Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2017: 18

# Assessment of dietary intake of phosphorus in relation to tolerable upper intake levels

**Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety**

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2017: 18
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Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety
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# Assessment of dietary intake of phosphorus in relation to tolerable upper intake level

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## Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM). Kristin Holvik (chair), Livar Frøyland, Margaretha Haugen, Sigrun Henjum, Martinus Løvik, Tonje Holte Stea and Tor A. Strand.

(Panel members in alphabetical order after chair of the panel)

## Acknowledgment

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou. Margaretha Haugen and Inger Therese L. Lillegaard are acknowledged for their valuable work on this opinion.

## Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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# Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), evaluated the intake of phosphorus in the Norwegian population. VKM has also conducted scenario calculations to illustrate the consequences of amending maximum limits for phosphorus (to 1000, 2000 or 2500 mg/day) in food supplements.

Phosphorus is an essential nutrient and is involved in many physiological processes, such as in the cell's energy cycle, in regulation of the body's acid-base balance, as a component of the cell structure, in cell regulation and signalling, and in the mineralisation of bones and teeth. In the human body, phosphorus is present in different forms. Serum contains mainly inorganic phosphates ($P_i$) (dihydrogen and monohydrogen phosphate), bone contains phosphorus largely in the form of hydroxyapatite, whereas the soft tissues and extracellular fluids contain organic phosphates in complex with carbohydrates, lipids and proteins. Phosphorus is the main mineral constituent of bones. About 85% of the body's phosphorus is in bones and teeth, and together with calcium account for around 80-90% of bone composition. The remaining 15% of the body's phosphorus is essential in functions ranging from the transfer of genetic information to energy utilisation. Phosphorus is a structural component of the nucleic acids DNA and RNA and thus involved in the storage and transmission of genetic material. It is an essential component of phospholipids (e.g. phosphatidylcholine) that form all membrane bilayers throughout the body. Phosphorus is also an essential component of adenosine triphosphate (ATP), the body's key energy source.

Currently there is no reliable biomarker of phosphorus status, and serum phosphorus increases for a short period after ingestion of a meal and then decreases and remains within a relatively narrow range as a result of homeostatic mechanisms.

The EFSA recommendations (2015) for adequate intake (AI) of phosphorus is 550 mg/day for adults, both sexes, whereas the recommended intake (RI) in the Nordic Nutrition Recommendations (2012) is 600 mg/day. Adolescents have a higher requirement of phosphorous because of bone accretion (640 mg/day EFSA and 700 mg/day NNR).

EFSA (2005) concluded that the available data were not sufficient to establish a tolerable upper level for phosphorus, however, data indicate that normal healthy individuals can tolerate phosphorus intakes up to 3000 mg/day. EFSA advised supplemental intake not to exceed 750 mg/day, because mild gastrointestinal symptoms have been reported when this dose was increased. EFSA gave no UL suggestions for children, lactating or pregnant women, while Institute of Medicine set a UL for total intake of phosphorous for children at 3000 mg/day and 4000 mg/day for adolescents and adults and 3500 mg/day for lactating women.

In accordance with EFSA (2005), VKM suggests to use 3000 mg/day as a provisional UL for total intake of phosphorous for adults, and suggests 750 mg/day as an upper level for supplements. Because of lack of data no provisional ULs are set for adolescents or children.

Accordingly, all the suggested doses from NFSA (1000, 2000 and 2500 mg/day) in supplements exceed 750 mg/day, the suggested UL for supplemental phosphorus for adults.

**Key words**: VKM, risk assessment, Norwegian Scientific Committee for Food Safety, phosphorus, food supplement, upper level, exposure.

# Sammendrag på norsk

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet vurdert inntaket av fosfor i den norske befolkningen i relasjon til øvre tolerable inntaksnivåer (UL). VKM har også gjort noen enkle scenarioberegninger og vurdert konsekvenser av å endre den eksisterende maksimumsgrensen for fosfor i kosttilskudd på 1500 mg/dag til 1000, 2000 eller 2500 mg/dag.

Fosfor er et essensielt næringsstoff, og er involvert i en rekke fysiologiske prosesser som cellenes energiomsetning, kroppens syre-basebalanse, som komponent i cellestrukturen, regulering av cellesignalering og i mineralisering av skjelett og tenner.

Fosfor finnes i ulike former i kroppen. I serum hovedsakelig som uorganiske fosfater ($P_i$) (dihydrogen og monohydrogen fosfat), i beinvev for det meste som hydroksyapatitt, mens bløtvev og ekstracellulære væsker inneholder organiske fosfater i ulike karbohydrat-, fett- eller proteinkomplekser.

Fosfor er det viktigste mineralet i beinvev. Om lag 85 % av kroppens fosfor inngår i skjelett og tenner, og utgjør sammen med kalsium 80-90 % av beinsubstansen. De resterende 15 prosenten av kroppens fosfor er essensielle for alt fra overføring av genetisk informasjon til energiutnyttelse. Fosfor inngår også som strukturell komponent i nukleinsyrene DNA og RNA, og er dermed involvert i lagring og overføring av genetisk materiale. Fosfor inngår i fosfolipider (for eksempel fosfatidylkolin) som utgjør alle dobbeltlag i kroppens cellemembraner. Fosfor er også nøkkelkomponent i adenosintrifosfat (ATP), kroppens viktigste energikilde.

Per i dag er det ingen god biomarkør for fosforstatus. Etter et måltid vil fosfatnivået i serumstige en kort stund for deretter å avta. Fosfatnivået i serum varierer lite på grunn av homeostatiske mekanismer.

EFSAs anbefalinger fra 2015 for adekvat inntak (AI) av fosfor er 550 mg/dag for voksne menn og kvinner, mens anbefalt inntak (RI) i de nordiske næringsstoffanbefalingene er 600 mg/dag. Ungdom har et større behov for fosfor på grunn av skjelettets utvikling (640 mg/dag i EFSA og 700 mg/dag i NNR).

