, 1997), Innophos, Inc., through me as its agent, hereby provides notice of a claim that the use of calcium acid pyrophosphate as described in the enclosed notification document is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because Innophos has determined that the intended use is generally recognized as safe (GRAS) based on scientific procedures.

While we are quite certain that calcium acid pyrophosphate may be regarded as an unlisted GRAS substance, FDA has never acknowledged its status as such and this notice is intended to address this situation.

As required, three copies of the notification are provided. Each copy also includes the summary conclusion of the GRAS expert panel as well as the signatures of the three panel members.

If you have any questions regarding this notification, please feel free to contact me at 804-742-5548 or jh@jheimbach.com.

Sincerely,

(b) (6)

James T. Heimbach, Ph.D., F.A.C.N.
President

Encl.

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GRAS Determination for the Addition of Calcium Acid Pyrophosphate to Baked Products As a Leavening Agent

Prepared for

Innophos, Inc.
Cranbury NJ

Prepared by

JHeimbach LLC
Port Royal VA

January 2012

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1. GRAS Exemption Claim

Innophos, Inc., through its agent JHEIMBACH LLC, hereby notifies the Food and Drug Administration that the use of calcium acid pyrophosphate described below is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Innophos has determined that such use is generally recognized as safe (GRAS) through scientific procedures. (b) (6)

James T. Heimbach, Ph.D., F.A.C.N.
President, JHEIMBACH LLC

2/3/12
Date

1.1. Name and Address of Notifier

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P.O. Box 8000
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Contact: Roy S. Lyon, Ph.D.
Telephone: (609) 366-1282
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E-mail: roy.lyon@innophos.com

1.2. Name of GRAS Substance

The common name of the substance that is the subject of this Generally Recognized As Safe (GRAS) notice is calcium acid pyrophosphate. It is also referred to as calcium pyrophosphate, calcium hydrogen diphosphate, diphosphoric acid calcium salt, and (systematic name) calcium dihydrogen pyrophosphate.

1.3. Intended Use and Consumer Exposure

Calcium acid pyrophosphate is produced and intended to be used in combination with the GRAS compound monocalcium phosphate, in approximately 3:1 proportions, for addition to baked products as a leavening acid, and will be used as a 1:1 alternative to sodium acid pyrophosphate. As a result, there will be no change in the consumer exposure to the pyrophosphate/orthophosphate anion or any change in the intake of phosphorus. The last food additive survey by the National Academy of Sciences in 1987 estimated that the *per-capita* intake of sodium acid pyrophosphate from all permitted food uses is 19.35 mg/kg bw/day (Clydesdale 1997). Since the calcium acid pyrophosphate/monocalcium phosphate mixture is simply intended as an alternative to sodium acid pyrophosphate, the estimated daily intake (EDI) of the combination product is the same. Since calcium acid pyrophosphate constitutes about 75%

of the mixture, its EDI from its intended use is approximately 75% of that of sodium acid pyrophosphate, or about 15 mg/kg bw/day.

1.4. Basis for GRAS Determination

Innophos's GRAS determination for the intended use of calcium acid pyrophosphate is based on scientific procedures as described under 21 CFR §170.30(b). A comprehensive search of the literature on calcium acid pyrophosphate and other inorganic phosphates through December 2011 was conducted by JHEIMBACH LLC, and served as the basis for preparation of this monograph summarizing the totality of the information available germane to determining the safety of the intended use of calcium acid pyrophosphate.

The EDI of calcium acid pyrophosphate has been determined to be safe, and has also been determined to be GRAS by demonstrating that the safety of this level of intake is based on generally available and accepted information and is generally recognized by experts qualified by scientific training and experience to evaluate the safety of substances added to food.

Therefore, the intended use of calcium acid pyrophosphate is determined to be safe and GRAS. Determination of the safety and GRAS status of calcium acid pyrophosphate for direct addition to food under its intended conditions of use was made through the deliberations of an Expert Panel consisting of Joseph F. Borzelleca, Ph.D., Walter H. Glinsmann, M.D., and Lucina Lampila, Ph.D., R.D., who reviewed the information in this monograph as well as other information available to them. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. They critically reviewed and evaluated the publicly available information on calcium acid pyrophosphate and other inorganic phosphates, including the potential human exposure to calcium acid pyrophosphate, and individually and collectively concluded that no evidence exists in the available information on calcium acid pyrophosphate or other inorganic phosphates that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public health when calcium acid pyrophosphate is used under its intended conditions of use.

It is the Expert Panel's opinion that other qualified scientists reviewing the same publicly available data would reach the same conclusion. Therefore, calcium acid pyrophosphate is GRAS by scientific procedures under the conditions of use described.

1.5. Availability of Information

The data and information that serve as the basis for the GRAS determination will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times at the office of James T. Heimbach, Ph.D., President, JHEIMBACH LLC, 923 Water Street, Box 66, Port Royal VA 22535, telephone 804-742-5548 and e-mail jh@jheimbach.com.

2. Identity of the Substance

2.1. Chemical Name

The product that is the subject of this GRAS notice is calcium acid pyrophosphate. It is also referred to as calcium pyrophosphate, acid calcium pyrophosphate, monocalcium pyrophosphate, calcium diphosphate, monocalcium diphosphate, calcium hydrogen diphosphate, monocalcium dihydrogen diphosphate, and diphosphoric acid calcium salt. Its IUPAC name is calcium dihydrogen pyrophosphate.

2.2. Trade or Common Name

Calcium acid pyrophosphate has no known trade name. The compound is produced and sold in combination with monocalcium phosphate in a product with the trade name Cal-Rise®. In this product, calcium acid pyrophosphate constitutes about 75% by weight while monocalcium phosphate constitutes about 25%. Food-grade monocalcium phosphate is regarded as GRAS (21 CFR §182.1217) with no use restrictions other than Good Manufacturing Practice.

2.3. CAS Registry Number

The Chemical Abstracts Services (CAS) registry number for calcium acid pyrophosphate is 14866-19-4.

2.4. Molecular and Structural Formula

The molecular formula of calcium acid pyrophosphate is $CaH_2P_2O_7$. Its molecular weight is 216.04 g/mol. The structural formula for this compound is shown in Figure 1, below.

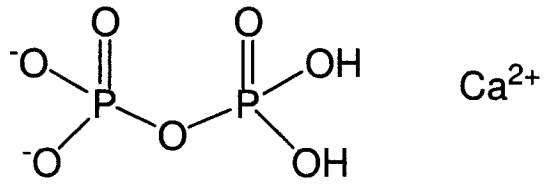

Figure 1. Structural Formula for Calcium Acid Pyrophosphate.

2.5. Physical and Chemical Properties

A brief summary of the physical and chemical properties of calcium acid pyrophosphate is provided in Table 1.

Table 1. Physical and Chemical Properties of Calcium Acid Pyrophosphate.

Physical/Chemical Property	Value
Appearance of powder	Fine white powder
Solubility in water	Insoluble or slightly soluble
Solubility in dilute acid	Moderately soluble
pH of 1% solution	2-4

2.6. Production Process

This section describes the manufacture of Cal-Rise®, a 3:1 mixture of calcium acid pyrophosphate and monocalcium phosphate. Food-grade phosphoric acid treated with small amounts of food-grade potassium hydroxide and sulfuric acid is pumped into a Stedman reactor (a rotating vessel with a stationary blade) containing a small charge of food-grade aluminum trioxide. Micronized food-grade calcium oxide is added slowly to the acid mixture and allowed to react. Near the end of the reaction, food-grade calcium hydroxide is used to complete the conversion to monocalcium phosphate. Sulfuric acid is used as a processing aid to seed the precipitation that influences the crystal morphology. The addition of aluminum and potassium compounds serve a technical function in the final product, discussed in Section 2.7.3. Product Stability.

The overall stoichiometric equations for this process are:

$$H_3PO_4 \text{ excess} + KOH \rightarrow H_3PO_4 + KH_2PO_4 + H_2O$$

$$H_3PO_4 \text{ excess} + Al_2O_3 \rightarrow H_3PO_4 + AlPO_4 + H_2O$$

$$H_2SO_4 + CaO \rightarrow CaSO_4 + H_2O$$

$$4H_3PO_4 + CaO + Ca(OH)_2 \rightarrow 2Ca(H_2PO_4)_2 + 3\,H_2O\uparrow$$

The completed batch of monocalcium phosphate is dried in a rotary dryer. In the dryer the monocalcium phosphate is converted to calcium acid pyrophosphate by the following reaction:

$$\text{Calcium dihydrogen phosphate} \underset{\Delta}{+} \text{heat} \rightarrow \text{Water} + \text{Calcium acid pyrophosphate}$$

$$Ca(H_2PO_4)_2 \rightarrow H_2O + CaH_2P_2O_7$$

This conversion percentage is targeted to result in a mixture of 75% calcium acid pyrophosphate and 25% monocalcium phosphate.

