Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population

Mona S Calvo and Jaime Uribarri

ABSTRACT
This review explores the potential adverse impact of the increasing phosphorus content in the American diet on renal, cardiovascular, and bone health of the general population. Increasingly, studies show that phosphorus intakes in excess of the nutrient needs of a healthy population may significantly disrupt the hormonal regulation of phosphate, calcium, and vitamin D, which contributes to disordered mineral metabolism, vascular calcification, impaired kidney function, and bone loss. Moreover, large epidemiologic studies suggest that mild elevations of serum phosphate within the normal range are associated with cardiovascular disease (CVD) risk in healthy populations without evidence of kidney disease. However, few studies linked high dietary phosphorus intake to mild changes in serum phosphate because of the nature of the study design and inaccuracies in the nutrient composition databases. Although phosphorus is an essential nutrient, in excess it could be linked to tissue damage by a variety of mechanisms involved in the endocrine regulation of extracellular phosphate, specifically the secretion and action of fibroblast growth factor 23 and parathyroid hormone. Disordered regulation of these hormones by high dietary phosphorus may be key factors contributing to renal failure, CVD, and osteoporosis. Although systematically underestimated in national surveys, phosphorus intake seemingly continues to increase as a result of the growing consumption of highly processed foods, especially restaurant meals, fast foods, and convenience foods. The increased cumulative use of ingredients containing phosphorus in food processing merits further study given what is now being shown about the potential toxicity of phosphorus intake when it exceeds nutrient needs. Am J Clin Nutr doi: 10.3945/ajcn.112.053934.

INTRODUCTION
Public health concern for excess phosphorus intake beyond nutrient requirements stems from the growing epidemiologic evidence showing a significant association between serum phosphate and cardiovascular disease (CVD) risk (1–4) and from the potential contribution of high dietary phosphorus to the development of osteoporosis even in healthy adults (5). The phosphorus content of the American diet is increasing as a result of the growing consumption of foods processed with phosphate additives (5, 6). Regrettably, there is little direct evidence to show this increase in phosphorus intake in the general population, even though we consume more processed foods now than in the past because of their widespread use and highly desirable functions in the processing of a large variety of foods. Despite our changes in food preferences for processed and fast foods, nationally representative surveys (NHANES) show little change in estimated phosphorus intake over the decades for any age or sex group. Earlier attempts to challenge the indirect estimates of phosphorus intake used in these surveys by comparison with direct chemical analyses showed gross underestimation of phosphorus intake (>20%) when software relying on nutrient content databases was used (7–9). High phosphorus intakes raised little public health concern until recently when the high serum phosphate concentrations in chronic kidney disease (CKD) patients were shown to be significantly linked to CVD and increased mortality (10–12). Both animal and clinical studies showed several compensatory hormonal changes after dietary phosphorus loading (13–23). These phosphate-regulating hormones include bone-derived fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH), both of which influence the renal production and circulating concentrations of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D (1,25D), which in turn affects bone metabolism, intestinal absorption of calcium and phosphorus, and factors influencing cardio renal function such as hypertension and vascular calcification (24). FGF-23, PTH, and 1,25D have all been shown to independently influence arterial calcification, hypertension, bone metabolism, and left ventricular function (24–27), even

1 From the Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, Department of Health and Human Services, Laurel, MD (MSC); and The Mount Sinai School of Medicine, New York, NY (JU).
2 The findings and conclusions presented in this article are those of the authors and do not necessarily represent the views and opinions of the US Food and Drug Administration. Mention of trade names, product labels, or food manufacturers does not constitute endorsement or recommendations or use by the US Food and Drug Administration.
3 Address correspondence to J Uribarri, One Gustave Levy Place, New York, NY 10029. E-mail: Jaime.uribarri@mssm.edu.
4 Abbreviations used: CKD, chronic kidney disease; CVD, cardiovascular disease; EAR, Estimated Average Requirement; FGF-23, fibroblast growth factor 23; GRAS, Generally Recognized as Safe; PTH, parathyroid hormone; UL, Tolerable Upper Intake Level; 1,25D, 1,25-dihydroxyvitamin D.

Received November 1, 2012. Accepted for publication April 29, 2013. doi: 10.3945/ajcn.112.053934.
when serum phosphate is within the normal range in healthy subjects. These findings confound our understanding of the role of dietary phosphorus in chronic bone and heart disease.

This review focuses on our current understanding of the regulation of phosphate homeostasis and how the changing inorganic phosphorus content of the foods we consume influences this hormonal regulation and affects the risk of hypertension, CVD, bone fragility, and renal disease. In this review, we evaluate the current evidence in healthy adults that supports this concept of potential nutrient toxicity of phosphorus, review the possible mechanisms by which excess dietary phosphorus influences adverse cardiovascular outcome and bone loss, review the sources of phosphorus in the current food supply and preferred foods, describe food-processing practices that influence the dietary phosphorus burden, and identify environmental factors that influence serum phosphate concentrations in normal subjects.

