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Safety assessment of the substance trimellitic acid, tris (2-ethylhexyl) ester, for use in food contact materials

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Abstract

This scientific opinion of the EFSA Panel on Food Contact Materials, Enzymes and Processing aids (CEP Panel) is on the safety assessment of trimellitic acid, tris(2-ethylhexyl) ester, intended to be used as a plasticiser in the manufacture of soft poly(vinyl chloride) (PVC) materials and articles, such as wrap films (single uses) and tubing (repeated uses) at up to approximately 10% and 40%, respectively. Under the tested conditions, the substance migrated up to 165 μg/kg food from wrap films and was not detected in food simulant in contact with tubing. Based on the three reported *in vitro* genotoxicity studies, the Panel concluded that the substance does not raise concern for genotoxicity. The lowest no observed adverse effect level (NOAEL), derived from a 90-day oral toxicity study, was 225 mg/kg body weight (bw) per day. Based on data on toxicokinetic and metabolism, the substance does not give rise to concern for accumulation in humans. The substance does not cause developmental effects as induced by phthalic acid, bis(2-ethylhexyl) ester (DEHP). Assuming that impurities migrate pro-rata to a migration of the substance up to 5 mg/kg food, their estimated migration does not raise a safety concern. The Panel concluded that the substance does not raise safety concern for the consumer when used in the manufacture of soft PVC under the conditions requested by the applicant for (i) single use wrap films in contact with food for which simulants A, B and D1 are assigned, as well as (ii) tubing for repeated contacts with food for which simulants A and B are assigned. Overall, the use of the substance does not raise a safety concern if its migration does not exceed 5 mg/kg food. Due to the additional contribution from other sources of exposures, the application of an allocation factor should be considered.

Keywords: trimellitic acid, tris(2-ethylhexyl) ester, plasticiser, CAS No 3319-31-1, FCM substance No 1078, PVC, food contact materials, safety assessment, evaluation

Requestor: Ministero della Salute, Italy

Question number: EFSA-Q-2017-00645

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Competing interests: Roland 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 (http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf), a waiver was granted to Roland Franz regarding his participation to the EFSA's Working Group on Food Contact Materials (FCM WG) in accordance with Article 21 of the Decision of the Executive Director on Competing Interest Management. Pursuant to Article 21(6) of the above-mentioned Decision, the involvement of Roland Franz is authorised as member in the FCM WG, 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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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 Ministero della Salute, Italy, requesting the evaluation of the substance tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate with the CAS number 3319-31-1 and the FCM substance No 1078. The dossier was submitted by Polynt S.p.A. on behalf of Polynt S.p.A. and Oxea 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 has submitted a dossier in support of its application for the authorisation of the substance tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, to be used in plastic FCMs.

Additional information was provided by the applicant during the assessment process in response to the request from EFSA sent on 14 February 2018 (see Documentation provided to EFSA').

Data submitted and used for the evaluation are:

Non-toxicological data

- Chemical identity of the substance and its impurities
- Description of the manufacturing process
- Physical and chemical properties
- Intended uses
- Existing authorisation(s)
- Migration of the substance
- Residual content of the substance

Toxicological data

- Bacterial gene mutation test
- *In vitro* mammalian cell gene mutation test
- *In vitro* mammalian chromosome aberration test
- Repeated dose 90-day oral toxicity study in rats
- Comparative toxicity study
- Data on toxicokinetic and metabolism
- Developmental toxicity study in rats
- Transcriptomic study.

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).

[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.

The methodology is based on the characterisation of the substance that is 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 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 Scientific Committee, 2009) and considering the relevant guidance from the EFSA Scientific Committee.

3. Assessment

According to the applicant, the substance 'tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate', named by the Panel 'trimellitic acid, tris(2-ethylhexyl) ester' for being listed in the Union list, is intended to be used as a plasticiser in the manufacture of soft poly(vinyl chloride) (PVC) materials and articles, such as wrap films and tubing. In wrap films' formulations, this substance is intended to be used up to approximately 10% w/w, generally with other plasticisers, weighting all together ca. 25% of the films. In formulations for tubing, it is intended to be used up to approximately 40% w/w. Typical thicknesses are 11 μm for wrap films and 0.5 mm for tubing. Trimellitic acid, tris(2-ethylhexyl) ester is not intended to be used in materials and articles for contact with infant foods. The following conditions of contact are foreseen by the applicant:

Wrap films for single use in contact with:

- foodstuffs for which food simulants A and B are assigned by the Regulation (EU) No 10/2011[2] for long-term storage at room temperature and below, including heating up to 70°C for up to 2 h, or heating up to 100°C for up to 15 min;
- foodstuffs for which food simulant D1 is assigned by the Regulation (EU) No 10/2011 for long-term storage at frozen conditions.
- The ratio of surface to volume in single use applications is indicated to be up to 10 dm^2/kg food.