The material exiting the dryer is screened and packaged under current Good Manufacturing Practice (cGMP) conditions.

2.7. Product Characteristics

2.7.1. Food-Grade Specifications

Innophos has developed food-grade specifications for Cal-Rise®, containing approximately 75% calcium acid pyrophosphate and 25% monocalcium phosphate. These specifications are intended to establish and maintain the food-grade status of the final product. The food-grade specifications established for Cal-Rise® are listed in Table 2.

Table 2. Food-Grade Specifications for Cal-Rise®.

Parameter	Specification	Method
Neutralizing value	NLT[1] 70.0	Observation
Cumulative on 100 mesh	NMT[2] 3.0%	Observation
Through 200 mesh	NLT 75.0%	Observation
Fluoride	NMT 30 mg/kg	JSFA, 6th Ed.
Arsenic	NMT 3 mg/kg	JSFA, 6th Ed.
Lead	NMT 2 mg/kg	JSFA, 6th Ed.
Cadmium	NMT 1 mg/kg	JSFA, 6th Ed.
Mercury	NMT 1 mg/kg	JFHA, 1990

1. Not less than
2. Not more than

2.7.2. Results of Analysis of Calcium Acid Pyrophosphate

In order to demonstrate conformance with the food-grade specifications listed in Table 2, Innophos analyzed five non-consecutive lots of Cal-Rise®. The results of these analyses are displayed in Table 3; Certificates of Analysis are in the Appendix.

Table 3. Results of Analysis of Five Non-Consecutive Lots of Cal-Rise®.

Parameter	Specification	Lot Number				
		40	52	55	58	61
Mfg. Date	--	10/22/08	9/11/09	11/17/09	3/26/10	4/15/10
Neutralizing value	NLT[1] 70.0	72.4	71.8	71.0	70.9	72.0
Cumulative on 100 mesh	NMT[2] 3.0%	0.0	0.0	0.0	0.0	0.0
Through 200 mesh	NLT 75.0	79.7	83.9	90.4	92.3	92.8
Fluoride	NMT 30 mg/kg	Conforms	Conforms	Conforms	Conforms	Conforms
Arsenic	NMT 3 mg/kg	Conforms	Conforms	Conforms	Conforms	Conforms
Lead	NMT 2 mg/kg	Conforms	Conforms	Conforms	Conforms	Conforms
Cadmium	NMT 1 mg/kg	Conforms	Conforms	Conforms	Conforms	Conforms
Mercury	NMT 1 mg/kg	Conforms	Conforms	Conforms	Conforms	Conforms

1. Not less than
2. Not more than

All five lots were fully within established food-grade specifications. In order to confirm the low level of heavy metals, an additional three non-consecutive lots were tested for arsenic, cadmium, and lead, using more sensitive analytical methods in order to better characterize the low levels of these elements in the product. These results are shown in Table 4.

Table 4. Results of Heavy Metals Analysis of Three Additional Lots of Cal-Rise®.

Parameter	Sample ID		
	31024039	33013022	35013024
Mfg. Date	2/10/08	4/21/08	8/14/08
Arsenic (mg/kg)	0.4	0.2	0.4
Cadmium (mg/kg)	0.3	0.2	0.3
Lead (mg/kg)	0.025	0.042	0.065

2.7.3. Product Stability

During the processing of Cal-Rise®, aluminum trihydrate ($Al_2O_3 \cdot 3H_2O$) and potassium hydroxide are added to the phosphoric acid prior to the lime addition to help extend the shelf life of the final product by keeping the material from caking. The mechanism of caking is the hydration of monocalcium phosphate, during which the heat of hydration fuses the particles together, causing Cal-Rise® to cake.

$$Ca(H_2PO_4)_2 + H_2O \rightarrow Ca(H_2PO_4)_2 \cdot H_2O + \text{heat}$$

The aluminum trihydrate reacts to form an acidic aluminum phosphate while the potassium hydroxide forms monopotassium phosphate. These compounds coat the surface of the Cal-Rise® during drying to block the hydration reaction. As well as preventing caking, this coating gives Cal-Rise® a unique and useful reaction profile by delaying generation of carbon dioxide when mixed with a base, such as sodium bicarbonate or baking soda, commonly used as neutralizing agents in both the bakery industry and the household.

Samples from one lot of Cal-Rise®,(b) (4) l, were stored in a Nashville (TN) Warehousing facility under typical warehouse conditions (no record of temperature or humidity is available) for at least 3 years; one bag from the pallet was removed quarterly beginning after 14 months, visually inspected for flow characteristics, and analyzed for free acid content, loss on ignition, neutralizing value, and Baking Powder Rate of Reaction (BPRR) in 2, 4, 10, and 15 minutes. The results, shown in Table 5, demonstrate that the product remained within typical values of these characteristics over the full 41 months of warehouse storage.

Table 5. Stability of Warehoused Cal-Rise® Over Three Years.

Months After Packaging	Flow (Visual)	Free Acid (%)	Loss On Ignition (%)	Neutral-izing Value	Baking Powder Rate of Reaction			
					2 Minutes	4 Minutes	10 Minutes	15 Minutes
14	Free	0.08	10.69	68.4	30	43	70	90
17	Free	0.08	10.98	68.3	32	46	74	96
20	Free	0.08	10.62	65.7	35	49	84	104
23	Free	0.09	10.97	66.7	32	45	74	96
26	Free	0.06	10.78	69.1	28	42	70	90
29	Free	0.05	10.74	67.7	30	43	74	98
35	Free	0.11	11.53	70.4	32	44	68	86
38	Free	0.06	10.78	68.6	31	43	70	90
41	Free	0.05	10.84	70.4	34	47	75	94

3. Intended Use and Consumer Exposure

3.1. Intended Uses of Calcium Acid Pyrophosphate

Cal-Rise®, consisting of approximately 75% calcium acid pyrophosphate and 25% monocalcium phosphate, is intended for addition to baked products as a leavening agent [21 CFR §170.3(o)(17)] as an alternative to sodium acid pyrophosphate. Other potential intended uses include the following currently permitted uses of sodium acid pyrophosphate [with each use preceded by its paragraph number in 21 CFR §170.3(o)]:

4	coloring adjunct
6	dough strengthener
8	emulsifier or emulsifier salt
12	flavoring adjuvant
13	flour treating agent
14	formulation aid
22	oxidizing and reducing agent
26	sequestrant

In these uses, the combination of calcium acid pyrophosphate and monocalcium phosphate is intended to serve as an alternative to sodium acid pyrophosphate and is not intended to be used in any applications not already served by sodium acid pyrophosphate.

3.2. Consumer Exposure

Cal-Rise® (75% calcium acid pyrophosphate and 25% monocalcium phosphate) is intended for use as a 1:1 alternative to sodium acid pyrophosphate. As a result, there will be no change in the consumer exposure to the pyrophosphate/orthophosphate anion or any change in the intake of phosphorus[1]. The last-food additive survey by the National Academy of Sciences in 1987 estimated that the per-capita intake of sodium acid pyrophosphate from all permitted food uses is 19.35 mg/kg bw/day (Clydesdale 1997). Since Cal-Rise® is simply intended as an alternative to sodium acid pyrophosphate, its estimated daily intake (EDI) is the same. Further, since calcium acid pyrophosphate constitutes about 75% of the mixture, its EDI from the intended use of Cal-Rise® is approximately 75% of that of sodium acid pyrophosphate, or about 15 mg/kg bw/day.

The International Food Additives Council (IFAC) continued to track disappearance data for phosphorus through 1994 based on industry production data. IFAC's data (Lampila and Godber 2001) indicate that production of phosphorus compounds was little greater in 1994 than in 1987. It thus is clear that the use of phosphates is not expanding rapidly and the figures from the last food-additive survey still provide reasonable estimates of consumer exposure to phosphates.

