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Safety assessment of the substance phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters for use in food contact materials

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), Vittorio Silano, Claudia Bolognesi, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Wim Mennes, Maria Rosaria Milana, André Penninks, Andrew Smith, Maria de Fátima Tavares Poças, Christina Tlustos, Detlef Wölfle, Holger Zorn, Corina-Aurelia Zugravu, Martine Kolf-Clauw, Eugenia Lampi, Kettil Svensson, Eric Barthélémy and Laurence Castle

Abstract

This scientific opinion of the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) deals with the safety assessment of the substance phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters. The substance was evaluated by the CEF Panel in 2011 and 2,4-di-*tert*-amylphenol, an impurity and hydrolysis product was re-evaluated by the CEF Panel in 2015. In this application, the applicant requested an increase of the specific migration limit of the substance, currently established at 5 mg/kg food, to 10 mg/kg food, and provided new toxicological studies. Findings from three new *in vitro* mutagenicity assays on the oxidation products support the conclusion from 2011 that the substance and its oxidation products are not genotoxic. A new toxicokinetic study on the substance supports the consideration from the evaluation in 2011 that the substance does not raise concern for accumulation. The outcome of a new delayed neurotoxicity study on a structurally related substance, phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester, which was considered not to cause neurotoxicity in hens, strengthens the conclusion of the Panel in 2011 that the substance does not represent a concern for neurotoxicity. From a new two-generation reproduction toxicity study and a prenatal developmental toxicity study on the substance, a new subchronic toxicity study on its oxidation products that completes the one submitted in 2011 on the substance itself, and a 2-year oral toxicity study on the structurally related substance, the lowest NOAEL was 58–147 mg/kg bw per day (from the 2-year oral toxicity study). Compared to the requested increase of the migration limit, this gives an acceptable margin of safety of 348. Therefore, the CEF Panel concluded that an increase of the specific migration limit of the substance from 5 to 10 mg/kg food is not a safety concern for the consumer.

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Keywords: phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters, CAS number 939402-02-5, FCM substance No 974, food contact materials, safety assessment, evaluation

Requestor: Food Standards Agency, United Kingdom

Question number: EFSA-Q-2016-00006

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Panel members: Claudia Bolognesi, Laurence Castle, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Wim Mennes, Maria Rosaria Milana, André Penninks, Vittorio Silano, Andrew Smith, Maria de Fátima Tavares Poças, Christina Tlustos, Detlef Wölfle, Holger Zorn and Corina-Aurelia Zugravu.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Before a substance is authorised to be used in food contact materials (FCM) and included in a positive list, EFSA's opinion on its safety is required. This procedure has been established in Articles 8, 9 and 10 of Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food.

According to this procedure, the industry submits applications to the Member States' competent authorities which transmit the applications to the European Food Safety Authority (EFSA) for their evaluation.

In this case, EFSA received an application from Food Standards Agency, the United Kingdom, requesting a re-evaluation of the substance phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters, with the CAS number 939402-02-5, the PM Ref. No 74050 and the FCM substance No 974. The dossier was submitted on behalf of Addivant.

According to Regulation (EC) No 1935/2004 of the European Parliament and of the Council on materials and articles intended to come into contact with food, EFSA is asked to carry out an assessment of the risks related to the intended use of the substance and to deliver a scientific opinion.

2. Data and methodologies

2.1. Data

The applicant has submitted a dossier in support of their application for a revision of the authorisation of phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters, to be used in FCM. Data submitted and used for the evaluation are:

Non-toxicological data and information:

- Chemical identity
- Intended use
- Existing authorisation(s).

