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Safety assessment of the active substances cyclooctene homopolymer and cobalt stearate in combination for use in active 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 combined use of cyclooctene homopolymer (PCOE) and cobalt stearate (CoS) intended as a oxygen scavenger in the packaging of all kinds of food stored at room temperature or below for up to 6 months. The CoS is the oxidation catalyst and the PCOE is intentionally oxidised for the oxygen scavenging function. They are incorporated into a plastic layer that is intended to be either in direct or indirect contact with the food. The potential migration of cobalt and cyclooctene monomer were below their respective specific migration limit (SML). The potential migration of PCOE non-oxidised oligomeric low molecular weight fraction (LMWF) < 1,000 Da was estimated to be up to [redacted] The Panel concluded that this fraction does not raise concern for genotoxicity potential and that the no observed adverse effect level (NOAEL) derived from a subchronic toxicity study would ensure a margin of exposure large enough to not raise a safety concern. However, the Panel considered the analysis of the oxidised PCOE LMWF not sufficiently comprehensive, i.e. that additional oxidation products of different nature may be formed, and that the limit of detection corresponding to ca. [redacted] for individual substances is too high. The oxidised PCOE LMWF was not covered by the genotoxicity tests or the 90-day study on the PCOE oligomers. The assessment of the identified potential oxidised migrants was considered conclusive, but not that of the migrants having remained undetected. Therefore, the CEP Panel was not able to conclude on the safety of the proposed use of cyclooctene homopolymer and cobalt stearate together as active substances in a layer for scavenging oxygen, either in direct contact with the food or separated from the food by a passive layer of polymer.

Keywords: cyclooctene homopolymer, cobalt stearate, food contact materials, plastic, active, oxygen scavenger, safety assessment

Requestor: Federal public service of the Health, Food Chain Safety and Environment, Belgium

Question number: EFSA-Q-2019-00387

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Note: The full opinion will be published in accordance with Article 10(6) of Regulation (EC) No 1935/2004 once the decision on confidentiality, in line with Article 20(3) of the Regulation, will be received from the European Commission. The following information have been provided under confidentiality and they are deleted awaiting the decision of the Commission: the trade names of the applied and tested mixtures, the identity and amount of the impurities in the active components, the manufacturing process of the applied PCOE, purity specifications of cobalt stearate, the maximum process temperature of the polymer containing the active components, information on bioaccumulation of unoxidised oligomers and read-across to another compound, information and safety assessment of the oxidised oligomers, consolidated list of migrants from PCOE and from the matrix, percentage of PCOE and cobalt stearate.

Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Competing interests: R. Franz declared that Fraunhofer institute at which he is employed provides advisory services to private business operators active in the sector on food contact materials. In line with EFSA's Policy on Independence (http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf) and the Decision of the Executive Director on Competing Interest Management, a waiver was granted to R. Franz regarding his participation to the EFSA's Working Group on Food Contact Materials (FCMWG) in accordance with Article 21 of the Decision of the Executive Director on Competing Interest Management (http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf). Pursuant to Article 21(6) of the above-mentioned Decision, the involvement of R. Franz is authorised as member in the FCMWG, allowing him to take part in the discussions and in the drafting phase of the scientific output, but he is not allowed to be, or act as, a chairman, a vice-chairman or rapporteur of the working group.

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† Deceased.

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1. Introduction

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

Regulation (EC) No 450/2009[1] of the Commission of European Communities is a specific measure that lays down specific rules for active and intelligent materials and articles intended for contact with foodstuffs in addition to the general requirements established in Regulation (EC) No 1935/2004[2] of the European Parliament and of the Council on materials and articles intended to come into contact with food. Active materials and articles are intended to extend the shelf life or to maintain or improve the condition of packaged food; they are designed to deliberately incorporate components that would release or absorb substances into or from the packaged food or the environment surrounding the food.

The substance(s) responsible for the active and/or intelligent function of the material should be included in a positive list by the Commission following a safety evaluation by the European Food Safety Authority (EFSA) according to the procedure described in the above-mentioned regulations.

According to this procedure, the industry submits applications to the Member States competent authorities which transmit the applications to EFSA for their evaluation. The application is supported by a technical dossier submitted by the industry following the EFSA 'Guidelines on submission of a dossier for safety evaluation by EFSA of active or intelligent substances present in active and intelligent materials and articles intended to come into contact with food' (EFSA CEF Panel, 2009) .