Tubing for repeated uses in contact with:

- foodstuffs for which food simulants A and B are assigned by the Regulation (EU) No 10/2011 for up to 24 h at temperatures up to 40°C.

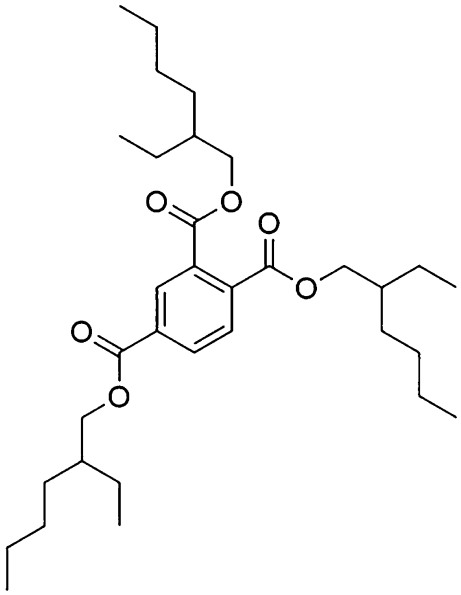
Trimellitic acid, tris(2-ethylhexyl) ester was not evaluated by the SCF and the EFSA in the past. It is listed in the notified draft for a German regulation on printing inks for FCMs[3] with an specific migration limit (SML) of 0.05 mg/kg food on the basis that it was evaluated to be not genotoxic. Trimellitic acid, tris(2-ethylhexyl) ester is also covered by the FDA Food Contact Notification (FCN) No 1587 with the limitation/specifications that the substance '…is intended to be used as a plasticizer at levels not to exceed 30% by weight in repeated-use food-contact vinyl chloride polymers intended to contact all types of food. The finished product is not for use in contact with infant formula and breast milk. Such uses are not included as part of the intended use of the substance in the FCN'.[4]

[2] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1.
[3] http://ec.europa.eu/growth/tools-databases/tris/en/index.cfm/search/?trisaction=search.detail&year=2016&num=333&mLang=EN
[4] https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=ENV-FCN&id=1587

According to the applicant, trimellitic acid, tris(2-ethylhexyl) ester is widely used for a range of non-FCMs, such as PVC medical devices and medical tubing, car interior components and wire insulations. According to the European Chemicals Agency (ECHA), the 'substance is manufactured and/or imported in the EU area in 10,000 to 100,000 tonnes per year'.[5]

3.1. Non-toxicological data

Chemical formula: $C_{33}H_{54}O_6$
Molecular weight: 546.76 Da
Chemical structure:



Trimellitic acid, tris(2-ethylhexyl) ester is manufactured by esterification of trimellitic anhydride (CAS No 552-30-7; EC FCM No 349; total specific migration limit (SML(T)), 5 mg/kg food) and 2-ethylhexanol (CAS No 104-76-7; EC FCM No 209; SML, 30 mg/kg food).

According to the applicant, the minimum purity of trimellitic acid, tris(2-ethylhexyl) ester is 98%. Impurities are di(2-ethylhexyl) terephthalate (CAS No 6422-86-2; EC FCM No 798; SML(T), 60 mg/kg food), phthalic acid, bis(2-ethylhexyl) ester (DEHP, CAS No 117-81-7; EC FCM No 283; SML, 1.5 mg/kg food, plus restriction on the uses), 2-ethylhexanol (CAS No 104-76-7; EC FCM No 209; SML, 30 mg/kg food), di(2-ethylhexyl) isophthalate (CAS No 137-89-3), tetra(2-ethylhexyl) pyromellitate (CAS No 3126-80-5) and tricarboxylic esters < C8 and > C8. The Panel noted the ongoing mandate from the European Commission to update the 2005 AFC Panel risk assessment of 5 phthalates[6] that may affect the existing SML on DEHP noted here as impurity.

