Safety assessment of the substance benzophenone-3,3′,4,4′-tetracarboxylic dianhydride, 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 benzophenone-3,3′,4,4′-tetracarboxylic dianhydride (BTDA), FCM substance No 1083, as co-monomer for the production of polyimides used in repeated use materials and articles that are in contact with acidic and fatty foods at temperatures up to 250°C. Migration of BTDA from a polyimide containing 43% BTDA, into olive oil was below the limit of quantification of about 3 µg/kg food, and in 3% acetic acid it decreased from 30.3 µg/kg in the first test to 22.1 µg/kg in the third test (2 h/100°C). In a semi-quantitative screening using acetonitrile and acetonitrile/water to extract the polymer powder, linear and cyclic oligomers were detected at levels below 1 mg/kg material. In thermal desorption of the polymer powder at 250°C, phenol, tentatively identified were found, but the modelled migrations of these were far below a level of potential concern. The substance did not induce gene mutations in bacterial and mammalian cells. In an in vitro chromosomal aberration test, the substance was found to be directly clastogenic in the absence of metabolic activation. In an in vivo follow-up, the substance did not induce the formation of micronuclei in experimental conditions associated with evidence of systemic exposure and therefore the Panel considered that the substance does not raise concern for genotoxicity. The CEP Panel concluded that the use of the substance BTDA is not of safety concern for the consumer if it is applied at up to 43% as a co-monomer in the production of polyimides for repeated use contact with acidic or fatty foods at temperatures up to 250°C. In addition, the migration of BTDA should not exceed 50 µg/kg.

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Keywords: benzophenone-3,3′,4,4′-tetracarboxylic dianhydride, BTDA, CAS No 2421-28-5, co-monomer, food contact materials, safety assessment, evaluation

Requestor: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany

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**Competing interests:** R. Franz declared that Fraunhofer institute at which he was 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 R. 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 R. 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.

**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 has been provided under confidentiality and it is redacted awaiting the decision of the Commission: composition of sample used for migration/extraction/thermal desorption tests; results of (i) screening for impurities, (ii) screening of polymer powder extracts, (iii) thermal desorption analysis of the polymer powder, (iv) migration modelling; details of study conduction and results of *in vitro* and *in vivo* genotoxicity tests.

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# Table of contents

Abstract ................................................................................................................................................... 1  
1. Introduction ................................................................................................................................4  
  1.1. Background and Terms of Reference as provided by the requestor ........................................ 4  
2. Data and methodologies .............................................................................................................. 4  
  2.1. Data ........................................................................................................................................... 4  
  2.2. Methodologies ............................................................................................................................. 4  
3. Assessment ................................................................................................................................. 5  
  3.1. Non-toxicological data ............................................................................................................... 5  
    3.1.1. Identity of the substance ....................................................................................................... 5  
    3.1.2. Physical and chemical properties ........................................................................................ 6  
    3.1.3. Specific migration ................................................................................................................. 6  
    3.1.4. Screening of migrating reaction products related to the substance ..................................... 6  
  3.2. Toxicological data .................................................................................................................... 7  
    3.2.1. Genotoxicity ....................................................................................................................... 7  
      3.2.1.1. Bacterial reverse mutation test ....................................................................................... 7  
      3.2.1.2. In vitro mammalian cell gene mutation test ..................................................................... 7  
      3.2.1.3. In vitro mammalian chromosomal aberration test ....................................................... 8  
      3.2.1.4. In vivo mammalian erythrocyte micronucleus test ....................................................... 8  
      3.2.1.5. Genotoxicity of non-listed impurities/reaction products ............................................... 9  
      3.2.1.6. Conclusions on genotoxicity ......................................................................................... 9  
4. Discussion .................................................................................................................................. 9  
5. Conclusions ............................................................................................................................... 10  
Documentation provided to EFSA .............................................................................................................. 10  
References ............................................................................................................................................... 10  
Abbreviations ........................................................................................................................................... 11

Benzophenone-3,3',4,4'-tetracarboxylic dianhydride, for use in food contact materials
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 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 Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, requesting the evaluation of the substance benzophenone-3,3',4,4'-tetracarboxylic dianhydride (BTDA), with the CAS number 2421-28-5, and the FCM substance No 1083. The dossier was submitted by MDCTec Science GmbH on behalf of Evonik Fibres 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 their application for the authorisation of benzophenone-3,3',4,4'-tetracarboxylic dianhydride (BTDA) to be used in FCM.

Additional information was provided by the applicant during the assessment process in response to a request from EFSA sent on 02 July 2019 and was consequently provided (see ‘Documentation provided to EFSA’).