In this case, EFSA received an application from the Federal Public Service (FPS) Health, Food Chain Safety and Environment, Belgium, requesting the evaluation of the active substances cyclooctene homopolymer and cobalt stearate, with the CAS number 25267-51-0 and 13586-84-0, respectively. The dossier was submitted on behalf of Evonik Resource Efficiency GmbH.

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 submitted a dossier in support of its application for the authorisation of the active substances cyclooctene homopolymer and cobalt stearate to be used in active food contact materials (FCM).

Additional information was provided by the applicant during the assessment process in response to the requests from EFSA sent on 16 October 2019 and 21 October 2021 (see Documentation provided to EFSA).

Data submitted and used for the evaluation are:

Non-toxicological data and information

- Chemical identity
- Physical and chemical properties
- Manufacturing process of the substances/FCM
- Function, intended uses and existing authorisation(s)
- Residual content of the substances
- Identification, quantification and estimated migration of reaction products and impurities

Toxicological data

- Bacterial reverse mutation test (cyclooctene)
- *In vitro* mammalian cell gene mutation test (cyclooctene)
- *In vitro* mammalian chromosome aberration test (cyclooctene)
- Subacute (28-day) oral toxicity study (cyclooctene)
- Bacterial reverse mutation test (oligomers [redacted])
- *In vivo* micronucleus test (oligomers [redacted])

[1] Commission Regulation (EC) No 450/2009 of 29 May 2009 on active and intelligent materials and articles intended to come into contact with food. OJ L 135, 30.5.2009, p. 3–11.

[2] 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.

- Subchronic (90-day) oral toxicity study for polyoctenamer ([redacted])
- Report of different approaches to establish the lack of accumulation in human

2.2. Methodologies

The safety evaluation was conducted in line with the EFSA 'Guidelines on the submission of a dossier for safety evaluation of active or intelligent substances present in active and intelligent materials and articles intended to come into contact with food' (EFSA CEF Panel, 2009). The assessment focuses on the risks related to dietary exposure to chemicals arising from the intended application. It neither considers the efficacy nor the microbiological aspects of the proposed application.

The dossier submitted for evaluation by the applicant was in line with the above-mentioned EFSA Guidelines (EFSA CEF Panel, 2009).

The methodology is based on the characterisation of the composition, structure and working principle of the active and intelligent material or article, on the characterisation of the substance(s) that are the subject of the request for safety assessment, its/their impurities, reaction and degradation products, the evaluation of the exposure to those substances through migration and the definition of sets of toxicity data required for safety assessment. For active substances that are intended to be released themselves or to cause the release of other substances into foods, additional considerations apply with respect to their safety and status as direct food additives. These considerations are described in the 'EFSA guidelines on active or intelligent substances' (EFSA CEF Panel, 2009).

As for monomers and additives used to make plastics, 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 same tiered approach as described in the guidelines of the Scientific Committee on Food (SCF) (European Commission, 2001) for the presentation of an application for safety assessment of a substance to be used in FCM prior to its authorisation has to be followed. 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 Scientific Committee, 2009) and considering the relevant guidance from the EFSA Scientific Committee.

3. Assessment[3]

According to the applicant, the active substances, cyclooctene homopolymer (or polycyclooctene, PCOE) and cobalt stearate (CoS), are intended to be used together in multilayer applications as an oxidisable substrate and an oxidation catalyst, respectively, for the scavenging of oxygen. They are incorporated at up to [redacted] and [redacted] respectively, into a plastic layer (typically polypropylene (PP) or polyethylene (PE)) to form an active layer of up to 30 μm in thickness. The active layer is intended to be either in direct contact with the food or separated from the food by a passive layer of polymer (e.g. PP or PE layer of not less than 10 μm). Final articles are intended for use with all kinds of foods stored at room temperature or below for up to 6 months. The intention is that the active mixture reacts with oxygen from the headspace of the packaging in order to maintain a low oxygen level and allow a longer shelf life of the packaged food.

[3] Technical dossier/ADD DATA_220221/Revised PSDS/Sections 1, 2, 5 and 6; related annexes.

The monomer used in the manufacture of PCOE, i.e. cyclooctene, is listed in Regulation (EU) No 10/2011[4] under the FCM No 381 with a specific migration limit (SML) of 0.05 mg/kg food and with the further restriction that it is to be used only in polymers contacting foods for which simulant A is laid down. Cobalt stearate is also covered by Regulation (EU) No 10/2011 as follows: stearic acid is listed under FCM No 106 as monomer and additive without any restriction; the respective cobalt salt is authorised with a SML of 0.05 mg/kg food (Annex II).

