Brief profiles on systemic toxicological effects of common counter-ions in metal substances:

10.Phosphate

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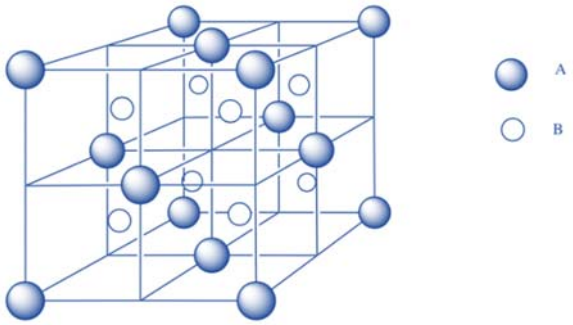

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Phosphate: Brief profile on systemic toxicological effects

For information on background, scope and use of this document, see accompanying cover-note!

1. Identification

Name: phosphate (anion)
Chemical formula: PO_4^{3-}
Molecular mass: 94.97 g/mol

2. Introductory remarks

As an ion, phosphate is not a substance under REACH, so that toxicological information is not available on the ion on its own. Phosphate is a common anion in salts of cationic metals. The aim of this summary on the systemic toxicity of phosphate is to assist the assessor of health hazards of phosphate containing substances, in determining whether the phosphate moiety contributes to the overall toxicity of the substance. This document does not discuss primary literature or studies in great detail. Instead, reference is made to most recently published authoritative reviews, such as from the European Food Safety Authority. Unless stated otherwise, EFSA (2019) is the source of the information summarised in this document.

3. Natural occurrence, physiological function and dietary intake

Phosphate is a naturally occurring anion which is abundantly present in the environment and in the human body. It is essential for all living organisms. In humans, the intracellular activity of phosphate ions participates in the acid base balance. Phosphate is intrinsically involved with regulation of metabolic processes via phosphorylation of proteins and supplying energy by means of nucleotides triphosphates (e.g. ATP, GTP, CTP and UTP) which serve as energy depots supporting protein and polysaccharide synthesis, ion pumps, cell signalling, muscle contractility. Phosphate is also component of second messengers such as cyclic adenosine monophosphate (cAMP), inositol polyphosphates (IP3) and cyclic guanine monophosphate (cGMP). Phosphate is further fundamental for the structure and function of DNA and ribonucleic acid (RNA).

Phosphates and polyphosphates are both naturally present in food, as well as being added to a wide range of food items as food additives (e.g. E 338–341, E 343, E 450–452). EFSA (2019) has summarised dietary exposures, as presented in the following table. This exposure assessment includes all sources of phosphorous in the diet, i.e. naturally contained phosphorous, the food additives named above and other further phosphorous containing additive.

Table 10b: Summary of dietary exposure to phosphorus from the diet,* in seven population groups (minimum–maximum across the dietary surveys in mg P/kg bw per day)

	Infants (< 16 weeks)	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
• Mean	64	32–85	55–74	33–62	18–33	16–22	16–20
• 95th percentile	83	56–106	85–123	55–92	31–56	25–36	24–35

bw: body weight.
*: Using analytical data except for chewing-gum (FC 05.3) and sugars and syrups (FC 11.1).

Source for table: EFSA (2019)

4. Toxicokinetics

Phosphate is well absorbed mainly as free orthophosphate mostly in the small intestine with amounts ranging between 55 and 90%. Intestinal absorption occurs by passive diffusion and sodium-dependent active transport and may be limited by the calcium content of the diet. The whole human body phosphorous content is 500–700 g. Fifteen percent of the phosphate in the body is involved in the above-mention ed metabolic function and control, whereas the largest pool of phosphates (approximately 85%) is found together with calcium in the skeleton. Excretion is via the kidney through glomerular filtration and tubular handling.

5. Toxicological effects

EFSA (2019) has reviewed toxicology data on most of the phosphates used as food additives (e.g. phosphoric acid, magnesium-, sodium- and potassium mono-, di- and tri-phosphates). The cations of these phosphates are constituents of human tissues that occur naturally in food stuffs, and intake of them does not cause adverse human health effects, providing that the intake is not so high as to disturb the homeostatic mechanisms controlling the electrolyte balance of the body. Therefore, the toxicity of these cations is not discussed in the EFSA opinion.

5.1. Acute toxicity

Studies are available on all phosphates evaluated by EFSA as food additives. Overall, the acute oral toxicity of phosphates is very low with LD_{50} values generally exceeding 2,000 mg/$kg_{bw.}$

5.2. Sensitisation

No specific studies relating to sensitisation of phosphates could be found in a quick search, and this topic is not addressed by EFSA (2019), nor by other publicly available reviews on phosphates. Phosphate is a naturally occurring anion which is abundantly present in the environment and in the human body. It is essential for all living organism. Many phosphates are approved for use in various applications, from food additives to use in cosmetics, cleaners and detergents and in fertilisers. Phosphate buffered saline is a commonly used buffer solution in biological research and is used for example in the local lymph node assay as a vehicle to inject a tritiated marker into the mice, and also to wash and store excised lymph nodes. In consideration of the above, there is no reason to assume that sensitisation is of any concern for phosphate.

