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SCIENTIFIC OPINION

Safety assessment of the substance 'phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol and polypropylene glycol, C10–16 alkyl esters', for use in food contact materials

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Abstract

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) assessed the safety of the substance 'phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol and polypropylene glycol, C10–16 alkyl esters', when used as an additive in all types of polyolefins. The substance is a polymer containing ≤ 13% w/w of a low molecular weight fraction (LMWF, < 1000 Da). A polyethylene sample with 0.15% w/w of the substance was used in a comprehensive set of migration tests with food simulants. The specific migration was up to 0.014 and 0.023 mg/kg in 4% acetic acid and 10% ethanol, respectively. Migration into olive oil was estimated by the Panel to be up to 5.3 mg/kg under worst-case conditions of use. The migrating LMWF species were comprehensively identified. Those without phosphorous were either without alerts for genotoxicity or listed in Regulation (EU) 10/2011 with worst-case migrations well below their respective specific migration limits. Toxicological studies were performed using phosphite and phosphate versions of the substance enriched in its LMWF. The substance does not raise a concern for genotoxicity. From a repeated dose 90-day oral toxicity study in rats with a 50:50 phosphite:phosphate blend, the Panel identified a NOAEL of 250 mg/kg bw per day for each component of the blend. No delayed neurotoxicity in hens was observed. The CEP Panel concluded that the substance does not raise a safety concern for the consumer if its LMWF is not higher than 13% w/w, if it is used at up to 0.15% w/w in polyolefin materials and articles intended for contact with all food types, except for infant formula and human milk, for long-term storage at room temperature and below, after hot-fill and/or heating up to 100°C for up to 2 h, and if its migration does not exceed 5 mg/kg food.

KEYWORDS

C10–16 alkyl esters, CAS No. 1821217-71-3, evaluation, FCM substance No. 1084, food contact materials, phosphorous acid, polymer with 1,4-cyclohexanedimethanol and polypropylene glycol, safety assessment, triphenyl ester

CONTENTS

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 is 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[1] 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 the German competent authority (Federal Office of Consumer Protection and Food Safety), requesting the evaluation of the substance 'phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol and polypropylene glycol, C10–16 alkyl esters', FCM substance No. 1084, CAS number 1821217-71-3. The dossier was submitted on behalf of Dover Chemical Corporation, 3676 Davis Road N.W. Dover, Ohio 44,622-0040 - United States of America.

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 the authorisation of 'triphenyl phosphite, polymer with CHDM and polypropylene glycol, C10-16 alkyl esters' renamed by the Panel 'phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol (CHDM) and polypropylene glycol, C10-16 alkyl esters' to be used in plastic FCM.

Additional information was provided by the applicant during the assessment process in response to requests sent by EFSA on 04 April 2023 (see Section 5).

In accordance with Art. 38 of the Commission Regulation (EC) No 178/2002[2] and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation and of the Decision of the EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[3] the non-confidential version of the dossier is published on Open.EFSA.[4]

According to Art. 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations,[5] EFSA carried out a public consultation on the non-confidential version of the application from 7 to 28 February 2024, for which no comments were received.

Data submitted and used for the evaluation are:

Non-toxicological data and information

- Chemical identity
- Description of manufacturing process of substance/FCM
- Physical and chemical properties
- Intended use
- Existing authorisation(s)
- Migration of the substance
- Content and migration of oligomers
- Identification, quantification and migration of reaction products and impurities

Toxicological data

- Bacterial gene mutation tests
- In vitro mammalian cell gene mutation tests
- In vitro mammalian cell micronucleus tests
- 28-day oral toxicity studies in Wistar rats

[1]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 and repealing Directives 80/590/EEC and 89/109/EEC. OJ L 338, 13.11.2004,p. 4-17.

[2]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–48.

[3]Decision available at https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements

[4]The non-confidential version of the dossier, following EFSA's assessment of the applicant's confidentiality requests, is published on Open.EFSA and is available at the following link: https://open.efsa.europa.eu/dossier/FCM-2022-6990

[5]Decision available at: https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-pre-submission-phase-and-public-consultations.pdf

– A 90-day oral toxicity study in Wistar rats
– Reasoning on potential accumulation in human
– Delayed neurotoxicity studies following acute exposure in white Leghorn hens

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 (EC, 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 that is/are the 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 up to 1 kg of food per day 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 guidance from the EFSA Scientific Committee.

