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Provisional Peer-Reviewed Toxicity Values for

Inorganic Phosphates
(Orthophosphoric Acid and Inorganic Phosphate Compounds, Including Ortho- and Condensed Phosphates)
(Various CASRNs included in the text)

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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS[1]

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

[1]Table A.1 provides a list of inorganic phosphate compounds and their acronyms.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR INORGANIC PHOSPHATES (ORTHOPHOSPHORIC ACID AND INORGANIC PHOSPHATE COMPOUNDS, INCLUDING ORTHO- AND CONDENSED PHOSPHATES) (VARIOUS CASRNS INCLUDED IN THE TEXT)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility

in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The focus of this document is on the development of oral p-RfD values to be used in assessing health risks associated with the ingestion of inorganic phosphates in water. Any other exogenous cumulative inorganic phosphate from dietary sources or enriched phosphate products needs to be taken into account during toxicity assessment of inorganic phosphorus in water. This analysis does not include elemental phosphorus in any form due to the fact that human exposure to elemental phosphorus in a typical environmental setting is unlikely to occur (elemental phosphorus [P] has a very short half-life in water) and because the toxicity of elemental phosphorus is much higher than that of inorganic phosphorus compounds, to which individuals are more likely to be exposed. Phosphorus is most commonly found in nature in its pentavalent form in combination with oxygen, as phosphate (PO_4^{3-}). Phosphorus (as phosphate) is an essential constituent of all known protoplasm, and its content is quite uniform across most plant and animal tissues. Orthophosphate is the basic unit for all phosphates. Orthophosphate can form many polymeric ions or condensed phosphates (pyro-, meta-, and other polyphosphates). Inorganic phosphates (ortho- and condensed phosphate anions) can be grouped into four classes based on their cations including monovalent cations (sodium, potassium, and hydrogen), bivalent cations (calcium and magnesium), ammonium, and aluminum. The phosphoric acids have been grouped with the other monovalent cations based on valence state. There are about 30 chemicals with inorganic phosphate as an anion. Figure 1 shows the basic structure of ortho- and condensed phosphates, and Appendix A, Table A.1 presents a list of ortho- and condensed phosphate names, their CASRNs, and acronyms for each compound. The classification scheme is based on the similar chemical and toxicological properties of inorganic phosphates within a given class. In each class, ortho- and condensed phosphate salts are grouped together. This secondary grouping is based on the chemicals' similar toxicological properties and on the fact that in vivo, condensed phosphates break down into orthophosphates. Thus, ortho- and

condensed phosphate salts can be viewed as having commonality by their cations (Weiner et al., 2001; WHO, 1982). In this document, "statistically significant" denotes a *p*-value of <0.05.

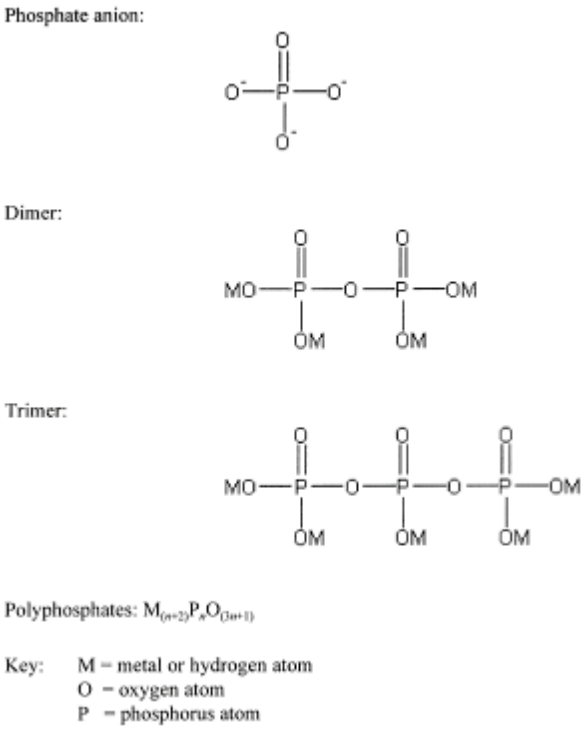

Figure 1. Basic Structure of Ortho- and Condensed Phosphates (Weiner et al., 2001)

OCCURRENCE, HOMEOSTASIS, AND DIETARY REQUIREMENTS

Phosphorus homeostasis and dietary requirements must be considered alongside toxicity studies to determine appropriate toxicity values. It is atypical for a healthy individual to have a deficiency in phosphorus because (1) phosphorus is readily available through ingestion of most food sources and (2) endogenous phosphorus is recycled indefinitely (IOM, 1997). Phosphorus is readily bioavailable from all foods except seeds (i.e., beans, peas, unleavened cereals, nuts). Seeds contain phosphorus in the form of phytic acid, which can only be released in the presence of phytase; phytase is found in intestinal bacteria and in certain foods. Gastrointestinal (GI) absorption of phosphorus is 55−70% in adults and 65−90% in children, and it does not vary by diet (except for those high in phytic acid) or with phosphorus dosage up to 3 g (100 mmol)/day. Aluminum and unabsorbed calcium in the GI tract (such as calcium carbonate from antacids) inhibit phosphorus absorption through complex formation.

In humans, 85% of the endogenous phosphorus is bound together with oxygen and calcium in the form of crystalline hydroxyapatite [$Ca_5(PO_4)_4(OH)$] in bone (Lewis, 2009a). Most of the remaining phosphorus is found in the form of organic phosphate in the intracellular compartment of soft tissues (e.g., adenosine diphosphate, adenosine triphosphate, nucleic acids, and membrane phospholipids). A small fraction of the total phosphorus is also found in plasma as inorganic phosphate. The small plasma inorganic phosphate compartment is critical to the tightly interrelated homeostasis of phosphate and calcium in bone and soft tissue.

Unlike calcium, phosphorus concentration in the plasma is only loosely regulated (IOM, 1997) and is primarily a function of phosphorus intake. Increases in plasma inorganic phosphorus can result in increased parathyroid hormone (PTH) secretion (leading to decreased renal resorption of phosphorus[2], increased bone resorption, and, potentially, increased plasma calcium) and decreased 1,25-dihydroxy vitamin D[3] (leading to decreased transport of calcium from the intestine, and, potentially, decreased plasma calcium). According to IOM (1997), these changes are not adverse when calcium intake is adequate. The normal range of inorganic phosphate concentrations in the plasma of an adult human is 2.5−4.5 mg/dL (0.81−1.45 mmol/L) (Lewis, 2009a). Levels are 50% higher in infants and 30% higher in children. In adults, hypophosphatemia[4] is considered to occur when plasma phosphate concentrations fall below 2.5 mg/dL; hyperphosphatemia[5] is defined by plasma phosphate concentrations that exceed 4.5 mg/dL.

Plasma calcium concentration is more stringently regulated than phosphorus concentration. It is controlled primarily by PTH and vitamin D, and secondarily by calcitonin (Lewis, 2009b). Normal total plasma concentrations of calcium in an adult human are in the range of 8.8−10.4 mg/dL (2.0−2.6 mmol/L). Hypocalcemia is defined by total plasma calcium concentrations <8.8 mg/dL; hypercalcemia is defined by total plasma calcium concentrations that exceed 10.4 mg/dL (Lewis, 2009b).

The product of the plasma calcium and phosphate ($Ca \times PO_4$) concentrations is an important determinant of soft-tissue calcification. When the $Ca \times PO_4$ product exceeds 70 mEq/L, precipitation of $CaPO_4$ crystals in soft tissue is more likely to occur; a value of 60 mEq/L is considered to be normal (Lewis, 2009b). However, calcification of vascular tissue may occur at $Ca \times PO_4$ values as low as 55 mEq/L in patients with chronic renal disease.

The Food and Nutrition Board of the Institute of Medicine (IOM, 1997) has published the following recommended daily allowances (RDAs) for phosphorus:

- Children 1−3 years: 460 mg (14.8 mmol) P/day
- Children 4−8 years: 500 mg (16.1 mmol) P/day
- Adolescents 9−18 years: 1250 mg (40.3 mmol) P/day
- Men and women 19−>70 years: 700 mg (22.6 mmol) P/day

[2]Phosphorus is excreted primarily through the kidneys (IOM, 1997). It is filtered out of the plasma in the glomerulus and resorbed in the proximal tubules. The rate of resorption is limited and can be described by the tubular maximum for phosphate (TmP), which is inversely proportional to PTH concentration: high plasma phosphorus results in high PTH and reduced TmP (less phosphorus is resorbed).
[3]Vitamin D (calciferol, includes both D_2 and D_3 forms) must be converted to its biologically active form (1,25-dihydroxy vitamin D) by two hydroxylations that occur in the liver and kidney (IOM, 1997). 1,25-Dihydroxy vitamin D regulates intestinal absorption of calcium and phosphorus.
[4]Fairly rare condition that may occur in hospitalized patients receiving parenteral feeding, burn patients, acute alcoholism, recovery phase of diabetic ketoacidosis, severe respiratory alkalosis, hyperparathyroidism, long-term administration of antacids or diuretics, or following prolonged malnutrition (Lewis, 2009a).
[5]Occurs as a result of decreased renal excretion of phosphate; some causes are glomerular filtration rate <30 mL/minute as in chronic renal failure, hypoparathyroidism, pseudohypoparathyroidism, excessive oral phosphate administration, overzealous use of enemas containing phosphate, or shifts of phosphate into the extracellular space in end-stage disease states or overwhelming systemic infection (Lewis, 2009a).

As determined by IOM (1997), the values for children are based on concentrations believed to be necessary for adequate bone and soft tissue growth, and the values for adults are based on the concentrations necessary for normal plasma inorganic phosphate concentrations. Due to the lack of evidence for increased phosphorus demand during pregnancy and lactation, the RDA values for pregnancy and lactation are the same as the age-based requirements, according to IOM (1997). These values are considered to be adequate for residents of the United States and Canada. Phosphorus deficiency is typically seen only in cases of acute alcoholism, chronic malnutrition, diabetic ketoacidosis, kidney disease, advanced cancer, or hospitalized patients fed parenterally (Lewis, 2009a).

REGULATORY ACTIVITY REGARDING THE TOXICITY OF INORGANIC PHOSPHATES

No oral RfD is available on the EPA IRIS database for inorganic phosphate; orthophosphoric acid; or any of the calcium, sodium, potassium, or magnesium salts (U.S. EPA, 2009). Similarly, no values are available for any of these compounds on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) or the HEAST database (U.S. EPA, 1997). EPA (1989) reviewed the health effects of inorganic phosphorus compounds but did not derive toxicity values. There are no other EPA documents having the ability to inform toxicity value derivation for inorganic phosphates included in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994).

Orthophosphoric acid and inorganic phosphate salts are used as food ingredients and are considered to be Generally Recognized as Safe (GRAS) by the Food and Drug Administration (U.S. FDA, 1979). The toxicity of orthophosphoric acid or its sodium, calcium, or potassium salts has not been reviewed by ATSDR (2009). The World Health Organization (WHO, 1971, 1965) reported that a 375-mg P/kg body-weight[6] was a "level causing no significant toxicological effect in the rat" based on a 90-week study of three generations in rats (Bonting and Jansen, 1956) and estimated a maximum tolerable daily intake (MTDI) for humans of 70 mg P/kg from all sources of phosphorus (JECFA, 2009; WHO, 1982). It is important to note that MTDI is not an acceptable daily intake (ADI); rather, it applies to the sum of phosphate additives and phosphates that occur naturally in food. The MTDI is based on an assumption of adequate dietary calcium; WHO (1982) notes that if calcium intake were higher, then the intake of phosphate could be proportionately higher; if calcium intake were lower, then the intake of phosphate that could be tolerated would be proportionately lower.

The IOM (1997) derived Tolerable Upper Intake Levels (ULs) for dietary phosphorus as follows:

- Children 1−8 years: 3 g (96.8 mmol) P/day
- Adolescents 9−18 years and adults 19−70 years: 4 g (130.0 mmol) P/day
- Adults >70 years: 3 g (96.8 mmol) P/day
- Pregnancy 14−50 years: 3.5 g (112.9 mmol) P/day
- Lactation 14−50 years: 4.0 g (130.0 mmol) P/day

[6]This value is based on a NOAEL of 7500 mg P kg-day of orthophosphoric acid in the diet; 375 mg P kg-day is the WHO estimate of the equivalent dose of phosphorous.