Toxicological data:

- Bacterial gene mutation test on the phosphate form of the substance
- *In vitro* mammalian cell gene mutation test on the phosphate form of the substance
- *In vitro* mammalian chromosome aberration test on the phosphate form of the substance
- 91-day oral toxicity study in rats on the phosphate form of the substance
- Two-generation reproduction toxicity study on the substance (phosphite form)
- Prenatal development toxicity study on the substance (phosphite form)
- ADME on the substance (phosphite form)
- ADME on a structurally related substance (phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester)
- Delayed neurotoxicity study in hens on a structurally related substance (phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester)
- Combined chronic/carcinogenicity oral rat study on a structurally related substance (phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester).

2.2. Methodologies

The assessment was conducted in line with the principles laid down in Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food. This Regulation underlines that applicants may consult the Guidelines of the Scientific Committee on Food (SCF) for the presentation of an application for safety assessment of a substance to be used in FCM prior to its authorisation (European Commission, 2001), including the corresponding data requirements. The dossier that the applicant submitted for evaluation was in line with the SCF guidelines (European Commission, 2001).

The methodology is based on the characterisation of the substance(s) that is subject of the request for safety assessment prior to authorisation, its impurities and reaction and degradation products, the evaluation of the exposure to those substances through migration, and the definition of minimum sets of toxicity data required for safety assessment.

To establish the safety from ingestion of migrating substances, the toxicological data indicating the potential hazard and the likely human exposure data need to be combined. Exposure is estimated from studies on migration into food or food simulants and considering that a person may consume daily up to 1 kg of food in contact with the relevant FCM.

As a general rule, the greater the exposure through migration, the more toxicological data is required for the safety assessment of a substance. Currently, there are three tiers with different thresholds triggering the need for more toxicological information as follows:

- a) In case of high migration (i.e. 5–60 mg/kg food), an extensive data set is needed.
- b) In case of migration between 0.05 and 5 mg/kg food, a reduced data set may suffice.
- c) In case of low migration (i.e. < 0.05 mg/kg food), only a limited data set is needed.

More detailed information on the required data is available in the SCF guidelines (European Commission, 2001).

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA, 2009) and considering the relevant existing guidance from the EFSA Scientific Committee.

3. Assessment

The substance phosphorous acid mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters was evaluated for its use as an antioxidant in all polymers by the CEF Panel in 2011 (EFSA CEF Panel, 2011). The CEF Panel concluded that the substance is not of concern if its migration does not exceed 5 mg/kg food (expressed as the sum of the phosphite and phosphate forms of the substance and the hydrolysis product 4-*tert*-amylphenol). The Panel also concluded that migration of the hydrolysis product 2,4-di-*tert*-amylphenol should not exceed 0.05 mg/kg food.

In 2015, the CEF Panel re-evaluated 2,4-di-*tert*-amylphenol, impurity and hydrolysis product of the substance, and concluded that it is not a safety concern for the consumer if its migration does not exceed 1 mg/kg food and it is included in the existing 5 mg/kg food restriction for the phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters (EFSA CEF Panel, 2015). It was proposed to express the restriction of phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters as the sum of the phosphite and phosphate forms of the substance, 4-*tert*-amylphenol and 2,4-di-*tert*-amylphenol; in addition the migration of 2,4-di-*tert*-amylphenol should not exceed 1 mg/kg food.

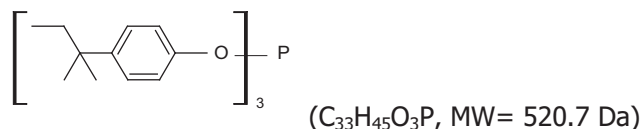
In this application, the applicant requests a re-evaluation of the specific migration limit (SML) for phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters, currently established at 5 mg/kg food, with a view to increase it to 10 mg/kg food. The final plastics containing the antioxidant are intended to come into contact with all types of food for short term contact at high temperatures and long term storage at or below room temperature.