EFSA (2005) konkluderte med at det ikke var tilstrekkelig data til å fastslå tolerable øvre inntaksnivåer (UL) for fosfor, men data indikerer at normale friske personer kan tolerere inntak opp til 3000 mg/dag. EFSA foreslår dette som en midlertidig UL for inntak av fosfor fra all kost, inkludert kosttilskudd. EFSA uttaler videre at fosfor fra kosttilskudd ikke bør overstige 750 mg/dag fordi det er rapportert om milde gastrointestinale plager ved høyere doser. EFSA har heller ikke foreslått UL for barn, gravide og ammende, mens Institute of Medicine (USA) har fastsatt UL for totalt inntak av fosfor for barn på 3000 mg/dag, for ungdom og voksne på 4000 mg/dag og for ammende 3500 mg/dag.

VKM foreslår at 3000 mg/dag brukes som midlertidig UL for totalt inntak av fosfor for voksne, og at 750 mg/dag brukes som øvre nivå for kosttilskudd som er i samsvar med EFSA (2005). VKM kan ikke foreslå midlertidig UL for ungdom eller barn på grunn av for dårlig datagrunnlag.

De foreslåtte dosene fra Mattilsynet (1000, 2000 og 2500 mg/dag) overstiger 750 mg/dag som er foreslått som øvre nivå for tilskudd.

# Abbreviations and/or glossary

## Abbreviations

AI – adequate intake
AR – average requirement
ATP - adenosine triphosphate
bw – body weight
cAMP – cyclic adenosine monophosphate
cGMP – cyclic guanosine monophosphate
CI – confidence interval
DNA – deoxyribonucleic acid
DRI – dietary reference intake
DRV – dietary reference value
EAR – estimated average requirement (IOM).
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
IOM – Institute of Medicine, USA
$IP_3$ - Inorganic phosphorus
IU – international unit
JECFA – Joint Expert Committee on Food Additives
LOAEL – lowest observed adverse effect level
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
PRI – population reference intakes
PTH – parathyroid hormone
RDA – recommended dietary allowances
RNA – ribonucleic acid
RI – recommended intake
SCF – Scientific Committee for Food
SUL – safe upper intake level
UF – uncertainty factor
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee for Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet]

## Glossary

**P5, P25, P50, P75 or P95-exposure** is the calculated exposure at the 5, 25, 50, 75 or 95-percentile.

**Percentile** is a term for visualising the low, medium and high occurrences of a measurement by splitting the whole distribution into one hundred equal parts. A percentile is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value (or score) below which 95 percent of the observations are found.

### *EFSA - Dietary Reference Values (DRVs) (EFSA, 2010)*

**Average Requirement (AR)** is the level of intake of a defined group of individuals estimated to satisfy the physiological requirement of metabolic demand, as defined by a the specific criterion for adequacy for the nutrient, in half of the heathy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate.

If an AR cannot be determined than an Adequate Intake is used.

**Adequate Intake (AI)** is defined as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of a nutrient intake, by a group (or groups) of apparently healthy people, and therefore assumed to be adequate. The practical implication of an AI is similar to that of a population reference intake, i.e. to describe the level of intake that is considered adequate for health reasons. The terminological distinction relates to the different ways in which these values are derived and to the resultant difference in the "firmness" of the value.

**Population Reference Intake (PRI)** is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals.

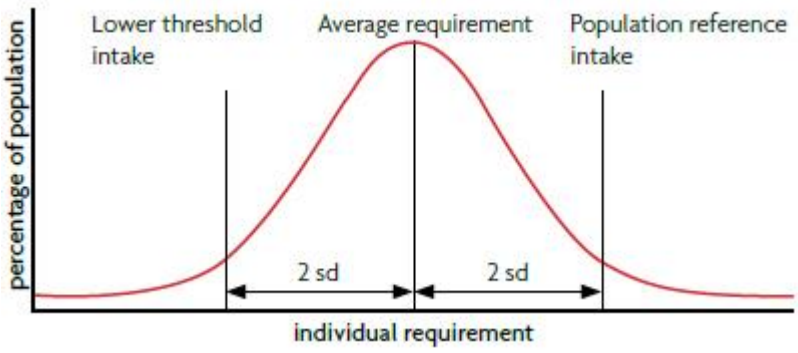


**Figure 1**: Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

**Lower Threshold Intake (LTI)** is the lowest estimate of requirement from the normal distribution curve, and is generally calculated on the basis of the AR minus twice its SD. This will meet the requirement of only 2.5% of the individuals in the population.

**Tolerable Upper intake Level (UL)** is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

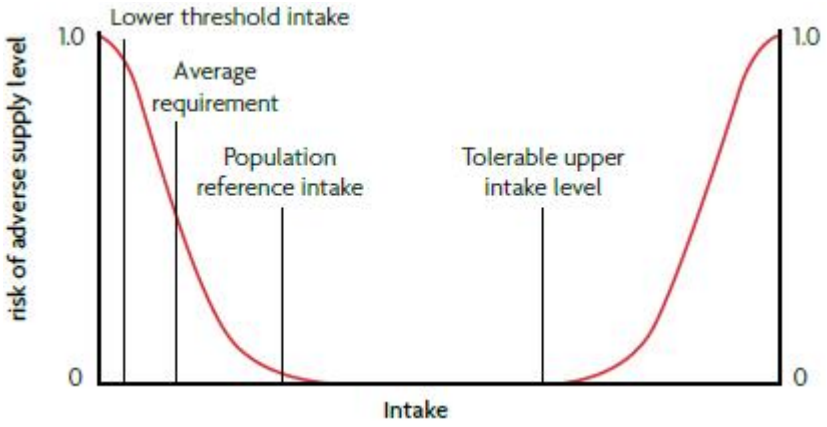


**Figure 2**: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake using EFSA terminology.

### *IOM - Dietary Reference Intakes (DRIs) (IOM, 2000)*

**Estimated Average Requirement (EAR)** is a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a life stage and gender group.