Trimellitic acid, tris(2-ethylhexyl) ester is a liquid (melting point determined as −43°C). The boiling point is indicated as 430°C. It has a log $P_{o/w}$ estimated in the range of 6–9, hence is soluble in organic solvents and has limited solubility in water (3 μg/L at 25°C as given by the applicant; 130 μg/L at 25°C from the OECD SIDS, 2002). It may be subject to hydrolysis, trans-esterification and oxidation. Trimellitic acid, tris(2-ethylhexyl) ester is thermally stable at the maximum temperature operated in the manufacture of soft PVC, indicated to be approximately 180°C.

The migration of trimellitic acid, tris(2-ethylhexyl) ester was tested by immersion of a 11-μm wrap film in single use condition and a tubing of 0.5 mm thickness/3 mm inner diameter in repeated use condition under representative conditions of time and temperature. Its contents were measured in both wrap film and tubing samples and were representative of the intended formulations. For both articles, the surface to volume ratio was 10 dm^2/L simulant. The migration from the film samples during 10 days at 60°C in contact with 10% ethanol (simulant A) and 3% acetic acid (simulant B) was up to 0.165 mg/kg food. Migration during 10 days at 20°C into 50% ethanol (simulant D1) was 0.085 mg/kg. For repeated use applications, a tubing was tested with 10% ethanol and 3% acetic acid for 24 hours at 40°C. In the third migration solution, trimellitic acid, tris(2-ethylhexyl) ester was not detectable at a detection limit of 0.020

[5] https://echa.europa.eu/it/substance-information/-/substanceinfo/100.020.019
[6] EFSA-Q-2017-00588/-00589/-00590, EFSA-Q-2018-00800/-00801, see EFSA webpage http://registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin?5.

mg/kg. The surface to volume ratio applied in the test (10 dm^2/L) does not cover narrow tubing (e.g. 133 dm^2/L for a 3-mm inner diameter tubing) but was considered acceptable for dynamic conditions and taking the solubility-controlled migration into account.

With regard to the potential migration of the above-mentioned six impurities, three of them are authorised with a SML and the three remaining (di(2-ethylhexyl) isophthalate, tetra(2-ethylhexyl) pyromellitate and tricarboxylic esters < C8 and > C8) have a solubility similar to that of trimellitic acid, tris(2-ethylhexyl) ester. Consequently, sbased on their respective percentage in trimellitic acid, tris(2-ethylhexyl) ester (up to ca. 0.35%), their migration can be estimated pro-rata with the measured migration of trimellitic acid, tris(2-ethylhexyl) ester to be each in the range of 1 μg/kg food.

The use of trimellitic acid, tris(2-ethylhexyl) ester for soft PVC in contact with fatty and dry foods was not requested. The Panel noted that the migration into fatty food[7] is expected to be very high, whereas migration into dry foods[7] is expected to be low, if any.

3.2. Toxicological data

3.2.1. Genotoxicity

To evaluate the genotoxic potential of trimellitic acid, tris(2-ethylhexyl) ester, three *in vitro* genotoxicity assays were performed, an Ames test, a mouse lymphoma TK mutation test and a chromosomal aberration in cultured human lymphocytes test.

In an Ames test, trimellitic acid, tris(2-ethylhexyl) ester (purity: 98.37%; diluted in ethanol) was tested for its ability to induce gene mutation in four histidine-requiring strains of *Salmonella* Typhimurium (TA1535, TA1537, TA98 and TA100) and one tryptophan-requiring strain of *Escherichia coli* (WP2 *uvrA*). These assays were conducted both in the absence and in the presence of metabolic activation (rat liver S9 fraction). Assays were performed in accordance with Good Laboratory Practice (GLP) and following OECD TG No 471 (adopted July 1997) at the following five doses: 313, 625, 1,250, 2,500 and 5,000 μg/plate using the plate incorporation method. Trimellitic acid, tris(2-ethylhexyl) ester did not induce relevant increases in numbers of revertants at any tested dose with or without metabolic activation. An assay with preincubation performed in the same conditions led to the same conclusions. The Panel concluded that trimellitic acid, tris(2-ethylhexyl) ester was not mutagenic in bacteria under the conditions employed in this study.