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[1] This is not precisely true. The molecular weight of sodium acid pyrophosphate is 221.94 while the weighted average molecular weight of the two components of Cal-Rise® is 220.54, so the use of Cal-Rise® will increase the number of phosphate molecules added by 0.63%. Further, phosphorus constitutes 27.9% of the weight of sodium acid pyrophosphate but 28.1% of the weight of Cal-Rise®, and so the addition of phosphorus will increase by 1.35%. These differences, however, are well within the variability of phosphate addition to foods under current Good Manufacturing Practice and are of no significance.

4. Safety

4.1. Phosphate Chemistry and Metabolism

4.1.1. Chemistry

The basic anionic unit of all phosphates is the orthophosphate anion—often called simply the phosphate anion. This tribasic anion (PO_4^{3-}; molecular weight = 94.97) forms a tetrahedron structure which allows the formation of phosphate polymers, including diphosphates—also known as pyrophosphates. The pyrophosphate anion [$(P_2O_7)^{4-}$; molecular weight 173.94] is tetravalent. Molecular structures of the two anions are shown in Figures 2 and 3.

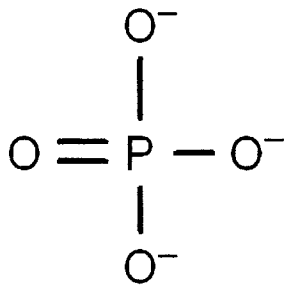

Figure 2. Orthophosphate Anion.

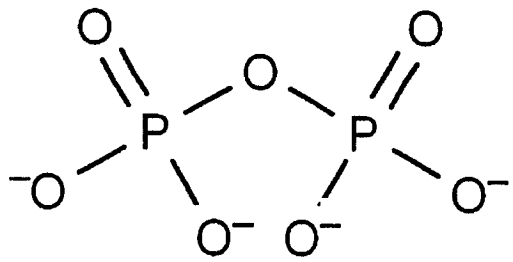

Figure 3. Pyrophosphate Anion.

4.1.2. Metabolism

Phosphorus is ingested in both inorganic form—including such phosphate salts as calcium acid pyrophosphate—and organic forms, but the organic forms are hydrolyzed by intestinal phosphatases, with the result that most phosphorus absorption occurs as inorganic phosphate (IOM 1997). Approximately 70% of dietary phosphorus is absorbed, principally in the jejunum (Goodman 2005). It is widely recognized that phosphate absorption occurs through both passive diffusion and saturable facilitated uptake, but there is some disagreement about which route dominates (Goodman 2005). For example, Bringhurst and Leder (2006) argued that active uptake (facilitated by 1,25-dihydroxyvitamin D) would always seem to predominate while the IOM Standing Committee on the Scientific Evaluation of Dietary Reference Intakes concluded that "the fact that fractional phosphorus absorption is virtually constant across a broad range of intakes suggests that the bulk of phosphorus absorption occurs by passive, concentration-dependent processes" (IOM 1997, pp 147-148).

When diphosphate salts such as calcium acid pyrophosphate are ingested, some of the diphosphate anions are hydrolyzed to orthophosphate in the gastrointestinal tract while the remainder are almost completely absorbed and hydrolyzed to orthophosphate in the serum (Fourman 1959). Since the estimated half-life for the hydrolysis of pyrophosphate at pH 2 and 39°C is about 400 hours (Mahoney and Hendricks 1978), it would appear that most diphosphate anions are absorbed intact and hydrolyzed only after absorption. Datta et al. (1962), in a toxicity study discussed in the next section, found that male Wistar rats fed sodium pyrophosphate had no pyrophosphate in their feces or urine; pyrophosphate was almost completely absorbed (either before or after hydrolysis to orthophosphate) and excreted in the urine as orthophosphate.

In the blood, about 70% of the phosphorus is in organic form—mostly as phospholipids or lipoproteins, while the remainder (about 3.1 mg/dl) is present as inorganic phosphate (IOM 1997; Bringhurst and Leder 2006). Of the inorganic phosphate, about 10% is ionically bound to protein; of the 90% non-bound phosphate, about 5% is in the form of divalent phosphate salts (calcium or magnesium), 20% as sodium salt, and 65% in free ionic form—80% of which is HPO_4^{-2} and 20% is $H_2PO_4^{-1}$ (Bringhurst and Leder 2006). Regardless of the form in which the phosphorus was originally ingested, it enters circulation and is distributed in these same forms.

4.2. Toxicity

4.2.1. Toxicological Equivalence of Inorganic Phosphates

The JECFA panel that reviewed the safety of food uses of phosphoric acid and inorganic phosphate salts (ammonium, calcium, magnesium, potassium, and sodium, including salts of mono-, di-, tri, and polyphosphates), concluded that the effects of these salts would not be significantly different and that same toxicity issues apply to all of them (JECFA 1982). Specifically, adverse effects seen in feeding studies involving high doses of inorganic phosphate salts are primarily due to excess phosphorus; the phosphate salts merely provide a source of the various cations and the phosphate anion. On this basis, the panel determined that "the present monograph is applicable to all the inorganic phosphates listed." Since no tested phosphate salt produced mutagenic or teratogenic effects, a maximum tolerable daily intake for both naturally occurring and all listed inorganic phosphates (including calcium pyrophosphate) was set at 70 mg/kg bw/day based on the lowest level of phosphate that produced nephrocalcinosis in the rat.

In reaching its conclusion that phosphate salts do not differ significantly in toxicity, and that the oral toxicity of these salts is low, the JECFA (1982) panel confirmed the determination made by the U.S. Select Committee on GRAS Substances seven years previously (SCOGS 1975). SCOGS had concluded that :

> "There is no evidence in the available information on ammonium phosphate, dibasic; ammonium phosphate, monobasic; calcium phosphate, monobasic; calcium phosphate, tribasic; calcium pyrophosphate; phosphoric acid; potassium phosphate, dibasic; potassium phosphate, monobasic; potassium phosphate, tribasic; potassium polymetaphosphate; potassium pyrophosphate; potassium tripolyphosphate; sodium acid pyrophosphate; sodium phosphate, dibasic; sodium phosphate, monobasic; sodium phosphate, tribasic; tetrasodium pyrophosphate; sodium tripolyphosphate; and straight-chain sodium poly-phosphates (including sodium hexametaphosphate, sodium metaphosphate, and sodium tetraphosphate) that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future" (SCOGS 1975).

After an extensive toxicological review of 29 inorganic phosphates—including calcium pyrophosphate—Weiner et al. (2001) reached similar conclusions, as follows:

- All of the tested inorganic phosphates are practically non-toxic following acute oral, dermal and inhalation exposures. In subchronic and chronic studies, high doses of the

inorganic phosphates did not cause severe toxicological effects. All of the inorganic phosphates were negative in a variety of genotoxicity assays and reproductive toxicity and teratogenicity studies.

- The adverse effects seen are not direct toxic effects of the inorganic phosphates, but rather effects of increased calcium excretion at high doses of inorganic phosphates as part of a physiological regulatory mechanism.
- The toxicological database on the inorganic phosphates is very robust. Based on the similar chemistry and similar toxicological results within and between classes of inorganic phosphates, the toxicities of similar inorganic phosphates are readily predicted from the available toxicological data.

4.2.2. Toxicity Studies of Inorganic Phosphates

Both the JECFA (1982) and Weiner et al. (2001) reviews included surveys of available toxicity studies, published and unpublished, of inorganic phosphates. Many of the unpublished studies were conducted by the Food and Drug Research Laboratory, Inc., under contract with FDA. Although these studies were not published in scientific journals, they were made freely available to the scientific community through the National Technical Information Service (NTIS). The JECFA review addressed only oral toxicity; Weiner et al. reviewed oral, inhalation, dermal, and ocular toxicity, but only oral toxicity is discussed in this document.

4.2.2.1. Acute Oral Toxicity

JECFA (1982) reported seven studies of monophosphate salts, three unpublished studies each in the mouse and the rat and one published study in the guinea pig, six of diphosphate salts—two in the mouse, three in the rat, and 1 in the hamster; one rat study was published. Unpublished studies were also reported of sodium tripolyphosphate in the mouse, rat, and rabbit and sodium hexametaphosphate in the mouse and rat. Reported oral LD_{50}s ranged from 1300 to 4100 mg/kg bw for the different phosphate salts and in different species.