**Recommended Dietary Allowances (RDA)** is the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. RDA = EAR + 2 $SD_{EAR}$ or if insufficient data to calculate SD a factor of 1.2 is used to calculate RDA; RDA = 1.2*EAR

**Adequate Intake (AI)** is the recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined

**Tolerable Upper Intake Level (UL)** is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population.

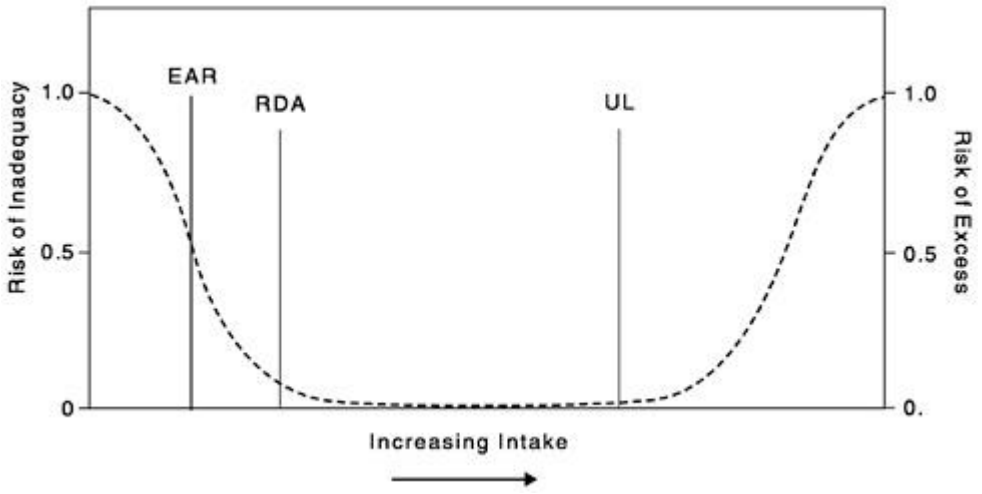


**Figure 3**: Dietary reference intakes using IOM terminology.

### *NNR -Recommended Intake (NNR Project Group, 2012)*

**Average Requirement (AR)** is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual i.e. the level of a nutrient that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement.

$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$

**Recommended Intake (RI)** is defined as the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. $RI = AR + 2SD_{AR.}$

$RI_{NNR} = RDA_{IOM} = PRI_{EFSA}$

**Upper Intake Level (UL)** is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans.

$UL_{NNR} = UL_{IOM} = UL_{EFSA}$

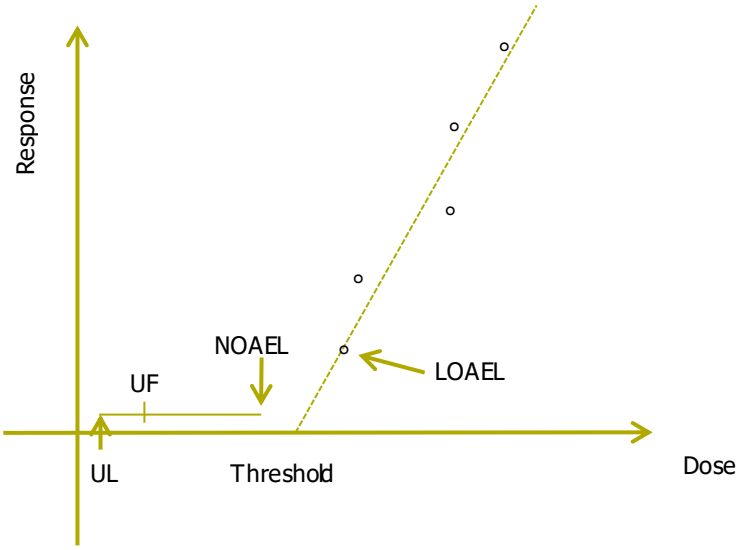


**Figure 4**: Derivation of Upper Intake Level (UL).

UF: Uncertainty factor

### *Expert group on vitamins and minerals (EVM), UK (EVM, 2003)*

**Safe Upper Intake Level (SUL):** EVM used SUL instead of UL and defined SUL as the determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provided a framework within which the consumer could make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative.

# Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented in Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Pursuant to Directive 2002/46/EC, common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU.

National maximum limits for vitamins and minerals were established in the former vitamin and mineral supplements regulation from 1986 and were continued in the 2004 regulation.

The European Commission started establishing common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

Maximum limits for levels of vitamins and minerals in food supplements shall be set on the basis of the following criteria, pursuant to article 5 in Directive 2002/46/EC:

- Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups
- Intake of vitamins and minerals from other dietary sources

When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Pending establishment of common maximums limits in the EU, the Norwegian Food Safety Authority is evaluating the national maximum limits for vitamins and minerals in food supplements.

**Assessment of phosphorus**

The Norwegian Food Safety Authority will evaluate the national maximum limits for phosphorus in the food supplement regulation. The minimum and maximum limits for the content of vitamins and minerals in food supplements are listed in Annex 1 to the food supplement regulation:

**Background Table:** Minimum and maximum limits for phosphorus in the food supplement regulation (October 2015).

| | Minimum amount per recommended daily dose | Maximum amount per recommended daily dose |
|---|---|---|
| **Phosphorus, mg** | 200 | 1500 |

Permitted phosphorus substances which may be used in the manufacture of food supplements are listed in "Forskrift om kosttilskudd 2012", http://www.lovdata.no/cgi-wift/ldles?doc=/sf/sf/sf-20040520-0755.html.

# Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA, Mattilsynet) requests the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of phosphorus from the diet, including fortified products, in all age groups in the population above 1 year (mean intakes, median, P5, P95).

VKM is also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for phosphorus (to 1000, 2000 or 2500 mg/day, as examples) in food supplements, and to evaluate these scenarios against already established tolerable upper intake levels.

# Assessment phosphorus

# 1 Introduction

Phosphorus is an essential nutrient and is involved in many physiological processes, such as in the cell's energy cycle, in regulation of the body's acid-base balance, as a component of the cell structure, in cell regulation and signalling, and in the mineralisation of bones and teeth. In the human body, phosphorus is present in different forms. Serum contains mainly inorganic phosphates ($P_i$) (dihydrogen and monohydrogen phosphate), bone contains phosphorus largely in the form of hydroxyapatite, whereas the soft tissues and extracellular fluids contain organic phosphates in complex with carbohydrates, lipids and proteins (Bansal, 1990, cited in EFSA report on DRVs for phosphorus, 2015). Phosphorus is the main mineral constituent of bones. About 85% of the body's phosphorus is in bones and teeth, and together with calcium account for around 80-90% of bone composition. Phosphorus does not occur in nature as a free element because of its high reactivity, but is found in the form of phosphate minerals.

Phosphorus homeostasis is linked to that of calcium because of the actions of calcium-regulating hormones, such as parathyroid hormone (PTH) and 1,25-dihydroxy-vitamin D ($1,25(OH)_2D$), at the level of the bone, the gut and the kidneys. The kidney plays a predominant role in the regulation of systemic phosphorus homeostasis. About 80% of filtered phosphorus is reabsorbed in the proximal tubule. The phosphorus reabsorption capacity adapts to altered intake of phosphorus within hours (acute adaptation) (Bindels, 2012 cited in EFSA report on DRVs for phosphorus, 2015).

The remaining 15% of the body's phosphorus is essential in functions ranging from the transfer of genetic information to energy utilisation. Phosphorus is a structural component of the nucleic acids DNA and RNA and thus involved in the storage and transmission of genetic material. It is an essential component of phospholipids (e.g. phosphatidylcholine) that form all membrane bilayers throughout the body. Phosphorus is also an essential component of adenosine triphosphate (ATP), the body's key energy source. Other phosphorylated molecules (e.g. creatine phosphate in muscle) serve as a rapid source of phosphate for ATP production. Many intracellular signalling processes depend on phosphorus-containing compounds such as cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) and inositol polyphosphates (e.g. inositol triphosphate ($IP_3$)). Cellular phosphate is the main intracellular buffer and therefore is essential for pH regulation in the human body (O'Brien, 2014 cited in EFSA report on DRVs for phosphorus, 2015).

Phosphate contents in foods correlate somewhat to protein content, but distinct differences exist. Milk and dairy products have the highest phosphate-to-protein ratio (close to 30 mg/g protein). Chicken and fish are at the low end (6-16 mg/g protein). Processed foods like cheese, and colas and some other sodas, are important sources. Much of the large amounts

of phosphate in plant-derived foods is bound to inositol (phytate and related forms) and is not absorbed. Based on data from 13 dietary surveys in nine European Union countries, mean phosphorus intakes range from 1000 to 1767 mg/day in adults (≥ 18 years) (EFSA, 2015).

Serum phosphorus concentration is not a reliable marker of intake as it increases for a short period after ingestion of a meal and then decreases and remains within a relatively narrow range as a result of homeostatic mechanisms. Currently there is no reliable biomarker of phosphorus status.

# 2 Recommendations and tolerable upper intake levels

## 2.1 Recommendations

### 2.1.1 Institute of Medicine (IOM, 1997), USA

IOM (1997) has set estimated average requirements (EAR) and recommended dietary allowances (RDA) for children and adolescents based on tissue accretion in balance studies. For adults EAR and RDA was set based on the relationship between serum $P_i$ and absorbed intake within the range typically considered normal. Absorption rate was set to 60-65%.

**Table 2.1-1** IOM RDA recommendations for phosphorus intakes (mg/day), both sexes.

| Age, both sexes | mg/day | |
|---|---|---|
| | Men | Women |
| 6-11 mo. | 275 | 275 |
| 1-3 years | 380 | 380 |
| 4-8 years | 500 | 500 |
| 9-13 years | 1250 | 1250 |
| 14-18 years | 1250 | 1250 |
| 18- >75 years | 700 | 700 |
| Pregnant >18 years | 700 | 700 |
| Lactating > 18 years | 700 | 700 |

### 2.1.2 Nordic Nutrition Recommendation (NNR, 2012)

NNR Project Group (2012) based the recommended intake (RI) of phosphorus on recommended calcium intake, on the view of an equimolar relationship (1:1) between calcium and phosphorus for both adults, children and adolescents (1 mmol calcium=40 mg, 1 mmol phosphorus=30.9 mg). No information is presented concerning pregnancy or lactation.

**Table 2.1-2** Recommended intakes (RI) for phosphorus (mg/day) in the Nordic Nutrition Recommendations 2012, both sexes.

| Age, both sexes | mg/day | |
|---|---|---|
| | Men | Women |
| 6-11 mo. | | |
| 1-2 years | | |
| 2-5 years | 470 | 470 |

| Age, both sexes | mg/day | |
|---|---|---|
| **6-9 years** | 540 | 540 |
| **mmol10-13 years** | 700 | 700 |
| **14- >75 years** | 600 | 600 |

### 2.1.3 European Food Safety Authority (EFSA, 2015)

EFSA (2015) considers that the available data are insufficient to derive average requirements (ARs) and population reference intakes (PRIs) for phosphorus, and therefore proposes to set adequate intakes (AIs) for all population groups. AIs for phosphorus are based on the AI (for infants aged 7–11 months) and the PRIs (for all other ages) for calcium (EFSA NDA Panel, 2015), with use of a molar calcium to phosphorus ratio of 1.4:1. AIs for all age groups were set after rounding up to the nearest 10 mg/day. The EFSA Panel considered that the AIs proposed for infants and children cover the quantity of phosphorus estimated for accretion in bone.