Trimellitic acid, tris(2-ethylhexyl) ester (purity: 98.37%; diluted in ethanol) was tested for its ability to induce mutation in L5178 TK+/- mouse lymphoma cells using the fluctuation method in the absence and in the presence of metabolic activation (rat liver S9 fraction). These experiments were performed in accordance with GLP and following OECD TG No 476 (adopted July 1997). Two separate experiments were performed, one assay was performed after a 3-h treatment time with or without metabolic activation and one assay was performed after a 24-h treatment time in the absence of metabolic activation. The following doses were tested: 78.1, 156, 313, 625, 1,250 and 2,500 μg/mL. With regard to mutation frequencies, no statistically significant increase was observed at any dose levels or treatment time and with or without metabolic activation compared to negative control. The Panel concluded that trimellitic acid, tris(2-ethylhexyl) ester did not induce gene mutation under the conditions used in this study.

Trimellitic acid, tris(2-ethylhexyl) ester (purity: 98.37%; diluted in ethanol) was tested for its ability to induce chromosomal aberration in cultured human lymphocytes after *in vitro* treatment, in the presence and in the absence of metabolic activation (rat liver S9 fraction). These experiments were performed following OECD TG No 473 (adopted July 1997) and according to GLP. The following doses in two separate experiments were tested: 39.1, 78.1, 156, 313, 625, 1,250, 2,500 and 5,000 μg/mL. For the first experiment, the treatment time was 3 h both in the presence and in the absence of metabolic activation. For the second experiment, the treatment time was 24 h in the absence of metabolic activation. Based on the mitotic index, the doses selected for scoring were 1,250, 2,500 and 5,000 μg/mL. Hundred metaphase spreads were scored for chromosomal aberration for each culture. Without metabolic activation, two endoreplicated cells were found in the control and one in the 1,250 μg/mL group and one polyploïd cell was found in the 2,500 μg/mL dose group. With metabolic activation, one endoreplicated cell was found in the 1,250 μg/mL dose group and one in the 2,500 μg/mL dose group. The Panel concluded that these increases were incidental considering the lack of dose–response relationship and concluded that trimellitic acid, tris(2-ethylhexyl) ester did not induce structural and numerical chromosomal aberration under the conditions used in this study.

[7] As assigned in Annex III of the Regulation (EU) No 10/2011.

Therefore, based on the negative results observed in the three reported *in vitro* studies, the Panel concluded that trimellitic acid, tris(2-ethylhexyl) ester does not raise concern for genotoxicity.

3.2.2. Repeated dose 90-day oral toxicity study in rats

The safety of trimellitic acid, tris(2-ethylhexyl) ester was examined in a subchronic (13-week) oral toxicity study in Sprague–Dawley rats, conducted following OECD TG No 408 (adopted September 1998). Four dose groups comprising 10 males and 10 females each received trimellitic acid, tris(2-ethylhexyl) ester (purity 98.67%) in the diet at the following approximate doses: 0 (control), 50, 225 and 1,000 mg/kg body weight (bw) per day. Mean daily achieved doses were for males: 51, 226 and 992 mg/kg bw and for females: 52, 233 and 1,023 mg/kg bw. Ten additional males and 10 additional females were added to the 1,000 mg/kg bw per day dose group for recovery assessment.

No mortality was observed during the study. Sensory reaction and motor activity assessments performed at the end of the study did not show statistically significant differences between treated animals and controls. Food consumption was not affected by trimellitic acid, tris(2-ethylhexyl) ester and no statistical differences in body weight or body weight changes were observed between control and treated animals. Ophthalmoscopy did not reveal any treatment-related ocular changes. Thrombocytosis and neutrophilia were observed in the 1,000 mg/kg bw per day treated animals after the dosing phase but not after the recovery period. Clinical chemistry revealed a statistically significant increase of alkaline phosphatase, γ-glutamyl transferase, cholesterol and sodium, and a decrease of globulin in male rats treated with 225 or 1,000 mg/kg bw per day. These changes were reversible. In females treated with 225 or 1,000 mg/kg bw per day, a decrease of alanine and aspartate transaminases, bilirubin, protein and globulin bile acids were observed as well as an increase of urea and chloride. These changes were reversible except those observed for aspartate aminotransferase and chloride but were of minimal severity. Reversible non-dose-related proteinuria was observed in the treated males. Histopathological evaluations revealed no treatment-related findings on reproductive organs in males and females of the control and the high-dose groups.

Decreases in absolute and relative spleen weights were observed in males treated with 1,000 mg/kg bw per day but were reversible. Significant increases of the absolute weight of the liver were observed in the females treated with 1,000 mg/kg bw per day. Relative weights of the liver were statistically significantly increased in males and females of the high-dose group. Absolute and relative weights of the liver in females of the high-dose group were still statistically significantly increased at the end of the recovery period.