For infants, IOM (1997) did not derive a UL but recommended that the source of phosphorus intake should be solely food and breast milk or formula (the phosphorus content of cow's milk is too high and results in hypocalcemia in approximately 30 out of 10,000 neonates).

The IOM (1997) UL values are based on the empirical relationship between phosphorus intake and serum phosphorus concentrations established in adult volunteers (Nordin, 1988) and in infants and young children. In adults, assuming 65% GI absorption, the upper boundary for oral intake associated with the upper boundary for normal serum inorganic phosphorus is 3.4 g (110 mmol)/day. Given that serum phosphorus values in infancy are naturally much higher than adult values and are safe, and that there is no reason to assume major differences in critical toxicity (i.e., metastatic mineralization) at different ages, IOM (1997) used the regression equation for adult intake versus serum concentration along with the upper boundary for infant serum value to project an equivalent adult intake of >10.2 g (330 mmol)/day. Thus, the adult UL value is based on a predicted NOAEL of 10.2 g/day. In deriving the UL value, the point of departure (POD) of 10.2 g/day was divided by an uncertainty factor (UF) of 2.5; the partial UF accounts for possible interindividual differences in pharmacodynamics, given that the relationship between intake and serum concentration is known. The UL for children 1−8 years old is based on the POD of 10.2 g/day divided by a UF of 3.3 to account for potentially increased susceptibility associated with smaller body size. The UL for adults over the age of 70 years is based on the POD of 10.2 g/day divided by a UF of 3.3 because IOM felt that it was prudent to lower the value to account for the increasing prevalence of impaired renal function. IOM (1997) did not offer any specific numerical evidence to support this decision. The UL for pregnancy is based on an observation that the absorption efficiency of phosphorus increases by 15% in pregnancy, and therefore, the intake associated with the upper end of the normal range for serum phosphorus would be approximately 3.5 mg (112.9 mmol)/day. Given that the phosphorus economy of a lactating woman is not discernibly different from a nonlactating woman, IOM (1997) assumed the upper limit was to be the same as for a nonlactating woman.

A cancer assessment for orthophosphoric acid or other inorganic phosphates is not available on the IRIS database (U.S. EPA, 2009), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or the HEAST database (U.S. EPA, 1997). The carcinogenic potential of orthophosphoric acid or other inorganic phosphates has not been studied or reviewed by the National Toxicology Program (NTP, 2009, 2005), the International Agency for Research on Cancer (IARC, 2009), or CalEPA (2009).

LITERATURE SEARCH

Literature searches were conducted from 1960s through September 16, 2010 for studies relevant to the derivation of provisional toxicity values for orthophosphoric acid. Databases searched include the following: MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months). Additional searches of PubMed (through August 17, 2009) were conducted to establish the availability of studies relevant to sodium and potassium salts of orthophosphoric acid, including dibasic sodium phosphate (Na_2HPO_4), dibasic potassium phosphate (K_2HPO_4), monobasic sodium phosphate (NaH_2PO_4), and monobasic potassium phosphate (KH_2PO_4), as well as mono-, di-, and tricalcium phosphate, trisodium and tripotassium phosphate, ammonium phosphate (mono- and di-), magnesium phosphate (mono- and di-), phosphate (restricted to exclude phosphine, organic phosphates, and organophosphate pesticides), and phosphorus (restricted to exclude phosphorus pentoxide, phosphorus trichloride

and pentachloride, elemental phosphorus, etc.). Elemental phosphorus was excluded from consideration because of its short half-life in water and resultant transformation to phosphate. The IOM (1997) Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride was searched for additional relevant citations.

REVIEW OF PERTINENT DATA

Based on the existing human and animal studies, the primary concerns for phosphate-induced toxicity are disruption of calcium economy, soft-tissue mineralization, and kidney damage. Disruption of calcium economy is the most commonly observed effect of phosphate ingestion in both humans and animals. While soft-tissue mineralization and kidney damage are common consequences of phosphate ingestion in laboratory animals, these changes are rare in humans, occurring most often (but not exclusively) in people who are already in end-stage kidney failure or other chronic disease states (IOM, 1997; Nordin, 1988).

HUMAN STUDIES OF ORAL EXPOSURE

The primary types of human studies encountered in the literature include studies of dietary supplementation and their effects on calcium balance, studies of the use of phosphate-containing solutions that are administered in high doses to cause bowel evacuation prior to surgery or colonoscopy, and carbonated beverage consumption studies. The carbonated beverage studies are potentially relevant because phosphoric acid is commonly used as an acidifying agent, particularly in cola beverages. There are also many studies of calcium and phosphorus balance in patients with end-stage chronic kidney disease. Following are summaries of these findings.

Controlled Supplementation or Dietary Studies that Assess Effects on Calcium Balance

There have been many studies designed to assess the effects of phosphorus supplementation or deficiency on the calcium economy. Appendix A, Table A.2 summarizes key studies of this type. The common finding of these studies is that increased dietary phosphate can cause small—but statistically significant—decreases in serum calcium (<3%), small (2-fold or less)—but statistically significant—increases in serum PTH or markers for PTH (e.g., urinary cAMP), and small—but statistically significant—increases in markers for bone resorption (Kemi et al., 2009, 2008; Calvo et al., 1990, 1988; Zemel and Linkswiler, 1981). Increasing dietary calcium appears to mitigate the changes produced by administration of high phosphate alone (Kemi et al., 2008; Zemel and Linkswiler, 1981; Heaney and Nordin, 2002). The aforementioned studies reported exposure durations from 24 hours (Kemi et al., 2008; Calvo et al., 1988) to 6 weeks (Grimm et al., 2001). Kemi et al. (2009) is a cross-sectional study of premenopausal females that relied upon 4-day food records from which dietary phosphorus and calcium intakes were calculated; subjects were sorted into quartiles based on phosphorus intake, and the first and fourth quartiles were compared. This and the studies by Calvo et al. (1990, 1988) are the only studies that reported significant decreases in serum calcium.

One 10-day study that used a high dietary phosphorus concentration of 1600 mg P/day with adequate dietary calcium found no significant effects on serum PTH or bone resorption (Bizik et al., 1996). The study using the highest dietary phosphorus concentration (3008 mg/day) and adequate-high dietary calcium (1700−1995 mg/day) for the longest duration

of exposure (6 weeks) found no significant changes in serum PTH, bone resorption, or indicators of renal function (Grimm et al., 2001) in healthy young women, who appear to be more sensitive to these effects than young men (Calvo et al., 1988). Intestinal upsets including soft stools and mild diarrhea were observed in all subjects during the period of high-phosphorus exposure (Grimm et al., 2001). These effects are likely due to bolus dosing (high phosphorus was achieved with supplemental tablets administered with orange juice, rather than through food sources); as discussed below, inorganic phosphate tablets are used for bowel cleansing. Studies designed specifically to assess calcium balance found no consistent critical effects of increased dietary phosphate on calcium balance in either males or females (Heaney and Recker, 1982; Spencer et al., 1978). According to WHO (1971) and Schrödter et al. (1991), a study (published in German) on ingestion of phosphoric acid reported that no marked urinary changes indicative of a detrimental effect on metabolism were seen in students who drank 2000−4000 mg P/day for 10 days (29−57 mg P/kg-day) or 3900 mg P/day for 14 days (56 mg P/kg-day) in fruit juices (Lauerson, 1953). Doses in parentheses were calculated assuming a 70-kg body weight in accordance with EPA (1988).

Studies of the Use of Phosphate-containing Solutions Administered as Bowel-Cleansing Agents

Sodium phosphate is commonly used as a bowel-cleansing agent prior to diagnostic imaging and surgical procedures, and there are many case reports of severe adverse effects in patients following acute administration of sodium phosphate tablets (28−40 tablets at 1.5 g sodium phosphate monobasic and 0.398 g sodium phosphate dibasic each, equivalent to 0.474 g P/tablet; 13.3−19 g P total dose) or two bottles of oral sodium phosphate solution (92 g sodium phosphate equivalent to 23 g phosphorus) for bowel cleansing prior to surgery or colonoscopy (Ori et al., 2008; Medoff et al., 2004). A rare syndrome of clinical and pathological effects known as acute phosphate nephropathy has been described in approximately 30 cases. This syndrome includes formation of calcium-phosphate depositions in the renal tubules, interstitial fibrosis, hypertension, and acute tubular degeneration and regeneration. This condition is irreversible and occurs in people with previously normal renal function as well as those with recognized risk factors including female gender, older age, hypertension, and renal failure.

In a study designed to investigate the efficacy of sodium phosphate (NaP) in treating constipation, 43 individuals (age and gender not provided) consumed 4−8 NaP tablets/day for 28 days (Medoff et al., 2004). Each tablet had 1.5 g NaP from a combination of mono- and dibasic sodium orthophosphate, equivalent to 0.474 g P/tablet. After 48 hours of treatment, the dose was increased or decreased to a minimum of 2 or a maximum of 12 tablets/day, yielding doses of 0.95−5.7 g P per person per day; assuming a 70-kg body weight, this is equivalent to a dose of 13.5−81 mg P/kg-day. Baseline serum calcium, inorganic phosphorus, and potassium readings were taken for each individual. The study authors did not consider any changes from baseline values to be clinically significant or requiring treatment. This study is limited by the small number of participants, variable dosing, and the lack of in-depth investigation of effects on kidney and bone.

Carbonated Beverage Consumption Studies

Due to the use of phosphoric acid as an acidifying agent, cola drinks and some brands of root beer and other popular soft drinks contain phosphorus. Values from common soft drinks have been determined (Massey and Strang, 1982), and they range from <1 mg P/100 mL for

7-Up and Ginger Ale to 8.9 mg P/100 mL for Kool-Aid (lemonade flavor) and 19.7 mg P/100 mL for Coca-Cola. There is no measurable calcium in these drinks (Mazariegos-Ramos et al., 1995).

Data on 1810 children (ages 12−18 years) collected in a national food intake survey suggest that soft drinks displace milk and fruit juice in the diets of children and adolescents (Hamack et al., 1999). A number of case-control and cross-sectional studies have been conducted to address the potential impact of consumption of carbonated beverages on health. Some of the studies found correlations between carbonated beverage consumption and the following:

- changes in calcium economy (decreased serum Ca, increased PTH) in children (Mazariegos-Ramos et al., 1995) and postmenopausal women (Guerrero-Romero et al., 1999);
- increased incidence of chronic kidney disease (Saldana et al., 2007);
- increased percentage of urinary stone recurrence (Shuster et al., 1992); and
- increased occurrence of bone fractures among active adolescent girls (Wyshak, 2000; Wyshak and Frisch, 1994).

While some of the above studies attempted to distinguish between consumption of beverages acidified with phosphoric acid and those that were not, only two addressed phosphorus intake in a manner that could inform toxicity value derivation. There were no significant differences in phosphorus intake between cases and controls in the two studies that quantified phosphorus intake (i.e., Guerrero-Romero et al., 1999; Mazariegos-Ramos et al., 1995). One other cross-sectional study found no significant difference in bone mineral density in older women who consumed carbonated beverages (either one daily serving for >1 year, or more than one serving daily) compared with those who did not (Kim et al., 1997). In that study, there were no differences in daily mineral intakes (621−668 mg Ca/day; 1163−1214 mg P/day) between nonconsumers or occasional consumers and daily or frequent consumers of carbonated beverages.

While some of the above studies suggest potential impacts of carbonated beverage consumption on health, there is no clear evidence that any such effect is due to intake of inorganic phosphate.

Weiner et al. (2001) reported that a handful of human studies have been conducted with inorganic phosphates. The review of human studies indicated that no adverse effects were associated with consuming 4−6 g of inorganic phosphate in the form of phosphoric acid (PA) or monosodium phosphate (MSP) daily for 10 days. The results of these studies provided evidence that inorganic phosphates exhibit low oral toxicities.