EFSA accepted that physiological adaptive processes ensure sufficient phosphorus for normal fetal growth and breast milk production. Thus, additional dietary phosphorus is not required for pregnant and lactating women as long as AI for adults is met.

**Table 2.1-2** EFSA recommendations for phosphorus intakes mg/day. Adequate intake (AI) for infants 7-11 months and Population reference intakes (PRIs) for all other groups, both sexes.

| Age, both sexes | mg/day | |
|---|---|---|
| | **Men** | **Women** |
| **7-11 mo.** | 160 | 160 |
| **1-3 years** | 250 | 250 |
| **4-10 years** | 440 | 440 |
| **11-17 years** | 640 | 640 |
| **Adults ≥18 years** | 550 | 550 |
| **Pregnant** | | 550 |
| **Lactating** | | 550 |

## 2.2 Tolerable upper intake levels (UL)

### Institute of Medicine (IOM, 1997), USA

IOM (1997) define tolerable upper intake level (UL) as an intake associated with the upper boundary of adult normal values of serum $P_i$. Adverse effects attributed to hyperphosphatemia are: (1) adjustments in the hormonal control system regulating the calcium economy, (2) ectopic (metastatic) calcification, particularly in the kidneys, (3)

increased porosity of the skeleton in some animal models, and (4) a suggestion that high phosphorus intakes could reduce calcium absorption by binding calcium in the chyme. Most of these effects require high intake leading to increased serum $P_i$.

It is stated that no reports exist of adverse effects following high dietary phosphorus intakes in humans. Essentially all instances of dysfunction (and, hence, all instances of hyperphosphatemia) in humans result from non-dietary causes (for example, end-stage renal disease, vitamin D intoxication).

The upper boundary of adult normal values of serum $P_i$ is reached at a daily phosphorus intake of 3.5 g (113 mmol). Infants, children, and adolescents have higher upper boundaries for normal serum $P_i$ values than adults, which indicates that their tissues tolerate higher $P_i$ levels well. With use of the upper normal $P_i$ boundary in children, a NOAEL for adults was assumed to be over 10.2 g (330 mmol)/day. A pharmacokinetic approach with a relationship between intake and blood level was used and an uncertainty factor (UF) of 2.5 was chosen, deriving at a UL for adults of 4.0 g/day (10.2 g/day divided by 2.5=~4.0 g (~130 mmol)/day).

During pregnancy, absorption efficiency for phosphorus is elevated by about 15%, and thus, the UL associated with the upper end of the normal range was argued to be about 15% lower than adults, that is, about 3.5 g (112.9 mmol)/day. During lactation, the phosphorus economy of a woman does not differ detectably from the non-lactating state. Hence, the UL was set to 4.0 g (130 mmol)/day during lactation.

For toddlers and children, a UL of 3.0 g (96.8 mmol)/day was calculated by dividing the NOAEL for adults (10.2 g [330 mmol]/day) by a UF of ~3.3 to account for potentially increased susceptibility due to smaller body size.

**Table 2.2-1** Tolerable upper intake levels for phosphorus intake from diet and supplements in different age groups. Institute of Medicine (1997).

| Age (years) | UL mg/day |
|---|---|
| **1-3** | 3000 |
| **4-8** | 3000 |
| **9-13** | 3000 |
| **14-18** | 4000 |
| **19 and older** | 4000 |
| **Pregnancy** | 3500 |

It was recognised that population groups such as professional athletes, military trainees, or those whose energy expenditure exceeds 6000 kcal/day, may have dietary phosphorus intakes above these levels. In such individuals with phosphorus intakes above the UL, no harm is known to result.

No vulnerable group for high phosphorus intakes was reported.

## Expert Group on Vitamins and Minerals (EVM, 2003), UK

EVM (2003) stated that there are no data on chronic toxicity of dietary forms of phosphorus in the literature. EVM concluded that there are insufficient data from human and animal studies to establish a Safe Upper Level for inorganic phosphates. A few studies have reported diarrhoea and mild gastrointestinal symptoms at doses of 750 to 2250 mg supplemental phosphorus/day (Godlsmith 1968, Brixen et al., 1992, Whybro et al., 1998 cited in EVM, 2003). The osmotic diarrhoea reported in these supplementation studies was mild and reversible in nature. Because persons with hypovitaminosis D are vulnerable to hyperparathyroidism, an uncertainty factor of 3 was applied to the NOAEL of 750 mg/day to allow for inter-individual variation. Based on these limited studies, and for guidance purposes only, a supplemental intake of 250 mg/day was expected not to produce adverse effects, including mild gastrointestinal upset. Assuming a maximum intake of 2100 mg/day (97.5 percentile) from food and water, EVM (2003) estimated that a total intake of 2400 mg/day phosphate (equivalent to 40 mg/kg bw/day in a 60 kg adult) would not be expected to result in any adverse effects.

## European Food Safety Authorities (EFSA, 2005), EU

The inorganic phosphate fraction in the extracellular fluid is under endocrine control of the parathyroid-vitamin D axis. Excess phosphorus intake might result in hyperphosphatemia and a consequent increase in serum parathyroid hormone (PTH) level. Secondary hyperparathyroidism leads to increased bone resorption which might reduce bone mineral density and impair skeletal integrity, and result in ectopic calcification. Such phosphorus induced effects have been observed in animal studies, but not in humans, except in patients with end-stage renal disease. As long as renal capacity is adequate, excess phosphate is excreted.

