National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Dutch Committee for Safety Assessment of Food Contact Materials

CBVV

Opinion

on an application for authorisation under the Dutch Commodities Act Decree on packaging and consumer articles for

2-Butyl-2-ethyl-1,3-propanediol

CAS Number: 115-84-4

Submitting applicant: Synthomer Specialty Additives

CBVV-S1030-D0042

Adopted

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1. Introduction

Before a substance is authorised to be used in food contact materials (FCM) and is included in a positive list, an opinion on its safety is required. This is laid down in Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food[1], and implemented in the Dutch Commodities Act Decree on packaging and consumer articles (Warenwetbesluit verpakkingen en gebruiksartikelen)[2] and its corresponding Regulation (Warenwetregeling verpakkingen en gebruiksartikelen)[3]. In case industry seeks authorisation for a substance that is not yet on a positive list and which is used in a material for which so far no harmonized EU legislation applies, it may submit an application for authorisation to the Dutch Committee for Safety Assessment of Food Contact Materials (CBVV) for its evaluation. Such an application may also be submitted for a modification of a current entry on a positive list. The CBVV will carry out an assessment of the risks related to the intended use of the substance and deliver a scientific opinion.

In this case, the CBVV received an application from Synthomer Specialty Additives, requesting the evaluation of the substance 2-butyl-2-ethyl-1,3-propanediol (CAS No 115-84-4) for inclusion in Chapter X (Coatings; (sub)section not specified) of Part A of the Annex to the Commodities Act Regulation on packaging and consumer articles.

2. Data and methodologies

2.1 Data

The applicant has submitted a dossier in support of their application for the authorisation of 2-butyl-2-ethyl-1,3-propanediol (3,3-bis(hydroxymethyl)heptane; BEPD) as a monomer in the preparation of a polyester resin, which is then further used to manufacture a coating for metal substrates used as FCM. A dossier on BEPD has also been submitted to the German authorities, for inclusion of BEPD into Recommendation XXVIII on cross-linked polyurethanes as adhesive layers for food packaging materials. Additional information was provided by the applicant during the assessment process in response to requests from the CBVV sent on 6 July 2020 and 11 November 2021 (see 'Documentation provided to CBVV').

Data submitted and used for the evaluation are:

Non-toxicological data
- Data on chemical identity
- Data on physical and chemical properties
- Data on intended use and existing authorisation(s)
- Data on the manufacturing process of the substance/FCM
- Data on the residual content of the substance

[1] Regulation (EC) No 1935/2004 of the European parliament and of the council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC. OJ L 338, 13.11.2004, p. 4-17.

[2] Besluit van 30 mei 2005, houdende vaststelling van het Warenwetbesluit verpakkingen en gebruiksartikelen in verband met Verordening (EG) nr. 1935/2004 van het Europees Parlement en de Raad van de Europese Unie van 27 oktober 2004 inzake materialen en voorwerpen bestemd om met levensmiddelen in contact te komen en houdende intrekking van de richtlijnen 80/590/EEG en 89/109/EEG (PbEU L 338) (Warenwetbesluit verpakkingen en gebruiksartikelen). Staatsblad van het Koninkrijk der Nederlanden, 2005, 420.

[3] Regeling van de Minister van Volksgezondheid, Welzijn [en Sport] van 14 maart 2014, kenmerk 328583-117560-VGP, houdende vaststelling van de Warenwetregeling verpakkingen en gebruiksartikelen die in contact komen met levensmiddelen (Warenwetregeling verpakkingen en gebruiksartikelen). Staatscourant, 2014, 8531.

• Data on the potential migration of the substance

Toxicological data
• Bacterial gene mutation test
• In vitro mammalian cell gene mutation test
• In vitro mammalian chromosomal aberration test
• In vivo micronucleus test
• 90-Day oral toxicity study
• 28-Day oral toxicity study
• Oral developmental toxicity study
• Acute oral toxicity study
• Eye irritation test
• Skin irritation test
• Skin sensitisation test
• Reasoning for absence of bioaccumulative potential in humans

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) and the Note for Guidance of the European Food Safety Authority (EFSA) for the preparation of an application for the safety assessment of a substance to be used in plastic FCM (EFSA CEF Panel, 2021).