3 | ASSESSMENT

According to the applicant, the substance 'phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol (CHDM) and polypropylene glycol, C10-16 alkyl esters' is a polymeric additive to be used as an antioxidant/stabiliser at a maximum use level of 0.15% w/w in all types of polyolefins intended for contact with aqueous, acidic, fatty and low alcohol foods for long-term storage at room temperature including hot fill and/or heating conditions up to 100°C for a maximum of 2 h. The contact with infant formulae and human milk was not specified as intended application of the substance and therefore it was not considered in the evaluation.

The substance has not been evaluated in the past by the SCF or EFSA.

3.1 | Non-toxicological data

3.1.1 | Identity of the substance[6]

Chemical structure/formula:

[redacted]

[6]Technical report, section 'Identity of Substance'.

[redacted]

The substance is a polymeric additive that is synthesised from triphenyl phosphite, polypropylene glycol, 1,4-cyclohexanedimethanol (CHDM) and aliphatic C10-16 alcohols. Phenol is released during the reaction and is removed by [redacted] the substance has a molecular weight distribution ranging from ~ 500 to ~ 95,000 g/mol [redacted] The low molecular weight fraction (LMWF), that is the fraction below 1000 Da, is ≤ 13% w/w.

The purity of the substance is > 99% w/w, which is derived by subtracting the fraction of detected impurities from 100%. Impurities are CHDM (< 0.1% w/w), phenol (< 0.05% w/w), C10-16 alcohols (< 1% w/w), alkyl phenyl ethers (< 0.1% w/w) and triphenyl phosphite (< 0.05% w/w). The level of residual polypropylene glycol was not determined.

The substance contains 1% w/w triisopropanolamine used as a stabiliser.

3.1.2 | Physical and chemical properties[7]

The substance is highly lipophilic with log $P_{o/w}$ values greater than 9 for the individual low molecular weight (LMW) constituents. It is virtually insoluble in water and in the aqueous food simulants 10% ethanol and 4% acetic acid (solubility < 0.05 mg/L), but very soluble in organic solvents, such as hexane, toluene and xylene (solubility > 1 g/10 mL). It is a liquid at room temperature and has no defined melting point and no boiling point because of decomposition starting at 304°C, as shown by thermogravimetric analysis (TGA). Taking into account the evaporation of volatiles and the short duration of the heat treatment in processing plastics, the Panel concluded that the additive is thermally stable for the proposed use in polyolefins with typical processing temperatures of 220–260°C and a maximum of 300°C.

The substance is used as antioxidant/stabiliser and is oxidised from phosphite to phosphate during melt processing of the polymer.

Phosphites are known to slowly hydrolyse in the presence of moisture. The hydrolytic stability of [redacted] trialkyl phosphites and phosphates ([redacted]) was studied in gastric juice simulant. While trialkyl phosphates were stable against hydrolysis, trialkyl phosphites were quickly turned into dialkyl phosphates with removal of alkyl alcohols.

3.1.3 | Screening and identification of migrating species[8]

For the identification of migrating reaction products and in particular LMW constituents, migration tests were performed with a linear low-density polyethylene (LLDPE) sample, formulated with the substance at 0.15% w/w. The formulation was compounded at 180°C and then processed through an additional extrusion step at 280°C, with the intention to convert all phosphites into their corresponding phosphates. Migration tests were conducted at 100°C for 2 h and at 40°C for 10 days with the simulant 95% ethanol to facilitate the identification and quantification of the migrating species.

In order to identify and quantify the individual migrating phosphorous-containing species, the migration solutions were analysed by high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS) and evaporative light scattering detection (HPLC-ELSD). The chemical identities of the individual phosphate esters were determined by molecular weight assignment and using synthesised standards. These analyses identified essentially monophosphates and dimers as migrating species. The monophosphates consist of [redacted] The dimers consist of a group of diphosphates composed of [redacted] Additionally, [redacted] species with higher molecular weight largely consisting of trimers (triphosphates, [redacted]) was identified. An average P content was calculated for each chemical class, resulting in a P content of 5.05% for monophosphates, of 6.1% for dimers and 6.64% for trimers. The total migration of the monophosphates for the migration test at 40°C for 10 days was 1.96 mg/kg food [redacted]. The migration of oligomers was not measured but calculated by subtraction of the migration of monophosphates from the total migration of the additive measured by inductively coupled plasma-optical emission spectrometry (ICP-OES) (3.18 mg/kg food) as 1.22 mg/kg food.