The oxygen scavenger mixture has obtained a US FDA Food Contact Notification No. 1997[5] for the intended uses 'As an oxygen scavenger in blends with low-density polyethylene or polypropylene as a non-food contact layer in multilayer food contact articles, except for use in contact with infant formula and human milk'.

3.1. Non-toxicological data

3.1.1. Identity of the substances[6]

The cyclooctene homopolymer (PCOE; CAS No. 25267-51-0) intended to be used has a purity above 99.9%. It has a number-average molecular weight of 14–15 kDa and a low molecular weight fraction (LMWF) below 1,000 Da of about 2% w/w, corresponding potentially to [redacted] when PCOE is incorporated at [redacted] in the active layer. The monomer cyclooctene used to manufacture PCOE has a molecular mass of 110 Da and so the LMWF < 1,000 Da would be up to and including the cyclic nonamer (n = 9,990 Da).

Cobalt stearate (CoS; CAS No. 13586-84-0) has a molecular mass of 626 Da and a cobalt content of about [redacted] when calculated stoichiometrically. A certificate of analysis was provided for one lot and the content of Co was reported to be [redacted] The purity and impurities in the CoS were otherwise not addressed by the applicant. CoS is incorporated at up to [redacted] of the active layer.

The chemical structures of PCOE and CoS are shown in Figures 1 and 2, respectively.

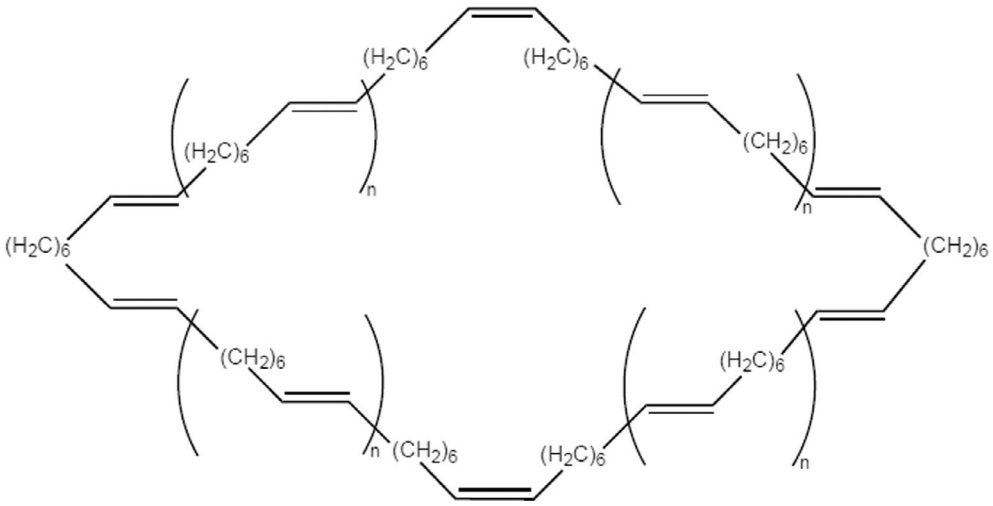

Figure 1: Chemical structure of PCOE ($(C_8H_{14})_n$)

[4] Regulation (EU) No 10/2011 (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. OJ L 12, 15.1.2011, p. 1–89.
[5] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FCN&id=1997
[6] Technical dossier/ADD DATA_220221/Revised PSDS/Section 1 and related annexes.

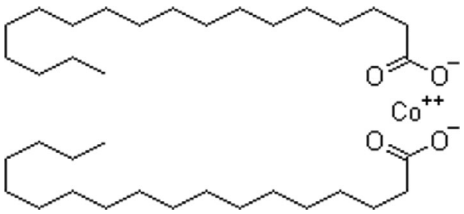

Figure 2: Chemical structure of cobalt stearate ($Co^{2+}(C_{17}H_{35}COO^{-})_2$)

3.1.2. Physical and chemical properties of the substances[7]

According to the applicant, PCOE is lipophilic with log P_{ow} measured to be 8.8 for the dimer and with values rising to > 24 when estimated by extrapolation for the higher oligomers/polymer.

PCOE and cobalt stearate are thermally stable up to and even above the maximum intended extrusion temperature for the plastics envisaged, which is stated to be [redacted] Therefore, no thermal degradation of the substances is expected during the manufacture of articles. However, reaction with air is expected during the manufacture and storage of articles prior to their use, and reaction (oxidation) of the PCOE is intentional when the substances perform their active function of scavenging oxygen.

3.1.3. Migration of the active substances and the reaction products from the oxygen scavenging system[8]

Specific migration tests were conducted for metals only.

