SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 4 June 2019*

doi: 10.2903/j.efsa.2019.5674

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

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Abstract

The Panel on Food Additives and Flavourings added to Food (FAF) provided a scientific opinion re-evaluating the safety of phosphates (E 338–341, E 343, E 450–452) as food additives. The Panel considered that adequate exposure and toxicity data were available. Phosphates are authorised food additives in the EU in accordance with Annex II and III to Regulation (EC) No 1333/2008. Exposure to phosphates from the whole diet was estimated using mainly analytical data. The values ranged from 251 mg P/person per day in infants to 1,625 mg P/person per day for adults, and the high exposure (95th percentile) from 331 mg P/person per day in infants to 2,728 mg P/person per day for adults. Phosphate is essential for all living organisms, is absorbed at 80–90% as free orthophosphate excreted via the kidney. The Panel considered phosphates to be of low acute oral toxicity and there is no concern with respect to genotoxicity and carcinogenicity. No effects were reported in developmental toxicity studies. The Panel derived a group acceptable daily intake (ADI) for phosphates expressed as phosphorus of 40 mg/kg body weight (bw) per day and concluded that this ADI is protective for the human population. The Panel noted that in the estimated exposure scenario based on analytical data exposure estimates exceeded the proposed ADI for infants, toddlers and other children at the mean level, and for infants, toddlers, children and adolescents at the 95th percentile. The Panel also noted that phosphates exposure by food supplements exceeds the proposed ADI. The Panel concluded that the available data did not give rise to safety concerns in infants below 16 weeks of age consuming formula and food for medical purposes.

Keywords: phosphates, phosphorus, food additive, acceptable daily intake, risk assessment, safety

Requestor: European Commission

Question numbers: EFSA-Q-2011-00532; EFSA-Q-2011-00533; EFSA-Q-2011-00534; EFSA-Q-2011-00535; EFSA-Q-2011-00536; EFSA-Q-2011-00537; EFSA-Q-2011-00538; EFSA-Q-2011-00539; EFSA-Q-2011-00540; EFSA-Q-2011-00541; EFSA-Q-2011-00542; EFSA-Q-2011-00543; EFSA-Q-2011-00618; EFSA-Q-2011-00619; EFSA-Q-2011-00620; EFSA-Q-2011-00621; EFSA-Q-2011-00622; EFSA-Q-2011-00623; EFSA-Q-2011-00624; EFSA-Q-2011-00625; EFSA-Q-2011-00626; EFSA-Q-2011-00628; EFSA-Q-2011-00629; EFSA-Q-2011-00630; EFSA-Q-2018-00597.

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* This opinion was first adopted by the FAF Panel on 27 March 2019, as reflected in the minutes of the FAF Panel Plenary Meeting of 27–29 March 2019: http://www.efsa.europa.eu/sites/default/files/event/190326-m.pdf. However, the adopted version was withdrawn prior to publication and the current version was adopted by the FAF Panel on 4 June 2019.

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Acknowledgements: The Panel wishes to thank Dominique Turck, Agnès de Sesmaisons-Lecarré and Valeriu Curtui for the support provided to this scientific output. The ANS Panel wishes to acknowledge all European competent institutions, Member State bodies and other organisations that provided data for this scientific output.

Suggested citation: EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Frutos Fernandez MJ, Fürst P, Gürtler R, Husøy T, Mennes W, Moldeus P, Oskarsson A, Shah R, Waalkens-Berendsen I, Wölfle D, Aggett P, Cupisti A, Fortes C, Kuhnle G, Lillegaard IT, Scotter M, Giarola A, Rincon A, Tard A and Gundert-Remy U, 2019. 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

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

The present opinion document deals with the re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) when used as a food additive.

Phosphates are authorised food additives in the European Union (EU) in accordance with Annex II and III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012. E 338, E 339, E 340 and E 341 are also authorised in food category 13.1 foods for infants and young children.