The Panel noted that the substances migrating into 95% ethanol include the dimers with an estimated average MW of [redacted], that is slightly above the upper MW limit that is conventionally used to identify substances of toxicological interest (1000 Da). As the MW of the various migrating species is an average derived from estimated individual MW, the Panel decided to consider the dimers as part of the LMWF. The Panel considered that the contribution of species of higher molecular weight, such as triphosphates, to the total migration is very low.

[7]Technical report, section 'Physical and Chemical Properties of Substance'.

[8]Technical report, section 'Data on Migration of Substance'.

3.1.4 | Specific migration of the substance and impurities[9]

Migration tests in total immersion mode were carried out with a 508-µm-thick LLDPE sample. The sample was formulated with the substance at 0.15% w/w and compounded at 180°C. Migration tests were conducted with the food simulants 10% ethanol, 4% acetic acid and olive oil at 100°C for 2 h as well as at 40°C for 10 days. The chosen conditions did not match the testing conditions required by Regulation (EU) 10/2011[10] (i.e. 60°C for 10 days).

The migration of the additive was calculated based on the determination of total phosphorous (P) in the simulant by ICP-OES, which was calibrated using a certified P standard. The analytical method was, therefore, able to detect all species containing P, that is the additive, its reaction products (phosphates) and all impurities containing P.

The highest specific migration was 0.009 mg/kg food in 3% acetic acid, 0.016 mg/kg food in 10% ethanol and 4.25 mg/kg food in olive oil. The higher migration determined in olive oil compared to that in 95% ethanol (3.18 mg/kg food) may be attributed to the higher solubility of the migrating species in olive oil.

The Panel noted that the specific migration was determined by the applicant based on a P content of 7.3%, that is the P content of the additive. However, the P content of the fraction migrating into food simulants is expected to be lower, as the P content of the migrating species identified in tests with 95% ethanol (see Section 3.1.3) ranged between 5.05% (monophosphates/phosphites) and 6.64% (trimers). Regarding the migration into aqueous simulants, a worse-case P content of 5.05% can be assumed, as the migrate is expected to consist almost entirely of monophosphites/phosphates. The resulting corrected specific migration was up to 0.014 mg/kg food for 3% acetic acid and up to 0.023 mg/kg food for 10% ethanol.

Regarding the migration into olive oil, the P content of the migrate could not be exactly estimated. Therefore, the resulting specific migration is expected to be between 4.25 (using 7.3%, the P content of the additive) and 6.14 (using 5.05%, the P content of monophosphates) mg/kg food. A fraction of this migration consists of monophosphites/phosphates. The migration of monophosphates was determined in migration tests with 95% ethanol (Section 3.1.3) as 1.96 mg/kg food. Assuming that their migration in olive oil is pro-rata to that in 95% ethanol and using the specific migration determined with ICP-OES, the specific migration of monophosphites/phosphates in olive oil would be 2.62 mg/kg food (= 1.96 × 4.25/3.18). The migration of oligomers would then be between 1.63 and 3.52 mg/kg food.

The Panel noted that the applicant calculated the specific migration assuming that migration occurs independently from both sides of the LLDPE sample. However, under the used testing conditions, the substance is almost fully extracted and one-sided contact should have been used. This approach, together with the milder testing conditions (10 days at 40°C) compared to those recommended by Reg. (EU) 10/2011 (10 days at 60°C), is expected to underestimate the real specific migration. To understand the magnitude of this underestimation, the Panel applied migration modelling, considering as a worst-case scenario the migration of trialkyl phosphites/phosphates ([redacted]) from a LLDPE sample of the same thickness (508 µm) into olive oil for 10 days at 60°C assuming a LMWF of 13% w/w [redacted]. The resulting modelled specific migration was 5.3 mg/kg food. Considering a 250-µm-thick sample, the resulting modelled specific migration was 2.61 mg/kg food.

The migration in aqueous simulants is expected to be limited by the low solubility of the substance. The Panel considered that potential migration into solid foods will be far below 5 mg/kg food due the low volatility of migrating species. Therefore, it is covered by the set of migration data provided.