Nineteen years later, Weiner et al. (2001) located and reviewed 96 studies of acute oral toxicity of inorganic phosphates (including those that had been cited by JECFA [1982]), including 13 studies in the mouse; one each in the hamster, guinea pig, and rabbit; and the remainder in the rat. Only five of these studies were published, while four were conducted under FDA auspices and are generally available through NTIS. The range of reported oral LD_{50}s ranged from 1380 mg/kg bw for tetrasodium pyrophosphate to >10,000 for several phosphates. Sixteen acute oral toxicity studies dealt with pyrophosphates, nine with sodium acid pyrophosphate, six with tetrasodium pyrophosphate, and one with calcium pyrophosphate. The test with calcium pyrophosphate was one with an LD_{50} > 10,000 mg/kg bw. The authors concluded that the acute oral toxicity of inorganic phosphates is low and that "differences observed between compounds and between studies for the same compound are probably due to methodological differences" (Weiner et al. 2001).

Seo et al. (2011) evaluated the acute oral toxicity of tetrasodium pyrophosphate in a fixed-dose study compliant with OECD guideline 420, in which 6-week-old female Sprague-Dawley rats were given the test article by gavage at doses of 0 or 2,000 mg/kg bw (n = 5 rats/ dose). Animals were observed for signs of toxicity at 1 and 3 hours post-gavage and daily for 14 days. There were no mortality, adverse clinical signs, or abnormal necropsy findings, leading to the conclusion that the LD_{50} of tetrasodium pyrophosphate in the female rat is > 2,000 mg/kg bw.

4.2.2.2. Short-Term and Subchronic Oral Toxicity

Sodium acid pyrophosphate and disodium phosphate were administered in the diets of 90-115-g male and female Birmingham-Wistar rats (20 rats/sex/group) at concentrations of 0, 1.0, 2.5, or 5.0% for 16 weeks (Datta et al. 1962). Half of the animals in each group were caged individually while the other were housed 5/cage. At termination, the pyrophosphate content of fecal matter and urine was measured, liver and kidney function were assessed, blood was drawn for hematological analysis, organs were excised, weighed, and examined macroscopically. All test groups developed kidney lesions as shown in Table 6. Among the rats receiving sodium acid pyrophosphate, all but the 1% group exhibited increased kidney weights and decreased renal function. The lowest observed adverse effect level (LOAEL) for sodium acid pyrophosphate in this study was 1% dietary concentration, equivalent to approximately 450 mg/kg bw/day. The NOAEL for disodium phosphate was 2.5% dietary concentration, equivalent to approximately 1250 mg/kg bw/day (Datta et al. 1962).

Table 6. Microscopic Appearance of Kidneys of Rats Fed Sodium Acid Pyrophosphate or Disodium Phosphate (Datta et al. 1962).

Description of Damage	Percent (%) of Each Group with Abnormality				
	Control	Sodium Acid Pyrophosphate			5% Mono-sodium Phosphate[1]
		1%	2.5%	5%	
Any renal damage	25	95	100	100	100
Cortical atrophy	15	60	60	15	15
Cortical hyaline degeneration	10	55	55	20	10
Cortical calcification	0	5	10	10	5
Medullary calcification	0	5	30	70	75
Medullary necrosis	0	5	10	60	65
Tubular casts	5	0	30	55	55
Hemorrhages and exudate	5	45	50	60	60
chronic inflammatory changes	0	0	5	70	70

1. Datta et al. 1962 did not report the results for the 1% and 2.5% monosodium phosphate groups.
Source: Datta et al. 1962

Hodge (1964) fed diets containing 0 or 5.0% concentrations of disodium phosphate (equivalent to 2571 mg/kg bw/day) to weanling rats (5 rats/group; strain not reported) for 1 month. No effects were seen on body or kidney weight, but histopathological analysis revealed tubular necrosis in the kidneys. Hodge (1964) also fed weanling male rats (5 rats/group) 0, 0.2, 2.0, or 10.0% dietary concentrations of sodium hexametaphosphate, sodium tripolyphosphate, sodium trimetaphosphate, or sodium tetrametaphosphate for 1 month. Growth was significantly retarded, relative kidney weights were increased, and tubular necrosis in the kidneys was seen in rats receiving 10% levels of any of the 3 compounds. Some of the rats receiving phosphates at 2.0% of the diet showed similar but lesser changes. The NOAEL for each phosphate salt tested in this study was 0.2% , equivalent to approximately 100 mg/kg bw/day.

In a third study reported by Hodge (1964), young adult dogs (strain not reported) received diets providing 100 mg/kg bw/day of sodium hexametaphosphate, sodium tripolyphosphate, sodium trimetaphosphate, or sodium tetrametaphosphate (1 dog/compound) for 1 month. Other young adult dogs received the same condensed phosphates with the dose beginning at 1000 mg/kg bw/day and increasing to 4000 mg/kg bw/day over 5 months. No adverse effects were seen in the first study, but all four dogs in the second study exhibited weight loss, increased eosinophil and decreased neutrophil counts, increased heart weight, hypertrophy of the left ventricle, and tubular kidney damage. No NOAEL could be determined in the 5-month study.

Four-year-old medium wool Merino wethers (castrated sheep) were given 0, 45, 130, or 260 mg/kg bw/day (5 sheep/group) of monosodium phosphate by gavage for 70 days (McMeniman 1973). The sheep had free access to grass and water and were weighed weekly. No treatment-related adverse effects were noted in any group. The NOAEL for monosodium phosphate in this study was 260 mg/kg bw/day, the highest dose tested.

JECFA (1982) reported that "many" short-term studies, both published and unpublished, have been conducted to determine the toxicity of inorganic phosphates in the rat and did not undertake to report on all of them. Generally, adverse effects such as nephrocalcinosis occurred only inconsistently and with diets providing phosphates at more than 5% dietary concentration and grossly distorted balances of potassium, magnesium, calcium, and phosphorus. JECFA concluded that "Optimum ratios of calcium to phosphorus, or of magnesium and potassium to phosphorus, most likely explain why the diets of some studies required higher levels of phosphates in order to demonstrate adverse physiological effects."

Weiner et al. (2001) reported an unpublished study in which 75 male Sprague-Dawley rats (age and weight not reported) were given diets containing 0, 0.7, or 3.0% sodium aluminum phosphate (25 rats/group) for 28 days. No effects were seen in any groups on clinical observations, weight gain, intake of feed and water, hematology, clinical chemistry, gross necropsy, or histopathological findings. The NOAEL for sodium aluminum phosphate in this study was 3.0%, equivalent to 1543 mg/kg bw/day, the higher dose tested. In another unpublished study cited by Weiner et al. (2001), rats (number, strain, sex, age, and weight not reported) were given the same compound at dietary concentrations of 0, 1.0, 3.0, 5.0, or 7.0% for 30 days. Significant reduction in feed intake and weight gain were noted at concentrations of 5.0 and 7.0%, but no effects were seen at lower doses. The report did not discuss what other parameters were measured nor whether the weight-gain decrement was fully explained by the reduction in feed intake and did not report the NOAEL

Weiner et al. (2001) reported a third unpublished study of the oral toxicity of sodium aluminum phosphate in which albino rats (number, strain, sex, age, and weight not reported) were fed diets containing 0, 0.3, 1.0, or 3.0% of the compound for 90 days. Aside from microconcretions of aluminum in the renal tubules of female rats in all three test groups, no abnormalities were reported. In a follow-up study in which female rats (number, strain, age, and weight not reported) were fed the compound at concentrations of 0, 0.03, or 0.1%, no effects were reported in survival, growth, or kidney lesions. In another unpublished study, Beagle dogs (number, sex, age, and weight not reported) received sodium aluminum phosphate as a dietary admixture at levels of 0, 0.3, 1.0, or 3.0% for 90 days. No significant treatment-related effects were reported (Weiner et al. 2001).