SHORT-TERM, SUBCHRONIC-DURATION, AND CHRONIC-DURATION ANIMAL STUDIES

Appendix A, Table A.3 summarizes studies of note that were cited by WHO (1982, 1971, 1965) and IOM (1997), and selected relevant studies published in 1997 or later (after the IOM publication). Exposure to high concentrations of dietary phosphate has been associated with increased kidney damage and calcification in dogs, cats, rats, and rabbits (Cockell and Belonje, 2004; Cockell et al., 2002; Matsuzaki et al., 2002, 1999, 1997; Bushinsky et al., 2000;

DiBartola et al., 1993; Schneider et al., 1981, 1980a,b; MacKay and Oliver, 1935); increased bone porosity in rabbits (Jowsey and Balasubramaniam, 1972); and increased soft tissue calcification involving tissues other than kidney in rabbits and guinea pigs (Jowsey and Balasubramaniam, 1972; House and Hogan, 1955). The observed effects appear to occur regardless of the form of inorganic phosphate, are greater in females than in males, and, in some studies, are mitigated by the presence of adequate or increased dietary calcium.

In a 7-year study of wild-caught Cinnamon-tailed monkeys, Anderson et al. (1977) found no clinical radiographic or histological indicators of bone disease in monkeys fed high-phosphate diets (1.2% P in the diet equivalent to 600 mg P/kg-day) for 7 years. Bonting and Jansen (1956) did not observe significant effects on growth, hematology; pathology; or calcium, phosphorus, or nitrogen balances in three generations of rats fed up to 0.946% dietary phosphorus (equivalent to a dose of 792 mg P/kg-day); did not observe effects in three generation reproduction of rats exposed to 1.06% dietary phosphorus (equivalent to a dose of 888 mg P/kg-day). The dietary composition in this study, which was used by WHO to set an MTDI for phosphorus, was designed to emulate the calcium and phosphorus composition of a normal Dutch diet. Food and Drug Research Laboratories, Inc. (1975a,b) did not report any marked developmental effects in rats and mice fed phosphate in the diet at doses up to 106 and 95 mg P/kg-day, respectively.

Additionally, a toxicological review of inorganic phosphates by Weiner et al. (2001) including data on the acute, subchronic, and chronic toxicity; genotoxicity; teratogenicity; and reproductive toxicity from the published literature and from unpublished studies by the manufacturers is considered for the assessment. Based on toxicity data and similar chemistry, the inorganic phosphates can be separated into four major classes: monovalent salts, divalent salts, ammonium salts, and aluminum salts. The classification scheme supports the use of the oral toxicity data because compounds within a particular class can be used to assess the toxicity of another compound in the same class (Weiner et al., 2001; WHO, 1982).

Subchronic Toxicity of Inorganic Phosphates

Results from multiple studies in rats, dogs, and sheep ranging from 28 to 100 days demonstrated that the kidney is a target organ of inorganic phosphate at high doses. At high phosphate loads, excess phosphate can cause increased bone demineralization and release of calcium as part of a physiological regulatory mechanism. Excess phosphate and calcium loads result in nephrocalcinosis and other renal effects. All of the phosphates, with the exception of SALP (sodium aluminum phosphate), exhibited similar NOAELs. SALP had a NOAEL that was significantly higher than the NOAELs for other inorganic phosphates—presumably due to the high contribution of the aluminum ion to the salt's molecular weight and the poor absorption of the aluminum ion. For the majority of the tested inorganic phosphates, the NOAELs were based on renal effects. Because the renal effects are due to excess phosphate and calcium loads and not a direct effect of the cation, Weiner et al. (2001) suggested that all four classes of inorganic phosphates could produce the same critical effect at high doses. Therefore, a single subchronic Weiner et al. (2001) stabled NOAELs for all four classes of inorganic phosphates based on the available data. Based on the lowest subchronic NOAELs observed for three inorganic phosphates (sodium tripolyphosphate [STP], sodium trimetaphosphate [STMP], and sodium hexametaphosphate [SHMP]), the group subchronic NOAEL was established at greater than or equal to 103 mg/kg-day. Appendix A, Table A.4 presents the summary of subchronic-duration oral toxicity studies of inorganic phosphates reported by Weiner et al. (2001).

Chronic Toxicity of Inorganic Phosphates

Based on the Weiner et al. (2001) review, results of multiple studies in rats, dogs, and rabbits ranging from 21 to 104 weeks demonstrated that the kidney is a target organ at high doses. Excess phosphate loads cause increased bone demineralization and release of calcium as part of a physiological regulatory mechanism. Excess phosphate and calcium loads result in nephrocalcinosis and other renal effects. A wide range of chronic NOAELs was established for inorganic phosphates. The difference between the lowest NOAEL and the highest was over an order of magnitude. Despite this range, the majority of the NOAELs were based on the same endpoint (i.e., renal effects). Weiner et al. (2001) reported that, because the renal effects were due to excess phosphate and calcium loads and not a direct result of the cation, it was expected that all four classes of inorganic phosphates would produce the same critical effect at high doses. Therefore, a single chronic NOAEL was established for all four classes of inorganic phosphates based on the available data. Also, based on the lowest chronic NOAEL observed for two inorganic phosphates (STP and SHMP), the group chronic NOAEL was established at 0.5% (257 mg/kg-day). Appendix A, Table A.5 presents a summary of chronic-duration oral toxicity studies reviewed by Weiner et al. (2001). The two studies used as the basis for the selected NOAEL of 257 mg/kg-day are summarized below:

STP

In a chronic-duration oral toxicity study, 50 weanling rats (strain not specified) of both sexes were fed a basal diet of 0 (control group), 0.05, 0.5, or 5.0 % STP (purity not specified), respectively, for each group in the diet for 104 weeks. Animals in the highest dose group exhibited retarded growth, increased food consumption, signs of anemia, slightly increased liver and kidney weights, reduced bone growth, and renal lesions. Histopathological changes in the kidney consisted of dilated convoluted tubules, hyaline casts, and interstitial fibrosis between the dilated tubules; fibrotic glomeruli and intertubular calcification occurred in all rats in the highest dose group. In control rats and those administered 0.05% and 0.5% STP, the kidney changes were indistinguishable from chronic pyelonephritis of old rats. Mortality was high principally because of epidemics that occurred at various times. The highest mortality (80%) over the 2-year period was observed in female rats in the highest dose group and the lowest in mortality (exact percent not reported) in females of 0.05% STP. There was no indication that STP is carcinogenic. Tumor incidence and type observed were typical of those found in old rats and were similar in controls and treated animals. The NOAEL for this study was 0.5% in diet, which is equivalent to 257 mg/kg-day, assuming a 0.35-kg rat consumes 18 g food/day (Weiner et al., 2001).

SHMP

Rats (strain not specified) (50/sex/group) were administered 0, 0.05, 0.5, or 5.0% SHMP (purity not specified) in the diet for 2 years. Decreased growth and increased food consumption were noted in animals fed 5% SHMP. Increased kidney-to-body-weight ratios were noted in the 0.5 and 5%-groups; however, the study authors stated that the organ-weight changes were difficult to interpret due to a varied incidence of kidney infection. Calcification of the renal tubules was noted in most rats in the 5%-group and one rat in the 0.5%-group. Hematological and urine parameters and bone growth were normal in all animals. Tumor incidence and type were similar in control and treated animals. No effects were noted in the 0.05%-group. Because the increased kidney-to-body weight ratio in the 0.5%-group was not accompanied by a significant observation of histopathological renal damage (i.e., only one animal exhibited renal

calcification), the NOAEL for this study is 0.5% in the diet, equivalent to 257 mg/kg-day, assuming a 0.35-kg rat consumes 18 g food/day (Weiner et al., 2001).

DEVELOPMENTAL STUDIES

Weiner et al. (2001), in a peer-reviewed journal, summarized results of 18 teratogenic studies for inorganic phosphates including mono- and divalent ortho- and condensed inorganic phosphates in pregnant rats, mice, rabbits, and hamsters in different strains. All the 18 teratogenic studies summarized by Weiner et al. (2001) are gavage studies with five dose levels (including a control) in the range of 0 to 465 mg/kg-day. Weiner et al. (2001) reported these phosphates lacked teratogenic potential when tested in pregnant rats, mice, rabbits, and hamsters using standard protocols for teratogenic studies. Based on these results, Weiner et al. (2001) reported that it was not expected that other inorganic phosphates would be teratogenic. Similar results are reported by WHO (1982).

In other studies, WHO (1982), in a peer-reviewed document, reported the absence of maternal or developmental effects after administration of the following phosphates: (i) monocalcium phosphate (MCP) at dose levels up to 465 mg/kg-day body weight (bw) in mice and 410 mg/kg bw in rats, (ii) monosodium phosphate (MSP) at dose levels up to 370 mg/kg bw in mice and 410 mg/kg bw in rats (strain not specified), (iii) sodium acid pyrophosphate (SAPP) at dose levels up to 355 mg/kg bw in mice, 169 mg/kg bw in rats, 128 mg/kg bw in rabbits, and 166 mg/kg bw in hamsters, (iv) TSPP at dose levels up to 130 mg/kg bw in mice and 138 mg/kg bw in rats, and (v) SHMP at dose levels up to 370 mg/kg bw in mice, 170 mg/kg bw in rats, 250 mg/kg bw in rabbits, and 141 mg/kg bw in hamsters.

REPRODUCTIVE TOXICITY

Weiner et al. (2001) summarized a two-generation reproductive study with a monovalent inorganic phosphate (e.g., PA) and one three-generation reproductive study with three condensed phosphates (e.g., STP, STMP, or SHMP).

As reported by Weiner et al. (2001), an unspecified number of male and female rats (strain not specified) were administered 0.4 or 0.75% PA (purity not specified) in the diet for 29 weeks. Basel diets contained 1.9% tricalcium phosphate (TCP) (purity not specified) and 0.8% disodium phosphate (DSP) (purity not specified). After 29 weeks of treatment, the rats were mated. Eleven weeks after the first mating, the rats were mated again. The study authors did not indicate whether the parents received a treated diet during the 11 weeks between the first and second mating. The offspring were maintained on the parental diet for 29 weeks starting at 3 weeks of age. All reproductive parameters, including weight of the mothers, number of living young, and stillborn per litter, average birth weight of the living young, and number of young left at weaning, were comparable between controls and treated animals for both generations. There were no remarkable body-weight changes or gross or histopathological differences between controls and treated animals. Blood parameters, which were only determined for controls and the 0.4%-group, were similar between the two groups.

For condensed inorganic phosphates, Hodge (1964) summarized a three-generation reproductive study, in which 16 female and 8 male rats (strain not specified) per group were administered and maintained on a diet containing 0, 0.05% STMP (purity not specified), 0.5% STP (purity not specified), or 0.5% SHMP (purity not specified) from weanling to 100 days. Two litters from each generation were examined. Matings were carried out between

16 females and 8 males of each group when weanling rats were 100 days old. None of the inorganic phosphates affected fertility, litter size, or growth or survival of the offspring. A slight increase in kidney weight was observed in rats administered 0.5% STP, but the authors indicated it was not statistically significant (data not reported). For the third generation, organ weights and gross and histopathological findings were comparable between controls and treated animals. These studies were also included in the Weiner et al. (2001) toxicological review of inorganic phosphates.

Weiner et al. (2001) reported that the study results demonstrated that none of the tested inorganic phosphates are reproductive toxicants in rats. Also, based on those data, it was not expected that other inorganic phosphates would be reproductive toxicants. Therefore, it is suggested that all four classes of inorganic phosphates are grouped together in regards to reproductive toxicity (Weiner et al., 2001; Hodge, 1964).

DERIVATION OF SUBCHRONIC AND CHRONIC p-RfD VALUES FOR PHOSPHORUS FROM INORGANIC PHOSPHATES

Phosphorus in the human body is present in both organic and inorganic forms, but its absorption mostly occurs as inorganic phosphate. Inorganic phosphorus occurs as orthophosphate (PO_4^{3-}), pyrophosphate molecule ($P_2O_7^{4-}$), and phosphate linked through an organic compound (RPO_4^{2-}). Inorganic phosphate in extracellular fluids is the measure of phosphorus intake toxicity. Orthophosphate, as the central unit, is the source of phosphorus exposure from agricultural and chemical products, and diet. For better clarity, all subsequent calculations are based on elemental phosphorus, which is contained in inorganic phosphate (PO_4^{3-}) (Nordin, 1988; IOM, 1997; Weiner, 2001).