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) and the EFSA Scientific Committee recommendations on genotoxicity

testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011).

3. Assessment

The substance has not been evaluated in the past by the SCF or EFSA, and it is not listed in the Dutch Commodities Act Regulation on packaging and consumer articles. The US Food and Drug Administration (FDA) has authorised BEPD as a polyol monomer in the synthesis of polyester resins used to produce coatings, specifically coating binder resins, for use as can coatings and adhesives for single use in food contact applications (Food Contact Notification (FCN) No. 420).

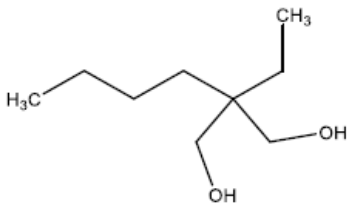
The purpose of the present application is to increase the range of authorisation. Specifically, authorisation is sought for BEPD as a monomer in the preparation of a polyester resin, which is then used to manufacture coatings for metal substrates (cans) used as FCM. The packaging materials coated with BEPD containing coatings are intended for all food types, for direct food contact applications. The foodstuffs in the cans will be heat treated by sterilisation (121°C - 130°C) and then stored at room temperature (20°C - 40°C).

3.1 Non-toxicological data

3.1.2 Identity of the substance

Molecular formula: $C_9H_{20}O_2$

Structural formula:



BEPD is a di-functional alcohol used as a monomer to react with di-functional acids (such as isophthalic acid) to produce a polyester polymer resin. This resin is subsequently used to prepare a coating for metal substrates for use as FCM.

3.1.2 Physical and chemical properties

BEPD is white crystalline solid with a mild odour at 20 °C and 101.3 kPa. Due to the structural composition of BEPD it is not considered to be oxidising or susceptible to photolysis or hydrolysis. BEPD has a molecular weight of 160.3 g/mol. It is used at a purity higher than 99%. The substance has hydrophilic characteristics with a log Po/w (octanol/water partition coefficient) determined as 2.2 at 25 °C and a water solubility of 8.8 g/L at 20 °C. BEPD has a melting point of 314 K (41 °C) and a boiling point of 264 °C at 101.3 kPa. It doesn't decompose up to 264 °C. The substance is stable to hydrolysis at temperatures of 20 °C and 50 °C, an at pH 4, 7 and 9.

3.1.3 Migration data

Based on worst-case migration simulation, migration studies (including specific migration, overall migration of BEPD and NIAS determination) into 20% and 50% aqueous ethanol have been carried out on typical BEPD coated metal panels. The specific migration of BEPD in 20% and 50% aqueous ethanol (v/v) was 2.6 and 2.2 mg/6 dm^2, respectively, at condition 2 hours at 130 °C, then left to cool down to < 60 °C and placed in an oven for 10 days at 60 °C. The results suggested that under the very demanding conditions, the polymer is beginning to break down and transesterification reactions are taking place in the presence of ethanol. The specific migration of BEPD is well below the specific migration limit (SML) of 5 mg/kg. The overall migration in 20% and 50% aqueous ethanol (v/v) was 90.3 and 155.6 mg/6 dm^2, respectively, with blank corrected values of 90.3 and 144.9 mg/6 dm^2 measured for 20% and 50% aqueous ethanol (v/v), respectively. It suggested that under the very demanding conditions of the overall migration exposure experiments, the polymer coating is beginning to break down and come away from the metal panel. There were in total five unidentified NIAS, all with estimated concentration of less than 50 µg/6 dm^2 and it is very unlikely that these substances are associated with the presence of BEPD.