After reviewing the body of published and unpublished subchronic studies of oral toxicity in the rat, dog, and sheep, Weiner et al. (2001) concluded that the only adverse effects seen in response to administration of inorganic phosphates were renal effects due to excess phosphate and calcium load and these effects were not a direct effect of the cation. The authors' review stated:

> "All of the phosphates, with the exception of [sodium aluminum phosphate] SALP, exhibited similar NOEL/NOAELs. SALP had a NOEL that was significantly higher than the NOEL/NOAELs for the other inorganic phosphates, presumably due to the high contribution of aluminum ion to the salt's molecular weight and the poor absorption of aluminum ion. For the majority of the tested inorganic phosphates, the NOEL/NOAELs were based on renal effects. As the renal effects are due to excess phosphate and calcium load and not a direct effect of the cation, it is expected that all four classes[1] of inorganic phosphates would produce the same critical effect at high doses. Therefore, a single NOEL/NOAEL can be established for all four classes of inorganic phosphates based on the available data. Based on the lowest subchronic NOEL/NOAELs observed for three inorganic phosphates (i.e., [sodium tripolyphosphate, sodium trimetaphosphate, and sodium hexametaphosphate]), the group subchronic NOEL/NOAEL is established at greater or equal to 103 mg/kg/day" (Weiner et al. 2001).

Weiner et al. (2001) also noted that this likely underestimates the true NOAEL due to the wide dose spacing used in the studies.

Calcium pyrophosphate can be sintered to assume crystalline forms, referred to as alpha, beta, or gamma phase. The beta form, known as β-calcium pyrophosphate, has a number of medical applications including as a bone-graft extender and a toothpaste abrasive. For this reason, Lee et al. (2009) performed a subchronic study of its oral toxicity. Forty 6-week-old Sprague-Dawley rats (20 of each sex) were randomly assigned to receive 0 or 30 mg β-calcium pyrophosphate/kg bw/day. (Caging arrangements were not described, and the method of administration was not specified but appears to have been gavage.)

Clinical observations were made twice daily and feed and water intake and body weights were measured weekly. Ophthalmological examinations were conducted at baseline and prior to euthanasia. After sacrifice, urine was collected for assessment of volume and color, specific gravity, pH, leukocyte esterase, nitrite, protein, glucose, ketone bodies, urobilinogen, bilirubin, and occult blood. Blood was analyzed for hematological parameters including red and white blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, prothrombin times, activated partial thromboplastin time, and differential blood cell counts (lymphocytes, neutrophils, basophils, eosinophils, and monocytes) and for biochemical measures including total protein, albumin, glucose, total cholesterol, triacylglycerol, total bilirubin, blood urea nitrogen, creatinine, alanine transaminase, aspartate transaminase, alkaline phosphatase, chloride, calcium, potassium, and phosphorus. The necropsy included external body macroscopic examination and measurement of the weights of heart, liver, lung, kidneys, spleen, adrenal glands, brain, thymus, pituitary gland, testes, and ovaries. The following tissues and organs were sectioned and stained: digestive system (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, liver, gall bladder, salivary gland, and pancreas), urinary system (kidney and urinary bladder), respiratory

[1] In their data presentation and discussion, Weiner et al. (2001) separated inorganic phosphates into four major classes: monovalent salts, divalent salts, ammonium salts, and aluminum salts.

system (lung and trachea), cardiovascular system (heart and aorta), hematopoietic system (spleen, thymus, lymph nodes, and bone marrow), endocrine system (adrenal, pituitary, thyroid, and parathyroid glands), nervous system (brain and spinal cord), muscular skeletal system (skeletal muscle, femur, and sternum), male reproductive system (testes, epididymides, prostate, and seminal vesicle), female reproductive system (ovaries, uterus, mammary glands, and vagina), skin, tongue, and eyes.

There were no deaths; and no treatment-related adverse effects on clinical signs, feed or water intake, body weights, hematology, clinical chemistry, urinalysis, ophthalmologic parameters, absolute or relative organ weights, or in macro- and microscopic pathology. The NOAEL in this study was the single dose tested, 30 mg calcium pyrophosphate/kg bw/day.

In another published study, Seo et al. (2011) tested the oral toxicity of tetrasodium pyrophosphate in a 90-day study compliant with OECD guideline 408. Six-week-old Sprague-Dawley rats were gavaged 5 times/week with tetrasodium pyrophosphate suspended in distilled water at doses of 0, 250, 500, or 1000 mg/kg bw/day with n = 10 rats/sex/dose. (The authors noted that doses were selected based on the results of a 14-day ranging study, in which no mortality or toxicity was observed in any of the 5 male and female rats tested.)

The animals were housed in groups of 2-3 rats/cage, observed daily, and weighed weekly; feed consumption by each group was monitored. Urinalyses were performed on 5 rats/sex/group during the last week, including glucose, bilirubin, ketone bodies, specific gravity, occult blood, pH, protein, urobilinogen, nitrite, and leukocyte levels. The animals were euthanized and blood samples were taken for hematology (total and differential leukocyte counts, total red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte ratio, platelet count, prothrombin time, and activated partial thromboplastin time) and clinical chemistry (total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine, blood urea nitrogen, total cholesterol, triacylglycerol, glucose, calcium, phosphorus, creatine kinase, chloride, sodium, and potassium). Necropsies were performed on all animals; organs were excised and weighed (liver, kidneys, adrenals, testes, ovalies, and brain) and prepared for histopathology (brain, pituitary, eye, thyroids, heart, lung, liver, kidney, spleen, adrenals, stomach, testes, urinary bladder, femur, and ovaries).

There was no test-article-related mortality; the only clinical sign observed was a tendency for hair loss in female rats in the mid- and high-dose groups. Male rats receiving the high dose of 1000 mg tetrasodium pyrophosphate/kg bw/day exhibited significantly reduced feed consumption and gain in bodyweight; no significant differences were seen in feed intake or bodyweight gain in the other groups. There were no treatment-related effects on urinalysis. In the hematological evaluation, significantly increased counts of white blood cells and neutrophils and significantly reduced counts of lyphocytes were seen in both sexes in the high-dose group. Males in the high-dose group also had significantly reduced levels of red blood cells, hemoglobin concentration, hematocrit, prothrombin time, and activated partial thromboplastin time; significantly reduced prothrombin time was also seen in male rats in the mid-dose group.

Rats of both sexes in the mid- and high-dose groups had significantly reduced total protein while males in both groups had significantly reduced albumin, as did females in the high-dose group. High-dose females also had significantly increased total bilirubin and reduced

alkaline phosphatase and alanine aminotransferase. Aspartate aminotransferase was significantly increased in high-dose males. High-dose rats of both sexes showed significantly increased triacylglycerol and reduced calcium, phosphorus, sodium, potassium, and chloride. The necropsy and histopathology found no adverse findings or lesions other than higher incidences of cortical tubular basophilia of the renal tubule in high-dose males and mineralization of the kidney in high-dose females; the statistical significance of these differences was not tested. Both absolute and relative liver weights were significantly increased in mid- and high-dose females and relative liver weights were significantly increased in mid- and high-dose males.

Based on these findings, the authors concluded that "the no observed effect level (NOEL) and the no observed adverse effect level (NOAEL) were 250 and 500 mg/kg/day respectively."

4.2.2.3. Chronic Oral Toxicity

Individually caged male Wistar rats weighing 50-60 g were fed dipotassium phosphate as a dietary admixture at levels of 0.87 or 5.1% (12 rats/group) for 150 days (Dymsza et al. 1959). Feed and water were available *ad libitum*. No effects were seen at the 0.87% level. Absolute kidney weights were significantly increased in the 5.1% treatment group but there was no associated histopathology, changes in hematology or clinical chemistry, or other treatment effects. The NOAEL was determined to be 5.1%, equivalent to 2600 mg/kg bw/day.

Twelve individually housed male Wistar rats/group, received sodium hexametaphosphate as a dietary admixture at levels of 0, 0.93, or 3.5% for 150 days (Dymsza et al. 1959). Feed and water were freely available. Although absolute kidney weights were significantly increased in the 3.5% group, this was unaccompanied by histopathological findings and there were no adverse effects reported. The increased kidney weights were considered physiological adaptation. The NOAEL in this study was 3.5%, equivalent to approximately 1800 mg/kg bw/day.

Fifty Rochester rats/sex/group received sodium tripolyphosphate as a dietary admixture at levels of 0, 0.05, 0.5, or 5% for 2 years (Hodge 1964). Adverse effects—decreased growth, anemia, increased absolute kidney weight, and renal lesions (including calcification)—were seen only in the 5.0% group. The NOAEL for this study was 0.5% dietary concentration, equivalent to approximately 250 mg/kg bw/day.

In a second study (Hodge 1964), the same numbers of rats received the same dietary levels of sodium hexametaphosphate for 2 years. Significantly decreased growth was seen in the 5.0% group, along with increased relative kidney weights and calcification of the renal tubules. The 0.5% group also showed increased relative kidney weights, but this was difficult to interpret due to variable incidences of kidney infections. Since no other effects were noted, and the increase in relative kidney weight was not accompanied by histopathology, the NOAEL was determined to be 0.5% in the diet, approximately equivalent to 250 mg/kg bw/day.