Information on average intake, Estimated Average Requirements (EARs), Recommended Dietary Allowances, and Tolerable Upper Intake Levels (ULs) of phosphorus by sex and age is shown in Table 1.

**MARKERS OF DIETARY PHOSPHORUS EXCESS AND ADVERSE CLINICAL OUTCOME IN HEALTHY ADULTS: CAUSE OR ASSOCIATION?**

Proposed mechanisms of high dietary phosphorus in adverse outcomes

In both animal models and clinical studies, a diet high in phosphorus can induce secondary hyperparathyroidism and bone loss (13, 14) and FGF-23 release from bone (30). Both PTH and FGF-23 are thought to have a pathogenic cardiovascular effect with increased metastatic calcification (31). These changes in PTH and FGF-23 can occur with high dietary phosphorus consumption over weeks, but without measurable change in serum phosphate concentrations in normal adults and in animal studies (32). Due to the presence of a pronounced circadian rhythm, serum phosphate concentrations correct back to the previous morning’s fasting concentrations, even with high dietary burdens of phosphorus (17, 18). Unless a circadian design using multiple blood sampling over at least 8 h is used, serum phosphate concentrations cannot be relied on to accurately reflect whether the dietary burden is high or low (17, 32). The confounding effect of the circadian variation and the return to morning fasting concentrations complicates the interpretation of cross-sectional epidemiologic data examining the link between dietary phosphorus intake and serum phosphate and disease outcomes.

Dietary phosphorus intake or oral phosphate loading stimulated increases in PTH and FGF-23 in human studies (17, 19–23). PTH changes rapidly in response to an elevation in serum phosphate and a decrease in serum ionized calcium with chronic high dietary phosphorus intake (16, 17). Vervloet et al (22) showed that an increased dietary phosphorus intake from 800 to 2880 mg/d was accompanied by a significant increase in FGF-23. Ito et al (33) showed a failure of FGF-23 concentrations to increase when serum phosphate concentrations were elevated directly by intravenous infusion, suggesting that dietary phosphorus regulates FGF-23 production and secretion through some unknown intestinal receptors communicating to bone.

Elevated tissue phosphate concentrations have been shown to increase oxidative stress in endothelial cells (34), and acute hyperphosphatemia induces acute impairment in endothelial function as assessed by decreased flow-mediated vasodilatation in healthy subjects (34). Elevated serum phosphate has an inhibitory effect on the renal activation of 25-hydroxyvitamin D to the active metabolite 1,25D, and lower concentrations of 1,25D have been associated with adverse cardiovascular outcome (31). Direct effects of elevated phosphate on the cellular and matrix components of the vascular smooth muscle cells that promote calcification have also been postulated (35). Specifically, elevated phosphate has been implicated as a key factor in the transdifferentiation of contractile vascular smooth muscle cells to a bone-forming phenotype, a process termed *osteochondrogenic differentiation* (35). The roles that PTH and FGF-23 play in this transition of vascular smooth muscle cells to bone-forming cells are yet unclear.

**Evidence in animal models showing that excess dietary phosphorus causes bone loss, loss of renal function, and cardiovascular calcification**

High phosphorus consumption has been shown to reduce bone mass in a number of species including mice, rats, cats, rabbits, dogs, horses, and baboons (7, 14), and hyperparathyroidism has been established as the mechanism through which excess phosphorus consumption reduces bone mass in growing dogs (7) and rabbits (13). Experimental dietary phosphorus–loading studies in rodents were critical to establishing the classical endocrine feedback regulation of FGF-23 secretion from osteocytes (36, 37) and in showing how FGF-23 inhibits renal synthesis of 1,25D from 25-hydroxyvitamin D (38, 39). Through chronic phosphorus