Three starting points (or options) are considered for development of the subchronic and chronic p-RfDs:

- Option1: The chronic p-RfD of 1.5 g P/day calculated from animal studies summarized by Weiner et al. (2001)
- Option 2: The UL of 4.0 g P/day for adults developed by IOM (1997) as the chronic p-RfD
- Option 3: The subchronic and chronic p-RfD of 3.4 g P/day derived from human study data reported by Nordin (1988)

The derivation process of the subchronic and chronic p-RfD considered for each option is described below.

p-RfD CALCULATED FROM WEINER ET AL. (2001)

Option 1: The Chronic p-RfD of 1.5 g P/day Calculated from Animal Studies Summarized by Weiner et al. (2001)

Based on the chronic-duration toxicity data of various inorganic phosphates summarized by Weiner et al. (2001) (see Appendix A, Table A.5), the lowest chronic NOAEL was selected as the POD for deriving a chronic p-RfD. No subchronic p-RfD is developed because the established subchronic NOAEL of 103 mg/kg-day for inorganic phosphates was considered

unrealistic and most likely substantially greater than 103 mg/kg-day. This was justified by a log-fold difference between the NOAEL and LOAEL in the three studies (STP, STMP, and SHMP) used to determine the group chronic NOAEL. Based on Weiner et al. (2001), the large-dose spacing was used because these studies were simply preliminary studies used to establish a dose range for chronic-duration studies with these compounds (Hodge, 1964). Therefore, the subchronic NOAEL for STP, STMP, and SHMP was most likely considerably higher than estimated from the preliminary studies. This is supported by the NOAEL established for the chronic-duration studies on STP, STMP, and SHMP, which are several fold greater than the NOAEL established in subchronic-duration studies (Weiner et al., 2001).

Weiner et al. (2001), based on the lowest chronic NOAELs observed for two inorganic phosphates (i.e., sodium triphosphate [STP] and sodium hexametaphosphate [SHMP]), established the group chronic NOAEL of 257 mg/kg-day and a LOAEL of 2571 mg/kg-day due to renal calcification in rats. The assumption for unit conversion by Hodge (1964); Weiner et al. (2001) included an average body weight of 0.35 kg and a daily food consumption of 18 g/day and that a rat consuming a diet containing 0.5% of STP or SHMP would ingest 257 mg STP or SHMP/kg-day (Hodge, 1964; Weiner et al., 2001). Also, the phosphorus atomic weight of 31 g/mol, the STP molecular weight of 368 g/mol, and the SHMP molecular weight of 612 g/mol were used to express the NOAEL as mass of phosphorus contained in inorganic phosphate (after accounting for the percentage of P in each compound) as follows:

Adjusted to Daily Average Dose

$NOAEL_{ADJ}$

The following dosimetric adjustments are made for each dose in the Hodge (1964) study for diet treatment in adjusting for daily average dose.

Conversion factors: 1% = 10,000 ppm and 1 ppm = 1 mg/kg of food; 0.5% is equivalent to 5000 mg/kg.

Weiner et al. (2001) used a rat body weight of 0.35 kg, and average daily food consumption was 18 g/day for both sexes.

$NOAEL_{ADJ}$ (mg/kg-day) = $NOAEL_{Hodge, 1964}$ × [food consumption per day (kg/day) ÷ body weight (kg)] × (days dosed ÷ 7 days per week)

$NOAEL_{ADJ}$ (mg/kg-day) = 5000 mg/kg × [(0.018 kg/day)] ÷ (0.35 kg) × (7 days dosed ÷ 7 days per week)

$NOAEL_{ADJ}$ = 257.1 mg/kg-day × 1

$NOAEL_{ADJ}$ = 257.1 mg/kg-day = 0.257 g/kg-day

STP

STP = (0.257 g/kg-day × 93 g/mol ÷ 368 g/mol) = 6.5×10^{-2} g P/kg-day
= 65 mg/kg-day of P contained in a STP mol.

SHMP

SHMP = (0.257 g/kg-day × 186 g/mol ÷ 612 g/mol = 7.8×10^{-2} g P/kg-day
= 78 mg/kg-day of P contained in a SHMP mol.

Among the two proposed NOAELs, the lowest (i.e., **65 mg P/kg-day)** is used as the POD to derive the chronic p-RfD to allow protection of both groups.

$$\textbf{p-RfD} = \textbf{POD (NOAEL)} \div \textbf{UF}_C$$
$$= \textbf{(65 mg P/kg-day)} \div \textbf{3}$$
$$= \textbf{21.6 mg P/kg-day}.$$

The phosphorus p-RfD of 21.6 mg P/kg-day is equivalent to a human intake of 1512 mg P/day or 1.52 g P/day as illustrated below:

(21.6 mg P/kg-day) × 70 kg human body weight = 1512 mg P/day of human intake.

The composite UF (UF_C) of 3 is used. Table 1 below summarizes the UFs.

Table 1. Uncertainty Factors for the Chronic p-RfD of Inorganic Phosphates Using Animal Data Summarized by Weiner et al. (2001)

UF	Value	Justification
UF_A	1	A UF_A is selected for the following reasons: 1) No significant difference in toxicodynamics of phosphate metabolism between humans and laboratory animals is expected. 2) Normal blood P_i concentration is higher in laboratory animals than in humans, which represents a toxicokinetic difference. However, this higher concentration results in greater sensitivity to renal calcification, because the base level of P_i is higher. Therefore, there is no justification to use an UF for animal-to-human extrapolation.
UF_D	1	A UF_D of 1 is selected because the database includes two acceptable multigeneration reproduction studies in rats (Bonting and Jansen, 1956; Hodge, 1964) and multiple acceptable developmental study summaries in rats, mice, rabbits, and hamsters (Weiner et al., 2001), and there is no indication of other specific endpoint studies that may be relevant.
UF_H	3	A UF_H of 3 is selected because the analysis was developed based on healthy human adults, who are more sensitive to phosphate poisoning than children, but the degree of sensitivity is arguable. The normal plasma levels of phosphate are higher in children than adults, but toxicity is not observed at these levels, which reduce with age (IOM, 1997; Nordin 1988). However, adults with kidney impairment and the elderly are more sensitive. The UF_H of 3 takes these factors into account.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because exposure duration is independent of the critical endpoint (renal effects) (Hodge, 1964).
UF_C ≤3000	3	

p-RfD CALCULATED FROM IOM (1997)

Option 2: The UL of 4.0 g P/day for Adults Developed by IOM (1997) as the Chronic p-RfD

IOM (1997) calculated the UL of ~4 g (~130 mmol) P/day for adults by dividing a NOAEL of 10.2 g P/day by a UF of 2.5. IOM (1997) selected a UF of 2.5 based on the following rationale:

> *No benefit is evident from serum inorganic phosphate values above the usual normal range in adults. Moreover, information is lacking concerning adverse effects in the zone between normal inorganic phosphate and levels associated with ectopic mineralization. Therefore, in keeping with the pharmacokinetic practice where the relationship between intake and blood level is known* (page 187).

UL = NOAEL ÷ UF
= 10.2 g P/day ÷ 2.5
= ~4.08 g P/day

The UL of 4.0 is for adults ages 19−70 years old. Assuming a human body weight of 70 kg for an adult, the UL of 4.0 g P/day is equivalent to 57 mg P/kg-day as illustrated below:

4000 mg P/day ÷ 70 kg = 57 mg P/kg-day.

Appendix A, Table A.6 presents the ULs for different lifestages, as taken from IOM (1997).

p-RfD CALCULATED FROM NORDIN (1988)

Option 3: The Subchronic and Chronic p-RfDs of 3.4 g P/day Derived from Human Study Data Reported by Nordin (1988).

IOM (1997) estimated a NOAEL of 10.2 g P/day (equivalent to 145.7 mg/kg-day) based on the upper boundary of adult normal values of serum P_i related to the daily phosphorus intake obtained from an intravenous infusion experiment of neutral phosphate solution at a steadily increasing rate in adults with normal renal function by Nordin (1988). According to IOM (1997), the NOAEL of 10.2 g P/day was the highest inorganic phosphate ingested intake in adults considered normal and the threshold above which elevated inorganic phosphate in the extracellular fluid (ECF) could result in toxicity.

Figure 2 demonstrates the general relationship between absorbed phosphorus intake and serum P_i in adults, which was derived from Nordin (1988) from a study of neutral phosphate solution that was intravenously infused at a steadily increasing rate in adults with normal renal function, thus producing a controlled hyperphosphatemia. Thus, the achieved serum P_i is directly related to the quantity entering the circulation. Serum P_i rises rapidly at low intakes because the filtered load will be below the tubular maximum for phosphate (TmP) and little of the absorbed phosphorus can be lost in the urine (see Figure 2). The solid curve can be empirically approximated by the following equation:

$P_i = 0.00765 \times \text{AbsP} + 0.8194 \times (1 - e^{(-0.2635 \times \text{AbsP})})$, in which P_i = serum inorganic phosphate (in mmol/liter), AbsP = absorbed phosphorus intake (mmol), and 1 mmol phosphorus = 30.9 mg.

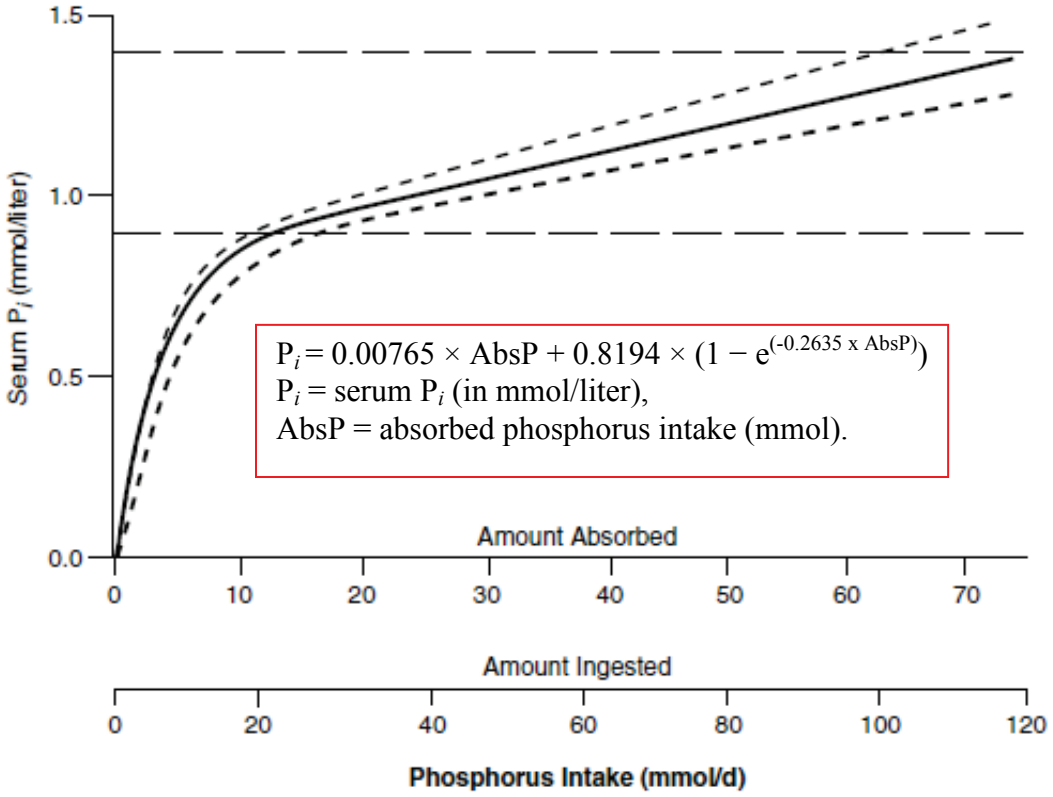

Figure 2. Relation of Serum Inorganic Phosphate to Absorbed Intake in Adults with Normal Renal Function (IOM, 1997)[a]

[a]P_i = inorganic phosphate, PO_4^{3-} = orthophosphate anion, which is the representation of dietary phosphate in 1 mol (95 g) of inorganic phosphate anion (PO_4^{3-}) that exists as 1 mol (31 g) of inorganic phosphorus (P). 1 mol is equal to 0.001 mmol and 1 L = 10 dL. From Figure 2, the upper boundary of adult normal values of serum P_i is reached at a daily phosphorus intake of 3.5 g (113 mmol), and the corresponding ingested intake in an adult would be over 10.2 g (330 mmol) P/day.