Fifty Rochester rats/sex/group received sodium trimetaphosphate as a dietary admixture at concentrations of 0, 0.1, 1.0, or 10.0% for 2 years (Hodge 1964). Both males and females receiving 10% concentrations showed significant growth retardation and decreased absolute liver weights, and females exhibited retarded bone growth, but hematological, histopathological, and urinanalytical parameters were normal. Males in the 1% group exhibited growth retardation during the first year, but normal growth during the second; no other effects were reported. No

adverse effects were noted in the 0.1% group. The NOAEL in this study was 1.0%, equivalent to approximately 500 mg/kg bw/day.

JECFA (1982) reported a 1952 study in which "over 700 rats" (strain, sex, age, and weight not reported) covering 3 generations were given diets containing up to 0.75% concentrations of phosphoric acid. JECFA reported that "no adverse effects were observed" (but did not indicate whether a NOAEL was established), and noted that, "The study was reported to include examination of the blood, tissues, mineral balance, nitrogen retention, and the acidic conditions of the digestive tract."

JECFA (1982) also cited a study in which high-phosphorus/low-calcium diets supplemented with concentrations of 0, 0.5, 1.0, 2.5, or 5% of a mixture containing 2/3 sodium acid pyrophosphate and 1/3 sodium trimetaphosphate were fed to male and female rats (10 rats/sex/ concentration). Dosing was continued through 3 generations. Up to the 2.5% level, no effects were seen on growth, fertility, or average life span, although some nephrocalcinosis was seen at levels of 1% and above. No adverse effects were seen at 0.5% , equivalent to approximately 375 mg/kg bw/day and this was considered the NOAEL.

JECFA (1982) cited a third study in which 30 male and 10 female weanling rats/dose were placed on a very-high-phosphorus/low-calcium diet supplemented with concentrations of 0.5, 1, 2.5, or 5% of 2/3 sodium acid pyrophosphate and 1/3 sodium trimetaphosphate. The diet was maintained to the end of their life spans and continued through 2 successive generations. Growth and fertility were significantly inhibited in rats receiving 5% supplementation, but not in the other groups. The 2.5% group showed significant reduction in erythrocyte count in the second generation only, and all groups receiving polyphosphates at levels over 0.5% showed dose-dependent increases in renal calcification. JECFA did not report whether a NOAEL was identified in this study.

JECFA (1982) also cited two unpublished feeding studies in which weanling rats (50 rats/sex/treatment; strain and weight were not reported) were given diets containing 0, 0.05, 0.5, or 5% of either sodium tripolyphosphate (Experiment 1) or sodium hexametaphosphate (Experiment 2). Adverse effects on survival, growth, hematology, histology, and reproduction were seen only at the 5% level, and the NOAEL was 0.5%, equivalent to approximately 375 mg/kg bw/day. In the control and 0.5% treatment groups, feeding continued over 3 generations with 2 litters/generation. No adverse effects were seen, and the NOAEL for this multigeneration study was also 0.5%, equivalent to approximately 375 mg/kg bw/day.

Weiner et al. (2001) cited a published 1954 study in which 10 female rabbits were given 300-700 mg/kg bw/day of monosodium phosphate in drinking water in increasing doses for 5-16 months; the only endpoint assessed was the weight of the parathyroid glands. Increased parathyroid weights were seen, a physiological response to the added phosphate load. The study was not regarded as suitable for setting a NOAEL. Weiner et al. (2001) also reported an FDA-sponsored study in which rats were fed sodium orthophosphate or sodium metaphosphate for 7 months at 8% dietary concentration. Bone decalcification, hypertrophy and hyperplasia of the parathyroid glands, and renal calcification were seen at this level, equivalent to about 4100 mg/kg bw/day.

Weiner et al. (2001) also cited a study in which 15 beagle dogs received diets providing 800 mg/kg bw/day of dipotassium phosphate for either 14 or 38 weeks along with an unspecified

number of controls. The test dogs had elevated creatine and blood urea as well as renal tubular atrophy and nephrocalcinosis. No NOAEL was identified in this study.

In another study described by Weiner et al. (2001), 34-36 male rats/group (strain, age, and weight were not reported) were administered 0, 3, or 5% dietary concentrations of disodium phosphate, sodium tripolyphosphate, or tetrasodium pyrophosphate for 6 months. In one side experiment, 36 male rats/group were given 0 or 1.8% disodium phosphate or tetrasodium pyrophosphate in the diet for 6 months. In a second side experiment, male rats received 0 or 1.1% dietary concentrations of disodium phosphate, sodium tripolyphosphate, or tetrasodium pyrophosphate for 39 weeks. Significantly decreased growth and renal calcification were seen in the groups receiving 3% or 5% concentrations of any of the tested phosphates. In the first side experiment, all three phosphates produced statistically significant increases in absolute kidney weights at 1.8% (an effect apparently not observed in the main study), but no other effects were reported. During the second side experiment, slight growth retardation was seen. The LOAEL for all three compounds in these studies was regarded as 1.1% in the diet, equivalent to about 560 mg/kg bw/day, the lowest dose tested.

Weiner et al. (2001) reported an unpublished study in which male and female beagle dogs (4 dogs/sex/group) received diets containing 0, 0.3, 1.0, or 3.0% sodium aluminum phosphate for 26 weeks. Significantly decreased feed intake and body weights were noted in males of the 3.0% group, along with histopathological changes including hepatocyte vacuolation and hypertrophy, and milk glomerulonephritis. There were no treatment-related adverse effects on hematology, clinical chemistry, urinalysis, or necropsy findings. The NOAEL in this study was 1.0%, equivalent to doses of 390 and 323 mg/kg bw/day for males and females, respectively. In another cited study from the same laboratory, 6 beagle dogs/sex/group were given the same compound at the same dietary concentrations for 27 weeks. In this study, no changes were seen in clinical observations, feed consumption, weight gain, hematology, biochemistry, urinalysis, gross necropsy, fecal occult blood, ophthalmic findings, or histopathology. The NOAEL was 3% dietary concentration, equivalent to 1034 and 1087 mg/kg bw/day for males and females, respectively (Weiner et al 2001). Weiner et al. (2001) did not directly comment on the differences in the findings of these two similar studies from the same laboratory, but reported that the effects observed in the first study "appeared to be an indirect result ... resulting from the decreased food consumption and weight gain."

Weiner et al. (2001) noted the wide variation in the NOAELs established in the various chronic studies, but also noted that a) the variability for the same compound across studies was just as great as the variability across compounds, and b) the NOAELs were nearly all based on the same endpoint—renal effects, which were due to excess phosphate and calcium load and not a direct effect of the phosphate cation. They suggested that "a single NOEL/NOAEL can be established for all four classes of inorganic phosphates based on the available data. Based on the lowest chronic NOEL/NOAELs observed for two inorganic phosphates (i.e., [sodium tripolyphosphate and sodium hexametaphosphate]), the group chronic NOEL/NOAEL is established at 225 mg/kg/day."

4.2.2.4. Teratogenicity and Reproductive Toxicity

Verrett et al. (1980) tested the toxicity of 80 food-additive chemicals in developing chick embryos. The tested compounds included monosodium phosphate, monopotassium phosphate, monocalcium phosphate, tricalcium phosphate, tetrasodium pyrophosphate, and sodium hexa-

metaphosphate. Four conditions were used for each test chemical: injection into the yolk or into the air cell and preincubation for 0 or 96 hours. Five or more dose levels were tested with each chemical, with at least 100 embryos tested per dose. All embryos and hatched chicks were subjected to gross necropsy. No teratogenic effects were seen with monopotassium-, monocalcium-, or tricalcium phosphate; weak teratogenic effects were seen with the other compounds.

Under FDA contract, and made available to the public through the NTIS, teratogenicity studies were conducted in mice, hamsters, rats, and rabbits with a variety of inorganic phosphate salts, including monosodium phosphate, monopotassium phosphate, sodium acid pyrophosphate, tetrasodium pyrophosphate, sodium tripolyphosphate, sodium hexametaphosphate, and monocalcium phosphate (Weiner et al. 2001). Phosphates were administered by gavage at doses as high as 465 mg/kg bw/day from day 6 to day 10-18 of gestation, depending on the test species. In all studies, the sex, body weights of live pups, and numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. All fetuses were examined for skeletal defects and external congenital abnormalities, and a third of the fetuses of each litter were subjected to visceral examinations. In no study was any indication of teratogenicity observed, and Weiner et al. (2001) concluded that, "Based on these results, it is not expected that other inorganic phosphates would be teratogenic."