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
- Migration of the substance
- Residual content of the substance
- Identification, quantification and migration of reaction products and impurities

Toxicological data
- Bacterial gene mutation test
- In vitro mammalian cell gene mutation test
- In vitro mammalian chromosome aberration test
- Mammalian erythrocyte micronucleus test

2.2. Methodologies

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

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

3. Assessment

According to the applicant, the substance benzophenone-3,3',4,4'-tetracarboxylic dianhydride (BTDA) is intended to be used as a co-monomer in the production of polyimides along with other... [niteword]

In the mixture of monomers to produce polyimides, BTDA amounted to 43%, which is stated to be the maximum percentage in the formulation.

Due to its heat stability and creep resistance, the final polymers are used in frictional elements of baking ovens and bearings of food processing equipment (e.g. cutter for meat and sausage processing). Potential food contact conditions for these repeated use applications were specified as up to 60°C for up to 2 h with acidic or fatty foods or up to 250°C for up to 1 h.

The use of the substance has not previously been authorised for food contact in Europe or elsewhere.

3.1. Non-toxicological data

3.1.1. Identity of the substance

Chemical formula: C_{17}H_{6}O_{7}

![Chemical structure of BTDA](image)

**Figure 1:** Chemical structure of BTDA
The substance BTDA has a molecular mass of 322 g/mol. It is synthesised by reaction of o-xylene with acetaldehyde in the presence of sulfuric acid, through which 1,1-bis-(3,4-dimethylphenyl)ethane (di-xylylethane) is formed.\(^2\) Using nitric acid, the latter is oxidised to 3,3',4,4'-benzophenone tetracarboxylic acid (BTA), which is converted by heating to BTDA (the anhydride). The purity of the thus produced substance is \(\geq 98\%\) (determined by gas chromatography (GC)/flame ionisation detector (FID)). According to specifications, the main impurity, BTA, has to be below 1.2\%.\(^3\)

The applicant provided data on screening for impurities in the substance using GC/FID, GC/mass spectrometry (MS), high-performance liquid chromatography (HPLC)/ultra violet (UV) and HPLC/MS analysis.\(^4\) Various and were found. Furthermore, two were tentatively identified. In the absence of authentic standards, their level was estimated to be in the range of (depending on the method of analysis).

### 3.1.2. Physical and chemical properties\(^5\)

BTDA has a melting point of 218°C; decomposition starts at 360°C and is slightly soluble in water. BTDA rapidly hydrolyses to BTA; in the presence of alcohols, esters are formed. Reaction of BTDA with amines generates amic acids that can be further dehydrated to imides.

### 3.1.3. Specific migration\(^6\)

Specific migration of the substance (measured as BTA) into food was determined for a polyimide made from 43\% (w/w) BTDA, . It was simulated by three consecutive tests with 3\% acetic acid and olive oil for 2 h at 100°C, 2 h at 70°C and 10 days at 40°C. Migration solutions were analysed via HPLC/MS. Under all conditions, migration into olive oil was below the limit of quantification (LOQ) of about 3 \(\mu\)g/kg food (food contact surface area to volume (s/v) ratio: 6 dm\(^2\)/kg). In the first test, the migration into 3\% acetic acid after 2 h/100°C was 30.3 \(\mu\)g/kg (s/v ratio: 6 dm\(^2\)/kg); in the third, it was 22.1 \(\mu\)g/kg. After 2 h at 70°C, migration in the third test into 3\% acetic acid was below the LOQ of 3 \(\mu\)g/kg food.

### 3.1.4. Screening of migrating reaction products related to the substance

Low molecular mass constituents in the powdered polyimide were screened in extracts obtained from the same polyimide with acetonitrile and acetonitrile/water (1:1) during 4 h at 100°C by GC/MS, GC/FID and HPLC/MS.\(^7\) were identified by HPLC/MS. In a semi-quantitative analysis by GC/MS and GC/FID, monomers used to manufacture the polyimide, impurities from these monomers and condensation products of these monomers (linear and cyclic oligomers) were detected below 1 mg/kg polyimide.

The polyimide was also tested for migration of selected oligomers and 2,4-toluene diamine (2,4-TDA; from ) into the food simulant 3\% acetic acid and acetonitrile (for oligomers) under the following time/temperature conditions: 2 h at 70°C and 2 h at 100°C for 2,4-TDA as well as 2 h at 100°C for oligomers.\(^8\) The migrates were analysed by HPLC/MS. No linear or cyclic oligomers were detected at a detection limit of around 30 \(\mu\)g/kg. No migration of TDA into 3\% acetic acid was detected for the test conducted at 70°C (detection limit, 1.5 \(\mu\)g/kg), but at 100°C, the migration varied between 2.2 and 3.5 \(\mu\)g/kg food (s/v ratio: 6 dm\(^3\)/kg; similar results in three consecutive tests).