3.1.3.1. Cobalt stearate

The migration of cobalt was tested using 3% acetic acid as the food simulant. The samples tested were 3-layer LDPE and PP laminates with each layer being 10 μm thick and with the middle (active) layer containing [redacted] PCOE and [redacted] CoS, these being the maximum use levels proposed. Film samples were tested both aged (storage in air for 24 days at 40°C and therefore subject to oxidation) and 'fresh' (having been protected from air by storage under nitrogen prior to the migration tests). The migration test conditions were 10 days at 40°C and the surface area: food mass (SA:M) ratio was 10 dm^2/kg. The exposed simulant was analysed by inductively coupled plasma mass spectrometry (ICP-MS) after acid digestion. There was no migration of cobalt at the limit of detection of 0.0006 mg/kg food for the LDPE tests. There was no migration of cobalt at the limit of quantification of 0.0024 mg/kg food for the PP tests. Thus, potential migration of cobalt from LDPE and PP laminates (indirect contact) was well below the SML of 0.05 mg/kg food assigned in Annex II of the Plastics Regulation.

No tests were performed for the migration of cobalt from samples where the active layer was in direct contact with the food/simulant. However, based on a worst-case assumption of 100% mass transfer from a 30 μm active layer containing [redacted] CoS ([redacted]) and a SA:M ratio of 6 dm^2/kg, the calculated migration of cobalt would be [redacted], which is below the SML for Co.

[redacted]

3.1.3.2. PCOE and the reaction products from the oxygen scavenging

Because of its high molecular mass, the PCOE itself is not expected to migrate and so the evaluation focuses on the LMWF and the reaction products resulting from the oxygen scavenging that are of toxicological relevance. To assess the potential migration of organic substances, the applicant opted to measure the content of organic substances in the plastic materials and to estimate their migration assuming total mass transfer.

[7] Technical dossier/ADD DATA_220221/Revised PSDS/Section 3 and related annexes.
[8] Technical dossier/ADD DATA_220221/Revised PSDS/Section 7 and related annexes.

A wide range of analytical techniques were used to aid the detection, identification and quantification of organic substances. These included [redacted] The samples analysed included analysis of the PCOE itself, an oligomer fraction obtained by extraction of the PCOE, [redacted] and plastic samples with- and without the active system incorporated. These tests used both fresh and aged (i.e. oxidised) samples for comparison, to help pinpoint residual components, their impurities, transformation and reaction products of the active system (i.e. of the PCOE and the cobalt stearate) along with any unintentional products from chemical interactions with the host plastics (LDPE and PP). Some tests also used [redacted]

Based on the results obtained from the analysis of these materials, worst-case calculations were made assuming total mass transfer (100% migration) from a 30-μm thick active plastic layer with a density of 1 g/cm^3, containing [redacted] PCOE and [redacted] cobalt stearate in the active layer and with an SA:M ratio of 6 dm^2/kg. This assumption of total mass transfer of the contents measured in the plastics was made for those specific substances that had been found in the analyses performed. **The findings are summarised below for the different categories of substances that were detected and attributed to the presence and function of the active substances PCOE and CoS**.

For hydrocarbons, the worst-case migration of **cyclooctene** itself (the PCOE monomer) was [redacted] well below its SML of 50 μg/kg.

Other hydrocarbons detected, mainly impurities in PCOE, were [redacted] for which the worst-case migration was in the range of [redacted]

Concerning the **PCOE oligomers**, the potential migration was estimated to be [redacted] amounting to a migration potential of totally ca. [redacted] Oligomers higher than the hexamer (660 Da) could not be analysed by [redacted] methods used, but it can be estimated that the whole oligomer fraction < 1,000 Da has a migration potential of ca. [redacted] The analyses and these calculations are for fresh samples and the potential migration of PCOE oligomers will decline as the active system oxidises. Indeed, the PCOE oligomers were largely absent from aged samples.

The substances that can be described as **LMW oxygenates**, potentially coming from the active oxygen-scavenging function, but possibly also arising in part from the cobalt-catalysed oxidation of the host polyolefin, comprised [redacted] When calculated for a 30-μm aged layer, the worst-case migration for these substances was [redacted] for each, with the exception of [redacted]). The summed migration potential of these [redacted] oxygenates, amounted to [redacted], using upper-bound setting for the concentration equal to the LoQ for substances that were detected but not quantified.