---

**Table 1**

<table>
<thead>
<tr>
<th>Sex and age</th>
<th>Usual phosphorus intake (mg/d)</th>
<th>EAR (mg/d)</th>
<th>UL (mg/d)</th>
<th>RDA (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 1–3 y</td>
<td>1030 ± 26.3 a 1</td>
<td>380</td>
<td>3000</td>
<td>460</td>
</tr>
<tr>
<td>4–8 y</td>
<td>1145 ± 27.4</td>
<td>405</td>
<td>3000</td>
<td>500</td>
</tr>
<tr>
<td>9–13 y</td>
<td>1321 ± 35.4</td>
<td>1055</td>
<td>4000</td>
<td>1250</td>
</tr>
<tr>
<td>14–18 y</td>
<td>1681 ± 61.5</td>
<td>1055</td>
<td>4000</td>
<td>1250</td>
</tr>
<tr>
<td>19–30 y</td>
<td>1656 ± 53.4</td>
<td>580</td>
<td>4000</td>
<td>700</td>
</tr>
<tr>
<td>31–50 y</td>
<td>1727 ± 25.0</td>
<td>580</td>
<td>4000</td>
<td>700</td>
</tr>
<tr>
<td>51–70 y</td>
<td>1492 ± 30.0</td>
<td>580</td>
<td>4000</td>
<td>700</td>
</tr>
<tr>
<td>≥71 y</td>
<td>1270 ± 27.6</td>
<td>580</td>
<td>3000</td>
<td>700</td>
</tr>
<tr>
<td>Women 1–3 y</td>
<td>1030 ± 26.3 a 1</td>
<td>380</td>
<td>3000</td>
<td>460</td>
</tr>
<tr>
<td>4–8 y</td>
<td>1145 ± 27.4</td>
<td>405</td>
<td>3000</td>
<td>500</td>
</tr>
<tr>
<td>9–13 y</td>
<td>1176 ± 57.5</td>
<td>1055</td>
<td>4000</td>
<td>1250</td>
</tr>
<tr>
<td>14–18 y</td>
<td>1067 ± 29.8</td>
<td>1055</td>
<td>4000</td>
<td>1250</td>
</tr>
<tr>
<td>19–30 y</td>
<td>1120 ± 40.8</td>
<td>580</td>
<td>4000</td>
<td>700</td>
</tr>
<tr>
<td>31–50 y</td>
<td>1197 ± 25.0</td>
<td>580</td>
<td>4000</td>
<td>700</td>
</tr>
<tr>
<td>51–70 y</td>
<td>1106 ± 34.0</td>
<td>580</td>
<td>4000</td>
<td>700</td>
</tr>
<tr>
<td>≥71 y</td>
<td>985 ± 28.8</td>
<td>580</td>
<td>3000</td>
<td>700</td>
</tr>
</tbody>
</table>

1 Usual daily phosphorus intake data are from What We Eat in America, NHANES 2005–2006 (28). The Dietary Reference Intake amounts for phosphorus were established by the Institute of Medicine, Food and Nutrition Board, in 1997 [Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride, National Academies Press, Washington, DC (29)]. EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance; UL, Tolerable Upper Intake Level.

2 Mean ± SE (all such values).
loading in rats, Ben-Dov et al (40) found that elevated FGF-23 inhibits PTH secretion and that dietary phosphorus restriction exerts the opposite effect, decreasing FGF-23, increasing renal phosphate reabsorption, and increasing renal synthesis of 1,25D.

Most recently, apolipoprotein E knockout mice fed atherogenic diets with varying phosphorus content, showed significant increases in serum phosphate and FGF-23, with significantly more atheroma developed at the aortic sinus in the high-compared with low-phosphorus–fed mice (41).

Another recent study was able to show simultaneous bone loss and arterial calcification with long-term high phosphorus feeding in a rat model for CKD (42). Rats (7/8 nephrectomized) fed a high-phosphorus diet showed histologic evidence of vascular calcification (positive Von Kossa staining) and low distal and proximal tibia bone density after 20 wk of consuming a high-calcification (positive Von Kossa staining) and low distal and proximal tibia bone density after 20 wk of consuming a high-phosphorus diet. By using microarray analyses of aortic tissue for both muscle-related and bone-related genes, Román-García et al (42) observed that the rats showing the greatest histologic evidence of vascular calcification presented the strongest signal log ratio for the bone-related genes. This is compelling preclinical evidence for high-phosphorus, diet-induced osteochondrogenic change or transition of the vascular smooth muscle cells to bone-like cells that calcify while simultaneously losing mineral from bone. These findings of switches of genome expression in animal models have major significance for human subjects.

Clinical evidence in subjects with normal renal function

In Table 2 we describe 14 published studies that showed an effect of dietary phosphorus or phosphate loading on markers of bone and/or CVD in healthy subjects (15–23, 43–46). The only caveat is that, except for 3 studies (15–17), all of them used phosphate supplements added to a control diet or meal rather than using the actual phosphorus content of commercially available foods to modulate oral phosphate intake. These 3 studies (15–17) used processed (high-phosphorus) compared with unprocessed foods (low-phosphorus), which is consistent with the foods available in the market place, and 2 of these studies used processed foods purchased from local groceries (16, 17).

Two studies in Table 2 did not show a negative effect of dietary phosphate intake on CVD variables. In one study, high dietary phosphorus at baseline was associated with lower systolic blood pressure and on follow-up with less incidence of hypertension (43). However, secondary analyses of this study showed that only higher phosphate intake from dairy products, not from other dietary sources, presumably more processed, was consistently associated with lower systolic blood pressure and lower risk of hypertension. This finding could be indicative of an effect of phosphorus in conjunction with other dietary constituents or of dairy itself, even without the involvement of phosphorus. In fact, there is a body of literature suggesting that higher consumption of dairy products is associated with lower risk of hypertension (47).