Microscopic observations revealed treatment-related findings in the liver of animals of both sexes of the high-dose group as well as in the spleen of females of the same dose group. In liver, findings were diffused hepatocytic hypertrophy and increase incidence of extramedullary haematopoiesis compared to animals of the control, low- and mid-dose groups. Extramedullary haematopoiesis was also observed in the spleen of females of the high-dose group. These changes were not observed after the 4-week recovery period. These findings in relation to the increase of the relative weight of the liver (up to 14% in females and 20% in males in the high-dose group) were considered as adverse.

The Panel concluded that based on the effects observed in the liver in the high-dose group, the no observed adverse effect level (NOAEL) for trimellitic acid, tris(2-ethylhexyl) ester under the condition of the study was 225 mg/kg bw per day.

3.2.3. Comparative toxicity between DEHP and trimellitic acid, tris(2-ethylhexyl) ester

Due to similar structure between the applied substance and DEHP, Shehata et al. (2013) compared the effects of the administration of 300 mg/kg by oral gavage to male rats for 4 weeks of either DEHP or trimellitic acid, tris(2-ethylhexyl) ester diluted in corn oil. GLP status was not claimed. Three groups of 12 animals were established: Group I was the control group, rats in group II received DEHP and those in group III received trimellitic acid, tris(2-ethylhexyl) ester. Rats were treated for 4 weeks (6 days/week). At the end of the treatment period, half of the rats were sacrificed, and half were left for a 4-week recovery period.

Histological examination of the livers from the trimellitic acid, tris(2-ethylhexyl) ester-treated rats showed clear differences with those from the rats treated with DEHP. After DEHP administration, some hepatocellular changes at different degrees appeared. The more severe changes were the loss of normal lobular architecture, periportal cellular infiltration, congestion and dilatation of the portal veins. These changes were still observed after the 4-week recovery period but were less pronounced. After

administration of trimellitic acid, tris(2-ethylhexyl) ester, the lobular architecture of the liver was preserved, however some effects on the vascular hepatic system were observed (prominent Kupffer cells in the congested blood sinusoids). These were not observed in the liver of rats from the recovery subgroup. Immunohistochemical analyses using anti Hep Par1 antibody (a sensitive marker for hepatocellular carcinoma) revealed narrow immunoreaction around the central veins in livers from the control and the trimellitic acid, tris(2-ethylhexyl) ester-treated groups and wide in livers from the DEHP group.

In conclusion, the Panel noted that some of the histopathological effects (e.g. loss of normal lobular architecture) observed after the administration of 300 mg DEHP/kg bw per day were not observed after the administration of the same dose of trimellitic acid, tris(2-ethylhexyl) ester under the condition used in this study.

3.2.4. Developmental toxicity and transcriptomic studies

A pre- and post-natal developmental toxicity study was performed in Sprague–Dawley rats according to OECD TG No 414 (Renauta and Whiteley, 2017). The study investigated the effects of 100, 500 and 1,050 mg of trimellitic acid, tris(2-ethylhexyl) ester/kg bw per day (oral gavage) and of 750 mg DEHP/kg bw per day (equimolar to 1,050 mg of trimellitic acid, tris(2-ethylhexyl) ester) on embryo–fetal development and post-natal development of the offspring through sexual maturity (termination at 6 weeks for females and 15 weeks for males). Trimellitic acid, tris(2-ethylhexyl) ester or DEHP was administered to 35 mated females per group from gestational days (GD) 6–19 inclusive. On GD 20, 20 females were sacrificed, and the remaining females were treated until lactation day 20.

A wide range of developmental findings observed in the DEHP-treated rats were not found in rats treated with trimellitic acid, tris(2-ethylhexyl) ester. The only effect reported for trimellitic acid, tris(2-ethylhexyl) ester is retained areolar regions in male offspring of the highest dose group.

Based on the findings (retained areolar regions in males) in the 1,050 mg/kg bw per day dose group, the NOAEL was set at 500 mg/kg bw per day.