Hodge (1964) fed male and female Rochester rats (8 males and 16 females/group) diets containing 0 or 0.5% sodium tripolyphosphate or sodium hexametaphosphate, or 0 or 0.05% sodium trimetaphosphate, from weaning to 100 days of age for 3 generations. Two litters from each generation were examined. None of the treatments had any observable effect on fertility, litter size, survival or growth of the offspring, organ weights, gross necropsy, or histopathological findings. The NOAELs were the tested levels—0.5% dietary concentration for sodium tripolyphosphate and sodium hexametaphosphate and 0.05% for sodium trimetaphosphate. Based on this published study, Weiner et al. (2001) concluded that "it is not expected that other inorganic phosphates would be reproductive toxicants."

4.2.2.5. Genotoxicity

Ishidate et al. (1984) conducted Ames tests and Chinese hamster fibroblast cell line chromosomal aberration tests on 242 food additives used in Japan. The Ames tests were conducted with S. *typhimurium* tester strains TA92, TA94, TA98, TA100, TA1535, and TA1537, both with and without S9 metabolic activation. Chromosomal aberration tests included both 24- and 48-hour exposures without metabolic activation. Inorganic phosphates tested included disodium phosphate and sodium acid pyrophosphate. None of the results was positive.

Weiner et al. (2001) reviewed a large number of genotoxicity studies of inorganic phosphates; *in vitro* tests included Ames/*Salmonella* and *Saccharomyces cerevisiae* mutagenicity assays (all both with and without metabolic activation), chromosome aberrations in Chinese hamster fibroblasts, and cytogenetics in human lung cells, while *in vivo* tests included dominant lethal tests in rats, host-mediated assays in mice, and mouse translocation tests. Phosphates tested included monosodium phosphate, monopotassium phosphate, dipotassium phosphate, tripotassium phosphate, sodium acid pyrophosphate, tetrasodium pyrophosphate, sodium tripolyphosphate, tetrapotassium pyrophosphate, sodium hexametaphosphate, monocalcium phosphate, dicalcium phosphate, and ammonium polyphosphate. All results were negative, and

Weiner et al. (2001) concluded that the phosphate ion "is not genotoxic or mutagenic in standard test systems."

4.2.2.6. Summary of Toxicity Studies of Inorganic Phosphates

An extensive body of data on the safety of inorganic phosphates exists, including studies published in the scientific literature and studies sponsored by FDA and generally available through NTIS, supported by unpublished studies. This body of research includes acute and short-term, subchronic, and chronic studies of oral toxicity, developmental and reproductive toxicity studies, and *in vitro* and *in vivo* genotoxicity tests. Test articles included all the mono- and condensed phosphates of sodium, potassium, calcium, magnesium, ammonium, and aluminum. Test species included mice, rats, hamsters, guinea pigs, rabbits, dogs, and sheep. The data consistently demonstrate the lack of developmental or reproductive toxicity, or genetic toxicity and low oral toxicity under all test conditions. The limiting factor in phosphate ingestion is increased calcium excretion at high doses as part of a physiological regulatory mechanism, leading to calcification of the kidney. This is a physiological effect of the phosphate ion and not a toxicological one. This finding allows generalization of toxicological characteristics across classes of inorganic phosphates.

Based on this conclusion, JECFA (1982) was able to derive a maximum tolerable daily intake (MTDI) for man of 70 mg total phosphorus/kg bw/day, which applies to the sum of the phosphates naturally present in food and to all evaluated inorganic phosphates. The JECFA reviewers stated that "the rat is exquisitely susceptible to calcification and hydronephrosis upon exposure to acids forming calcium chelates or complexes." They then concluded, "The lowest level of phosphate that produced nephrocalcinosis in the rat (1% P in the diet) is used as the basis for the evaluation and, by extrapolation based on the daily food intake of 2800 calories, this gives a dose level of 6600 mg P per day as the best estimate of the lowest level that might conceivably cause nephrocalcinosis in man."

Weiner et al. (2001), critically evaluated the data available to JECFA and nearly two decades of additional research and recommended an acceptable daily intake (ADI) for total phosphorus of 63 mg phosphorus/kg bw/day. This is equivalent to 4410 mg phosphorus/day for a 70-kg individual. For comparison, the IOM (1997), using data from the Continuing Surveys of Food Intakes by Individuals, estimated total daily phosphorus intake for the U.S. population, including both naturally occurring and added phosphorus, as 1222 mg at the mean and 1790 mg at the 90th percentile.

5. Safety Assessment and GRAS Determination

5.1. Introduction

This section presents an assessment that demonstrates that the addition of calcium acid pyrophosphate to conventional foods under the conditions of use described is safe and is GRAS.

This safety assessment and GRAS determination entail two steps. In the first step, the safety of the intended use of calcium acid pyrophosphate is demonstrated. Safety is established by demonstrating a reasonable certainty that the exposure of consumers to calcium acid pyrophosphate under its intended conditions of use is not harmful. In the second step, the intended use of calcium acid pyrophosphate is determined to be GRAS by demonstrating that the safety of this compound under its intended conditions of use is generally recognized among qualified scientific experts and is based on publicly available and accepted information.

The regulatory framework for establishing whether the intended use of a substance (or organism) is GRAS, in accordance with Section 201(s) of the Federal Food Drug and Cosmetic Act, is set forth under 21 CFR §170.30. This regulation states that general recognition of safety may be based on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. A GRAS determination may be made either: 1) through scientific procedures under §170.30(b); or 2) through experience based on common use in food, in the case of a substance used in food prior to January 1, 1958, under §170.30(c). This GRAS determination employs scientific procedures established under §170.30(b).

A scientific procedures GRAS determination requires the same quantity and quality of scientific evidence as is needed to obtain approval of the substance as a food additive. In addition to requiring scientific evidence of safety, a GRAS determination also requires that this scientific evidence of safety be generally known and accepted among qualified scientific experts. This "common knowledge" element of a GRAS determination consists of two components:

1. data and information relied upon to establish the scientific element of safety must be generally available; and
2. there must be a basis to conclude that there is a consensus among qualified experts about the safety of the substance for its intended use.

The criteria outlined above for a scientific-procedures GRAS determination are applied below in an analysis of whether the addition of calcium acid pyrophosphate to foods is safe and is GRAS.

5.2. Safety Evaluation

The body of evidence supporting the safety of ingestion of inorganic phosphates, including calcium acid pyrophosphate, at current or reasonably contemplated levels of intake, is large and convincing and includes acute, subacute, subchronic, chronic, reproductive and developmental, and genotoxicity. Test animals included mice, rats, dogs, and sheep. The only consistently observed treatment-related adverse effect at high levels of phosphate exposure is calcification of the kidney resulting from increased calcium excretion as part of a physiological regulatory mechanism. This physiological response was recognized by JECFA (1982) and by Weiner et al (2001). JECFA (1982) set an MTDI for phosphorus of 70 mg/kg bw/day, while

Weiner et al. (2001) set an ADI for phosphorus at 63 mg/kg bw/day. All available evidence demonstrates clearly that there is no reason to suspect harm to individuals consuming foods containing calcium acid pyrophosphate at the anticipated daily intake level of 15 mg/kg bw/day, or of Cal-Rise® containing calcium acid pyrophosphate and monocalcium phosphate at 20 mg/kg bw/day.

5.3. Existing Regulatory Approvals of Inorganic Phosphates

Along with numerous other inorganic phosphates, calcium acid pyrophosphate in approved for use in the European Union under number E450.

Table 7. Phosphates Approved for Use in the EU.