No genotoxic effect of inorganic salts of phosphorus was identified (JECFA, 1982). JECFA reviewed the available data from studies in mice and rats and concluded that dosing with phosphoric acid and inorganic phosphate salts does not induce maternal toxicity or teratogenic effects. Maximum dose levels tested for the various inorganic phosphate salts varied between 130 and 410 mg phosphorus/kg body weight (JECFA, 1982).

Osmotic diarrhoea and other mild gastrointestinal effects, including dyspepsia, nausea and vomiting have been reported as side effects in some individuals participating in supplementation studies using high supplemental doses (between 750 to 2250 mg/day, total oral intakes up to 3000 mg phosphorus/day).

Consumption of soft drinks with added phosphoric acid has been associated with hypocalcaemia in children (Mazarlegos-Ramos, 1995 cited in EFSA, 2005), but no effect on calcium excretion was seen among 20-40 year old women (Heaney and Rafferty, 2001 cited in EFSA, 2005). There is no evidence that phosphorus intake interferes with calcium absorption. Clinical studies referred to in the EFSA report found no effects of high

phosphorus (phosphate) intake on markers of bone remodelling in subjects with hyperparathyroidism induced by inadequate calcium intakes, or with an inadequate vitamin D status.

EFSA (2005) concluded that the available data are not sufficient to establish a tolerable upper intake level for phosphorus. However, available data indicate that normal healthy individuals can tolerate phosphorus (phosphate) intakes up to at least 3000 mg/day without adverse systemic effects. Because, mild gastrointestinal symptoms have been reported in some individuals if exposed to supplemental intakes >750 mg phosphorus per day, supplements were advised not to exceed this amount. EFSA does not suggest any ULs for children, lactating or pregnant women.

### Nordic Nutrition Recommendations (NNR, 2012)

NNR Project Group (2012) set a provisional UL of 3000 mg/day based on the EFSA evaluation. No independent assessment of the literature was performed for the NNR.

### 2.2.1 Summary and discussion of tolerable upper intake levels

IOM (1997) used hyperphosphatemia as outcome to set a UL for total intake (diet and supplements) of phosphorous for children at 3000 mg/day and 4000 mg/day for adolescents and adults, and 3500 mg/day for lactating women. EFSA (2005) included clinical studies on markers of bone remodelling in the attempt to establish a tolerable upper intake level for phosphorus. Increased bone turnover was used as a surrogate marker of excess phosphorus because serum or blood phosphorus concentrations have been shown to be poor markers of phosphorus status. EFSA gave no special UL suggestions for children, lactating or pregnant women. EVM (2003) used the 97.5 percentile of dietary intake among adults as the basis for setting a guidance level.

Because of osmotic diarrhoea reported in supplementation studies with intakes of phosphorus at 750 - 2250 mg/day, EFSA (2005) suggested that supplemental phosphorus should not exceed 750 mg/day for supplements while EVM used a UF of three to assure no physiological changes in calcium and parathyroid hormone levels from phosphorus supplementation. NNR (2012) used the provisional upper level for phosphorus based on the EFSA opinion in 2005.

**Table 2.2.1-1** Overview of upper levels in adults set by various authorities.

| | UL/GL, mg/day | NOAEL mg/day | UF | Based on |
|---|---|---|---|---|
| **IOM, 1997** | 4000 (UL) | 10.2 g/day | 2.5 for adults and 3 for adolescents and children | Hyperphosphatemia |
| **EVM, 2003** | Guidance level (GL) 2400 and 250 mg/day for supplements | 750 mg/day for supplements | 3.0 for supplements | Safe intake = no gastrointestinal problems |
| **EFSA, 2005** | Data indicate upper level 3000 and 750 mg/day for supplements | | Not data to set a UL and no UF discussed | Safe intake = no gastrointestinal problems |
| **NNR, 2012** | 3000 | | | EFSA 2006 |

VKM suggests to use 3000 mg/day as a provisional upper level for the total intake of phosphorus for adults and 750 mg/day for supplemental phosphorus in accordance with the EFSA (2005) opinion. The suggested highest intake from supplements is in agreement with findings from clinical studies where osmotic diarrhoea and other mild gastrointestinal effects were found with an intake above 750 mg/day.

# 3 Intakes and scenarios

## 3.1 Short description of the Norwegian dietary surveys

The estimated intakes of phosphorus presented in this opinion are based on data from the national food consumption surveys in young children (2- and 4 year-olds), children and adolescents (9- and 13-year-olds) and adults (aged 18 to 70 years). The national food consumption surveys were conducted by the Department of Nutrition, University of Oslo in collaboration with the Directorate of Health, the Norwegian Food Safety Authority and the Norwegian Institute of Public Health. Different methodologies were used in the tree different surveys and direct comparisons between the age groups may be misleading.

A description of the food consumption surveys and the different methodologies used is given below.

Adults: "Norkost 3" is based on two 24-hour recalls by telephone at least one month apart. Food amounts were presented in household measures or estimated from photographs (Totland et al., 2012). The study was conducted in 2010/2011, and 1787 adults (925 women and 862 men) aged 18-70 participated.

9- and 13-year-old children/adolescents: "Ungkost 3" is based on a 4-day food intake registration with a web based food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 2016). The study was conducted in 2015 and 636 9-year-old children and 687 13-year-old adolescents participated.

4-year-old children: "Ungkost 3" is based on a 4-day food intake registration with a webbased food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 2017). The study was conducted in 2016, and 399 4-year-olds participated.

2-year-old children: "Småbarnskost 2007" is based on a semi-quantitative food frequency questionnaire. In addition to predefined household units, food amounts were also estimated from photographs. The study was conducted in 2007, and a total of 1674 2-year-olds participated (Kristiansen et al., 2009).