For **larger acids and diacids** resulting from the oxidation of PCOE, the predominant diacids were [redacted] with migration potentials from an aged 30-μm layer of [redacted] Other substances tentatively identified were [redacted] Collectively, these [redacted] acids/diacids, etc., summed up to a [redacted] migration potential (upper-bound) for an oxidised 30 μm layer.

No substances were detected and identified using [redacted] that were not already found using [redacted] methods, despite that the oxidation products might be expected to be rather intractable to analysis by [redacted] The LoD for [redacted] was established using known calibrants and estimated by the applicant to be in the region of [redacted] if a SA:M ratio of 6 dm^2/kg is assumed. This is a high LoD and leads

to the conclusion that the [redacted] method was insufficiently sensitive and the analysis of potentially migrating substances not sufficiently comprehensive.

3.2. Toxicological data

Cobalt stearate is authorised to manufacture plastic under the Regulation (EU) No 10/2011 under stearic acid and salts of cobalt. Stearic acid is authorised under the FCM No 106 as monomer and additive without any restriction, and the respective cobalt salt is authorised with a SML of 0.05 mg/kg food for cobalt (Art. 6.3.a). Moreover, in the safety assessment of similar oxygen scavengers also using cobalt stearate as catalyst (EFSA CEF Panel, 2012), the CEF Panel noted that the EFSA Panel on Additives and Products or Substances used in Animal Feed has evaluated cobalt compounds, concluding that a daily oral intake of 600 μg cobalt per person (based on a LOAEL of 1 mg/kg for polycythaemia) appears an acceptable safe amount for humans (EFSA FEEDAP Panel, 2009). Under the requested intended uses, migration of cobalt is expected to be below 0.05 mg/kg food (see Section 3.1.3).

Therefore, the toxicological assessment focuses on the oligomeric fraction below 1,000 Da of the PCOE and its reactions products.

In addition, the applicant provided the three genotoxicity studies on cyclooctene that had been assessed by the SCF (European Commission, 1999), namely a bacterial reverse mutation test, an *in vitro* mammalian cell gene mutation test and an *in vitro* mammalian chromosome aberration test. These resulted in the authorisation under Reg. 10/2011 (SML 0.05 mg/kg).[9] However, the bacterial reverse mutation test conducted in 1990 did not include *Salmonella* Typhimurium strain TA102 or *Escherichia coli*, thus was not in accordance with the current OECD 471 Test Guidelines. A new test with these strains was provided for assessing DNA oxidative damage and cross-linking. Therefore, the three compliant tests were also evaluated, and their assessment is reported below.

3.2.1. Genotoxicity of cyclooctene[10]

3.2.1.1. Bacterial reverse mutation test

Cyclooctene (purity 96.8%) was tested for its ability to induce gene mutation in a bacterial reverse mutation test (Ames test). The assay was performed according to Organisation for Economic Co-operation and Development (OECD) Test Guideline 471 (1997) and following Good Laboratory Practice (GLP). Five strains of *Salmonella* Typhimurium (TA98, TA100, TA102, TA1535 and TA1537) were used in the presence or absence of metabolic activation (S9-mix), applying the standard plate incorporation and preincubation methods. Two separate experiments were carried out using six concentrations of the substance (1, 3.16, 10, 31.6, 100 and 316 μg/plate). Cytotoxicity was observed at 316 μg/plate in all experiments. Upon treatment with the substance, there was no significant increase in revertant colony numbers above the control values in any strain with or without S9-mix. The Panel concluded that cyclooctene did not induce gene mutations in bacteria under the test conditions employed in this study.

3.2.1.2. *In vitro* mammalian cell gene mutation test

Cyclooctene (purity 96%) was tested in an *in vitro* mammalian cell gene mutation test performed according to OECD Test Guideline 476 (1984) and following GLP. Two assays were performed with and without metabolic activation (S9-mix) with Chinese hamster ovary (CHO) cells. Due to observed cytotoxicity, concentrations were limited to 30 μg/mL in the absence of S9-mix and to 125 μg/mL in the presence of S9-mix. Results showed that cyclooctene did not induce an increase of the mutation frequency at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus. The Panel concluded that cyclooctene did not induce gene mutations in mammalian cells under the test conditions employed in this study.

3.2.1.3. *In vitro* mammalian chromosomal aberration test

The *in vitro* mammalian chromosomal aberration test was carried out in Chinese hamster cell line V79 according to OECD Test Guideline 473 (1983) and following GLP. The dose-finding study was performed at concentrations ranging from 0.021 to 8.5 mg/mL with and without metabolic activation

[9] A subacute 28-day oral toxicity study for cyclooctene was also provided but not reported here as cyclooctene is listed in Regulation (EU) 10/2011 (FCM 381) with a specific migration limit set at 0.05 mg/kg food which is much higher than the reported migration in the current dossier.