The steep, ascending portion of the curve, thus, represents a filling up of extracellular fluid space with absorbed phosphate. At higher intakes, urinary excretion rises to match absorbed input, and plasma levels change much more slowly. The dashed horizontal lines represent approximate upper and lower limits of the normal range, while the dashed curves reflect the relationship between serum P_i and ingested intake for absorption efficiencies about 15 percent higher and lower than the average.

According to Figure 2, the upper boundary of adult normal values of serum P_i is reached at a daily phosphorus intake of 3.5 g, the corresponding ingested intake of 10.2 g P/day. This is the threshold above which elevated ECF serum P_i could result in toxicity (Nordin, 1988; IOM, 1997).

No indication has been found that exposure duration (subchronic relative to chronic) to the same dose level would present different health effects (Weiner et al., 2001), thus, a p-RfD value of 3.4 g P/day is derived for both subchronic- and chronic-duration exposures from

inorganic phosphates to human individuals in the age range 1−70 years old and older. Lack of data precludes derivation of a p-RfD for infants.

Subchronic and Chronic p-RfDs = NOAEL ÷ UF_C
= 10.2 g P/day ÷ 3
= 3.4 g P/day or 48.6 mg P/kg-day.

A UF_C of 3 is used. Tables 2 and 3, below, summarize the UFs and the confidence descriptors.

Table 2. Uncertainty Factors for Subchronic and Chronic p-RfDs of Inorganic Phosphates Using Human Data[a]

UF	Value	Justification
UF_A	1	A UF_A of 1 is applied because a human study is utilized in development of the POD.
UF_D	1	A UF_D of 1 is selected because the database includes two acceptable multigeneration reproduction studies in rats (Bonting and Jansen, 1956; Hodge, 1964) and multiple acceptable developmental study summaries in rats, mice, rabbits, and hamsters (Weiner et al., 2001), and there is no indication of other specific endpoint studies that may be relevant.
UF_H	3	A UF_H of 3 is selected because the analysis was developed based on healthy human adults who are more sensitive to phosphate poisoning than children but the degree of sensitivity is arguable. The normal plasma levels of phosphate are higher in children than adults, but toxicity is not observed at these levels, which reduce with age (IOM, 1997; Nordin, 1988). However, kidney-impaired and elderly adults are more sensitive. The UF_H of 3 takes these factors into account.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because the data utilized for derivation of a p-RfD were independent of exposure duration.
UF_C ≤3000	3	

[a]IOM (1997) and Nordin (1988).

The confidence of the subchronic and chronic p-RfDs for phosphorus in inorganic phosphate is medium, as explained in Table 3 below.

Table 3. Confidence Descriptors for Subchronic and Chronic p-RfDs for Phosphorus in Inorganic Phosphates

Confidence Categories	Designation[a]	Discussion
Confidence in the study	M	The confidence in the key study is medium. IOM (1997) is a well-respected scientific review that used data from Nordin (1988) to estimate the NOAEL. Also, Nordin (1988) used intravenous infusion experimental data from another previous study (Bijvoet, 1969, as cited by IOM, 1997). The relationship between serum P_i and absorbed P_i intake established by Nordin (1988) is well supported by results from other human studies (Heaney and Nordin, 2002) and animal studies (Weiner et al., 2001).
Confidence in the database	H	The confidence in the database is high. The database includes subchronic- and chronic-duration toxicity studies in more than two species (rats, mice, rabbits, dogs), with developmental toxicity studies and two multigeneration reproductive studies.
Confidence in the p-RfD[b]	M	The overall confidence in the p-RfD is medium.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than the lowest entry in the table.

The overall confidence in the p-RfD is medium, given the magnitude of the animal and human databases, and given the length of time and level of expertise that has gone into IOM's (2007) analysis and conclusions. Confidence is not high because there are no chronic- or subchronic-duration human studies that demonstrate a clear dose-response relationship between phosphorus intake and toxicity.

RATIONALE FOR SELECTION OF THE BEST APPROACH (OPTION 3) FOR DERIVING SUBCHRONIC AND CHRONIC p-RfDs

The chronic p-RfD of 1.5 g P/day (1.52 mg/kg-day) calculated from animal studies summarized by Weiner et al. (2001) is the lowest compared to a p-RfD of 3.4 g P/day (48.6 mg/kg-day) derived using Nordin (1988) human toxicity data, and a UL of 4.0 g P/day (57 mg/kg-day) for adults established by IOM (1997), but it cannot be considered as the best option for a subchronic and/or chronic p-RfD because phosphorus density of the diets fed to laboratory animals is much greater than that of humans, and animals are probably not good models for determining phosphorus toxicity in humans (IOM, 1997). For example, the median measured dietary density for phosphorus is 62 mg (2.0 mmol)/100 kcal for human adults (Cleveland et al., 1996, as cited by IOM, 1997). The corresponding values for rats and mice

(124−186 mg/100 kcal), cats and dogs (279 mg/100 kcal), and laboratory primates (155 mg/100 kcal) are much higher.

The definition and steps for deriving a UL (IOM, 1997) and for deriving a p-RfDs (U.S. EPA, 2002) are similar. However, the application and justification of UFs are notably different. For both the UL and the p-RfDs, a NOAEL of 10.2 g P/day as a POD has been used for all ages—except for infants. The UFs applied for the UL ranged from 2.5−3.3 depending on lifestage (see Appendix A, Table A.6), and a UF_C of 3 was applied for deriving RfD. The UFs for the UL identified the individual contributions of UF components (intrahuman variability, interspecies variability, subchronic-to-chronic duration, LOAEL-to-NOAEL extrapolation, and incomplete-to-complete database compensation). These differences between the UL and p-RfD derivation processes support the exclusion of the UL developed by IOM (1997) as the chronic p-RfD for phosphorus from inorganic phosphates.

The p-RfD of 3.4 g P/day (48.6 mg/kg-day) derived using a NOAEL of 10.2 g P/day (145.7 mg/kg-day) as the POD based on elevated ECF serum P_i (IOM, 1997; Nordin, 1988) is considered the best approach to adopt. This option is preferred because of the relevance of human data to the human health toxicity assessment, a NOAEL obtained from a regression curve based on data calculations that is inclusive of all the variables that affect inorganic phosphate absorption, distribution, and excretion, and it shows pharmacokinetic basis of phosphorus intake in humans. No benchmark dose (BMD) modeling has been performed because the Nordin (1988) data were unsuitable for BMD modeling (U.S. EPA, 2010).

Based on EPA RfD-derivation methodology (U.S. EPA, 2002), subchronic and chronic p-RfD values of 3.4 g P/day (48.6 mg P/kg-day) are established. Considering the fact that phosphorus is an essential nutrient, its p-RfD must take into account both deficiency (hypophosphatemia) and toxicity (hyperphosphatemia). The IOM (1997) established an RDA, which is the daily dietary intake level of a nutrient considered sufficient by the Food and Nutrition Board to meet the requirements of nearly all (97−98%) healthy individuals in each lifestage and gender group (see Appendix A, Tables A.6 and A.7). The RDA for adults ages 19−70 years old and older is 0.7 g P/day (10 mg P/kg-day). Thus, taken together, the RDA of 10 mg P/kg-day and the p-RfD of 48.6 mg P/kg-day constitute a range of 38.6 mg P/kg-day that is supportive of human health (i.e., avoids deficiency and protects against toxicity).

DERIVATION OF CHRONIC p-RfC

A chronic RfC of 1×10^{-2} mg/m^3 of phosphoric acid is available on the IRIS (U.S. EPA, 2010b) database, and it is based on a subchronic-duration inhalation toxicity study of rats by Aranyi et al. (1988). The last update of the assessment was in 1995 (U.S. EPA, 1995). The IRIS assessment was based on two 13-week inhalation studies of male rats exposed to the combustion products of 95% red phosphorus and 5% butyl rubber (Aranyi et al., 1988). The critical effect was bronchiolar fibrosis with a LOAEL and a NOAEL of 180 mg/m^3 and 50 mg/m^3, respectively. A chronic RfC of 0.01 mg/m^3 was derived based on a BMC_{10HEC} of 3.4 mg/m^3 as the POD, and a UF_C of 300, accounting for a UF_A of 3, a UF_H of 10, and a UF_S of 10. The IRIS assessment (U.S. EPA, 1995) states that,

…this RfC is for aerosols of phosphoric acid and phosphorus oxidation products and does not apply to elemental phosphorus or other forms of phosphorus, such as phosphorus, such as phosphorus salts. Because the site of deposition (and toxicity) of acid aerosol particulates is dependent on size distribution, and character, this RfC would be most appropriate for phosphoric acid aerosols in the range of 0.4−1.0 microns. (Section I.B.5., paragraph 1).

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR INORGANIC PHOSPHATES

WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Three chronic-duration studies reported by Hodge (1964) evaluated the carcinogenicity of inorganic phosphates in rats after administration via the diet of four dose levels ranging from 0 to 10% of STP (monovalent phosphate), and for SHMP and STMP (condensed phosphates). There was no indication that the three chemicals (STP, SHMP, STMP) were carcinogenic. The results indicated that tumor incidence and type were similar in controls to inorganic phosphate-treated animals. In addition, Hodge (1964) reported no particular concern with regard to genotoxic activity. Weiner et al. (2001) reached the same conclusion.

In a short-term study of 4 weeks, 5 to 6-week-old male lung cancer model mice (transgenic) were fed a diet containing 0.5% (normal) inorganic phosphate and 1% inorganic phosphate (high) (purity not provided) and were tested for effects of high dietary P_i on lung cancer development. Results indicated that high dietary inorganic phosphate activates Akt signaling and, subsequently, there is a strong correlation with increased lung tumorigenesis (Jin et al., 2009). These results were consistent with previous studies from the same group that examined the relationship between high dietary P_i intake and lung effects, and Akt signaling (Xu et al., 2008, 2009; Jin et al., 2007; Chang et al., 2006).

The chronic-duration studies performed by Hodge (1964) did not report information on lung testing and treatment-related health effects. The short-tem (4 weeks) animal study results are not sufficient to draw conclusions on the likelihood of inorganic phosphate carcinogenicity. No additional human or animal data have been located to inform on the potential carcinogenicity of inorganic phosphate. Thus, under the U.S. EPA (2005) *Guidelines for Carcinogen Assessment*, the data are considered to provide "***Inadequate Information to Assess Carcinogenic Potential"*** for inorganic phosphates. Appendix A, Table A.8 identifies the cancer WOE descriptor for inorganic phosphates.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for inorganic phosphate is precluded by the lack of available data.

