Risk Assessment — Phosphorus

General information

Chemistry

Phosphorus is a group 5 element of the periodic table and has an atomic weight of 30.97. Within this risk assessment, the phosphorus refers to ionic phosphorus except where specific phosphorus compounds are mentioned.

Natural occurrence

Phosphorus is most commonly found in nature in its pentavalent form in combination with oxygen, as phosphate (PO_4^{3-}).

Occurrence in food, food supplements and medicines

Phosphorus is widely found in many food groups, largely as phosphate(s). Dietary sources that are rich in phosphorus include red meats (1600 mg/kg), dairy products (> 900 mg/kg), fish (4000 mg/kg), poultry (2100 mg/kg) and bread and other cereal products (> 900 mg/kg). A number of phosphate salts are used in foods and soft drinks as additives (JECFA, 1994). Phosphorus is also used in food supplements (at levels up to a daily dose of 1100 mg/day) and licensed medicines, in the form of inorganic phosphate salts and sodium acid phosphate, respectively.

Other sources of exposure

Phosphorus is present in fertilisers, detergents, sewage effluent and surface waters. The Drinking Water in the Water Supply (Water Quality) Regulations 1989 specify a limit of 2.2 mg phosphorus per litre drinking water.

Recommended amounts

COMA (1991) noted that phosphorus requirements are conventionally set as equal to calcium, in mass terms i.e. 1 mg phosphorus : 1 mg calcium. However, these elements are present in the body in equimolar amounts and COMA took the view that the ratio in the diet should be set at 1 mmol phosphorus: 1 mmol calcium and considered that the Recommended Nutrient Intake (RNI) for phosphorus should be set equal to the calcium RNI in molar terms (1 mmol calcium = 40 mg, 1 mmol phosphorus = 30.9 mg).

COMA therefore calculated a RNI of 550 mg/day of phosphorus for males and females aged 19-50 years. COMA derived an increment of 440 mg/day for women during lactation, giving a total of 990 mg/day. The RNI for infants and children ranges from 400 to 775 mg/day.

Analysis of tissue levels and phosphorus status

Phosphorus is abundant in the body with largest amounts found in bone. It is also found in all soft tissues including muscle, liver, heart and kidneys. Serum total phosphorus levels are measured by colorimetric methods.

Overview of non-nutritional beneficial effects

Treatment with oral or intravenous phosphate causes a decrease in serum calcium in hypercalcaemic adults. Thus, it has been reported to be useful in reducing hypercalcaemia and hypercalciuria. It is also used for the treatment of conditions of the bone, such as fractures, Paget's disease and multiple myeloma.

Function

Phosphorus is a constituent of all major classes of biochemical compounds. Structurally, phosphorus occurs as phospholipids, which are a major constituent of most biological membranes, and as nucleotides and nucleic acids. Phosphorus plays an important role in carbohydrate, fat and protein metabolism and is essential for optimum bone health. The energy that is required for most metabolic processes is derived from the phosphate bonds of adenosine triphosphate and other high energy phosphate compounds.

Clinical studies employing chronic phosphorus supplementation were the first to show that high phosphorus intakes influence the parathyroid-vitamin D axis, which maintains calcium balance in the body. The phosphorus loading in humans operates through mechanisms of nutritional or secondary hyperparathyroidism similar to those observed in animals fed excess phosphorus.

Deficiency

Factors associated with phosphorus deficiency (hypophosphatemia) include liver disease, sepsis, alcoholism, diabetic ketoacidosis and the use of aluminium-containing antacids. The symptoms of a potentially fatal syndrome include anorexia, anaemia, muscle weakness, bone pain, rickets and ataxia. Hypophosphatemia in infants is known to occur in situations of poorly managed parenteral nutrition with inappropriate administration of fluid and electrolyte therapy or with rapid refeeding after prolonged dietary restriction. Preliminary studies have indicated that phosphate deficiency at birth is associated with the development of rickets in later life.