3.1. Non-toxicological data

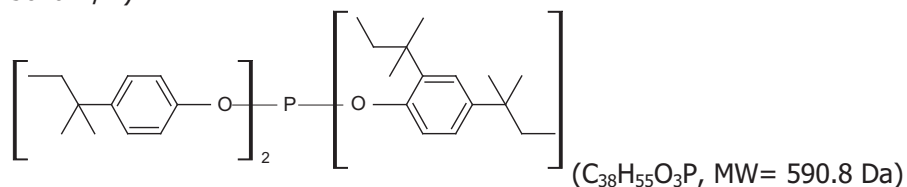
Note to the reader: Two different names are used in this Opinion to describe the same 5-carbon structural unit. These names are 1,1-dimethylpropyl- and *t*-amyl- which are common names for the moiety more systematically named as 2-methylbutan-2-yl. The two common names are used variously, in order to be consistent with the naming of the parent substances (i.e. substances containing that 5-carbon unit) in previous Opinions and in EU FCM Regulations.

The substance is a defined mixture in which the components are:

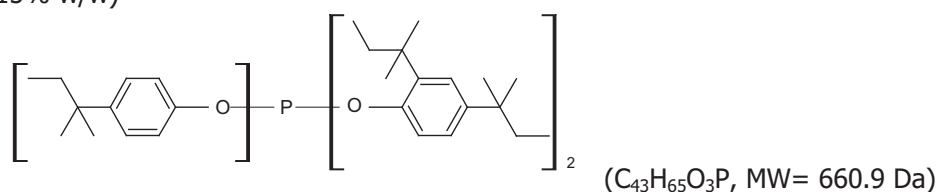
- Phosphorous acid, 4-(1,1-dimethylpropyl)phenyl triesters (24–60% w/w)



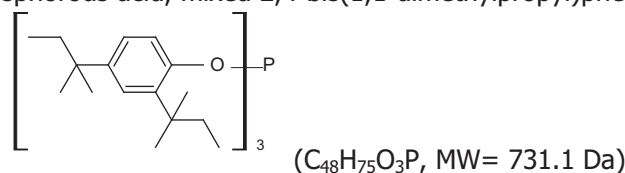
- Phosphorous acid, [2,4-bis(1,1-dimethylpropyl)phenyl] bis[4-(1,1-dimethylpropyl)phenyl] esters (25–50% w/w)



- Phosphorous acid, bis[2,4-bis(1,1-dimethylpropyl)phenyl] [4-(1,1-dimethylpropyl)phenyl] esters (1–15% w/w)



- Phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl triesters (0–5% w/w)



- Impurities and hydrolysis products, 4-*t*-amylphenol and 2,4-di-*t*-amylphenol

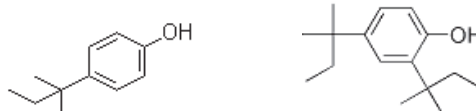


Figure 1: Chemical structures of the substance phosphorous acid mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters and of its impurities and hydrolysis products 4-*t*-amylphenol and 2,4-di-*t*-amylphenol

From the previous evaluations (EFSA CEF Panel, 2011, 2015), the migration of the substance from high-density polyethylene (HDPE) and linear low-density polyethylene (LLDPE) was not detectable in any simulans used (3% acetic acid, 10% ethanol, olive oil; after 2 h at 100°C followed by 10 days at 40°C) at the detection limit of 20 µg/kg. The oxidised form (phosphate form) was found in olive oil at levels up to 20.9 mg/kg. 4-*t*-Amylphenol was detected in water, 3% acetic acid, 10% ethanol and olive oil at levels up to 1.1 mg/kg. 2,4-di-*t*-Amylphenol was detected only in olive oil and was up to 0.1 mg/kg. In mixed-character foods (e.g. both fatty and acidic), hydrolysis of migrated antioxidant might result in higher concentrations.

3.2. Toxicological data

Data on the applied substance (phosphite form) and its oxidation products (phosphate form) have been provided for toxicokinetics, genotoxicity, subchronic toxicity, reproduction and prenatal developmental toxicity.