5.3. Repeated dose toxicity

Short-term and sub-chronic toxicology studies with most of the phosphates under EFSA evaluation are available, often in rats or dogs. Few chronic animal toxicity or carcinogenicity studies are available. EFSA has further reviewed a comprehensive database of human data on the effects of phosphates on cardiovascular health, kidney, the gastrointestinal tract and bone health. Considering all available information, EFSA concluded that the critical adverse effect of phosphates is kidney calcification. The Panel noted that the highest reliable NOAEL for kidney effects of 116 mg P/kg_{bw}/d, was identified in a 90-day rat study with tetrasodium diphosphates performed according to OECD guidelines (Seo et al., 2011). In the same study, a dose of 1,000 mg/kg_{bw}/d of this test item, corresponding 233 mg P/kg_{bw}/d was demonstrated to induce effects in the kidney, thus being the LOAEL. However, since this study was only a sub-chronic study, EFSA concluded that the most suitable point of departure for deriving an ADI was the lowest NOAEL from a chronic study, which was conducted in rats with sodium hexametaphosphate (Hodge, 1960). Based on treatment related kidney calcification and reduced body weight gain, the NOAEL in this chronic study was 250 mg/kg_{bw}/d sodium hexametaphosphate, corresponding to 76 mg/kg_{bw}/d phosphorus.

In the context of their opinion, the EFSA Panel was in the special situation to assess the safety of food additives, phosphate salts, while phosphate is also an essential nutrient already naturally present in food. EFSA therefore considered that the derivation of an ADI should also consider the phosphate intake with

the base diet of the rats. However, this data was not available for the 1960 study by Hodge. Instead EFSA used the phosphorous content of the base rat diet that was used in a recent OECD guideline compliant 90-day oral toxicity study with tetrasodium diphosphate (Seo et al., 2011; information on the diet obtained by EFSA via personal communication from Cargill Agri Purina Korea, 29 January 2019). Based on this information, it was estimated that the rats received 91 mg P/kg_{bw}/d with the bases diet. The EFSA Panel considered the content of phosphorus retrieved for the Seo et al. study as an appropriate estimate of a standard animal diet which is also in conformity with the phosphorus content in laboratory animal diets from different sources.

This dose of phosphorous received with the base diet was added to the NOAEL of 76 mg P/kg_{bw}/d, resulting in 167 mg P/ kg_{bw}/d. To this value, a chemical-specific adjustment factor for phosphate of 4 is applied resulting in an ADI value of 42 mg P/kg_{bw}/d, rounded to 40 mg P/kg_{bw}/d (for details on the adjustment factor, see also EFSA, 2019).

5.4. Mutagenicity/genotoxicity

Phosphoric acid, phosphates, diphosphates, triphosphates and polyphosphates have been tested for genotoxicity in a variety of in vitro and in vivo assays. In neither in vitro nor in vivo assays did any of the tested phosphates produce a positive response. The EFSA Panel concluded that available data clearly show that phosphate is not genotoxic in standard test systems (EFSA, 2019).

5.5. Reproductive toxicity

There are a number of studies, although generally not conducted according to current OECD guidelines, evaluating reproductive and developmental toxicity of the phosphates under evaluation by EFSA (2019). In oral studies performed in mice, rats, rabbits or hamsters, there are no signs of reproductive or developmental toxicity at any dose tested. The EFSA Panel thus concluded that exposure to phosphates do not present any risk for reproductive or developmental toxicity (EFSA, 2019).

5.6. Carcinogenicity

There are three 2-year carcinogenicity studies in rats available, one with sodium triphosphate and two with sodium polyphosphate. There was no relationship between treatment with the phosphates and tumour development in any of the studies. The EFSA Panel thus concluded that phosphates do not have any carcinogenic potential (EFSA, 2019).

6. Discussion and conclusion

Kidney calcification has been identified as the critical adverse systemic effects of excess exposure to phosphates. EFSA has established an acceptable daily intake of phosphate of 40 mg P/kg_{bw}/d. However, for example considering the natural food content of phosphate, according to exposure scenarios considered by EFSA, this ADI may potentially be exceeded in infants, children and adolescents up to 17 years of age, although usually not in adults (e.g. in workers) (EFSA, 2019).

Phosphate "in a nutshell":

Key / leading adverse systemic effect on human health:	Kidney calcification
Relevant (CLP) Hazard Classification(s) for systemic effects:	None
Numerical toxicological descriptor	ADI by EFSA (2019): 40 mg P/kg_{bw}/d Corresponding to ca. 123 mg PO_4^{3-}/kg_{bw}/d

References

EFSA (2019): FAF Panel (EFSA Panel on Food Additives and Flavourings): Scientific Opinion on the re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives and the safety of proposed extension of use. EFSA Journal 2019;17 (6):5674, 156 pp. https://doi.org/10.2903/j.efsa.2019.5674

Hodge (1960): Unpublished report. Chronic oral Toxicity Studies in Rats of Sodium Hexametaphosphate. Department of Pharmacology, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Seo et al. (2011): DS, Kwon M, Sung HJ and Park CB: Acute oral or dermal and repeated dose 90-day oral toxicity of tetrasodium pyrophosphate in Sprague Dawley (SD) Rats. Environmental Health and Toxicology, 26, e2011014. https://doi.org/10.5620/eht.2011.26.e2011014