The maximum possible migration of impurities was calculated by assuming a 100% migration from a LLDPE specimen of 250-µm thickness formulated with the substance at the maximum requested level of 0.15% w/w. The substances not containing phosphorous that are listed in Regulation (EU) No 10/2011 are either without a restriction (for C10–16 alcohols, polypropylene glycol, CHDM) or their worst-case migration (for phenol) was estimated to be well below the respective specific migration limit (SML). The maximum possible migration of the alkyl phenyl ethers and triphenyl phosphite would amount up to 0.0225 and 0.0110 mg/kg food, respectively.

3.2 | Toxicological data[11]

For the toxicity studies, two test items were synthesised in which the substance was enriched in its phosphite and phosphate LMWF (LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate, respectively). The test items were produced by adapting the process used for the synthesis of the substance and were used either individually or as a 50:50 blend for toxicity testing. The LMWF was determined by gel permeation chromatography (GPC) to be 40.6% w/w and 43.9% w/w in LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate, respectively. The major constituents of the LMWF determined by HPLC-MS and HPLC-ELSD analysis were [redacted]

The purities of the test items were calculated by subtracting the fraction of detected impurities from 100%, resulting in > 94.5% and > 97.6% for LMWF-[redacted]-phosphite and for LMWF-[redacted]-phosphate, respectively. For the 50:50 blend, a purity of > 95% was indicated.

[9]Technical report, section 'Data on Migration of Substance'.

[10]Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food Text with EEA relevance.

[11]Technical report, section 'Toxicological data'.

The Panel noted that according to the EFSA guidance on genotoxicity testing of complex mixtures (EFSA Scientific Committee, 2019), for mixtures not fully characterised, the inert, toxicologically irrelevant material, such as high-molecular-weight polymers (> 1000 Da), should be removed from the material tested to minimise the dilution of the components of interest in the tested sample. However, based on the information provided on the method used for chemical synthesis, the compositional analytical data and the information from the migration tests using 95% ethanol (see Section 3.1.4), the Panel concluded that the test items were sufficiently representative of the migrating fraction of the substance.

3.2.1 | Genotoxicity

LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate were tested in a basic battery of genotoxicity tests with and without metabolic activation.

3.2.1.1 | *Bacterial reverse mutation test*

The test items were tested in two independent studies with the bacterial reverse mutation test (Ames test) according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 471 (OECD, 1997) and following Good Laboratory Practice (GLP). Four strains of Salmonella Typhimurium (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvrA/*pKM101 were used. In each study, two separate experiments were performed applying the plate incorporation method, both in the absence and presence of metabolic activation (S9-mix). In a first toxicity-mutation experiment, the test items were suspended in dimethyl sulfoxide (DMSO) and tested in duplicate at eight concentrations from 0.0015 to 5 μL/plate. No precipitation was reported. Normal bacterial background lawn pattern and no increase in number of revertant colonies were observed in all the tested strains when compared with the concurrent vehicle control. In a second confirmatory mutation experiment, six concentrations of the test item between 0.16 and 5 μL/plate were tested in triplicate. No toxicity and no increase in the number of revertant colonies were observed in the presence or absence of S9-mix. Based on the results, it was concluded that the test items LMWF-[redacted]-phosphate and LMWF-[redacted]-phosphite did not induce gene mutations in bacteria under the test conditions applied. Based on the 'Harmonised approach for reporting reliability and relevance of genotoxicity studies' (EFSA, 2023), the studies were considered reliable without restrictions and the negative results obtained of high relevance.

3.2.1.2 | *In vitro mammalian cell gene mutation test*

The test items were tested in two independent studies with the in vitro mammalian cell gene mutation test, using the thymidine kinase gene according to OECD TG 490 (OECD, 2016) and following GLP. Duplicate cultures of L5178Y cells were treated for a period of 3 hours in the presence and absence of metabolic activation (S9-mix). The test items were suspended in DMSO and the ranges of concentrations to be used were established based on the results of a range finding test: 0.2, 0.4, 0.8, 1.4 and 1.6 μL/mL for LMWF-[redacted]-phosphite, and 0.125, 0.25, 0.5, 1 and 2 μL/mL for LMWF-[redacted]-phosphate. For LMWF-[redacted]-phosphite, cytotoxicity, evaluated as reduced suspension growth, was observed at the concentration of 1.6 μL/mL in the presence or absence of S9-mix. A statistically significant increase of mutation frequency was observed at 1.4 μL/mL in the presence of metabolic activation, which was in the range of negative historical controls. For LMWF-[redacted]-phosphate, no cytotoxicity was observed. The mutation frequency was comparable to that of the vehicle control group at all the tested concentrations, in the absence and presence of S9-mix. Based on the results, it was concluded that LMWF-[redacted]-phosphate and LMWF-[redacted]-phosphite did not induce gene mutation in mammalian cells under the test conditions applied. The studies were considered reliable without restrictions and the negative results obtained of high relevance.