Substances potentially migrating in high temperature applications were screened by thermodesorption from polyimide powder in a flow of nitrogen during 1 h at 250°C using Carbopack/Carbosieve as trap and GC/MS.\(^9\) Highest concentrations in the polymer were found for
No other nitrated compounds were detected (e.g. no benzophenones), but the Panel considered that their presence cannot be excluded, considering the limitations of the gas chromatographic analysis and the identification based on chemical structures which could be expected.

The migration of the tentatively identified to food under repeated use conditions for 1 h at 250°C and for an s/v ratio of 6 dm²/kg food was estimated by migration modelling for the third contact to be . It was assumed that thermodesorption extracted the whole content in the powder. The Panel considered the identification of these compounds as uncertain and that also mono-nitrated compounds as well as nitrated benzophenones could be present, but the total migration would still be expected to be low. Under the same conditions, the migration of detected as an impurity of the substance at , it was assumed by the applicant that would have been bonded into the polymer. Then, the migration from the polyimide to food under repeated use conditions for 1 h at 250°C was estimated to be food in the third test (s/v ratio: 6 dm²/kg food). The Panel considers that even an integration of the substance into the polymer lower than would result in a migration of no concern, as confirmed by not being detected by extraction or thermal desorption from the polymer.

3.2. Toxicological data

A full battery of genotoxicity tests for BTDA has been provided, i.e. a bacterial gene mutation assay (Ames test), an in vitro mammalian cell gene mutation test, an in vitro mammalian chromosomal aberration test and an in vivo mammalian erythrocyte micronucleus test.

The applicant also submitted summaries of a prenatal developmental toxicity study (OECD Guideline 414) and a repeated dose 90-day oral toxicity in rodents (OECD Guideline 408). However, no full study reports were available. In addition, the Panel noted the low migration of the substance (< 0.05 mg/kg food), in which case the submission of these toxicological studies is not required according to the tiered approach (European Commission, 2001), and therefore did not further consider these two studies in this assessment.

3.2.1. Genotoxicity

3.2.1.1. Bacterial reverse mutation test

The test substance BTDA ( ) was tested in a bacterial reverse mutation assay (Ames test) performed according to the OECD Test Guideline 471 (OECD, 1997) and following Good Laboratory Practice (GLP). Five strains of Salmonella Typhimurium (TA98, TA100, TA1535, TA1537 and TA102) were used in the presence or absence of metabolic activation by liver S9 from Aroclor1254-induced rats. Based on the results of preliminary cytotoxicity assays, 1,000 μg/plate was chosen as top dose for the main study. Two separate experiments were performed using the plate incorporation and the preincubation methods, with six concentrations of the test substance (3.16, 10.0, 31.6, 100, 316 and 1,000 μg/plate) tested in triplicate. Dimethyl sulfoxide (DMSO) was used as vehicle. Toxic effects, evident as a reduction in the number of revertants, occurred in all strains at 1,000 μg/plate. Upon treatment with the substance, there was no dose-related and/or statistically significant increase in revertant colony numbers above the control values in any strain with or without S9-mix.

The Panel concluded that the substance did not induce gene mutations under the test conditions employed in this study.

3.2.1.2. In vitro mammalian cell gene mutation test

The test substance BTDA ( ) was tested in a gene mutation assay at the thymidine-kinase (TK) locus in the mouse lymphoma L5178Y cell line following the OECD TG 490 (OECD, 2015) and GLP. A preliminary toxicity experiment was performed to select maximum
test concentrations, which were set at 1.4 and 1.5 mg/mL without and with metabolic activation, respectively. The main experiment was performed using a short (4 h) exposure period, with and without metabolic activation by liver S9 from rats induced with phenobarbital/β-naphthoflavone. Eight concentrations (0.05, 0.1, 0.2, 0.4, 0.8, 1.0, 1.1 and 1.4 mg/mL without S9, and 0.6, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3 and 1.5 mg/mL with S9) were tested in single cultures. Precipitation was observed at the top dose in the experiment with S9. A decrease of cell growth rate was observed in treated cultures both with and without metabolic activation: relative total growth was 10.7% at 1.4 mg/mL without S9, and 29.4% at 1.5 mg/mL with S9. No dose-related increase of mutation frequency, and no increase of mutant frequencies above the Global Evaluation Factor was observed in treated cultures, with and without metabolic activation. Spontaneous mutation frequencies were in the acceptable range.