A second negative study included in Table 2 looked specifically at the relation between dietary and serum phosphorus in participants from NHANES III (48). The authors found that serum phosphate was correlated with dietary phosphorus, but only weakly. In these subjects, the average difference between fasting and postconsumption serum phosphate, which must have resulted from dietary phosphate intake, was ~0.1 mg/dL.

Although this difference in mean serum phosphate concentrations is relatively small, several prior studies have reported an elevated risk of adverse renal and cardiovascular outcomes in association with comparably small increases in serum phosphate (1). It should be emphasized that the nutrient composition tables that are available to estimate survey participants or CKD patients’ phosphorus intake, including those in NHANES III and subsequent survey waves, do not accurately include the phosphorus contributed from the growing use of additives in processing, which results in a significant underestimation of total dietary phosphate intake (5).

The above-mentioned point was further addressed in another study with the same population (NHANES III) in which the authors found a clear association between an index of poverty and serum phosphate (46). Participants in the lowest income had the highest serum phosphate concentrations and the highest prevalence of hyperphosphatemia despite having the lowest estimated daily phosphate intake (46). Low socioeconomic status was also related to higher intake of meat products (particularly highly processed items such as hot dogs, bacon, and sausage), in which one would suspect a higher contribution by phosphorus additives not accounted for in the nutritional databases (46).

In addition, other publications describing an association between serum phosphate and cardiovascular outcome in healthy subjects would strengthen our conclusions from Table 2, but we have chosen not to include them because we cannot show with certainty that fasting serum phosphate concentrations reflect purely dietary phosphate intake (1–4, 49–54).

Sources of phosphorus in the American food supply

As mentioned above, dietary phosphorus can induce small elevations in serum phosphate that may be masked by its circadian rhythm. If sustained over time, such increases can have physiologic consequences including loss of bone mineral density and initiation of vascular calcification. Consideration needs to be given to the increasing phosphorus content of the US diet and to the increased intake of inorganic phosphate salts in processed foods used in restaurants and by fast-food providers that influence these increases in serum phosphate within the normal physiologic range.

Phosphorus intake in relation to phosphorus allowance

Clear guidance as to the needed amount of total phosphorus required by both sexes across all ages was established by the Institute of Medicine in 1997 (29). With the exception of men and women in their bone-forming years, daily phosphorus intake requirements (EAR) are well under 1000 mg/d (Table 1). As shown in Figure 1, usual median phosphorus intake data from NHANES 2005–2006 indicate that 50% of the US population consumes >1000 mg/d, far exceeding the requirements (28). The EAR comparison to usual nutrient intakes at the 50th percentile (median) of intake is traditionally used to evaluate the adequacy of the dietary intake of a nutrient in a population. Phosphorus intakes measured in the NHANES surveys over the past 3 decades are generally in excess of the requirements for all ages, except for rapidly growing young adults.
<table>
<thead>
<tr>
<th>First author, date (ref)</th>
<th>Population size</th>
<th>Type of study</th>
<th>Length of study</th>
<th>Dietary phosphorus</th>
<th>Markers measured</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell, 1977 (15)</td>
<td>8 healthy young subjects (3 women and 5 men)</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 4 wk each, with different amounts of phosphorus from foods</td>
<td>Daily phosphorus intake of 1000 or 2100 mg through food without or with phosphorus additives</td>
<td>Urinary cAMP and hydroxyproline</td>
<td>High-phosphorus diet increased all urinary parameters</td>
</tr>
<tr>
<td>Calvo, 1988 (16)</td>
<td>16 healthy young subjects (8 men and 8 women)</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 8 d each, with different amounts of phosphorus from grocery-store foods</td>
<td>Daily phosphorus intake of 930 or 1660 mg from foods without or with food phosphorus additives</td>
<td>Serum PTH and 1,25D</td>
<td>High-phosphorus diet increased serum PTH and 1,25D</td>
</tr>
<tr>
<td>Portale, 1989 (18)</td>
<td>7 healthy young men</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 8 d each, with different phosphorus dietary intakes</td>
<td>Daily phosphorus intake of 625 or 2300 mg through phosphorus salt loading and a baseline dietary phosphorus intake of 550 mg</td>
<td>Serum 1,25D</td>
<td>Low-phosphorus diet decreased 1,25D</td>
</tr>
<tr>
<td>Calvo, 1990 (17)</td>
<td>15 healthy young women</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 28 d each, with different amounts of dietary phosphorus from grocery-store foods</td>
<td>Daily phosphorus intake of 900 or 1700 mg through foods without or with phosphorus additives</td>
<td>Serum PTH and 1,25D; urinary cAMP</td>
<td>High-phosphorus diet increased urine phosphorus, cAMP, serum phosphorus, and PTH with no changes in 1,25D, despite decrease in serum ionized calcium</td>
</tr>
<tr>
<td>Ferrari, 2005 (19)</td>
<td>29 healthy young men</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 5 d each, with different phosphorus intakes</td>
<td>Daily phosphorus intake of 1400 mg plus either phosphorus binders or loading with phosphorus salts of 1000 mg daily</td>
<td>Serum FGF-23, PTH, and 1,25D</td>
<td>Phosphorus loading increased FGF-23 without affecting PTH or 1,25D</td>
</tr>
<tr>
<td>Antonucci, 2006 (20)</td>
<td>13 healthy young men</td>
<td>Dietary phosphorus intervention</td>
<td>3 periods, 10 d each, with different phosphorus intakes</td>
<td>Daily phosphorus dietary intake of 500 mg loaded with different amounts of phosphorus salts to provide daily oral phosphorus intake of 625, 1500, or 2300 mg</td>
<td>Serum FGF-23, PTH, and 1,25D</td>
<td>Phosphorus loading increased FGF-23 and PTH, but decreased 1,25D</td>
</tr>
<tr>
<td>Burnett, 2006 (21)</td>
<td>66 healthy men and women</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 5 d each, with different phosphorus intakes</td>
<td>Daily phosphorus intake of 500 mg plus either phosphorus binders or loading with phosphorus salts of 2000 mg daily</td>
<td>Serum FGF-23, PTH, and 1,25D</td>
<td>Phosphorus loading increased FGF-23 and PTH, but did not change 1,25D</td>
</tr>
<tr>
<td>Kemi, 2009 (43)</td>
<td>147 healthy premenopausal women</td>
<td>Cross-sectional</td>
<td>NA</td>
<td>NA</td>
<td>Dietary and serum phosphorus and serum PTH measurement</td>
<td>High habitual dietary phosphorus intake is associated with higher serum PTH</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 2 (Continued)