Interactions

Phosphorus absorption is reduced by ingestion of aluminium-containing antacids and by pharmacological doses of calcium salts. High phosphate diets cause a reduction in the urinary excretion of calcium.

Absorption

Net absorption of phosphorus from a mixed diet has been reported to range from 55 to 70 % in adults and from 65 to 90% in infants and children. The intestinal absorption of phosphorus is greatest in the jejunum and decreases along the length of the small intestine.

Distribution and metabolism

Approximately 80% of the body phosphorus is present in the skeleton and the remainder is distributed in soft tissues and extracellular fluid. About 70% of the phosphorus in blood is as a constituent of phospholipids; the remainder is present as inorganic phosphate, about 85% free and 15% protein-bound. Parathyroid hormone (PTH) is the major regulator of the balance of phosphorus and calcium. Thus, a low calcium and high phosphate diet induces the secretion of PTH, which decreases the serum concentration of phosphate by increasing its urinary excretion.

Excretion

Phosphorus is primarily excreted in the urine. The regulation of phosphorus excretion is apparent from early infancy. In infants, as in adults, the major site for the regulation of the amount of phosphorus retained by the body is the kidney.

Toxicity

Human data

The majority of the published data relating to the toxicity of phosphorus in humans focus on accidental or intentional ingestion of the more toxic forms of phosphorus that are not found in food or food supplements (e.g. elemental yellow phosphorus).

No human data on chronic toxicity of dietary forms of phosphorus were identified in the literature.

Supplementation trials

The predominant adverse reaction to orally administered phosphorus (as various phosphate salts, including sodium, potassium, ammonium and glycerol) in human supplementation studies is osmotic diarrhoea, which has been reported at intakes of 750 mg/day and above. Other mild gastrointestinal effects, including nausea and vomiting have been noted in some studies.

Animal data

There are a limited number of studies on the oral toxicity of inorganic phosphate salts in experimental animals. Kidney lesions have been reported in rats following the administration of acute doses of phosphates (approximately 5000 mg/kg bw/day, equivalent to about 1200 mg/kg bw/day phosphorus). Pathological effects in the parathyroids, kidneys and bone have also been reported in subchronic studies at high doses (approximately 4000 mg/kg bw/day, equivalent to about 1000 mg/kg bw/day phosphorus).

No adverse effects on growth and reproduction were reported in an abstract report of long-term studies with phosphoric acid.

Carcinogenicity and genotoxicity

No data on carcinogenicity or genotoxicity of dietary forms of inorganic phosphorus and phosphate salts were identified.

Mechanism of toxicity

No relevant data have been identified.

Dose-response characterisation

Data from human trials indicate a dose-related increase in osmotic diarrhoea from intakes of 750 mg/day and above.

Vulnerable groups

One study suggested that increased phosphorus intake may lead to increased bone resorption in postmenopausal women with osteoporosis (Goldsmith *et al*., 1976). However, a more recent study in postmenopausal women found no biochemical evidence of increased bone remodelling as a result of supplementation with phosphorus (Brixen *et al*., 1992).

Black and Asian people and older people may be susceptible to bone resorption as a result of high phosphorus intakes, as they are more susceptible to hypovitaminosis D, which decreases the absorption of calcium, and phosphorus has been shown to influence the parathyroid-vitamin D axis, causing an increase in serum calcium levels via bone resorption.

Genetic variations

No genetic variations conferring vulnerability to phosphate toxicity have been identified.

Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD)

Human data

Goldsmith et al., 1968

This was a study of the role of phosphate as an adjunct in the therapy of multiple myeloma. Phosphate supplements (given as mixtures of sodium and potassium salts and providing a daily dose of approximately 1000 to 2000 mg phosphorus) were given to 14 patients orally for up to 15 months, or intravenously (duration not stated). Reductions in bone pain and urinary calcium were reported by the authors. None of the patients developed any evidence of extra-skeletal calcification during follow-up periods of up to 15 months. One patient developed an increase in pedal and pretibial oedema, which subsided when the phosphate salts were discontinued. Another patient complained of dyspepsia

following the ingestion of phosphate supplements, although the same subject reported similar discomforts with other medications including placebo.