3.2.1.3 | *In vitro mammalian cell micronucleus test*

The test items were tested in two independent studies with the in vitro mammalian cell micronucleus test carried out with the cytokinesis block, according to the OECD TG 487 (OECD, 2016) and following GLP. Duplicate cultures of human peripheral blood lymphocytes were exposed to the test items, both in a short-term treatment (3 h exposure and 21 h recovery period), with or without metabolic activation (S9-mix), and in a long-term treatment (24 h exposure) without S9-mix. Based on the results of a range finding test, five concentrations of the test items suspended in DMSO (0.125, 0.25, 0.5, 1 and 2 μL/plate) were applied. No precipitation was reported. Cytotoxicity (evaluated as a reduction in replicative index) was observed at the highest concentration tested of 2 μL/mL: 19%, 16% and 24% for LMWF-[redacted]-phosphite and 32%, 33% and 50% for LMWF-[redacted]-phosphate in the short-term treatment in absence and presence of S9-mix and in the long-term treatment, respectively. The frequency of binucleated cells with micronuclei was not statistically significantly different from the negative controls at any concentration of the test items and condition of treatment. LMWF-[redacted]-phosphate and LMWF-[redacted]-phosphite did not induce increase in micronuclei frequency in mammalian cells under the test conditions applied. The studies were considered reliable without restrictions and the negative results obtained of high relevance.

3.2.1.4 | *Conclusion on genotoxicity*

LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate were tested in a basic battery of reliable in vitro genotoxicity studies. In the presence or absence of S9 mix, the test items did not induce gene mutations in bacteria (four strains of Salmonella Typhimurium, TA1535, TA1537, TA98 and TA100 and one strain of *Escherichia coli* WP2 *uvrA*) and in mammalian cells (mouse lymphoma L5178Y cells). They also did not induce chromosomal damage (evaluated as micronuclei frequency) in human peripheral blood lymphocytes. The dose-related cytotoxicity observed in the genotoxicity studies indicated that the test organisms (bacteria and cells) were adequately exposed to the test items under in vitro test conditions, which is an important consideration when evaluating mixtures (EFSA Scientific Committee 2019). Based on the results of the battery of genotoxicity studies provided, the Panel concluded that the test items did not raise a safety concern for genotoxicity.

3.2.2 | Sub-chronic toxicity

3.2.2.1 | *Repeated dose 28-day dose-finding studies*

Two 28-day dose-finding studies were conducted with LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate in preparation for the repeated dose 90-day toxicity study. The studies were conducted following GLP and using a protocol that was 'inspired from the OECD TG 407 (version 2008)'. After obtaining clarifications from the applicant, the Panel concluded that the conditions used in the study were appropriate.

The test items were administered by gavage to Wistar rats for 28 days at doses of 0, 100, 300 and 1000 mg/kg bw per day in corn oil. The treatment was followed by a 14-day recovery period.

In animals administered with LMWF-[redacted]-phosphite, an increase in thyroid with parathyroid absolute weights was observed in males of the high dose group (+ 22%) and in females of the low, mid and high dose groups (+ 13%, + 14% and + 30%, respectively). A similar increase in thyroid with parathyroid relative weight was observed in males of the high dose group (+ 28%) and in females of the low, mid and high dose groups (+ 10%, + 10% and + 30%, respectively). These increases were not accompanied by histopathological changes and were reversible after a recovery period of 14 days. No other effects were reported at doses up to 1000 mg/kg bw per day.

In animals administered with LMWF-[redacted]-phosphate, several treatment-related effects were reported. An increase in absolute weight of thyroid with parathyroid was observed in males of the high dose group (+ 24%) and females in the mid and high dose groups (+ 13% and + 23%, respectively). An increase of thyroid with parathyroid relative weight was also reported in males and females of the high dose group (+ 20% for both). These effects were reversible after a recovery period of 14 days and not associated with any macroscopic or microscopic changes. A dose-dependent fine yellowish and black granular deposit was observed in liver and spleen (minimal to moderate) in both males and females in all LMWF-[redacted]-phosphate dose groups. It was negative in haemosiderin, bilirubin and lipofuscin special staining methods. The granular deposit was still present after a 14-day recovery period. Scanning electron microscopy energy dispersive x-ray spectroscopy analysis (SEM–EDX) revealed that iron was part of the pigment in several samples and a positive correlation between iron concentration and phosphorus was detected, suggesting the presence of ferrous and/or ferric phosphate.