<table>
<thead>
<tr>
<th>First author, date (ref)</th>
<th>Population size</th>
<th>Type of study</th>
<th>Length of study</th>
<th>Dietary phosphorus</th>
<th>Markers measured</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinheiro, 2009 (44)</td>
<td>2420 healthy subjects older than 40 y</td>
<td>Cross-sectional; subjects answered a questionnaire from a trained investigator</td>
<td>NA</td>
<td>NA</td>
<td>Dietary intake and prevalence of fractures (by history)</td>
<td>Higher dietary phosphorus intake predicted the risk of fracture</td>
</tr>
<tr>
<td>de Boer, 2009 (48)</td>
<td>15513 participants in the NHANES III</td>
<td>Cross-sectional</td>
<td>NA</td>
<td>NA</td>
<td>Dietary phosphorus intake and CVD risk factors</td>
<td>Dietary phosphorus intake weakly correlated with serum phosphorus and not CVD</td>
</tr>
<tr>
<td>Alonso, 2010 (45)</td>
<td>9785 ARIC and 3659 MESA cross-sectional; 8208 ARIC and 2901 MESA follow-up</td>
<td>Cross-sectional and observation</td>
<td>Mean follow-up = 6.2 y</td>
<td>NA</td>
<td>Dietary phosphorus intake and BP</td>
<td>Higher dietary phosphorus associated with lower BP at baseline and less incident hypertension on follow-up</td>
</tr>
<tr>
<td>Vervloet, 2011 (22)</td>
<td>10 healthy young subjects (8 women and 2 men)</td>
<td>Dietary phosphorus intervention</td>
<td>2 periods, 36 h each, with different phosphorus intakes</td>
<td>Daily dietary phosphorus intake of 850 or 2880 mg with food adjustment to achieve phosphorus intake goal</td>
<td>Serum FGF-23, PTH, and 1,25D</td>
<td>Phosphorus loading increased FGF-23 but decreased PTH and 1,25D</td>
</tr>
<tr>
<td>Gutiérrez, 2011 (46)</td>
<td>1261 participants in the Health Professionals Follow-Up Study (mean ± SD age: 64 ± 9)</td>
<td>Cross-sectional</td>
<td>NA</td>
<td>NA</td>
<td>Dietary phosphorus intake and serum FGF-23</td>
<td>Higher dietary phosphorus intake was associated with higher FGF-23</td>
</tr>
<tr>
<td>Sigrist, 2012 (23)</td>
<td>12 healthy men (n = 6) and women (n = 6; median age: 40 y) and 18 CKD patients</td>
<td>Dietary phosphorus intervention</td>
<td>3 periods, 7 d each, with different phosphorus intakes</td>
<td>3 groups: dietary phosphorus intakes of 1) 2000 mg/d, 2) 750 mg/d, and 3) 750 mg/d plus phosphorus binders</td>
<td>Serum FGF-23, PTH, and 1,25D</td>
<td>Higher phosphorus loading increased FGF-23, but decreased 1,25D, and had no significant effect on PTH</td>
</tr>
</tbody>
</table>