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APPENDIX A. DATA TABLES

Table A.1. List of Inorganic Phosphate Compounds per Categories		
	Chemical	**CASRN**
I	**Monovalent salts: hydrogen, sodium, potassium**	
1	Orthophosphoric acid (PA)	7664-38-2
2	Polyphosphoric acid (PPA)	8017-16-1
3	Monosodium phosphate (MSP)	7558-80-7
4	Disodium phosphate (DSP)	7558-79-4
5	Trisodium phosphate (TSP)	7601-54-9
6	Sodium acid pyrophosphate (SAPP)	7758-16-9
7	Tetrasodium pyrophosphate (TSPP)	7722-88-5
8	Sodium tripolyphosphate (STP)	7758-29-4
9	Sodium trimetaphosphate (STMP)	7785-84-4
10	Sodium polyphosphate (SPP)	68915-31-1
11	Sodium hexametaphosphate (SHMP)	10124-56-8
12	Monopotassium phosphate (MKP)	7778-77-0
13	Dipotassium phosphate (DKP)	7758-11-4
14	Tripotassium phosphate (TKP)	7778-53-2
15	Tetrapotassium pyrophosphate (TKPP)	7320-34-5
16	Potassium tripolyphosphate (KTP)	13845-36-8
II	**Divalent salts: calcium and magnesium**	
17	Monocalcium phosphate (MCP)	7758-23-8
18	Dicalcium phosphate (DCP)	7757-93-9
19	Tricalcium phosphate (TCP)	7758-87-4
20	Calcium pyrophosphate (CPP)	7790-76-3
21	Monomagnesium phosphate (MMP)	7757-86-0
22	Dimagnesium phosphate (DMP)	7782-75-4
23	Trimagnesium phosphate (TMP)	7757-87-1
III	**Ammonium salts**	
24	Monoammonium phosphate (MAP)	7722-76-1
25	Diammonium phosphate (DAP)	7783-28-0
26	Ammonium polyphosphate (APP)	68333-79-9

Table A.1. List of Inorganic Phosphate Compounds per Categories		
	Chemical	**CASRN**
IV	**Aluminum salts**	
27	Monoaluminum phosphate (MALP)	13530-50-2
28	Aluminum metaphosphate (ALMP)	13776-88-0
29	Sodium aluminum phosphate (SALP) (tetrahydrate)	10305-76-7
30	Trialuminum sodium tetra decahydrogenoctaorthophosphate (dihydrate)	15136-87-5
31	Sodium aluminum phosphate (SALP) (anhydrous)	10279-59-1
32	Sodium aluminum phosphate (SALP) (acidic)	7785-88-8

Table A.2. Human Studies That Address the Effect of Dietary Phosphate and Calcium on Calcium Economy and Hormones That Affect Calcium Economy

Zemel and Linkswiler (1981)	
Study population	8 male university students (18−24 years of age)
Study protocol	Different combinations of Ca and P were given for four sequential 15-day periods of exposure; each subject received all dose combinations; diets were controlled and adequate for all nutrients except calcium, as noted below; each subject was his own control; Ca balance, hormones, and bone resorption were assessed
P and Ca doses (mg/day)	Low Ca (399), low P (1835) control diet Low Ca (399), high P (1835) supplemented with polyphosphate Low Ca (399), high P (1835) supplemented with orthophosphate High Ca (1194), high P (1835) supplemented with orthophosphate
Critical effects of increased P	Ca absorption was significantly lower with polyphosphate than with orthophosphate; both forms decreased the fractional renal tubular reabsorption of calcium, but only the orthophosphate supplement improved Ca balance. Ca equilibrium was only achieved with the orthophosphate supplement. Increase in PTH secretion (inferred from urinary cyclic AMP measurement); no effect on bone resorption (inferred from urinary hydroxyproline)
Critical effects of increased Ca	Diminished the increase in PTH secretion and bone resorption observed with high P, low Ca
Serum Ca and P levels[a]	Not specifically reported
Bizik et al. (1996)	
Study population	7 male university students (22−31 years)
Study protocol	Dietary Ca and P were manipulated with milk and cheese in two sequential 10-day dietary periods; each subject was his own control
P and Ca doses (mg/day)	1200 Ca, 800 P from food 1200 Ca, 1600 P from food (nitrogen and calories were controlled)
Critical effects of increased P	Nonsignificant increase in serum PTH; no effects on bone resorption (inferred from urinary deoxypyridinoline)
Critical effects of increased Ca	Not applicable
Serum Ca and P levels	Within normal ranges for all groups
Kemi et al. (2008)	
Study population	12 premenopausal females (21−40 years)
Study protocol	High P in association with low, adequate, or high Ca was given in the diet in three 24-hour study periods; each subject was her own control
P and Ca doses (mg/day)	480, 1080, or 1680 Ca with 1850 P from food
Critical effects of increased P	Not applicable
Critical effects of increased Ca	Significantly decreased serum PTH and bone resorption; no effect on bone formation
Serum Ca and P levels	No significant changes; within normal ranges for all groups

Table A.2. Human Studies That Address the Effect of Dietary Phosphate and Calcium on Calcium Economy and Hormones That Affect Calcium Economy

Kemi et al. (2009)	
Study population	147 premenopausal females (31−43 years)
Study protocol	Cross-sectional study; fasting blood samples were collected, and each subject kept a 4-day food record from which dietary intake P was calculated; subjects were sorted into quartiles based on P intake, and the first and fourth quartiles were compared
P and Ca doses (mg/day)	961 P for lowest quartile 1956 P for highest quartile; mean dietary Ca was 1056; mean dietary P was 1411
Critical effects of increased P	Decreased mean serum ionized Ca (2.5%) and increased serum PTH (2-fold), even after total dietary Ca was equalized
Critical effects of increased Ca	Not applicable
Serum Ca and P levels	Ionized Ca was within the normal range for all groups (~1.1−2.3 mmol/L)
Heaney and Nordin (2002)	
Study population	Data set 1: 191 Roman Catholic nuns (35−65 years) Data set 2: Mixed group of 88 women and five men (19−78 years)
Study protocol	Data set 1 was a longitudinal, observational, cohort design. Subjects completed seven-day diet diaries prior to each admission to the metabolic unit, and controlled diets were prepared for the eight-day inpatient stay to match the self-selected intakes of nitrogen, P and Ca of the subjects prior to admission. The diet was constant throughout the stay, and all excreta were collected and analyzed. Stool collections were timed and demarcated by the use of a nonabsorbable intake marker (polyethylene glycol), ingested with each meal. During the inpatient study, subjects maintained their usual intake of medications, vitamin and mineral supplements, health food preparations, etc. Each such product was analyzed for its Ca and P content, and those values were included in the total intake of the nutrients concerned. The methods for data set 2 were similar to data set 1 except that each balance study extended over two weeks, the first week for equilibrium, and the second week for daily fecal collections. The diets were the same every day during this two-week period, and the intake marker (polyethylene glycol) was fed from Day 1.
P and Ca doses (mg/day)	Data set 1: The mean intakes of P and Ca (1101 and 696) Dataset 2: P intake (~1101 and ~50% higher than the data set 1[1044])
Critical effects of increased P and interactions with Ca	Ca intake increases without a corresponding increase in P intake, P absorption falls, and the risk of P insufficiency rises. Intakes with high Ca:P ratios can occur with use of supplements or food fortificants consisting on nonphosphate calcium salts. Older patients with osteoporosis treated with current generation bone active agents should receive at least some of the calcium cotherapy in the form of a calcium phosphate preparation.
Serum Ca and P levels	Not reported

Table A.2. Human Studies That Address the Effect of Dietary Phosphate and Calcium on Calcium Economy and Hormones That Affect Calcium Economy

Grimm et al. (2001)	
Study population	10 females (20−30 years)
Study protocol	Each subject received the control diet for 4 weeks, followed by 6 weeks of supplementation with high P and Ca, then 4 weeks on control diet
P and Ca doses (mg/day)	Control diet: 1500 Ca, 1700 P Supplemental diet: 1995 Ca and 3008 P (supplements were tablets that contained NaH_2PO_4 and $Ca_5(PO_4)_3OH$; administered with orange juice)
Critical effects of increased P and Ca	Intestinal distress, soft stools, or mild diarrhea in all 10 subjects throughout the high-phosphorus period. No significant changes in serum PTH or indicators of bone resorption or renal function
Serum Ca and P levels	No significant changes; within normal ranges for all groups
Calvo et al. (1988)	
Study population	8 males, 8 females (18−25 years)
Study protocol	24-hour samples were collected following 8 days on a control diet; 24-hour samples were collected following a subsequent 8-day period on a low Ca, high P test diet
P and Ca doses (mg/day)	820 Ca, 930 P in control diet 420 Ca, 1660 P in test diet (controlled for calories, protein, carbohydrates, fat, sodium, and caffeine)
Critical effects of increased P and low Ca	Increased serum immunoreactive PTH in men (11%) and women (22%); increased serum 1,25-dihydroxy vitamin D, urinary cAMP (indicative of PTH) and hydroxyproline (indicative of bone resorption) only in women; decreased serum ionized Ca (−2%), and total Ca (−1.9%) only in women
Serum Ca and P levels	Within normal ranges for all groups
Calvo et al. (1990)	
Study population	15 females (18−25 years)
Study protocol	Participants were assigned to either a control or experimental protocol (low Ca, high P) diet. Controls consumed a basal diet for 56 days; subjects assigned to the experimental protocol consumed the basal diet for 28 days then a low Ca, high P diet for 28 days
P and Ca doses (mg/day)	Basal diet: 801−823 Ca, 884−934 P Low Ca, high P diet: 417−481 Ca, 1662−1764 P (controlled for calories, protein, carbohydrates, fat, sodium, and caffeine)
Critical effects of increased P and low Ca	Increased urinary P excretion; decreased urinary Ca excretion; decreased serum ionized Ca and total Ca (<3% lower compared with basal diet); increased serum intact and immunoreactive PTH (31 and 22%, respectively, compared with the basal diet); no effect on serum 1,25-dihydroxy vitamin D, 2,5-hydroxy vitamin D, osteocalcin, or alkaline phosphatase; no effects on glomerular filtration or on markers for bone resorption
Serum Ca and P levels	Within the normal range for Ca in all groups; high normal for P, all groups

Table A.2. Human Studies That Address the Effect of Dietary Phosphate and Calcium on Calcium Economy and Hormones That Affect Calcium Economy

Heaney and Recker (1982)	
Study population	170 premenopausal Roman Catholic nuns who volunteered as subjects for an ongoing study of osteoporosis (36−45 years)
Study protocol	Subjects were admitted to the hospital for 5-day examinations as part of the ongoing study; they received diets constructed to resemble their typical daily intake of Ca, P, nitrogen, caffeine, and Ca:P ratio. Calcium balance was studied, and mathematical relationships were estimated from the data through stepwise multiple linear regression
P and Ca doses (mg/day)	Mean (range): Ca = 0.660 (0.159−2.273); P = 1.145 (0.511−2.453)
Critical effects of increased P	There was no net association of phosphorus intake with calcium balance; higher phosphorus intake was associated with slightly higher intestinal secretion of calcium and slightly lower levels of urinary calcium
Serum Ca and P levels	Not reported
Spencer et al. (1978)	
Study population	19 males (38−65 years)
Study protocol	Each subject received a basal diet for 22−40 days, then an experimental diet for 28−48 days. Metabolic balances of calcium, phosphorus, and nitrogen were determined over a 6-day metabolic period. Calcium was varied by adding calcium gluconate tablets to the basal diet; phosphorus was varied by adding sodium glycerophosphate to the basal diet; Ca was monitored by [^{47}Ca] tracer
P and Ca doses (mg/day)	Low Ca, control P: 219 Ca, 854 P Low Ca, high P: 217 Ca, 2008 P Normal Ca, control P: 828 Ca, 845 P Normal Ca, high P: 823 Ca, 1977 P Intermediate Ca, control P: 1433 Ca, 768 P Intermediate Ca, high P: 1437 Ca, 1964 P High Ca, control P: 2018 Ca, 805 P High Ca, high P: 2019 Ca, 1003 P High Ca, control P: 2745 Ca, 938 P High Ca, high P: 2757 Ca, 2039 P
Critical effects of increased P and interactions with Ca	Calcium balance was not significantly affected by any combination. No change in calcium absorption was observed at any phosphorus concentration. Urinary calcium decreased significantly with phosphorus intake except during high calcium intake. Stool calcium significantly increased during phosphorus supplementation only when calcium was low. Urinary and fecal phosphorus increased significantly in all studies; phosphorus balance increased significantly only during high calcium intakes.
Serum Ca and P levels	Based on Table 3 of the study, multiplying percent dose/L plasma × Ca intake in mg/day yields plasma Ca values in mg/L; dividing by 10 gives Ca values in mg/DL. Using 8.8−10.4 mg/DL as the range for normal serum Ca levels in adults (Lewis, 2009b), most of the nine subjects for which values are reported in Table 3 of the study would be considered hypocalcemic regardless of phosphate intake and level of calcium supplementation.