Phosphates have been previously evaluated by the EU Scientific Committee on Food (SCF, 1978, 1991, 1994, 1997) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1974, 1982a,b, 2002). JECFA concluded that the allocation of an acceptable daily intake (ADI) was not appropriate for phosphates 'as phosphorus is an essential nutrient and unavoidable constituent of food' and it was decided, therefore, to assign a 'maximum tolerable daily intake' (MTDI) rather than an ADI. The MTDI allocated was 70 mg/kg body weight (bw) per day (expressed as phosphorus) for the sum of phosphates and polyphosphates, both naturally present in food and ingested as food additives (JECFA, 1982a). The SCF subsequently agreed with the JECFA MTDI estimate for phosphates and assigned the cations an ADI 'not specified' as they are natural constituents of man, animals and plants (SCF, 1991).

The Expert Group on Vitamins and Minerals (EVM) further concluded that a total intake of 2,400 mg/day (considering 2,110 mg/day inorganic phosphorus from food including food additives and water and 250 mg/day from supplemental phosphorus) does not result in any adverse effects (Expert Group on Vitamins and Minerals, 2003).

In the EFSA NDA Opinion on Tolerable Upper Intake level of phosphorus, the upper level for phosphorus was not established because available data were not sufficient and indicate that normal healthy adults can tolerate phosphorus (phosphates) intake up to at least 3,000 mg/day without adverse systemic effects (EFSA NDA Panel, 2005).

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (VKM) published an assessment of dietary intake of phosphorus in relation to tolerable upper intake levels suggesting 3,000 mg/day as provisional upper level (UL) for total phosphorus intake in adults and 750 mg/day as UL for supplements (VKM, 2017).

Phosphate is essential for all living organisms. Inorganic phosphate used as food additives assessed in this opinion is assumed to dissociate in the gastrointestinal tract. The inorganic phosphorus deriving from food additives is mainly absorbed in the amount of approximately 80–90% as free orthophosphate. Excretion is via the kidney through glomerular filtration and tubular handling.

The Panel considered phosphates to be of low acute oral toxicity and there is no concern with respect to genotoxicity and carcinogenicity.

In standard short-term, subchronic and chronic toxicity studies, the only significant adverse effect of phosphates is calcification of the kidney and tubular nephropathy. In the chronic rat study with sodium triphosphate, the no-observable-adverse-effect level (NOAEL) was 76 mg/kg bw per day phosphorus (Hodge, 1960). Adding the background dietary phosphorus of 91 mg/kg bw per day to the NOAEL of 76 mg P/kg bw per day gives a total value of 167 mg P/kg bw per day.

In studies performed in mice, rats, rabbits or hamsters, there are no signs of reproductive or developmental toxicity at any dose tested. The Panel thus concluded that exposure to phosphates do not present any risk for reproductive or developmental toxicity.

The epidemiological studies reviewed did not find consistent associations between dietary phosphorous intake and cardiovascular-related outcomes and do not provide sufficient and reliable data to assess the role of phosphate on bone health.

Clinical interventional trials in which the doses were given on top of the normal diet were performed over several months. No impairment of the renal function was reported with daily doses up to 2,000 mg phosphorus (28.6 mg/kg per day), whereas doses of 4,800 mg/day (68.6 mg/kg per day) elicited renal impairment. Histopathological examinations of human kidney specimens from exposed patients showed similar findings as seen in animals. In several of the studies using phosphorus doses up to 2,000 mg/day, the subjects had soft stools or diarrhoea which is not to be seen as adverse but is classified as discomfort. However, when higher doses are given, such as the doses for bowel cleansing in preparation for colonoscopy (e.g. 11,600 mg/kg or 165.7 mg/kg bw) these doses acted as a cathartic agent and this effect has to be clearly seen as adverse.

Several case reports indicate that a high acute single dose of phosphate (160 mg/kg bw and more) can induce renal impairment.

The evidence from epidemiological and human interventional studies is not suited to derive an ADI. The Panel therefore selected the 167 mg P/kg bw per day NOAEL identified by Hodge (1960) as the basis to derive the ADI. The chemical-specific adjustment factor for phosphate accounting for interspecies and interindividual differences in toxicokinetics (TK) and toxicodynamics (TD) is $2 \times 2 = 4$. To this value, the phosphorus-specific uncertainty factor of 4 is to be applied resulting in an ADI value of 42 mg/kg bw per day, rounded to 40 mg/kg bw per day.