ARIC, Atherosclerosis Risk in Communities Study; BP, blood pressure; cAMP, cyclic AMP; CKD, chronic kidney disease; CVD, cardiovascular disease; FGF-23, fibroblast growth factor 23; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not assessed; PTH, parathyroid hormone; ref, reference; 1,25D, 1,25-dihydroxyvitamin D.
Estimation of phosphorus intake

Whereas total phosphorus intakes from the nationally representative surveys show general excess, these estimates are thought to be underestimated, particularly in individuals consuming more restaurant, fast, and highly processed convenience foods. Phosphorus-containing food ingredients are used extensively in the current processing of food, but their contribution to total phosphorus intake is not usually captured in full in the nutrient intake estimates from national food consumption surveys.

Several key sources of evidence support this underestimation of phosphorus intake. First, a study conducted in the late 1980s compared accuracy of calculated estimates of dietary phosphorus and calcium by using popular software with direct chemical analyses (8). Duplicate meals consumed by 20 volunteers over a 24-h period (including restaurant and fast-food meals) were weighed and homogenized for direct chemical analysis. Phosphorus content was underestimated by >20%, whereas estimated calcium content was in good agreement with the direct chemical analyses. The USDA Nutrient Content Database (Standard reference, release 24: SR24; http://www.ars.usda.gov/ba/bhnrc/fsrg) serves as the basis for much of the software in use today, does not accurately reflect the use of inorganic or some organic phosphorus ingredients due in part to the constantly changing formulas and introduction of new convenience and fast foods. For these reasons, it is extremely difficult to establish accurate representative phosphorus-content values for use in the Nutrient Database updates. Even the use of brand-name foods does not completely address this problem, because some national brands use phosphate additives in some of their products but not in all of them.

Examples of discrepancies between food composition analyses and chemical analyses

Evidence supporting the inaccuracy of food composition tables exists for several food categories, including chicken products and meats (9). From label information and direct chemical analyses of 38 chicken products from local Midwestern grocery stores, the number of phosphorus-containing ingredients and the difference between estimated and direct chemical analyses were determined. Only 3 of the 38 products did not contain phosphate additives and the remaining 35 contained one or more phosphate additives. The additional phosphorus presumably contributed by the use of inorganic phosphate additives ranged from 12 to 165 mg/100 g.

Another group conducted 2 similar studies. In one study (55), they measured the phosphorus content of 44 food products, including 30 refrigerated or frozen precooked meat, poultry, and fish items, generally national brands, and found that the ratio of phosphorus to protein content in these items ranged from 6.1 to 21.5 mg phosphorus/g protein. The mean phosphorus-to-protein ratio in the 19 food products with a label listing phosphorus as an ingredient was 14.6 mg/g compared with 9.0 mg/g in the 11 items without phosphorus-containing ingredients. In a second study, they studied enhanced meats and observed that enhanced meat and poultry products had on average phosphorus:protein ratio that was 28.4% higher than that for “natural” products without enhanced phosphate salts (56). Further indirect evidence that current and past dietary databases underestimate dietary phosphorus intake is provided by other studies in which similar foods obtained in the market place and differing only by the presence or absence of phosphate additives showed significantly higher phosphorus content when chemically analyzed (16, 17). These examples support the inaccuracy of the current nutrient databases to estimate dietary phosphorus intake.

Potentially high unsafe intakes of phosphorus

To determine how close current extremes of phosphorus intake are to the actual UL for phosphorus (4000 g/d) set by the Institute of Medicine (29), we used existing NHANES data to estimate potential increases from use in processed food. In Figure 2A and B, we applied a conservative underestimation of a 30% contribution from additive use to the 95th percentile intake of phosphorus for men and women in the 2005–2006 NHANES. As shown in Figure 2B, the important point is that phosphorus intake in men with the highest percentile of intake approaches the UL of 4000 mg/d if the contribution of phosphorus from hidden additives is taken into account.

Why then are some individuals in the United States consuming dietary phosphorus at amounts that approach the UL? We believe that the main factor involves the extensive use of phosphorus-containing additives in food processing. We use the term “extensive use” because of the large number of phosphate ingredients with GRAS status and the large number of approved functional applications in food processing. Forty-eight commonly used phosphate ingredients out of 370 total different ingredients that were evaluated by the Select Committee on GRAS substances are presented in Table 3. The committee rendered both an opinion (report number) and a conclusion (score) about the safety of the GRAS ingredients (57). GRAS is an acronym for the phrase “Generaly Recognized as Safe,” a title that means that the substances are not subject to premarket review because they have been shown to be safe under conditions of their intended use by qualified experts from outside the US Food and Drug Administration. As shown in Table 3, the majority of the phosphate GRAS ingredients were given type 1 conclusions, a safety score defined...
as “no evidence in the available information on [substance] that demonstrates, or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future” (57).