[10] Technical dossier/ADD DATA_220221/Revised PSDS/Section 8.1 and related annexes.

(S9-mix). At concentrations 0.85 mg/mL and higher, only lysed cells were present. Based on these results, the cells were exposed to the substance at a range of concentrations from 0.05 to 0.5 mg/mL. Cells were treated for 5 h with and without metabolic activation (S9-mix) and harvested 12, 17 and 24 h after treatment. Two hundred cells were microscopically analysed. The frequency of structural and numerical chromosomal aberrations in treated cultures was comparable to the values detected in negative controls and within the range of the laboratory historical control data. The Panel concluded that the substance did not induce chromosome aberrations under the test conditions employed for this study.

Considering the results of the three above studies, the Panel concluded that cyclooctene does not raise concern for genotoxicity. This is in agreement with the assessment of the Scientific Committee on Foods (European Commission, 1999).

3.2.2. Genotoxicity of the PCOE oligomeric fraction[10]

Instead of the applied substance ([redacted]), the [redacted] oligomer extract was tested in a bacterial reverse mutation assay and in a mouse micronucleus test. [redacted] is a mixture of oligomers produced using a process very similar to that of the current application. FT-IR analyses showed that both mixtures are indistinguishable, but the Panel noted that the catalyst part of the substance (cobalt stearate) is not present. This appears as a drawback of this approach considering that potential oxidation products include epoxidised oligomers.

3.2.2.1. Bacterial reverse mutation test

[redacted] was tested for its ability to induce gene mutations in a bacterial reverse mutation assay (Ames test). The assay was performed according to OECD Test Guideline 471 (1997) and following GLP. Four strains of *Salmonella* Typhimurium (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* (WP2 *uvr*A) were used in the presence or absence of metabolic activation (S9-mix), applying the plate incorporation assay. Two separate experiments were carried out using seven different concentrations of the mixture (5, 15, 50, 150, 500, 1,500 and 5,000 μg/plate). Precipitate was observed at the highest dose tested. Upon treatment with the substance, there was no significant increase in revertant colony numbers above the control values in any strain with or without S9-mix. The Panel concluded that [redacted] did not induce gene mutations in bacteria under the test conditions employed in this study.

3.2.2.2. *In vivo* mouse micronucleus test

[redacted] was tested in the mouse erythrocyte micronucleus test, carried out in peripheral blood cells according to OECD Test Guideline 474 (1997) and following GLP. The substance was suspended in corn oil and administered orally at the three doses 500, 1,000 and 2,000 mg/kg on a single occasion to groups of six male CD1 mice. Bone marrow smears were harvested from the mice 24 h after administration from all dose groups and 48 h after administration from additional negative and high-dose groups. The presence of micronuclei was determined in 2,000 polychromatic erythrocytes and the proportion of polychromatic erythrocytes was determined based on the examination of at least 1,000 erythrocytes. The results showed no statistically significant decrease in the proportion of polychromatic erythrocytes and no statistically significant increase of the frequency of micronucleated polychromatic erythrocytes. The Panel concluded that [redacted] did not induce the formation of micronuclei in erythropoietic mouse cells under the test conditions employed in this study.

Considering the results of the two above studies, carried out at the limit doses recommended by the OECD guidelines, and the lack of genotoxicity of the cyclooctene monomer, the Panel concluded that non-oxidised cyclooctene oligomers do not raise concern for genotoxicity.

3.2.3. Subchronic oral toxicity of the PCOE oligomeric fraction[11]

A polyoctenamer ([redacted] containing 1.5–1.9% of low molecular weight (< 1,000 Da) oligomers) related to the PCOE substance was administered to rats in a subchronic toxicity study. The administered substance was shown to be representative enough to the substance under assessment in terms of composition of low molecular weight (< 1,000 Da) oligomers.

The repeated dose 90-day oral toxicity study was performed in accordance with OECD Test Guideline 408 (1981). No mention of the principles of GLP is present in the report; however, the

[11] Technical dossier/ADD DATA_220221/Revised PSDS/Section 8.2 and related annexes.

conduct of the study was inspected by the quality assurance unit of the test facility. Groups of 10 male and 10 female Wistar rats received the substance in feed at the following doses: 0 (control), 1,000, 2,000 and 4,000 mg/kg per day. These doses were equivalent to 1,018 mg/kg body weight (bw) per day in males and females of the low-dose group, 2,037 and 2,032 in males and females, respectively, of the mid-dose group and to 4,070 and 4,095 in males and females, respectively, of the high-dose group.