The Panel concluded that the substance did not induce mutations at the gene and/or chromosome level under the test conditions employed in this study.

### 3.2.1.3. *In vitro* mammalian chromosomal aberration test

The test substance BTDA was tested in an *in vitro* chromosomal aberration test carried out in human peripheral blood lymphocytes according to the OECD Test Guideline 473 (OECD, 2014) and following GLP.

The test substance was dissolved in and tested in a preliminary dose-finding experiment in the dose range 2.0 mg/mL (maximum recommended dose). Based on the results of the preliminary toxicity assay, the following doses were selected for the main experiment: 1.0, 1.5 and 2.0 mg/mL for the short-term treatment (4 h) with and without metabolic activation (by liver S9 from phenobarbital/β-naphthoflavone induced rats); 0.5, 1.0 and 1.5 mg/mL for the continuous treatment (24 h) in the absence of S9-mix.

In experiment I (short-term treatment), the relative mitotic index was (without and with S9) at the top dose, . In this experiment, no increase in the incidence of cells bearing structural chromosomal aberrations and/or polyploidy was observed in treated cell cultures compared to vehicle controls, at any dose without and with metabolic activation.

In experiment II (extended treatment), the relative mitotic index at the top dose was . A slight increase in cells with structural chromosomal aberrations (mainly chromatid breaks) was observed at all tested doses . The frequency of cells with aberrations in treated groups exceeded the historical control range and was statistically significant at the top dose ($p < 0.05$, Fisher exact test).

In both experiments, no treatment-related increase in polyploid cells was observed.

The Panel concluded that the test substance was directly clastogenic in this test system, inducing structural chromosome aberrations after continuous (24 h) exposure in the absence of metabolic activation.

### 3.2.1.4. *In vivo* mammalian erythrocyte micronucleus test

The test substance BTDA was tested in the mouse erythrocyte micronucleus test, carried out in peripheral blood cells according to OECD Test Guideline 474 (OECD, 2016) and following GLP.

The substance was suspended in corn oil and administered orally at the maximum recommended dose of 2,000 mg/kg body weight (bw) (selected in a preliminary toxicity experiment), and at two lower doses (1,000 and 400 mg/kg bw) to groups of NMRI mice. Peripheral blood samples were collected 44 h and 68 h after administration of the test item. At least 10,000 polychromatic (immature) erythrocytes (PCE) per animal were scored by flow cytometry to determine the incidence of micronucleated cells. As a measure of cytotoxicity, the ratio between immature and mature erythrocytes (PCE) per animal were scored by flow cytometry to determine the incidence of micronucleated cells. As a measure of cytotoxicity, the ratio between immature and mature erythrocytes (PCE) was also determined. Animals administered with 400 and 1,000 mg/kg bw did not show any sign of systemic toxicity. Animals in the highest dose group showed mild signs of systemic toxicity:

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13 Technical dossier/section 8.1.2; Appendix B – Technical dossier/Annex 23.

14 Technical dossier/section 8.1.3; Appendix B – Technical dossier/Annex 27.
reduction of spontaneous activity, piloerection and half eyelid closure. The flow cytometric determination of micronuclei in immature erythrocytes displayed similar values for untreated and treated mice, with all values within the historical control range. An adequate positive response, with a distinct increase of micronucleated PCEs and a reduction of immature erythrocytes, was elicited by the positive control substance.

The Panel concluded that the test substance BTDA did not induce the formation of micronuclei in erythropoietic mouse cells under the test conditions employed in this study.

### 3.2.1.5. Genotoxicity of non-listed impurities/reaction products

No experimental genotoxicity data were available for BTDA impurities and reaction products. The applicant provided a structure–activity relationship (SAR) analysis by the Toxtree tool (https://ec.europa.eu/jrc/en/scientific-tool/toxtree-tool, Version 3.1.0). No alerts for genotoxic carcinogenicity were identified according to the Benigni/Bossa rule base for mutagenicity and carcinogenicity in

The two identified in the polymer as potential migrants show a structural alert for genotoxic carcinogenicity according to the Benigni/Bossa rule base for mutagenicity and carcinogenicity, due to the nitro aromatic chemical functionality. However, the Panel noted that expected migration of would not exceed the threshold for toxicological concern (TTC) for genotoxic carcinogens, and considered it of no toxicological concern.