[a]Normal range for serum Ca in adults is 8.8−10.4 mg/DL (2.2−2.6 mmol/L); normal range for serum phosphate in adults is 2.5−4.5 mg P/DL (0.81−1.45 mmol/L) (Lewis, 2009a,b); 30−50% higher values for serum phosphate are considered normal for young children; ranges can vary between laboratories.

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997	
Anderson et al. (1977)	
Study population	Monkeys, 26 wild Cinnamon-tailed (*Cebus albifrons*), male and female
Study protocol	Groups were fed a purified diet with Ca:P ratios of 1:4 (Ca deficient, high PO_4), 1:2.1 (adequate Ca, high PO_4); 1:0.4 (adequate in both Ca and PO_4); or a commercial diet with a 1:0.5 Ca:P ratio for 3−88 months.
P and Ca doses	P concentrations: 1.2, 2.0, 0.4, and 0.47% Ca concentrations: 0.3, 0.95, 0.95, and 0.86%
Critical endpoints studied	Clinical, radiographic, and histologic indicators of bone disease were monitored throughout 7 years of study
Critical effects of increased P	None
Critical effects of increased Ca	None
Critical dose(s) as P	NOAEL: 600 mg/kg-day (from 1.2% diet, based on assumptions of 2 kg body weight and 150 g diet/day, from experimental values presented in the report)
Bonting and Jansen (1956)	
Study population	Rat (strain not reported), male and female
Study protocol	Three-generation 90-week study
P and Ca doses (mg/day)	Three successive generations of rats were fed diets containing 0.4 or 0.75% phosphoric acid for 90 weeks. The basal diet in this study was designed to emulate the average Dutch diet with 0.62% Ca and 0.82% P (Ca:P = 0.76). Total dietary P was 0.8, 0.946, and 1.06% in the control and two supplemented diets, respectively.
Critical endpoints studied	Reproduction, growth, hematology, pathology; Ca, P, and N balances
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 792 mg/kg-day (based on 0.946% P total in diet as the highest concentration tested for all critical endpoints; standard assumptions for body weight and food consumption per EPA [1988]) Reproductive NOAEL: 888 mg/kg-day (1.06% total dietary P)
Bushinsky et al. (2000)	
Study population	Rat, GHS, female (hypercalciuric strain of Sprague-Dawley)
Study protocol	18-week dietary study of P supplementation/reduction
P and Ca doses (mg/day)	0.225% P (low), 0.395% P (medium), or 0.565% P (high); Ca was constant and adequate
Critical endpoints studied	Effect of diminishing dietary P on urinary stone formation
Critical effects of increased P	Kidney stone formation
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 361 mg/kg-day (0.395% dietary P); LOAEL: 511 mg/kg-day (0.56% dietary P); uses EPA (1988) assumptions for body weight and food consumption

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997

Cockell et al. (2004)	
Study population	Rat, Sprague-Dawley, female weanlings
Study protocol	16-week dietary study; rats fed a control diet, a test diet, or test diet then control diet for combinations up to 16 weeks.
P and Ca doses (mg/day)	Control diet (5.2 g Ca + 3.7 g P/kg diet; molar ratio = 1.08); test diet (5.1 g Ca + 5.5 g P/kg diet; molar ratio = 0.72)
Critical endpoints studied	Nephrocalcinosis
Critical effects of increased P	Increased incidence and severity of nephrocalcinosis after as little as 0.5 weeks of the test diet; changes were not reversible, as switching to control diet had no effect on incidence and severity compared with 16 weeks on the control diet
Critical effects of increased Ca	Not reported
Critical dose(s) as P	Adverse Effect Level (AEL): 539 mg/kg-day (5.5 g P/kg diet; based on standard EPA [1988] assumptions for female Sprague-Dawley rats in a subchronic-duration study)
Cockell et al. (2002)	
Study population	Rat, Sprague-Dawley, male and female weanlings
Study protocol	16-week dietary study to determine the effect of increasing Ca and P together in commonly used standard laboratory diets
P and Ca doses (mg/day)	AIN-93G diet concentrations (5 g Ca + 3 g P/kg diet), with multiples of Ca and P at the same ratio (1.5× = 7.5 g Ca + 4.5 g P/kg diet, 2.5× = 12.5 g Ca + 7.5 g P/kg diet, 4.0× = 20.0 g Ca + 12.0 g P/kg diet), or Ca and P at concentrations found in the standardized AIN-76A diet (5 g Ca + 5 g P/kg diet), for 16 weeks.
Critical endpoints studied	Kidney calcium concentration and nephrocalcinosis
Critical effects of increased P	Incidence and severity of nephrocalcinosis and kidney Ca concentration in female rats increased with dietary Ca and P but not to levels in female rats fed at the AIN-76A Ca:P ratio. Male rats showed limited evidence of kidney Ca accumulation or nephrocalcinosis
Critical effects of increased Ca	Mitigates incidence and severity but not reversibility
Critical dose(s) as P	NOAEL: 294 mg/kg-day (5 g Ca + 3 g P/kg diet); LOAEL: 441 mg/kg-day (4.5 g P/kg diet: females only; doses based on standard assumptions by EPA [1988] for female Sprague-Dawley rats in a subchronic-duration study)
Dymsza et al. (1959)	
Study population	Rat, Wistar
Study protocol	0.46 or 1.2% P as orthophosphate and metaphosphate in the diet for up to 150 days
P and Ca doses (mg/day)	
Critical endpoints studied	Body weight, organ weights, clinical chemistry, hematology, or heart, kidney, or bone tissue
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 578 mg/kg-day (from 1.2% diet and measured body weight of 0.487 kg and food consumption of 0.02347 kg/day)

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997

DiBartola et al. (1993)	
Study population	Cats, adults fed commercial diets since weaning
Study protocol	0.71% phosphorous and 0.89% calcium in the diet (commercial cat food) from weaning until 2 years
P and Ca doses (mg/day)	
Critical endpoints studied	Renal status
Critical effects of increased P	Renal dysfunction and renal lesions
Critical effects of increased Ca	Not reported
Critical dose(s) as P	AEL: 0.71% diet; no controls
Food and Drug Research Laboratories Inc. (1975a)	
Study population	Rat, Wistar, pregnant females
Study protocol	Administration of anhydrous monopotassium phosphate (mixed in water) by daily gavage at doses of 0, 2.82, 13.1, 60.7, or 282 mg/kg-day on GDs (Gestation Days) 6−15, with a 5-day postexposure period prior to caesarean section on GD 20
P and Ca doses (mg/day)	
Critical endpoints studied	Developmental toxicity
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 64 mg/kg-day (from 282 mg/kg-day KH_2PO_4)
Food and Drug Research Laboratories Inc. (1975a)	
Study population	CD-1 mice, pregnant females
Study protocol	Administration of anhydrous monopotassium phosphate (mixed in water) by daily gavage at doses of 0, 3.2, 14.8, 68.9, or 320 mg/kg-day, with a 2-day postexposure period prior to caesarean section on GD 20
P and Ca doses (mg/day)	
Critical endpoints studied	Developmental toxicity
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 73 mg/kg-day (from 320 mg/kg-day KH_2PO_4)
Food and Drug Research Laboratories Inc. (1975b)	
Study population	Rat, Wistar, pregnant females
Study protocol	Administration of anhydrous monosodium phosphate (mixed in water) by daily gavage at doses of 0, 4.1, 19.0, 88.3, or 410 mg/kg-day on GDs 6−15, with a 5-day postexposure period prior to caesarean section on GD 20
P and Ca doses (mg/day)	
Critical endpoints studied	Developmental toxicity
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 106 (from 410 mg/kg-day NaH_2PO_4)

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997

Food and Drug Research Laboratories Inc. (1975b)	
Study population	CD-1 mice, pregnant females
Study protocol P and Ca doses (mg/day)	Administration of anhydrous monosodium phosphate (mixed in water) by daily gavage at doses of 0, 3.7, 17.2, 79.7, or 370 mg/kg-day, with a 2-day postexposure period prior to caesarean section on GD 20
Critical endpoints studied	Developmental toxicity
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 95 (from 370 mg/kg-day NaH_2PO_4)
Fettman et al. (1992)	
Study population	Cats, 3 adult
Study protocol P and Ca doses (mg/day)	Test diet: 1.7% dietary phosphoric acid (1.25% total dietary P) for 1 year; Controls: fed naturally occurring acidifying diet without added acidifiers (1.23% dietary P) for 1 year; Ca was 1.62 (control); 1.66% (test diet)
Critical endpoints studied	Mineral, bone, and taurine balances
Critical effects of increased P	None
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 44 mg/kg-day (from 1.25% dietary P based on measured mean body weight = 4.7 kg and food consumption rate of 16.6 g diet/day)
House and Hogan (1955)	
Study population	Guinea pigs, male and female
Study protocol	Groups of animals were fed diets that contained variable amounts of phosphorus, calcium, magnesium, and potassium for up to 24 months
P and Ca doses	0.70, 1.19, 0.72, 1.31, 1.74, and 1.25% P with 0.67, 0.60, 1.14, 1.14, 1.14, and 2.29% Ca, respectively; 0.9% P + 0.9% Ca with variable magnesium and potassium; 1.7% P + 0.9% Ca with variable potassium and constant magnesium
Critical endpoints studied	Stiffness and calcium deposition in joints
Critical effects of increased P	No apparent difference between groups with increasing P and unchanging Ca
Critical effects of increased Ca	Not specifically addressed
Critical dose(s) as P	Not determined; authors stated: The symptoms were most severe in the groups that contained 0.9% calcium, 1.75% phosphorus, 0.04% magnesium, and 0.41% potassium. When the ratios were changed to contain approximately 0.35% of magnesium and 1.5% of potassium, the damage to the animals was reduced remarkably

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997	
Jowsey and Balasubramaniam (1972)	
Study population	Rabbits
Study protocol	Groups of animals were fed a control diet for 10 days, given tibial fractures, then fed an experimental diet for 4 weeks, 8 weeks, or 6 months
P and Ca doses (mg/day)	Control diet for 4−8 weeks: 662 PO_4, 1125 Ca; experimental diet for 4 or 8 weeks: 2047 PO_4, 1125 Ca; control diet for 6 months: 83.6 PO_4, 89.7 Ca; experimental diet for 6 months: 207.7 PO_4, 87.7 Ca
Critical endpoints studied	Serum Ca and PO_4; ^{83}Sr uptake; histology
Critical effects of increased P	Short-term study: increased serum Ca and PO_4; calcification of kidney and thoracic aorta (increased Ca, ^{86}Sr uptake, and histological evidence); increased bone porosity Long-term study: increased serum Ca but not PO_4; increased ^{86}Sr uptake or Ca content in aorta and kidney, but no histological evidence of calcification; increased bone porosity
Critical effects of increased Ca	Not reported
Critical dose(s) as P	207.7 mg PO_4/rabbit/day, long-term study; 2047 mg PO_4/rabbit/day for 4−8-week study; based on average measured values
MacKay and Oliver (1935)	
Study population	Rat (strain not reported), female
Study protocol	Nine groups of rats were fed a basal diet alone or supplemented with phosphoric acid or combinations of mono- and dibasic sodium and potassium salts for up to 44 days
P doses	20 (basal diet), 110 (four groups), 155 (three groups), or 200 mEQ total phosphate/100 g food
Critical endpoints studied	Renal damage
Critical effects of increased P	Permanent renal lesions characterized by necrosis of the convoluted tubules followed by regeneration and calcification for all high phosphate diets regardless of the form of phosphate added
Critical effects of increased Ca	Not reported
Critical dose(s) as P	≥110 mEQ phosphate/100 g diet
Matsuzaki et al. (1997)	
Study population	Rat, Wistar males
Study protocol	Groups of animals were fed normal or high-phosphate diets for 5, 7, 14, and 21 days
P and Ca doses (mg/day)	0.5% P (normal diet) or 1.5% P (high-P diet)
Critical endpoints studied	Nephrocalcinosis
Critical effects of increased P	High-P diet: Nephrocalcinosis in 4/6 rats after 1 day of feeding and in 6/6 rats at each subsequent evaluation on Days 3, 5, 7, 14, and 21. Severity increased with duration of feeding. Nephrocalcinosis was not observed in any rats fed the normal P diet
Critical effects of increased Ca	Not reported