No mortality was observed. Males of the high-dose group showed a statistically significant lower body weight gain compared to those of the control group. This observation being limited to males and the difference being lower than 10%, the Panel considered it as not toxicologically relevant.

Clinical chemistry analyses revealed statistically significantly lower triglycerides concentrations in females from the high-dose group (−33.3% compared to control value). Additional statistically significantly differences were observed in males and females compared to respective control groups. Main differences were observed for inorganic phosphate in males from the low- and the high-dose groups (−6.7% and −10.9%, respectively) and in females of the mid-dose group (−14.2%); for aspartate transaminase in males of the high-dose group (−21.1%); for alanine aminotransferase in females from the low- and the high-dose groups (−13.4 and −11.8%, respectively) and for alkaline phosphatase in females from the low-dose group (−17.1%). These findings being observed in only one sex (except for inorganic phosphate) and/or not dose-related, the Panel considered them as not toxicologically relevant. No significant changes in haematology were reported.

In males from the high-dose group, statistically significantly lower absolute liver weights (−12.7%) were reported. Histopathological analysis revealed no substance-related findings in males and females of the high-dose group (low- and mid-dose groups organs were not analysed).

Body weight relative testicle weight in the mid- (12.8%) and high-dose (12.1%) groups were statistically significantly higher than those in control animals. This observation being not correlated with any histopathological findings, the Panel concluded this finding as not toxicologically relevant.

The Panel identified a no observed adverse effect level (NOAEL) at the high dose of 4,070 mg polyoctenamer/kg bw per day. Considering that low molecular weight oligomers represent between 1.5 and 1.9% of the administered substance, the Panel concluded that the NOAEL for the oligomers is at least 60 mg/kg bw per day.

3.2.4. Potential for accumulation in humans of the PCOE oligomeric fraction[12]

In vitro and *in silico* methodologies were used to demonstrate the lack of concern with regard to bioaccumulation potential of the substance. This includes log K_{ow} determination that is estimated to be 8.8 for the dimer and up to 24 for the heptamer and the nonamer. [redacted]

Several *in silico* approaches show that gastrointestinal absorption is expected to be low. [redacted]

Considering these different lines of evidence, the Panel concluded that accumulation of the PCOE oligomeric fraction does not give rise to safety concern.

3.3. Discussion

The applicant did not perform tests for overall migration or specific migration (except for metals, see above), but opted to measure the content of organic substances in materials containing the active substances, with and without oxidative ageing, and estimated migration based on those results making the assumption of total mass transfer. The Panel considered this assumption not unreasonable for the given polymer type and intended application.

For **cyclooctene** monomer, the worst-case migration was well below 50 μg/kg, thus, compliant with its SML.

For the **PCOE non-oxidised** oligomeric fraction < 1,000 Da, the potential migration from fresh material was estimated to reach up to [redacted]. The Panel concluded that it does not raise concern for genotoxicity potential. From the subchronic toxicity study, the NOAEL for the oligomeric

[12] Technical dossier/ADD DATA_220221/Revised PSDS/Section 8.3 and related annexes.

fraction < 1,000 Da of PCOE was estimated to be ca. 60 mg/kg bw per day (corresponding to 3,600 mg per person). The Panel concluded that the NOAEL and the potential migration of non-oxidised LMW PCOE oligomers would ensure a margin of exposure large enough to not raise a safety concern.

For the **oxidised PCOE LMWF**, the substances found in aged (oxidised) samples and described above as LMW oxygenates, larger acids, diacids and hydroxyacids, etc., summed up to a migration potential of approximately [redacted] Allowing for measurement uncertainty, as a first approximation it could appear that mass balance is approached, i.e. that the loss of the oxidisable substrate PCOE is fully accounted for by the identified and quantified newly formed products. In that regard, the applicant suggested that some losses might be due to [redacted] However, the Panel noted that, based on the high oxygen-consuming capacity of the active system, essentially all of the C = C double bonds in the oxidisable substrate PCOE (number-average molecular weight of 14–15 kDa) can be oxidised as the active system scavenges oxygen and becomes exhausted. It is expected that the PCOE will be partially oxidised to various degrees, resulting in different breakdown products. By reference to the PCOE structures in Figure 1, it is apparent that progressive oxidative cleavage of the C = C double bonds can release smaller oxidised fragments of the PCOE. The consequence is that the toxicologically relevant oxidation products (i.e. those of MW < 1,000 Da) may in principle be formed not only from the about 2% of the LMWF of PCOE, but from the whole MW range of the PCOE substrate. So, the possibility of using mass balance of the LMWF as a check on the completeness of the analysis conducted, is not applicable. Moreover, and notwithstanding the extensive experimentation conducted, the Panel considered that the analysis was not sufficiently comprehensive. The main limitation in the suite of analytical methods used was the relatively poor sensitivity (the detection limit and the identification capability) of the [redacted] method used ([redacted]) and the limited amenability of the polar substances to [redacted]. Moreover, no migration test was provided for direct or indirect contact that could have helped in refining the LoD for potentially undetected products. Therefore, there is a possibility that substances with the potential to migrate at levels of concern remained undetected and unidentified.