### 3.2.1.6. Conclusions on genotoxicity

In summary, the test substance BTDA was tested in a battery of in vitro and in vivo genotoxicity assays. All studies were adequately performed, in compliance with current technical guidelines and GLP. BTDA was evaluated as negative in gene mutation assays in bacteria (Ames test) and in mammalian cells (TK+/− system in mouse lymphoma cells), both with and without metabolic activation. Negative results were also obtained in a chromosomal aberration assay in human peripheral lymphocytes following short-term exposure, with and without metabolic activation. In the same test system, however, extended exposure of cells to BTDA in the absence of metabolic activation resulted in a weak increase of cells with structural chromosomal aberrations, in the absence of signs of overt toxicity. In vivo, the administration of BTDA up to the maximum recommended dose did not induce any detectable increase in the formation of micronuclei in erythropoietic cells in experimental conditions associated with evidence of systemic exposure, as shown by the significant depression of erythropoietic cell proliferation induced by treatment.

Among BTDA impurities and reaction products, no alerts for genotoxicity were identified by SAR analysis in; an alert for potential genotoxicity is highlighted in, but their migration is lower that the TTC for genotoxic carcinogens.

Overall, the Panel concluded that the substance benzophenone-3,3',4,4'-tetracarboxylic dianhydride, and its impurities and reaction products, do not raise concern for genotoxicity.

### 4. Discussion

The substance BTDA does not raise concern for genotoxicity. According to the tiered approach (European Commission, 2001), migration of up to 50 μg/kg food is not considered of safety concern. According to the applicant, polyimides produced with BTDA as co-monomer are intended for repeated use applications and, accordingly, migration data were provided for three consecutive tests. The Panel considered that the use of the substance in polyimides made with would not raise a concern even if used in non-repeated use applications, taking into account that the migration of BTDA measured in the first tests was below 50 μg/kg: migration into olive oil was below the LOQ of 3 μg/kg food for all different time/temperature conditions; migration into 3% acetic acid amounted to 8.1 and 30.3 μg/kg food for 2 h at 70 and 100°C, respectively. For applications represented by these simulants, the applicant only intended temperatures up to 60°C, but the available data show that also migration at 100°C is of no concern.
The migration of impurities and reaction products from the polyimide made from BTDA, was estimated to be low and the total exposure below 0.15 μg/person per day even in the first use, which is the threshold of toxicological concern (TTC) for genotoxic compounds (EFSA Scientific Committee, 2019).

The Panel noted numerous difficulties and uncertainties in the analysis of the impurities in the substance and the reaction/degradation products of low molecular mass in the final polymer, particularly when the polymer is used at high temperatures: probably not all constituents were eluted from the chromatographic column and a number of substances were not or only tentatively identified. However, the Panel noted that the migration would lead to exposure below the TTC even if the presence of reaction products and impurities would have been underestimated by one to two orders of magnitude.

The evaluation of impurities and reaction products refers to polyimides made with Benzophenone-3,3’,4,4’-tetracarboxylic dianhydride. No data were provided for polyimides with other comonomers, for which the migration behaviour and the type of reaction products could be different and therefore not covered by this specific evaluation.

5. Conclusions

Based on the above-mentioned data, the CEP Panel concluded that the use of the substance benzophenone-3,3’,4,4’-tetracarboxylic dianhydride is not of safety concern for the consumer if it is applied, as requested by the applicant, at up to 43% as a co-monomer in the production of polyimides for repeated use contact with acidic or fatty foods at temperatures up to 250°C. In addition, the migration of BTDA should not exceed 50 μg/kg food.

Remark to the Commission

The Panel noted that during the production of BTDA products may be formed some of which show structural alerts for genotoxicity (e.g. the tentatively identified and ).

Documentation provided to EFSA

1) Initial dossier. December 2018. Submitted by MDCTec Science GmbH on behalf of Evonik Fibres GmbH.
2) Additional data. February 2020. Submitted by MDCTec Science GmbH on behalf of Evonik Fibres GmbH.

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Abbreviations

BTA 3′,4′,4′-benzophenone tetracarboxylic acid
BTDA benzophenone-3,3′,4,4′-tetracarboxylic dianhydride
bw body weight
CAS Chemical Abstracts Service
CEP Panel EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
DMSO dimethyl sulfoxide
FCM food contact materials
FID flame ionisation detector
GC gas chromatography
GLP Good Laboratory Practice
HPLC high-performance liquid chromatography
LOQ limit of quantification
MS mass spectrometry
PCE polychromatic (immature) erythrocytes
Po/w octanol/water partition coefficient
SAR Structure activity relationship
SCF Scientific Committee on Food
s/v ratio food contact surface area to volume ratio
TDA toluene diamine
TK thymidine-kinase
TTC Threshold of Toxicological Concern
UV ultraviolet