The potential of trimellitic acid, tris(2-ethylhexyl) ester to induce testicular maldevelopment (TMD) in the rat was studied by the mean of the expression of the genes in pathways involved in steroidogenesis and testes development (shown to be involved in the induction of TMD by some phthalate esters). Pregnant rats received, by gavage, daily administration of different treatments between gestation days 12–19. Treatments were trimellitic acid, tris(2-ethylhexyl) ester (500 mg/kg bw), di(2-ethylhexyl) phthalate (DEHP, 500 mg/kg bw), mono(2-ethylhexyl) phthalate (MEHP, active metabolite of DEHP, 500 mg/kg bw), 2-ethylhexanol (metabolite of DEHP, 500 mg/kg bw) and a solution containing 0.05% DEHP (0.25 mg/kg bw, DEHP being a potential impurity of the applied substance technical grade at a maximum concentration of 0.05%). On GD 19, dams were sacrificed and fetuses decapitated. Fetal gonads were dissected and deep frozen prior to RNA isolation for microarray analysis. Results showed that DEHP and MEHP induced a repression of the genes involved in the induction of TMD in the testes of the offsprings whereas trimellitic acid, tris(2-ethylhexyl) ester or the solution containing 0.05% DEHP did not. 2-Ethylhexanol induced a weak but statistically significant decrease of the repression of these genes.

The Panel noted that this additional information provides some evidence that the TMD-related effects of DEHP are not induced by trimellitic acid, tris(2-ethylhexyl) ester.

3.2.5. Toxicokinetic and metabolism

One report and two published articles were provided.

The absorption and metabolism of [hexyl-2-^{14}C] tri(2-ethylhexyl) trimellitate in the rat was studied. The ^{14}C-radiolabelled trimellitic acid, tris(2-ethylhexyl) ester (radiochemical purity greater than 99%) was mixed with trimellitic acid, tris(2-ethylhexyl) ester (purity 91.7%) diluted in corn oil prior to the oral administration of 100 mg/kg bw by gavage to four male Sprague–Dawley rats. After dosing, rats were placed in metabolism chambers to collect exhaled air, faeces and urine and radioactivity was measured up to 144 h after administration. Analyses showed that the radioactivity was predominantly recovered in the faeces (75% of the administered dose). 16.3% of the radioactivity was recovered in the urine and 1.9% in the exhaled air. 144 h after administration, the total recovery of radioactivity was 94.1% of the administered dose. In the faeces, 85% of the radioactivity was trimellitic acid, tris (2-ethylhexyl) ester, 7% was di(2-ethylhexyl) trimellitate and 1% was mono(2-ethylhexyl) trimellitate. In urine, analyses demonstrated only the presence of the following metabolites: 2-ethylhexanol, 2-ethylhexanoic acid, 2-heptanone and mono(2-ethylhexyl) trimellitate. Elimination of $^{14}CO_2$ was

biphasic (half-lives estimated at 4.3 and 31 h). Urinary excretion of the radioactivity was also biphasic with elimination half-lives in the same order of magnitude (3.1 and 42 h).

Martis et al. (1987) reported the results of a disposition kinetics study of trimellitic acid, tris(2-ethylhexyl) ester following intravenous bolus administration of the radiolabelled trimellitic acid, tris(2-ethylhexyl) ester to male Sprague–Dawley rats. Plasma concentrations of trimellitic acid, tris(2-ethylhexyl) ester showed a biphasic decline. Distribution and apparent elimination half-lives were 46.2 min and 5.34 days, respectively. Volume of distribution was 7.49 L/kg. Excretion of the radioactivity in urine was low, since only 3.3% of the administered radioactivity was measured in urine over the entire experiment and 16.9% of the administered radioactivity was measured in the faeces over the entire experiment. With regard to tissue distribution, radioactivity was predominantly distributed in the liver, lungs and spleen (66.8, 13.1 and 3.8% of the administered radioactivity) at 48 h after drug administration. In the liver, radioactivity remained high 14 days after administration, 44.8% of the administered radioactivity was still present in the liver.

Höllerer et al. (2018) published the human metabolism and kinetic of trimellitic acid, tris(2-ethylhexyl) ester after oral administration to four healthy volunteers (2 males and 2 females). The metabolic pathway of trimellitic acid, tris(2-ethylhexyl) ester was postulated based on structural similarity with DEHP. Concentrations of all postulated metabolites were measured in urine and blood samples. Results showed that trimellitic acid, tris(2-ethylhexyl) ester is regioselectively hydrolysed to its diesters di(2-ethylhexyl) trimellitates (1,2-DEHTM, 2,4-DEHTM) and to its monoester isomers mono(2-ethylhexyl) trimellitates (1-MEHTM, 2-MEHTM). Trimellitic acid, tris(2-ethylhexyl) ester had a longer elimination half-life (27 h) compared to all measured metabolites. Overall 5.8% of the oral dose was recovered in urine. Renal excretion of metabolites was not complete for some metabolites at 72 h, especially for the main metabolite 2-MEHTM which accounted for 3.3% of the oral dose. This analysis identifies the metabolic pathway of trimellitic acid, tris(2-ethylhexyl) ester.