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997	
Critical dose(s) as P	NOAEL: 461 mg/kg-day (0.5% in diet based on EPA [1988] assumptions for bw and food consumption for a subchronic-duration study with male Wistar rats) LOAEL: 1380 mg/kg-day (1.5% in diet based on EPA [1988] assumptions as above)
Matsuzaki et al. (1999)	
Study population	Rat, Wistar males
Study protocol	Groups of animals were fed various diets supplemented with sodium dihydrogenphosphate (NaH_2PO_4), potassium dihydrogenphosphate (KH_2PO_4), or polyphosphate salts (sodium tripolyphosphate [$Na_5P_3O_{10}$] or potassium tripolyphosphate [$K_5P_3O_{10}$]), at levels representing a normal phosphorus diet (as in the previous study) or a high phosphorus diet (as in the previous study) for 21 days
P doses	0.5% P (normal diet) or 1.5% P (high-P diet)
Critical endpoints studied	Nephrocalcinosis and kidney function
Critical effects of increased P	Nephrocalcinosis was observed in all rats fed a high phosphorus diet, but the degree of nephrocalcinosis was more severe in rats fed $Na_5P_3O_{10}$ or $K_5P_3O_{10}$ than in rats fed NaH_2PO_4 or KH_2PO_4. Creatinine clearance, urinary albumin excretion, and *N*-acetyl-beta-D-glucosaminidase activity in urine were increased only in rats fed the high phosphorus diet with polyphosphate salts but not with monosodium or potassium salts
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 461 mg/kg-day (0.5% in diet based on EPA [1988] assumptions for bw and food consumption for a subchronic-duration study with male Wistar rats) LOAEL: 1380 mg/kg-day (1.5% in diet based on EPA [1988] assumptions as above)
Matsuzaki et al. (2002)	
Study population	Rat, Wistar males and females
Study protocol P doses	Groups of animals were fed diets containing 0.3, 0.6, 0.9, 1.2, or 1.5% P from KH_2PO_4 for 21 days
Critical endpoints studied	Gender differences in kidney mineral concentrations and function measured as urinary albumin excretion
Critical effects of increased P	0.6%: increased kidney weight (females); increased P and Ca in kidney (females), and increased albumin in urine (males and females); females fed≥0.6% dietary P had higher kidney calcium and P concentrations than comparable males. Females fed 1.2 or 1.5% P had higher urinary albumin excretion than comparable males
Critical effects of increased Ca	Not reported
Critical dose(s) as P	NOAEL: 308 mg/kg-day(from 0.3% dietary P based on EPA [1988] assumptions for female Wistar rats in a subchronic-duration study) LOAEL: 615 mg/kg-day (from 0.6% dietary P based on EPA [1988] assumptions as above)

Table A.3. Key Animal Studies Cited by WHO (1982, 1971, 1965) and IOM (1997), and Selected New Studies Published Post-1997	
Schneider et al. (1981) (based on abstract)	
Study population	Dog, Beagle
Study protocol and doses	Groups of dogs were fed equimolar amounts of K_2HPO_4, Na_2HPO_4, KCl, or NaCl daily by gavage for 9 or 22 weeks. Controls received no treatment (doses were not reported in abstract)
Critical endpoints studied	Kidney structure assessed by light and electron microscopy
Critical effects of increased P	Nephrocalcinosis with disseminated atrophy of the proximal tubule in dogs treated with the phosphates, but not in those treated with chlorides
Critical effects of increased Ca	Not reported
Critical dose(s) as P	Cannot tell from the abstract
Schneider et al. (1980a) (based on abstract)	
Study population	Dog, Beagle
Study protocol	Dogs were fed 8 g K_2HPO_4/kg diet (1.42 g P/kg diet) for up to 38 weeks to study phosphate-induced kidney nephropathy
Critical endpoints studied	Nephropathy
Critical effects of increased P	Nephropathy with severe tubular atrophy and significant glomerular selective and unselective proteinuria
Critical effects of increased Ca	Not reported
Critical dose(s) as P	LOAEL: 51−71 mg/kg-day (1.42 g P/kg diet from 8 g K_2HPO_4/kg diet; using EPA [1988] assumptions for Beagle dogs eating a dry or moist diet)

Table A.4. Summary of Animal Subchronic Oral Exposures by Weiner et al. (2001)

Inorganic Phosphate	Species	Duration (days)	Doses (% in diet or mg/kg-day)	NOAEL[a]	LOAEL	Reference[b]
Monovalent						
PA	Sheep	70	0, 35, 105, 211 mg/kg-day	105	−	McMeniman (1973)
MSP	Sheep	70	0, 43, 129, 258 mg/kg-day	258	−	McMeniman (1973)
DSP	Rat[c]	30	0 and 5%	−	<2571 (only dose tested)	Hodge (1964)
DSP	Rat	100	0 and 5%	−	<2571 (only dose tested)	Datta et al. (1962)
SAPP	Rat	100	0, 1.0, 2.5, 5%	−	<514 (lowest dose tested)	Datta et al. (1962)
STP	Rat	30	0, 0.2, 2.0, 10.0%	90		Hodge (1964)
SAPP	Rat	100	0, 1.0, 2.5, 5%		<514 (lowest dose tested)	Datta et al. (1962)
STP	**Rat**	**30**	**0, 0.2, 2.0, 10.0%**	**103**	−	**Hodge (1964)**
STP	Dog[d]	30	0, 100 mg/kg-day	100	−	Hodge (1964)
STMP	Rat	30	0, 0.2, 2.0, 10.0%	103	−	Hodge (1964)
	Dog	30	0, 100 mg/kg-day	100	−	Hodge (1964)
SHMP	**Rat**	**30**	**0, 0.2, 2.0, 10.0%**	**103**	−	**Hodge (1964)**
	Dog	30	0, 100 mg/kg-day	100	−	Hodge (1964)
Aluminum						
SALP	Rat	28	0, 0.7, 3.0%	1543	−	Stauffer (1986)
	Rat	30	0, 1.0, 3.0, 5.0, 7.0%	1543	−	Solutia (1972a)
	Rat	90	0, 1.0, 3.0%	Males: 1543	Females: 1543	Solutia (1973b)
	Rat	90	0, 0.03, 0.1%	514	−	Solutia (1973c)
	Dog	90	0, 0.3, 1.0, 3.0%	751	−	Solutia (1972c)

[a]The original table differentiated NOELs from NOAELs because a complete description of each study was not available, and to avoid misunderstanding , a NOAEL term is used to represent both the no-observed-effect level and the no-observed-adverse effect level.
[b]These references were cited by Weiner et al. (2001).
[c]The NOAELs or LOAELs were extrapolated from the level of compound in the diet assuming a 0.35-kg rat eats 18 g food/day.
[d]Extrapolated from the level of compound in the diet assuming a 12.7-kg dog eats 318 g food/day.

− Indicates not available/established.

Table A.5. Summary of Animal Chronic Oral Exposures by Weiner et al. (2001)

Inorganic Phosphate	Species	Duration (weeks)	Doses (% in diet or mg/kg-day)	NOAEL[a]	LOAEL	Reference[b]
PA	Rat[c]	>52	Up to 0.75%	338		Ellinger (1972)
MSP	Rabbit	22−70	300−700 mg/kg-day	Not determined		Fazekas (1954)
Sodium orthophosphate	Rat	30	0 and 8.0%		<3600	U.S. FDA (1975)
Sodium metaphosphate	Rat	30	0 and 8%		<3600	U.S. FDA (1975)
DKP	Dog	38	0, 800 mg/kg-day		<800	
DKP	Rat	21	0.87 or 5.1%	2295		Dymsza et al. (1959)
STP	Rat	39	0, 1.1, 1.8, 3.0, 5.0%		495	Hahn (1961)
STP	**Rat**	**104**	**0, 0.05, 0.5, 5.0%**	**257**		**Hodge (1964)**
SHMP	Rat	21	0, 0.93, 3.5%	1800		Dymsza et al. (1959)
SHMP	**Rat**	**104**	**0, 0.05, 0.5, 5.0%**	**257**		**Hodge (1964)**
STMP	Rat	104	0, 0.1, 1.0, 10%	514		Hodge (1964)
TSPP & DSP	Rat	39	0, 1.1, 1.8, 3.0, 5.0%		495	Hahn (1961)
Ammonium						
DAP	Rabbit	22−70	300−700 mg/kg-day	Not determined		Fazekas (1954)
Aluminum						
SALP	Dog	26	0, 0.3, 1.0, 3.0%	NOAEL: 323 Female, 390 Male		Stauffer (1987)
SALP	Dog	27	0, 0.3, 1.0, 3.0%	NOAEL: 1034 Female, 1087 Male		Stauffer (1981)

[a]The original table differentiated NOELs from NOAELs, because a complete description of each study was not available, and to avoid misunderstanding, a NOAEL term is used to represent both the no-observed-effect level and the no-observed-adverse effect level.
[b]These references were cited by Weiner et al. (2001).
[c]The NOAELs or LOAELs were extrapolated from the level of compound in the diet assuming a 0.35-kg rat eats 18 g food/day.

Table A.6. Derivation of Tolerable Upper Intake Levels for Different Lifestages by IOM (1997)

Lifestage (Years)	UF	UL (g P/day)[a]	UL (mg P/kg-day)	Uncertainty Factor Justification
Infants 0−1	Not established	Not established	Not established	There are no data relating to adverse effects of phosphorus intake for most of the first year of life. Therefore, it was impossible to establish a specific UL for infants.
Children 1−8	3.3	3.0	42.9	To account for potentially increased susceptibility due to smaller body size.
Adolescents 9−18	2.5	4.0	57.1	There is no evidence to suggest increased susceptibility to adverse effects during adolescence. Therefore, the same UL specified for adults is selected for adolescents, 4.0.
Adults 19−70	2.5	4.0	57.1	The relationship between intake and blood level is known.
Older adults >70	3.3	3.0	42.9	Because of an increasing prevalence of impaired renal function after age 70, a larger UF of 3.3 seems prudent.
Pregnancy 14−50	~2.9	3.5	50.0	During pregnancy, absorption efficiency for phosphorus rises by 15 percent, and, thus, the UL associated with the upper end of the normal range will be about 15 percent lower, which is about 3.5.
Lactation 14−50	2.5	4.0	57.1	During lactation, the phosphorus economy of a woman does not differ detectably from the nonlactating state. Hence, the UL for this physiologic state is not different from the nonlactating state.

[a]NOAEL of 10.2 g P/day (145.7 mg P/kg-day) as the threshold of daily phosphorus intake at which no evidence that a nominal adult individual may experience any untoward effects.

Table A.7. Lifestage-Based Recommended Dietary Allowance (RDA) Estimated by the Food and Nutrition Board (IOM, 1997)

Lifestage	Reference Body Weight (kg)[a]	RDA	
		(mg P/day)	(mg P/kg-day)[b]
Children 1−3 years	13	460	35
Children 4−8 years	22	500	23
Adolescents 9−18 years	50	1250	25
Adults 19−70 years	69	700	10
Adults >70 years	69	700	10
Pregnancy 13−18 years	NA	1250	NA
Pregnancy 19−50 years	NA	700	NA
Lactation 13−18 years	NA	1250	NA
Lactation 19−50 years	NA	700	NA

[a]From the third National Health and Nutrition Examination Survey (NHANES III, 1988−1994) in the United States; values are mean of male and female reference weights.
[b]RDA or UL/reference body weight.

Table A.8. Cancer WOE Descriptor for Inorganic Phosphates			
Possible WOE Descriptor	**Designation**	**Route of Entry**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human cancer studies are available.
"Likely to Be Carcinogenic to Humans"	N/A	N/A	No strong animal cancer data are available.
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	No human or animal cancer studies are available.
"Inadequate Information to Assess Carcinogenic Potential"	**X**	**Oral**	Chronic-duration studies did not show any differences related to tumor incidence and type between the control and treated groups. However, no test and responses were reported on lung cancer tumorigenesis. The studies suggest that high dietary P_i strongly activates Akt signaling, and increased lung tumorigenesis was only in weaning mice for an exposure duration of 4 weeks. No other studies were located that support the carcinogenicity.
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.