3.2.2.2 | *Repeated dose 90-day toxicity study*

The study was conducted following GLP and the OECD TG 408 (OECD, 2018). The test item was a 50:50 blend (by weight) of LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate. The applicant justified this choice 'to address and mimic this exposure situation of the phosphite and phosphate - and, at the same time, limit animal testing as scientifically feasible'. The Panel considered this justification appropriate. The test item (in corn oil) was administered to Wistar rats for 90 days by gavage at doses of 0, 15, 50, 150 and 500 mg/kg bw per day. As the test item was a 50:50 blend of LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate, the final doses for each were 0, 7.5, 25, 75 and 250 mg/kg bw per day. To assess the reversibility or delayed occurrence of toxicity, additional groups (30 males and 30 females at each dose level) were treated for 90 days and then further observed for an additional period of 28, 56 or 90 days without any treatment (10 males and 10 females from each group at each timepoint). The stability and concentration of the test item were verified regularly all along the study duration.

No mortality or morbidity were observed in male or female rats of any group throughout the study period, except for one male rat of the mid dose group that was found dead on Day 90. Macroscopic examination revealed a tissue mass in the kidney and autolytic changes in liver and spleen. Microscopic examination of the kidney mass revealed tubular carcinoma. The death of the animal was considered as an incidental finding.

Ophthalmological examination of the rats of all groups did not reveal any abnormalities.

No treatment-related changes were observed during the neurobehavioural and functional observational battery performed in rats from the treatment groups.

Mean body weight, mean body weight change and food consumption of male and female rats from the treatment groups were comparable with those of the respective vehicle control groups. Few statistical variations in food consumption, which were inconsistent and not dose-dependent, were observed intermittently. They were considered not treatment-related.

No significant changes were observed in haematology and clinical chemistry parameters of male and female rats of the treatment groups when compared with those of the respective vehicle control groups. An increase in low-density

lipoprotein (LDL) level (+ 57%) was observed in female rats of the high dose groups at Week 7 and at termination of the treatment period. This effect was test item-related, as it was consistently observed in the main and recovery groups. However, since similar alterations were not observed in other related parameters (i.e. high-density lipoprotein (HDL), cholesterol and triglyceride), the effect was considered not toxicologically relevant.

No treatment-related alterations were noted in urinalysis and hormone analysis (thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4)) at the end of the treatment (main groups), first recovery (28-day), second recovery (56-day) and third recovery (90-day) period for male and female rats of the different treatment groups.

No treatment-related alterations were revealed in terminal body weight, absolute organ weight and relative organ weight at the end of the treatment (main groups), first recovery (28-day), second recovery (56-day) and third recovery (90-day) period in male and female rats of the different treatment groups. The increase in thyroid with parathyroid absolute and relative weight (not accompanied by any histopathological changes) that was observed during the two preliminary 28-day studies (Section 3.2.2.1) was not confirmed during this 90-day study.

Macroscopic observation did not reveal any treatment-related findings. The histopathological examination of animals subjected to neuropathology did not reveal any lesions.

A yellowish black pigment deposition was observed in liver and equivocally in spleen. This observation was already reported (dose-dependent) in the preliminary 28-day study with rats administered with LMWF-[redacted]-phosphate, but not in the 28-day study with rats administered with LMWF-[redacted]-phosphite. The degree of pigment observations was minimal to mild without any other tissue reaction. In a battery of histological and histochemical stains, including a SEM-EDX analysis, the pigment was identified as mainly iron phosphate. It was considered not to be of biological organic origin and did not represent natural pigments (e.g. lipofuscin) that are indicative of toxicity. The pigmentation did not completely clear within the recovery periods and was observed mainly in macrophages and Kupffer cells, suggesting a continuous clearance mechanism from the circulation. Due to the chemical properties of phosphoproteins and their binding affinity to iron, the long-lasting appearance of pigment (iron phosphate) can be expected. In the absence of accompanying haematology and clinical chemistry changes (i.e. indicators of liver function), this deposition can be considered as not adverse at the tested doses.