Mostly inorganic phosphate salts are shown in Table 3, 17 of which also contain sodium; thus, phosphate additives are also significant sources of sodium because of their extensive use in food processing. The 3 organic phosphate ingredients with significant use shown in Table 3 include acetylated distarch phosphate, hydroxypropyl distarch phosphate, and monostarch phosphate. Modified starches do not always contain phosphate, and it is difficult to tell from the ingredients list if they are contributing phosphate. Modified starches have several functions and are critical to processing frozen foods. All of the phosphate ingredients in Table 3 have multiple functions that significantly improve the quality, taste, and texture of a variety of different food categories.

Another significant contributor to high phosphorus intake is the growing trend to eat out at either restaurants or fast-food establishments. A study from the Economic Research Service (58) reported that Americans are consuming a greater share of their total daily caloric intake from “food purchased and/or eaten away from home.” They reported an increase of 32% in away-from-home eating since the late 1970s and increased growth in the away-from-home market, which accounted for 50% of the total food expenditures in 2004; the highest frequency of eating out occurs for fast food in both children and adults. Fast foods and restaurant foods are processed and high in phosphate-containing ingredients, as are convenience foods, on which working families and single adults are increasingly becoming reliant because of lack of time for food preparation from scratch.

An important fact to consider is that the availability of unprocessed fresh foods may be limited for ethnic and racial minorities and for low-income populations with a high prevalence of type 2 diabetes. The availability of unprocessed fresh foods is relevant to the estimated 40% of diabetic patients who will progress to renal failure and ultimately to cardiovascular morbidity and mortality. Comparisons of the availability and cost of healthy foods recommended for patients with diabetes were made for a racial/ethnically diverse neighborhood in East Harlem and an adjacent, largely white, affluent Upper East Side neighborhood in New York City (59). Only 18% of the East Harlem stores stocked healthy foods recommended for patients with diabetes compared with 58% of stores in the Upper East Side.

Another factor to be considered is the distortion in the calcium:phosphorus intake ratio. The median calcium:phosphorus ratio for persons with lower calcium intakes ranged between 0.4 and 0.6 in the 1989–1991 Continuing Surveys of Food Intakes by Individuals conducted by the USDA; however, this finding raised little public health concern at the time (5). Although phosphorus intake estimates will be underestimated, it is critical to evaluate individual calcium:phosphorus intake ratios to determine the percentage of the population at potential risk of excess phosphorus intake and adverse health outcomes.

Increased dietary phosphorus intake is a larger and more serious problem for patients with impaired kidney function, especially those in the early stages who may not be aware of their impaired renal status (6). The National Kidney Foundation estimates that 26 million American adults have CKD; this population will have significant problems handling high phosphorus loads.

CONCLUSIONS

Adverse health effects are beginning to emerge in individuals with normal renal function, which questions the safety of the high cumulative use of phosphate ingredients in processed and prepared foods. The increasing evidence of an association between high dietary intake and heart disease calls for a more thorough investigation of this issue.

A barrier to the use of serum phosphate as a barometer of excess dietary phosphorus intake is variation a result of a pronounced circadian rhythm (phosphorus fluctuation of as high as
and the body’s ability to correct the elevated serum phosphate to fasting concentrations with high dietary phosphorus loads. Future studies using serum phosphate as a measure of dietary burden will need to be designed in a way to control these confounders. Accurate estimates of dietary phosphorus intake are essential to assess the contributions of serum phosphate to the development of chronic diseases.

The authors’ responsibilities were as follows—MSC and JU: participated in equal proportion in all the phases of this review. Neither of the authors had any conflicts of interest with regard to this article.

### TABLE 3

Alphabetical list of commonly used phosphate-containing GRAS substances and their SCOGS safety scores