In addition, data on toxicokinetics, combined chronic toxicity/carcinogenicity and delayed neurotoxicity have been submitted for phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester (Figure 2; FCM No 671, CAS No 31570-04-4), i.e. the 'source substance' to read across to the applied substance, i.e. the 'target substance' (one methyl group difference in each of the alkyl substituents). The source substance has been evaluated in the past by the SCF (European Commission, 1999) and was also considered in the evaluation by the EFSA CEF Panel in 2011 (EFSA CEF Panel, 2011). In view of the structural and physicochemical similarities, and a similar toxicokinetic behaviour (see below), the Panel considered the read across from the source substance acceptable.

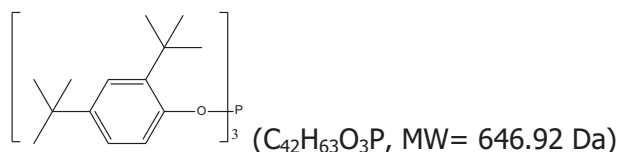


Figure 2: Chemical structure of the source substance for read-across; phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester

Toxicokinetics

In its evaluation in 2011 (EFSA CEF Panel, 2011), the CEF Panel considered a toxicokinetic study in Wistar rats performed on a structurally similar substance, i.e. ¹⁴C-bis(2,4-di-*tert*-butylphenyl) pentaerythritol diphosphite. Based on the results of that study, the CEF Panel concluded that the applied substance does not raise concern for accumulation despite its high log Po/w value.

In this application, a new toxicokinetic study (absorption, distribution, metabolism, and excretion (ADME)) in rats according to OECD TG No 417 was provided on the substance (non-oxidised form; phosphite). The substance was administered by oral gavage to Wistar rats (4 rats/sex per group) at single doses of 100 or 1,000 mg/kg, or a repeated dose for 14 days of 100 mg/kg per day. The test item was excreted within 48 h (81–92% of the dose) mainly via faeces, whereas excretion via urine was minor. Following single or repeated doses of the test item, animals were euthanised 48 h post-dosing. The average radioactivity remaining in blood, carcass and tissues was < 1% of the administered dose. In line with the results of the toxicokinetic study evaluated in 2011 on ¹⁴C-bis(2,4-di-*tert*-butylphenyl)pentaerythritol diphosphite, the data suggest that the substance was poorly absorbed and/or rapidly excreted and not accumulated in the body. These results support the 2011 conclusion that the applied substance does not raise concern for accumulation in human despite its high log Po/w value.

In view of the read across, the Panel also considered an ADME study on phenyl ring U-¹⁴C radiolabelled phosphorous acid, tris (2,4-di-*tert*-butylphenyl) ester. The fate of that source substance was investigated in male Sprague–Dawley rats administered by gavage with a single dose of 0.26 or 5.30 mg/kg body weight (bw). After 72 h, less than 0.02% of the dose was found in the body of the rats, the radioactivity being excreted nearly completely in the faeces (94.5–97.1% of the dose) and to a very small extent in urine (0.1–0.4% of the dose). Results between the source and target substances are basically consistent, although the Panel noted some minor uncertainties due to different dosing regimens applied in the studies and to quantitative differences in the urinary excretion levels.

Genotoxicity

In 2011, the CEF Panel evaluated the potential genotoxicity of the substance (i.e. in its phosphite form) from three *in vitro* genotoxicity tests and concluded that the substance was non-genotoxic (EFSA CEF Panel, 2011). The CEF Panel noted that under the conditions of the genotoxicity tests, also the oxidation products of the substance were tested.

In this application, three new *in vitro* genotoxicity assays were performed on the phosphate form of the substance (with a recorded purity of 100%) in the presence and absence of metabolic activation up to the solubility limit, according to OECD guidelines and Good Laboratory Practice (GLP). The substance, tested for bacterial mutation using *Salmonella* Typhimurium strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 uvrA, did not increase the number of revertants compared to the vehicle control. When the substance was tested for the ability to induce forward mutations at the thymidine-kinase locus (TK-locus) in L5178Y mouse lymphoma cells in two experiments, no increase in the mutation frequency compared to the vehicle control was observed. Likewise, when the substance

was tested in two separate experiments in an *in vitro* chromosomal aberration assay in human lymphocytes no increase of chromosomal damage compared to the vehicle control was observed.