In this study, a 50:50 blend of LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate did not produce any biologically significant toxicity or adverse effects at doses up to 250 mg/kg bw per day for each component of the blend when administered repeatedly for 90 days to Wistar rats by gavage. Therefore, under the conditions and procedure followed in the present study, the Panel identified a no observed adverse effect level (NOAEL) of 250 mg/kg bw per day (the highest dose tested) for each constituent of the test item (i.e. LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate) when administered by gavage up to 90 days in Wistar rats.

3.2.3 | Neurotoxicity

The applicant provided the reports of two neurotoxicity studies conducted with LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate administered to white Leghorn hens. The studies were conducted following GLP and the OECD TG 418 (OECD, 1995). The applicant justified the choice of performing neurotoxicity studies with hens following the OECD TG 418 with the known higher sensitivity of hens to organophosphorus esters (i.e. more prone to develop delayed neuropathy) compared to rats. Therefore, hens can be considered as the relevant animal model for testing potential neurotoxicity. As the test facility did not have sufficient historical positive control data, an additional study was performed with the positive control tri-ortho-cresyl phosphate (TOCP), as recommended by the OECD TG 418.

The studies were adequately conducted and reported. The animals received a single dose of 2000 mg test item/kg bw in corn oil administered by gavage, and a vehicle control was included in each study. In the positive control study, the animals received 750 mg TOCP/kg bw as a single dose. The controls (negative and positive) gave the expected results and the studies are considered valid. No gross pathological changes and histological alterations involving brain, spinal cord (cervical, thoracic and lumbo-sacral segments) and peripheral nerves (sciatic and tibial) were reported in animals receiving LMWF-[redacted]-phosphite or LMWF-[redacted]- phosphate. Under the conditions of these studies, no neurotoxic potential could be demonstrated for these two substances.

3.2.4 | Accumulation in human

As the LMWF constituents (i.e. phosphite esters and phosphate esters) of the substance are highly lipophilic (log $P_{o/w} > 9$), their potential for accumulation in human deserved evaluation.

Phosphite esters were shown to hydrolyse under simulated gastric conditions and are expected to be quickly metabolised during their passage through the digestive tract. Complete hydrolysis of the LMW constituent trialkyl phosphite produced substances listed in Regulation (EU) 10/2011 with an SML of 60 mg/kg food.

Phosphate esters were not hydrolysed under simulated gastric conditions. LMW alkyl phosphate esters are metabolised in liver cells as shown by modelling of the metabolism by cytochrome P450. Oxidation reactions catalysed by various cytochrome P450 isoforms were predicted by the modelling programme regarding metabolism of the trialkyl phosphate surrogate.

In three oral repeated-dose toxicity studies (two 28-day and one 90-day) performed with LMWF-[redacted]-phosphite and/or phosphate, yellowish black deposits were observed in a few tissues, primarily in the liver, and only in animals administered

with LMWF-[redacted]-phosphate. EDX point element analyses of these pigment deposits suggested that they were composed by iron phosphate (ferrous and ferric phosphates), that is that they are not organic phosphate esters. Considering their intra-cytoplasmic distribution, their size (< 1 μm) and their round shape, the pigments were considered to be stored in lysosomes. They were also observed in macrophages, pointing to a clearance mechanism from the circulation. Finally, the pigment-laden macrophages present in liver, spleen and mesenteric lymph nodes were not accompanied by any histopathological changes in the corresponding tissues.

The Panel concluded that the accumulation potential of LMWF-[redacted]-phosphite and phosphate in humans does not raise a toxicological concern.

3.2.5 | Discussion

The Panel noted that the use of the substance in contact with fatty foods may result in a specific migration exceeding 5 mg/kg food if some or all of the relevant parameters that influence migration are chosen worst-case: maximum intended use level, high polymer thickness (508 μm), a highly lipophilic food simulant (olive oil) and a polyolefin with the highest diffusivity (LLDPE). The Panel also considered that the modelled worst-case migration of the LMWF from a 250-μm-thick LLDPE sample using the testing conditions required in Regulation (EU) 10/2011 was 2.61 mg/kg food, hence below 5 mg/kg food. Similarly, other milder conditions of use (e.g. a lower use level, smaller LMWF, milder contact time and temperature) would result in lower migration levels. The migration into aqueous foodstuffs is limited by the low solubility of the substance in aqueous media.