## 3.2 Dietary intakes of phosphorus in the Norwegian population

Intakes of phosphorus in the various age groups and in users of phosphorus containing dietary supplements are presented in tables in Appendix 1. The tables in Appendix 1 also include estimates for P25 and P75.

### In adults (n=1787)

The mean intake of phosphorus from the diet alone is 1725 mg/day (median 1643 mg/day) in adults (n=1787). The P5 intake is 883 mg/day and the P95 intake is 2855 mg/day.

Only five participants (0.3%) reported use of phosphorus-containing supplements. Their mean total intake of phosphorus including that from supplements is 1924 mg/day.

Mean intake of phosphorus from supplements alone in adults reporting use of phosphorus-containing supplements is 97 mg/day.

### In 13-year-olds (n=687)

The mean intake of phosphorus from the diet alone is 1361 mg/day (median 1282 mg/day) in 13-year-olds. The P5 intake is 677 mg/day and the P95 intake is 2257 mg/day. No 13-year olds reported use of phosphorus-containing supplements.

### In 9-year-olds (n=636)

The mean intake of phosphorus from the diet alone is 1304 mg/day (median 1276 mg/day) in 9-year-olds. The P5 intake is 733 mg/day and the P95 intake is 1996 mg/day. No 9-year olds reported use of phosphorus-containing supplements.

### In 4-year-olds (n=399)

The mean intake of phosphorus from the diet alone is 1120 mg/day (1115 mg/day) in 4-year-olds. The P5 intake is 641 mg/day and the P95 intake is 1662 mg/day. Only one 4-year old reported use of phosphorus-containing supplements.

### In 2-year-olds (n=1674)

The mean intake of phosphorus from the diet alone is 1102 mg/day (median 1062 mg/day) in 2-year-olds. The P5 intake is 580 mg/day and the P95 intake is 1787 mg/day. No 2-year olds reported use of phosphorus-containing supplements.

## 3.3 Scenario calculations for phosphorus

For scenario calculations VKM added the suggested supplementation levels from NFSA (1000, 2000 and 2500 per day) to the respective 5- and 95-percentiles of estimated intakes from food in the national food consumption surveys. The existing maximum limit for phosphorus in food supplements (1500 mg) has also been included, see Tables 3.3-1 and 3.3-2.

**Table 3.3-1** Calculated total phosphorus intakes for various age groups in scenarios with 1000, 1500, 2000 and 2500 mg as supplements added to the P5 of intake from food alone (mg/day).

| Age group | P5 from food | Including 1000 mg from suppl | Including 1500 mg from suppl | Including 2000 mg from suppl | Including 2500 mg from suppl |
|---|---|---|---|---|---|
| Adults | 883 | 1883 | 2383 | 2883 | 3383 |
| 13 years | 677 | 1677 | 2177 | 2677 | 3177 |
| 9 years | 733 | 1733 | 2233 | 2733 | 3233 |
| 4 years | 641 | 1641 | 2141 | 2641 | 3141 |
| 2 years | 580 | 1580 | 2080 | 2580 | 3080 |

**Table 3.3-2** Calculated total phosphorus intakes for various age groups in scenarios with 1000, 1500, 2000 and 2500 mg as supplements added to the P95 of intake from food alone (mg/day).

| Age group | P95 from food | Including 1000 mg from suppl | Including 1500 mg from suppl | Including 2000 mg from suppl | Including 2500 mg from suppl |
|---|---|---|---|---|---|
| Adults | 2855 | 3855 | 4355 | 4855 | 5355 |
| 13 years | 2257 | 3257 | 3757 | 4257 | 4757 |
| 9 years | 1996 | 2996 | 3496 | 3996 | 4496 |
| 4 years | 1662 | 2662 | 3162 | 3662 | 4162 |
| 2 years | 1787 | 2787 | 3287 | 3787 | 4287 |

# 4 Assessment of the intakes of phosphorus

## 4.1 Evaluation of phosphorus intakes, including scenarios with supplementation

Dietary calculations have been performed for intake in P5, P25, mean, P50, P75 and P95 in children (2-, 4 and 9-year-olds), adolescents (13-year-olds) and in adults (Appendix I).

In all subjects in all age groups the 5th percentile of phosphorus intake was close to the recommended intake for phosphorus (EFSA, 2015). In adults the provisional upper level for phosphorus of 3000 mg/day was almost reached at the 95th percentile of food intake alone (Figure 4.1-1).

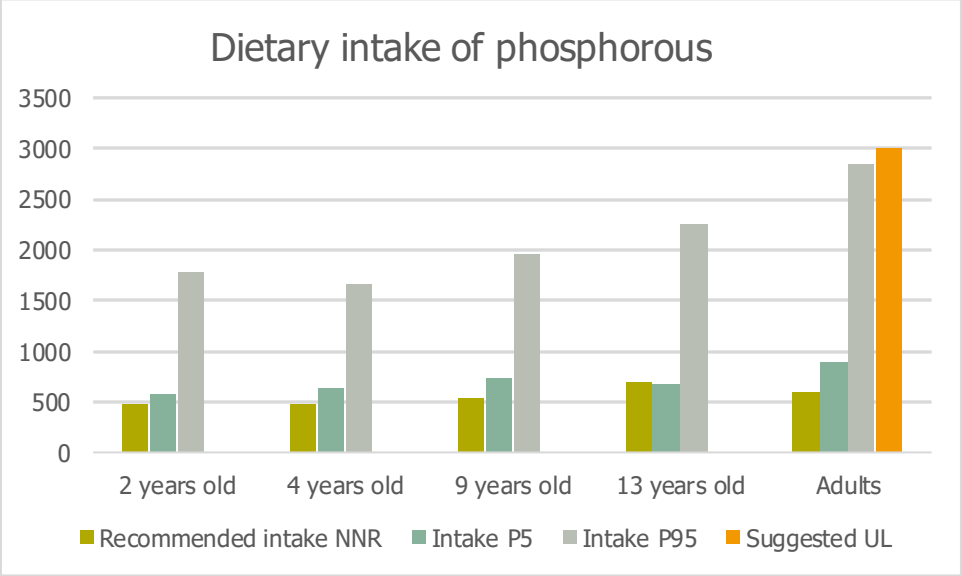


**Figure 4.1-1** Intake and recommendations of phosphorus.

To illustrate the consequences of phosphorus supplementation at high dietary intakes, the example doses 1000, 1500, 2000 and 2500 mg/day were added to the 95-percentile of phosphorus intake from diet alone for each age group. As illustrated in the scenarios (Table 3.3-2), the provisional upper level for phosphorus will be exceeded if a supplemented dose of 1000 mg phosphorus was given to the 95-percentile of intake in adults and adolescents.