Therefore, the above results confirm the conclusion drawn in 2011, that both the phosphite and the phosphate forms do not raise concern for genotoxicity.

Subchronic toxicity

In 2011, the CEF Panel evaluated a 90-day oral toxicity study carried out in rats with the phosphite form of the substance. It resulted in minor treatment-related changes. Increases in liver weights (approx. 10%) for the females treated with 20,000 ppm in the feed along with increased cholesterol levels (20%) and dose-dependent increases of alkaline phosphatase levels were considered adverse. The 'no observed adverse effect level' (NOAEL) was considered to be 10,000 ppm in the feed, equivalent to 759 mg/kg bw per day based on effects in liver.

In this application, the phosphate form of the substance was administered in a OECD TG No 408 guideline study by oral gavage to Sprague–Dawley rats, for 91 consecutive days, at dose levels of 0 (control), 100, 300 and 1,000 mg/kg bw per day followed by a recovery study of 28 days (0 and 1,000 mg/kg bw). Mild prolongations of activated partial thromboplastin time were noted at termination in both sexes of the 1,000 mg/kg bw per day group when compared to the control and prothrombin time was also minimally prolonged in the males at this dose level. There was a statistically significant increase of cholesterol in females (up to 22%) of the 1,000 mg/kg bw per day group when compared to control. These findings were considered treatment related by the Panel, since also increased cholesterol levels in the 90-day oral toxicity study carried out in rats with the phosphite form of the substance were identified in 2011. No other signs of either systemic toxicity or neurobehavioral effects were evident during the main or recovery phases of the study. Therefore, the NOAEL was determined to be 300 mg/kg bw per day.

Reproduction toxicity

In a two-generation reproduction toxicity study (OECD TG No 416) submitted in this application, the substance (phosphite form) was administered to Wistar Han rats orally in the diet at dose levels of 0 (control), 1,500 (87–116 mg/kg bw per day (m), 112–128 mg/kg bw per day (f)), 5,000 (278–399 mg/kg bw per day (m), 372–434 mg/kg bw per day (f)) and 15,000 ppm (943–1,254 mg/kg bw per day (m), 1,141–1,365 mg/kg bw per day (f)) from 10 weeks prior to mating until euthanasia (males) or 1 day before euthanasia (females). Higher relative kidney weights were noted in both sexes of the F₀ generation (10.8% males, 8.1% females), and increased absolute kidney weights were also noted in the F₀ males (7.4%) at the 15,000 ppm dose level. Reduced bodyweights (7.3% (F₁; m) and 6.3% (F₀ and F₁; f)) were observed despite an increased food consumption, indicating general systemic toxicity. Although the magnitude of the reduction was less than 10%, reduced body weights was also identified in the prenatal developmental study on this substance, therefore it was considered to be of toxicological relevance. The reproduction and developmental NOAELs were therefore considered by the Panel to be the 5,000 ppm dose level which corresponds for males to 278–399 mg/kg bw per day.

Prenatal developmental toxicity

In this application, the substance (phosphite form) was administered in a OECD TG No 414 prenatal developmental toxicity study orally (in the diet) to female Wistar Han rats from days 6 to 20 post-coitum at dose levels of 0 (control), 1,500, 5,000, 15,000 ppm, corresponding to a mean test substance intake of 0, 128, 439 and 1,266 mg/kg bw per day, respectively. Under the conditions of this prenatal developmental toxicity study, there were no effects on pregnancy and fetuses. The bodyweight decrease was close to 10% compared to controls, and a similar decrease in bodyweight was observed in the reproductive toxicity study. Therefore, the maternal NOAEL was considered by the Panel to be 5,000 ppm (439 mg/kg bw per day).