The Panel considered it likely that, based on the range of identified reaction and transformation products along with considerations of the likely mechanism(s) of oxidation of the PCOE substrate, there will be more oxidation products of similar character, but higher molecular mass/lower volatility. However, the Panel also considered it plausible that oxidation products of different nature, such as alpha, beta unsaturated carbonyl compounds or epoxides, may be formed and that the LoD corresponding to ca. [redacted] for individual substances is too high to rule-out a concern for such a possibility.

No data were provided to support that the PCOE oligomers tested in the toxicity studies were oxidised in an equivalent, comparable manner to the aged/oxidised or partially oxidised ones, especially when considering the oxygen scavenger catalyst (cobalt stearate). The oxidation that could happen in presence of the liver S9-mix or *in vivo* is expected to result in mono-oxygenation and not to be sufficient to represent the oxidation in plastic in presence of the catalyst and air. Thus, the oxidised oligomeric fraction < 1,000 Da and the other related reaction products are neither covered by the genotoxicity tests nor the 90-day study on the PCOE oligomers. The applicant provided an assessment of the potential migrants that were identified and those that could be anticipated while remaining undetected (and so unidentified) at the LoD of [redacted] The information (authorisation, literature, assessment by EFSA or other international safety institutions) presented by the applicant demonstrated the safety of the potential identified migrants. For the anticipated potential migrants, the applicant provided data for possible read-across that were not substantiated enough to perform the analysis (i.e. representativeness of the source versus the target substances), and hence, to rule out safety concern. Additionally, considering the LoD of [redacted] and according to the EFSA 'Note for Guidance' (2020), subchronic potential toxicity as well as the potential for accumulation of the substances should be addressed.

The application intends direct contact of the food with the active layer (covered by the total mass transfer assumed by the applicant) as well as indirect contact where a passive plastic layer is used between the active layer and the food. However, the Panel noted that the passive layer could rapidly become populated by the potential migrants (and/or their chemical precursors, considering the oxidation function) due to diffusion during storage and particularly during the high temperature during extrusion if (co)-extrusion was used in the manufacturing process of the multi-layer films/articles. Moreover, as this layer must be readily permeable for oxygen, its barrier efficiency against the

migration of reaction products cannot be high. Therefore, the aforementioned considerations apply to both the direct and the indirect modes of the proposed application.

3.4. Conclusions

Because of the insufficient characterisation of the oxidation products, the CEP Panel was not able to conclude on the safety of the proposed use of cyclooctene homopolymer and cobalt stearate together as active substances in a layer for scavenging oxygen, either in direct contact with the food or separated from the food by a passive layer of polymer, such as PP or PE, as requested.

Documentation provided to EFSA

1) Initial dossier. June 2019. Submitted on behalf of Evonik Resource Efficiency GmbH.
2) Additional data. March 2021. Submitted on behalf of Evonik Resource Efficiency GmbH.
3) Additional data. February 2022. Submitted on behalf of Evonik Resource Efficiency GmbH.

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Abbreviations

bw	body weight
CEF Panel	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CEP Panel	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
CHO	Chinese hamster ovary
CoS	cobalt stearate
FCM	food contact material
[redacted]	[redacted]
$K_{o/w}$	octanol/water partition coefficient
[redacted]	[redacted]
LDPE	low density polyethylene

LMWF	low molecular weight fraction
LOAEL	lowest observed adverse effect level
LoD	limit of detection
LoQ	limit of quantification
[redacted]	[redacted]
MW	molecular weight
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PCOE	Polycyclooctene
PE	Polyethylene
PP	Polypropylene
SA:M	Surface area:food mass
SCF	Scientific Committee on Food
SML	specific migration limit
US FDA	United State Food and Drug Administration
w/w	weight by weight