All example doses 1000, 1500, 2000 and 2500 mg/day exceed the proposed upper level of 750 mg/day in dietary supplements proposed by EFSA (2005) as the supplement dose shown to cause gastrointestinal symptoms.

# 5 Uncertainties

For the determinations of the upper levels for phosphorus, IOM, EVM and EFSA have not reached the same conclusions, indicating uncertainty regarding establishment of these upper levels for adults, and have not mentioned upper levels for children and adolescents.

It should be noted that the intakes have been calculated based on various dietary surveys for the different age categories and a comparison of calculations across age groups can be misleading. The calculated intakes in the higher and lower percentiles are always associated with a higher degree of uncertainty than mean or median intakes.

The percentile estimates of dietary intake are prone to random error due to the limited number of participants in the dietary surveys. The largest degree of uncertainty is present in the estimated percentiles for 4-year-olds with a sample size of n=399, corresponding to about 20 observations below the 5-percentile and above the 95-percentile, respectively.

Another issue is the validity of the estimated exposure data. Low participation rates in the national dietary surveys give rise to systematic errors and limit the representativeness of the participants compared with the background population in Norway. The participation rates among adults, 13-, 9-, 4- and 2-year-olds in the dietary surveys were 37%, 53%, 55%, 20%, and 56%, respectively. In general, those participating had a considerably higher education level than the background population, and they are expected to represent a health-conscious subgroup of the population. Some population subgroups are not covered, e.g. ethnic minorities.

# 6 Answers to the terms of reference

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of phosphorus from the diet, including fortified products, in all age groups in the population above 1 year.

VKM is also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for phosphorus in food supplements to 1000, 2000 or 2500 mg/day, as examples.

Dietary phosphorus intake at P5, P25, mean, P50, P75 and P95 has been estimated for 2-, 4- and 9-year-olds, 13-year-olds and among adult men and women.

VKM proposes to use 3000 mg/day of phosphorus as a provisional upper level for total daily intake and to use 750 mg/day as upper level for supplemental phosphorus to assure no gastrointestinal adverse effects. All the suggested doses from NFSA exceed the upper level for supplemental phosphorus at 750 mg/day.

No suggestions for of an upper levels for children are given.

An overview of the conclusions is presented in Table 6-1.

**Table 6-1** An overview of the conclusions for phosphorus according to doses in supplements.
Grey: No ULs available in previous reports.
Red: Exceedance of the UL.

| Doses in supplements / Age group | 1000 mg/day | 1500 mg/day | 2000 mg/day | 2500 mg/day |
|---|---|---|---|---|
| **Adults** | | | | |
| **13 years** | NO ULs available for children and adolescents, but all doses exceed UL set for supplements for adults | | | |
| **9 years** | | | | |
| **4 years** | | | | |
| **2 years** | | | | |

# 7 Data gaps

Because of lack of studies, no ULs could be set for children and adolescents.

More age groups should be included in dietary surveys in addition to subgroups like different ethnical groups.

# 8 References


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# Appendix I

## Summary tables of phosphorus intake for all age groups

Intakes of phosphorus in the various age groups are presented in the tables below. The tables summarise intakes from the diet alone, phosphorus-containing supplements alone (users only) and total intakes from both diet and supplements (Tables 1-2).

**Table 1** Phosphorus intakes from diet alone in various age groups (mg/day).

| | Adults (n=1787) | 13 years (n= 687) | 9 years (n=636) | 4 years (n=399) | 2 years (n=1674) |
|---|---|---|---|---|---|
| **Phosphorus from diet alone, mean** | 1725 | 1361 | 1304 | 1120 | 1102 |
| **Phosphorus from diet alone, median** | 1643 | 1282 | 1276 | 1115 | 1062 |
| **Phosphorus from diet alone, P5** | 883 | 677 | 733 | 641 | 580 |
| **Phosphorus from diet alone, P25** | 1293 | 1022 | 1029 | 903 | 840 |
| **Phosphorus from diet alone, P75** | 2057 | 1658 | 1547 | 1313 | 1290 |
| **Phosphorus from diet alone, P95** | 2855 | 2257 | 1996 | 1662 | 1787 |

**Table 2** Phosphorus supplement users intake of total phosphorus from diet and supplements, and from supplements alone (users only), in adults (mg/day).

| | Adults (n=5) |
|---|---|
| **Total phosphorus from diet and supplements, mean** | 1924 |
| **Total phosphorus from diet and supplements, median** | 1517 |
| **Total phosphorus from diet and supplements, P5** | - |
| **Total phosphorus from diet and supplements, P25** | - |
| **Total phosphorus from diet and supplements, P75** | - |
| **Total phosphorus rom diet and supplements, P95** | - |
| **Phosphorus from supplements alone, mean** | 97 |
| **Phosphorus from supplements alone, median** | 13 |
| **Phosphorus from supplements alone, P5** | - |
| **Phosphorus from supplements alone, P25** | - |
| **Phosphorus from supplements alone, P75** | - |
| **Phosphorus from supplements alone, P95** | - |