<table>
<thead>
<tr>
<th>No.</th>
<th>GRAS ingredient</th>
<th>Score</th>
<th>Report no.</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetylated distarch phosphate</td>
<td>2</td>
<td>115</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Ammonium phosphate dibasic</td>
<td>1</td>
<td>32</td>
<td>184.1141</td>
</tr>
<tr>
<td>3</td>
<td>Ammonium phosphate dibasic</td>
<td>1</td>
<td>34</td>
<td>184.1141</td>
</tr>
<tr>
<td>4</td>
<td>Ammonium phosphate monobasic</td>
<td>1</td>
<td>34</td>
<td>181.1141</td>
</tr>
<tr>
<td>5</td>
<td>Calcium glycophosphate</td>
<td>1</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Calcium hexametaphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Calcium hypophosphate</td>
<td>1</td>
<td>73</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Calcium phosphate dibasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Calcium phosphate monobasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Calcium phosphate tribasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>Calcium phytate</td>
<td>1</td>
<td>45</td>
<td>586.6219</td>
</tr>
<tr>
<td>12</td>
<td>Calcium pyrophosphate</td>
<td>1</td>
<td>32</td>
<td>182.8223</td>
</tr>
<tr>
<td>13</td>
<td>Dibasic magnesium phosphate</td>
<td>1</td>
<td>60</td>
<td>184.1434</td>
</tr>
<tr>
<td>14</td>
<td>Ferric phosphate</td>
<td>2</td>
<td>35</td>
<td>184.1301</td>
</tr>
<tr>
<td>15</td>
<td>Ferric pyrophosphate</td>
<td>5</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>Ferric sodium pyrophosphate</td>
<td>5</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>Hydropropyl distarch phosphate</td>
<td>3</td>
<td>115</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>Manganese glycophosphate</td>
<td>1</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>19</td>
<td>Manganese glycophosphate-package</td>
<td>1</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>Manganous hypophosphite</td>
<td>1</td>
<td>73</td>
<td>—</td>
</tr>
<tr>
<td>21</td>
<td>Monostarch phosphate</td>
<td>2</td>
<td>115</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>Phosphoric acid</td>
<td>1</td>
<td>32</td>
<td>182.1073</td>
</tr>
<tr>
<td>23</td>
<td>Potassium glycophosphate</td>
<td>1</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>24</td>
<td>Potassium hypophosphate</td>
<td>1</td>
<td>73</td>
<td>—</td>
</tr>
<tr>
<td>25</td>
<td>Potassium phosphate dibasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>26</td>
<td>Potassium phosphate monobasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>27</td>
<td>Potassium phosphate tribasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>28</td>
<td>Potassium polymetaphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>29</td>
<td>Potassium pyrophosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>Potassium tripolyphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>31</td>
<td>Riboflavin 5’-phosphate</td>
<td>1</td>
<td>114</td>
<td>—</td>
</tr>
<tr>
<td>32</td>
<td>Sodium acid pyrophosphate</td>
<td>1</td>
<td>32</td>
<td>182.087</td>
</tr>
<tr>
<td>33</td>
<td>Sodium aluminum phosphate, acidic</td>
<td>1</td>
<td>43</td>
<td>182.1781</td>
</tr>
<tr>
<td>34</td>
<td>Sodium aluminum phosphate, basic</td>
<td>1</td>
<td>43</td>
<td>182.1781</td>
</tr>
<tr>
<td>35</td>
<td>Sodium ferricytropyrophosphate</td>
<td>5</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>36</td>
<td>Sodium hexametaphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>37</td>
<td>Sodium hypophosphite</td>
<td>1</td>
<td>73</td>
<td>184.176</td>
</tr>
<tr>
<td>38</td>
<td>Sodium metaphosphate</td>
<td>1</td>
<td>32</td>
<td>182.6769</td>
</tr>
<tr>
<td>39</td>
<td>Sodium phosphate dibasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>40</td>
<td>Sodium phosphate monobasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>41</td>
<td>Sodium phosphate tribasic</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>42</td>
<td>Sodium phosphoaluminate-package</td>
<td>1</td>
<td>43</td>
<td>—</td>
</tr>
<tr>
<td>43</td>
<td>Sodium pyrophosphate</td>
<td>1</td>
<td>32</td>
<td>182.6760</td>
</tr>
<tr>
<td>44</td>
<td>Sodium tetrametaphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>45</td>
<td>Sodium tetraphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>46</td>
<td>Sodium trimetaphosphate</td>
<td>1</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>47</td>
<td>Sodium tripolyphosphate</td>
<td>1</td>
<td>32</td>
<td>182.1810</td>
</tr>
<tr>
<td>48</td>
<td>Tribasic magnesium phosphate</td>
<td>1</td>
<td>60</td>
<td>184.1434</td>
</tr>
</tbody>
</table>

1. CFR, Code of Federal Regulations; GRAS, Generally Recognized As Safe (this term is used to refer to a food substance that is not subject to premarket review and approval by the Food and Drug Administration because it is generally recognized, by qualified experts, to be safe under the intended conditions of use); SCOGS, Select Committee on GRAS Substances.

2. This score represents the SCOGS conclusion regarding the safety of the GRAS ingredient. For example, a score of 1 indicates no safety concerns under approved conditions of use.

3. The report number represents the number of the report that contains details of the safety studies that formed the basis of the opinion made by the committee.

4. The CFR number refers to the citation in Title 21 of the US Code of Federal Regulations if the substance is subject to a regulation.
REFERENCES

33. Kemi VE, Rita HJ, Karkkainen MU, Viljakainen HT, Laaksonen MM, Outila TA, Lamberg-Allardt C. Habitual high phosphorus intakes and foods with phosphate additives negatively affect serum parathyroid...