E-Number	Phosphate
E338	Phosphoric acid
E339	Monosodium phosphate Disodium phosphate Trisodium phosphate
E340	Monopotassium phosphate Dipotassium phosphate Tripotassium phosphate
E341	Monocalcium phosphate Dicalcium phosphate Tricalcium phosphate
E343	Monomagnesium phosphate Dimagnesium phosphate
E450	Disodium diphosphate Trisodium diphosphate Tetrasodium diphosphate Dipotassium diphosphate Tetrapotassium diphosphate Dicalcium diphosphate Monocalcium diphosphate
E451	Pentasodium triphosphate Pentapotassium triphosphate
E452	Sodium polyphosphate Potassium polyphosphate Sodium calcium polyphosphate Calcium polyphosphate
E541	Sodium aluminum phosphate, sour

The compound is also approved in Canada as an emulsifying and stabilizing agent, subject only to the JECFA limit of 70 mg/kg bw/day for phosphorus from all sources (Health Canada 2011). It is listed on the General Standard for Food Additives promulgated by the Codex Alimentarius Commission for use as an acidity regulator, emulsifier, humectant, raising agent, sequestrant, and stabilizer (Codex Alimentarius 2011).

The general safety and GRAS status of current uses of inorganic phosphates was addressed in a notice filed with FDA in 2003 on behalf of the International Food Additives Council (IFAC), informing the agency that IFAC had determined that potassium phosphate (mono-, di-, and tribasic), calcium hexametaphosphate, calcium pyrophosphate, tetrapotassium pyrophosphate, potassium tripolyphosphate, sodium hexametaphosphate, tetrasodium

pyrophosphate, and sodium tetraphosphate are GRAS for use in food generally, as multi-purpose ingredients, up to the limits of GMP. FDA's response letter (FDA 2003) noted that some of these salts—calcium hexametaphosphate, calcium pyrophosphate, sodium hexametaphosphate, sodium pyrophosphate, tetrasodium pyrophosphate, and dipotassium phosphate—were regulated under 21 CFR §182. FDA also stated that the remaining phosphate compounds, while not explicitly regulated under §182 or §184, had been reviewed by SCOGS and determined to be GRAS for their intended use. Finally, FDA concluded that, "The agency has no reason to question the GRAS determination performed by the SCOGS when used in accordance with good manufacturing practice."

In its evaluation of a petition for the inclusion of calcium acid pyrophosphate on the National [Organic] List of Allowed and Prohibited Substances for use as a leavening agent in baked goods (USDA 2010), the U.S. Department of Agriculture observed that the compound has long been approved for use as a poultry scald agent to remove feathers from poultry carcasses with its addition level stated as "sufficient for purpose." The review also noted that sodium acid pyrophosphate is approved for use as a leavening agent in organic products. (As of this date, calcium acid pyrophosphate has not been added to the National List.)

5.4. General Recognition of the Safety of Calcium Acid Pyrophosphate

The intended use of calcium acid pyrophosphate has been determined to be safe through scientific procedures set forth under 21 CFR §170.30(b). This safety was shown by establishing the identity and purity of the substance, reviewing the chemistry, metabolism, and published toxicological information on inorganic phosphates and the supporting unpublished information, and concluding that the expected exposure to calcium acid pyrophosphate by adults and children is without significant risk of harm. Finally, because this safety assessment satisfies the common knowledge requirement of a GRAS determination, this intended use can be considered GRAS.

Determination of the safety and GRAS status of the addition of calcium acid pyrophosphate to food has been made through the deliberations of an Expert Panel consisting of Joseph F. Borzelleca, Ph.D., Walter H. Glinsmann, M.D., and Lucina Lampila, Ph.D., R.D., who reviewed a monograph prepared by JHeimbach LLC as well as other information available to them. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. They critically reviewed and evaluated the publicly available information and the potential human exposure to calcium acid pyrophosphate anticipated to result from its intended uses, and individually and collectively concluded that no evidence exists in the available information on calcium acid pyrophosphate that demonstrates, or suggests reasonable grounds to suspect, a hazard to either adults or children under the intended conditions of use of calcium acid pyrophosphate.

It is the Expert Panel's opinion that other qualified scientists reviewing the same publicly available data would reach the same conclusion.

Therefore, the intended use of calcium acid pyrophosphate is GRAS by scientific procedures.

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CONCLUSION OF THE EXPERT PANEL: GRAS DETERMINATION FOR THE ADDITION OF CALCIUM ACID PYROPHOSPHATE TO BAKED PRODUCTS AS A LEAVENING AGENT

Prepared for:

Innophos, Inc.

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January 2012

CONCLUSION OF THE EXPERT PANEL: GRAS DETERMINATION FOR THE ADDITION OF CALCIUM ACID PYROPHOSPHATE TO BAKED PRODUCTS AS A LEAVENING AGENT

We, the members of the expert panel, have individually and collectively critically evaluated the publicly available information on inorganic phosphate salts, particularly calcium acid pyrophosphate, summarized in a monograph prepared by JHEIMBACH LLC, as well as other material deemed appropriate or necessary. Our evaluation included review of the identity and physical-chemical properties of the substance, including production methods, the potential exposure resulting from the intended use of Cal-Rise® containing calcium acid pyrophosphate, and published research bearing on the safety of calcium acid pyrophosphate. Our summary and conclusion resulting from this critical evaluation are presented below.

Summary

- The substance that is the subject of this GRAS determination is calcium acid pyrophosphate, also known as calcium dihydrogen pyrophosphate.

- Calcium acid pyrophosphate is produced by a chemical process that results in a 3:1 mixture of calcium acid pyrophosphate and monocalcium phosphate which is sold under the trade name Cal-Rise®.

- Cal-Rise® is intended for addition to baked products as a leavening agent as an alternative to sodium acid pyrophosphate; it may also serve other functions currently served by sodium acid pyrophosphate, including coloring adjunct, dough strengthener, emulsifier or emulsifier salt, flavoring adjuvant, flour treating agent, formulation aid, oxidizing and reducing agent, and sequestrant.

- Since Cal-Rise® (75% calcium acid pyrophosphate and 25% monocalcium phosphate) is intended for use as a 1:1 alternative to sodium acid pyrophosphate, there will be no change in the consumer exposure to the pyrophosphate/orthophosphate anion or any change in the intake of phosphorus. Further, since calcium acid pyrophosphate constitutes about 75% of the mixture, its EDI from the intended use of Cal-Rise® is approximately 75% of that of sodium acid pyrophosphate, or about 15 mg/kg bw/day.

- Approximately 70% of dietary phosphorus is absorbed, principally in the jejunum, through both passive diffusion and saturable facilitated uptake. When diphosphate salts such as calcium acid pyrophosphate are ingested, some of the diphosphate anions are hydrolyzed to orthophosphate in the gastrointestinal tract while the remainder are almost completely absorbed and hydrolyzed to orthophosphate in the serum.

- In the blood, about 70% of the phosphorus is incorporated into phospholipids or lipoproteins, while the remainder is present as inorganic phosphate, mostly in the free ionic forms of HPO_4^{-2} and $H_2PO_4^{-1}$.

- The U.S. Select Committee on GRAS Substances (SCOGS) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that the biological effects of a wide variety of inorganic phosphate salts are not significantly different and the same toxicity issues apply to all of them, with the result that a single ADI could be established covering all of them. This same conclusion was reached in later reviews.

- Inorganic phosphates are practically non-toxic following acute oral exposure; in subchronic and chronic studies, high doses of the inorganic phosphates did not cause severe toxicological effects. All of the inorganic phosphates were negative in a variety of genotoxicity assays and reproductive toxicity and teratogenicity studies.

- The adverse effects seen at high intakes of inorganic phosphates are not direct toxic effects of the phosphates, but rather effects of increased calcium excretion at high doses of inorganic phosphates as part of a physiological regulatory mechanism.

- The toxicological database on the inorganic phosphates is very robust, including acute, subacute, subchronic, chronic, reproductive and developmental, and genotoxicity studies in mice, rats, dogs, and sheep.

Conclusion

We, the undersigned expert panel members, are qualified by scientific education and experience to evaluate the safety of ingredients intended to be added to foods. We have individually and collectively critically evaluated the materials summarized above.

All available evidence demonstrates clearly that there is no reason to suspect harm to individuals consuming foods containing calcium acid pyrophosphate under its intended conditions of use, resulting in an estimated daily intake level of 15 mg/kg bw/day of calcium acid pyrophosphate and 20 mg/kg bw/day of Cal-Rise® containing calcium acid pyrophosphate and monocalcium phosphate.

It is also our opinion that other qualified and competent scientists reviewing the same publicly available information would reach the same conclusion. Therefore, the intended use of calcium acid pyrophosphate is safe, and is GRAS, via scientific procedures.

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SUBMISSION END