In conclusion, based on the studies reporting kinetic parameters after oral administration in rats and in humans, trimellitic acid, tris(2-ethylhexyl) ester is expected to be absorbed to a minor extent and excreted mainly unchanged in the faeces. Considering the low absorption and the elimination kinetics in rats and humans, the Panel concluded that the accumulation of trimellitic acid, tris(2-ethylhexyl) ester in humans is unlikely.

3.2.6. Conclusion on toxicity of trimellitic acid, tris(2-ethylhexyl) ester

Based on the data provided by the applicant, the Panel concluded that (i) trimellitic acid, tris(2-ethylhexyl) ester does not raise concern for genotoxicity; (ii) the lowest NOAEL identified in the studies is 225 mg/kg bw per day (derived from the 90-day oral toxicity study in rats) and (iii) trimellitic acid, tris(2-ethylhexyl) ester does not give rise to concern for accumulation in humans. The Panel also noted that trimellitic acid, tris(2-ethylhexyl) ester does not trigger developmental effects as induced by DEHP. Therefore, according to the SCF tiered approach, trimellitic acid, tris(2-ethylhexyl) ester itself does not raise a safety concern up to 5 mg/kg food.

3.2.7. Toxicity of the not listed impurities

No structural alerts for DNA reactivity are identified in di(2-ethylhexyl) isophthalate and tetra(2-ethylhexyl) pyromellitate (OECD QSAR ToolBox). No genotoxic potential is anticipated for tricarboxylic esters < C8 and > C8 by read across from trimellitic acid, tris(2-ethylhexyl) ester (a C8 tricarboxylic ester). The not listed impurities are evaluated to be of low toxicity (Cramer class I).

Assuming that these impurities migrate pro-rata to a migration of trimellitic acid, tris(2-ethylhexyl) ester up to 5 mg/kg food, their estimated migration does not raise a safety concern.

4. Conclusions

Based on the above-mentioned data, the CEP Panel concluded that the substance trimellitic acid, tris (2-ethylhexyl) ester does not raise a safety concern for the consumer when used in the manufacture of soft PVC under the conditions requested by the applicant for (i) single use wrap films in contact with food for which simulants A (10% ethanol), B (3% acetic acid) and D1 (50% ethanol) are assigned, as well as (ii) tubing for repeated contacts with food for which simulants A and B are assigned.

Overall, the use of trimellitic acid, tris(2-ethylhexyl) ester does not raise a safety concern if its migration does not exceed 5 mg/kg food. Due to the additional contribution from other sources that may add to the exposure from plastic FCMs, the application of an allocation factor should be considered.

FCMs made with trimellitic acid, tris(2-ethylhexyl) ester are not intended to be in contact with infant foods and the evaluation does not cover such uses. However, migration into water that may be used to reconstitute infant formula is expected to be negligible.

Documentation provided to EFSA

1) Initial dossier. September 2017. Submitted by Polynt S.p.A. on behalf of Polynt S.p.A. and Oxea GmbH.
2) Additional data. May 2019. Submitted by Polynt S.p.A. on behalf of Polynt S.p.A. and Oxea GmbH.

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Abbreviations

AFC	Scientific Panel on Additives, Flavourings, Processing Aids and Materials in Contact with Food
bw	body weight
CEP	Scientific Panel on food contact Materials, Enzymes and Processing Aids
DEHP	phthalic acid, bis(2-ethylhexyl) ester
DEHTM	di(2-ethylhexyl) trimellitate
ECHA	European Chemicals Agency
FCN	food contact notification
FCM	food contact materials
FDA	US Food and Drug Administration
GD	gestational days
GLP	good laboratory practice
MEHP	mono(2-ethylhexyl) phthalate
MEHTM	mono(2-ethylhexyl) trimellitate
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PVC	poly(vinyl chloride)
QSAR	quantitative structure–activity relationship
RNA	ribonucleic acid
SCF	Scientific Committee on Food
SML	specific migration limit
SML(T)	total specific migration limit
TMD	testicular maldevelopment