The Panel concluded that the migrating phosphorous-containing oligomers and other reaction/degradation products were adequately represented in the toxicity studies provided, which used the substance in the phosphite and phosphate form and enriched in its LMW components (LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate, respectively).

Regarding genotoxicity, the results of the assays did not show a genotoxic potential of the substance. The impurities include the starting substances used to manufacture the substance, which are either listed in Regulation (EU) 10/2011 without restrictions (polypropylene glycol as FCM substance No. 639; CHDM as FCM substance No. 210; C10-16 alcohols covered by FCM No. 3) or evaluated as non-genotoxic (triphenyl phosphite). Triisopropanolamine, used as a stabiliser for the additive, is listed in the Regulation under FCM No. 292 with a SML of 5 mg/kg. Phenol by oral route is devoid of biologically relevant genotoxicity in vivo (EFSA CEF Panel, 2013) and alkyl phenyl ethers do not present a concern for genotoxicity.

As regards sub-chronic toxicity, the results of the 90-day repeated oral toxicity study performed in Wistar rats with a 50:50 blend of LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate allowed to identify a NOAEL of 250 mg/kg bw per day, the highest dose tested, for each constituent of the test item (i.e. LMWF-[redacted]-phosphite and LMWF-[redacted]-phosphate).

The Panel concluded that the accumulation potential of LMWF-[redacted]-phosphite and of LMWF-[redacted]-phosphate in humans does not raise a toxicological concern.

Delayed neurotoxicity studies performed with white Leghorn hens did not show any concern regarding the induction of delayed neurotoxicity by the substance enriched in its LMW components.

Based on the above-mentioned considerations and following the tiered approach reported in the SCF guidelines (European Commission, 2001) and the relevant EFSA's Note for Guidance (EFSA, 2008), the Panel concluded that the substance does not raise safety concern if its migration does not exceed 5 mg/kg. The contact with infant formula and human milk was not specified as intended application of the substance and therefore it was not considered in the evaluation.

4 | CONCLUSIONS

The CEP Panel concluded that the substance 'phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol and polypropylene glycol, C10–16 alkyl esters' is not of safety concern for the consumer (i) if its LMWF (< 1000 Da) is not higher than 13% w/w, (ii) if it is used as an additive at up to 0.15% w/w in polyolefin materials and articles intended for contact with all food types, except for infant formula and human milk, for long-term storage at room temperature and below, including hot-fill and/or heating up to 100°C for up to 2 h and (iii) if the migration of the total of phosphite and phosphate species does not exceed 5 mg/kg food.

The Panel noted that the migration of the substance into fatty foods may exceed 5 mg/kg food.

For the determination of the specific migration via total P measurement, a P content not higher than 5.05% should be considered, to be conservative.

The Panel noted that the fat reduction factor (FRF) is applicable.

5 | DOCUMENTATION AS PROVIDED TO EFSA

- Dossier "phosphorous acid, triphenyl ester, polymer with 1,4-cyclohexanedimethanol and polypropylene glycol, C10–16 alkyl esters". March 2023. Submitted on behalf of Dover Chemical Corporation, United States of America.
- Additional information, October 2023, submitted on behalf of Dover Chemical Corporation, United States of America.

ABBREVIATIONS

bw	body weight
CAS	Chemical Abstracts Service
CEP Panel	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
CHDM	1,4-cyclohexanedimethanol
Da	Dalton
FCM	food contact materials
FRF	fat reduction factor
GLP	Good Laboratory Practice
HDL	high-density lipoprotein
HPLC-ELSD	high-performance liquid chromatography – evaporative light scattering detection
HPLC-MS	high-performance liquid chromatography – mass spectrometry
ICP-OES	inductively coupled plasma-optical emission spectroscopy
LDL	low-density lipoprotein
LLDPE	linear low-density polyethylene
LMW	low molecular weight
LMWF	low molecular weight fraction
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
Po/w	octanol/water partition coefficient
SCF	Scientific Committee on Food
SEM-EDX	scanning electron microscopy energy dispersive x-ray spectroscopy analysis
SML	specific migration limit
T3	triiodothyronine
T4	thyroxine
TGA	thermogravimetric analysis
TOCP	tri-ortho-cresyl phosphate
TSH	thyroid stimulating hormone

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

German competent authority (Federal Office of Consumer Protection and Food Safety).

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