Neurotoxicity

In its evaluation in 2011 (EFSA CEF Panel, 2011), the Panel noted that the oxidation products of the substance, i.e. the corresponding phosphate esters, have a structural similarity to known inducers of delayed neurotoxicity (i.e. *ortho*-esters of tricresyl phosphates and tri-*p*-ethylphenyl phosphate). In the absence of specific neurotoxicity studies, the Panel noted that no treatment-related effects in behaviour or in the functional performance tests were detected in the 90-day oral rat study. Additionally, the Panel considered the evaluation made in the past on the source substance and the tolerable daily intake (TDI) of 1 mg/kg bw derived from a 2-year oral rat study (European

Commission, 1999). The Panel at that time concluded that there was no concern for neurotoxicity of the applied substance.

In this application, a delayed neurotoxicity study in hens (OECD TG No 418) conducted with the source substance was provided to rule out any concern for this specific effect. The source substance was given at dose levels of 2,150 and 6,000 mg/kg twice at an interval of 21 days. These treatments revealed no toxic symptoms. Histopathological lesions of the nervous system were absent. Therefore, it was concluded that the source substance did not cause delayed neurotoxicity in hens. By read across, a potential concern for delayed neurotoxicity of the applied substance is removed.

Overall, the Panel confirmed that the applied substance does not raise concern for neurotoxicity.

Combined chronic/carcinogenicity study

No study examining the potential chronic toxicity/carcinogenicity of the applied substance (phosphite form) was provided. Instead the chronic/carcinogenicity study on the source substance that was reviewed by the SCF in 1999 (European Commission, 1999) was provided. The CEF Panel concurs with the TDI of 1 mg/kg bw per day that was derived from the NOAEL of 58–147 mg/kg bw per day (highest dose; no treatment related effects).

The Panel noted that the lowest NOAEL of 300 mg/kg bw per day from the subchronic toxicity study on the phosphate form of the target substance is higher than the NOAEL of 58–147 mg/kg bw per day from a 2-year oral rat study of the source substance. Therefore, instead of applying a default uncertainty factor to the NOAEL from the subchronic study on the target substance, the Panel considered more appropriate to use the lowest NOAEL from the chronic study on the source substance for risk assessment. This NOAEL of 58 mg/kg bw per day (corresponding to 3,480 mg/person per day) would give a margin of safety (MOS) of 348 compared to the requested migration limit to 10 mg/kg food (equivalent to 10 mg/person per day). This MOS is considered sufficient to cover the uncertainties related to the read across.

4. Conclusions

Having considered the above-mentioned data, the CEF Panel concluded that the substance phosphorous acid, mixed 2,4-bis(1,1-dimethylpropyl)phenyl and 4-(1,1-dimethylpropyl)phenyl triesters is not of safety concern for the consumer if used as an additive with a migration limit of 10 mg/kg food, expressed as the sum of the phosphite and phosphate forms of the substance, 4-*tert*-amylphenol and 2,4-di-*tert*-amylphenol. The migration of 2,4-di-*tert*-amylphenol should not exceed 1 mg/kg food.

As a remark for the Commission, the substance complies with the criteria for applying the fat reduction factor (FRF).

Documentation provided to EFSA

- 1) Initial dossier. February 2016. Submitted on behalf of Addivant.
- 2) Additional data. June 2016. Submitted on behalf of Addivant.
- 3) Additional data. February 2017. Submitted on behalf of Addivant.

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Abbreviations

ADME	absorption, distribution, metabolism, and excretion
AFC	Panel on additives, flavourings, processing aids and materials in contact with food
bw	body weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
FCM	food contact materials
FRF	fat reduction factor
GLP	good laboratory practice
HDPE	high-density polyethylene
LLDPE	linear low-density polyethylene
MOS	margin of safety
MW	molecular weight
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
Po/w	octanol/water partition coefficient
SCF	Scientific Committee on Foods
SML	specific migration limit
TDI	tolerable daily intake
TG	Test guideline
TK	thymidine-kinase