Brixen et al., 1992

This was a study of the effect of a short course of oral phosphate treatment on serum parathyroid hormone levels and markers of bone turnover. A group of postmenopausal women with reduced bone mineral density and a history of at least one fracture were randomised in a double-blind study and given oral phosphate (providing 750, 1500 or 2250 mg/day phosphorus) or placebo for 7 days; the subjects were followed for 4 months thereafter. The phosphate was administered as effervescent tablets containing a mixture of ammonium phosphate, potassium phosphate and glycerol phosphate. The urinary phosphate/creatinine ratio increased in a dose-related fashion whereas no significant changes were seen in serum phosphate or serum calcium. Serum parathyroid hormone rose significantly in the groups receiving 1500 and 2250 mg/day phosphorus. No effect on serum parathyroid hormone levels could be demonstrated with the lowest dose of phosphorus. Gastrointestinal side effects were noted in a dose-related fashion in 2 of 19 patients receiving 750 mg/day, in 3 of 19 patients receiving 1500 mg/day and in 7 of 20 patients receiving 2250 mg/day.

Whybro et al., 1998

This was a report of two studies carried out to test the effect of supplementation with phosphate on calcium homeostasis and bone turnover. Study 1 was a 1-week, randomised, controlled cross-over trial involving 10 healthy men supplemented with 1000 mg phosphorus (as sodium acid phosphate). The control diet for these men contained 800 mg/day of calcium and 800 mg/day of phosphorus. Study 2 (involving 12 healthy men) was an escalating dose study of 0, 1000, 1500 and 2000 mg/day phosphorus, given as phosphate for 1 week. The control diet contained 1000 mg/day of calcium and 1000 mg/day of phosphorus as phosphates. Both studies showed an increase in the urinary excretion of phosphate and a decrease in urinary calcium. Serum levels of parathyroid hormone were only elevated in the first study. There were no changes in serum phosphate, osteocalcin or urinary N-telopeptide. Diarrhoea was reported in one subject in study 2 when receiving phosphorus at 2000 mg/day.

Exposure assessment

Food:	Mean: 1260 mg/day (NDNS 1986/7) 97.5th percentile: 2110 mg/day
Drinking water:	4.4 mg/day (assuming 2 L/day at maximum level of 2.2 mg/L)
Supplements:	up to 1100 mg/day (Annex 4)
Estimated maximum daily intake:	2110 + 4.4 +1100 = 3200 mg

No potential high intake groups have been identified.

Risk assessment

In humans, changes in serum parathyroid hormone levels have been reported in supplementation studies in postmenopausal women with reduced bone mineral density and a history of fracture and in healthy men. Osmotic diarrhoea and other mild gastrointestinal symptoms have also been reported in supplementation studies. However, these symptoms were only reported in a limited number of studies.

There are limited data on the oral and general toxicity of inorganic phosphate salts in animals. Pathological effects in the parathyroid gland, kidneys and bones have been observed in mature male rats fed a diet containing an excessively high level of sodium orthophosphate for 7 months. No adverse effects on growth and reproduction were reported in long-term studies with phosphoric acid.

ESTABLISHMENT OF GUIDANCE LEVEL

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. The osmotic diarrhoea reported in these supplementation studies was mild and reversible in nature. In addition, physiological changes in calcium and parathyroid hormone levels have been associated with intakes of 1500 mg/day and above of supplemental phosphorus. Because persons with hypovitaminosis D are vulnerable to hyperparathyroidism, an uncertainty factor of 3 has been 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 would be expected not to produce adverse effects, including mild gastrointestinal upset. This is equivalent to 4.2 mg/kg bw in a 60 kg adult. Assuming a maximum intake of 2100 mg/day from food and water, an estimated total intake of 2400 mg/day (equivalent to 40 mg/kg bw/day in a 60 kg adult) would not be expected to result in any adverse effects.

References

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