Currently, phosphates (E 338–341, E 343, E 450–452) are authorised food additives in the EU with maximum permitted levels (MPLs) ranging from 500 to 20,000 mg/kg in 104 authorised uses and at *quantum satis* (QS) in four.

To assess the dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives, the exposure was calculated based on two different sets of concentration data: (1) MPLs as set down in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario*).

While analytical data were used to consider the exposure to phosphorus from all dietary sources.

In the context of this opinion, the Panel was in the special situation to assess the safety of food additives, phosphate salts, which are also nutrients. The Panel based its assessment on the toxicity of phosphorus (phosphate moiety). Since the ADI encompasses the phosphorus intake from natural sources and from food additives sources, the usual exposure assessment using the reported use levels of the food additives was not appropriate to characterise the risk linked to the exposure to phosphorus and the exposure assessment was based on analytical data of the total phosphorus content of foods. In this scenario, the exposure exceeds the ADI of 40 mg/kg bw per day in infants from 12 weeks to 11 months, toddlers and children both at the mean and high level. In adolescents, the high level is also exceeding the ADI of 40 mg/kg bw per day.

Based on the reported use levels, the Panel calculated two refined exposure estimates: a *brand-loyal consumer scenario* and a *non-brand-loyal scenario*. The Panel considered that the refined exposure assessment approach resulted in more realistic long-term exposure estimates and that the refined non-brand loyal scenario is the most relevant exposure scenario for the safety evaluation of phosphates. In the *non-brand-loyal exposure assessment scenario*, estimated exposure to phosphates ranged between 1 and 48 mg P/kg bw per day at the mean and between 3 and 62 mg P/kg bw per day at the 95th percentile for all population groups.

The derived ADI 40 mg P/kg bw per day results in a exposure to phosphorus of 2,800 mg/person per day for an adult of 70 kg which is within the safety level of exposure of 3,000 mg/person per day set by the EFSA NDA Panel (2005).

The Panel concluded that the group ADI of 40 mg/kg bw per day, expressed as phosphorus, is protective for healthy adults because it is below the doses at which clinically relevant adverse effects were reported in short-term and long-term studies in humans. However, this ADI does not apply to humans with moderate to severe reduction in renal function. Ten per cent of general population might have chronic kidney disease with reduced renal function and they may not tolerate the amount of P per day which is at the level of ADI.

The Panel noted that in the exposure estimates based on analytical data exceeded the proposed ADI for infants, toddlers and children at the mean level and for infants, toddlers, children and adolescents at the 95th percentile. The Panel also noted that P exposure from food supplements exceeds the proposed ADI.

The Panel concluded that the available data did not give rise to safety concerns in infants below 16 weeks of age consuming formula and food for medical purposes. When receiving data on the content of contaminants in formula, the Panel noted that the high aluminium content may exceed the tolerable weekly intake (TWI).

The Panel recommends that:

- The EC considers setting numerical Maximum Permitted Level for phosphates as food additives in food supplements.
- The European Commission considers revising the current limits for toxic elements (Pb, Cd, As and Hg) in the EU specifications for phosphates (E 338–341, E 343, E 450–452) in order to ensure that phosphates (E 338–341, E 343, E 450–452) as a food additive will not be a significant source of exposure to those toxic elements in food.
- The European Commission considers revising the current limit for aluminium in the EU specifications for the use of calcium phosphate (E 341).

- The European Commission to consider revising the current EU specifications for calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and calcium dihydrogen diphosphate (E 450(vii)) to include characterisation of particle size distribution using appropriate statistical descriptors (e.g. range, median, quartiles) as well as the percentage (in number and by mass) of particles in the nanoscale (with at least one dimension < 100 nm) present in calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and calcium dihydrogen diphosphate (E 450(vii)) used as a food additive. The measuring methodology applied should comply with the EFSA Guidance document (EFSA Scientific Committee, 2018).
- The development of analytical methods for the determination of phosphate additives in the range of foods and beverages permitted to contain them should be considered.
- The EFSA Scientific Committee reviews current approaches to the setting of health-based guidance values for regulated substances which are also nutrients to assess if a coherent harmonised strategy for such risk assessments should be devised.