3.2 Toxicological data

3.2.1 Genotoxicity

3.2.1.1 Bacterial reverse mutation test

BEPD was tested in a bacterial reverse mutation test with 4 Salmonella typhimurium strains (TA1537, TA1535, TA98, and TA100), performed with and without metabolic activation. No substantial increases in revertant colony numbers over control counts were obtained with any of the tester strains following exposure to BEPD at any concentration up to and including 5000 µg/plate in either the presence or absence of S9 mix. BEPD thus did not show evidence of mutagenic activity under the test conditions used. The test is performed in 1995 and was conducted in accordance with OECD TG 471 as it was in place at the time (so, without testing an additional Escherichia coli WP2 or Salmonella typhimurium TA 102 strain, as required in OECD TG 471 from 1997 onwards).

3.2.1.2 In vitro mammalian cell gene mutation assay

BEPD was tested in vitro for its potential to induce gene mutations at the TK-locus of cultured mouse lymphoma L5178Y cells, in both the absence and the presence of a metabolic activation system (S9-mix) and in accordance with OECD TG 476 as it was in place in 2009 when the test was conducted. The maximum concentrations tested (5.0 and 7.2 mmol/L in the absence of S9 mix and 7.2 and 10.0 mmol/L in the presence of S9 mix) were limited by cytotoxicity. No relevant increase in the number of mutations at the TK-locus was observed at any test substance concentration evaluated. It is concluded that, under the test conditions used, BEDP is not mutagenic at the TK-locus of mouse lymphoma L5178Y cells. It is noted that in the current OECD TG 476 the TK-locus is no longer recommended for testing.

3.2.1.3 In vitro mammalian chromosomal aberration test

BEPD was tested in an in vitro chromosomal aberration assay in the absence and presence of an S9-activation system, using Chinese hamster ovary (CHO) cells. The test was performed according to OECD TG 473. The maximum concentrations tested (up to

2 mg/mL in the absence of S9 mix and up to 5 mg/mL in the presence of S9 mix) were limited by cytotoxicity. The percentage of cells with structural but not numerical aberrations was significantly increased in the absence of metabolic activation at the highest non-toxic dose, 1.25 mg/mL. In the presence of metabolic activation, no increase in the percentage of cells with structural or numerical aberrations was observed at 1.6 mg/mL, the highest non-toxic dose. It was concluded that under the conditions of the assay BEPD was positive for structural chromosome aberrations.

3.2.1.4 In vivo micronucleus test

BEPD was tested in an in vivo micronucleus assay in NMRI mice. The study was conducted according to OECD TG 474. Doses were selected based on toxicity observed in pre-experiments with mice given 1000-2000 mg BEPD/kg bw. In the main experiment mice received a single oral dose of 312.5, 625 or 1250 mg BEPD/kg bw. No significant increase in micronuclei was seen in bone marrow cells. The PCE/NCE ratio was not increased, but symptoms of general toxicity were seen in the mice. Moreover, in the 90-day rat study organ toxicity is seen at doses below the lowest dose tested in this MN-test, indicating that BEPD became systemically available. The micronucleus test is considered negative.

3.2.2 General toxicity

3.2.2.1 Repeated dose 90-day oral toxicity study

BEPD was tested in an 90-day repeated oral dose toxicity study in rats at 15, 150 and 1000 mg/kg bw/day. The study was performed in accordance with OECD TG 408, except for the large dose spacing in the study. BEPD-related minimal nephropathy in male rats showed a dose related increase in incidence, in combination with increase in urea and total protein in blood. No nephropathy was seen in female rats. The NOAEL of 15 mg/kg bw/day in this study was checked by calculating the $BMDL_{10}$ of blood parameters indicative for kidney function (increase in urea & total protein); both were above 15 mg/kg bw/day. The NOAEL is therefore derived at 15 mg/kg bw/day, based on the observed nephropathy in male rats.

3.2.2.2 Other toxicity studies

In addition, an acute, sub-acute and a prenatal developmental oral toxicity study in rats, an eye irritation (positive) and a skin irritation (negative) study in the rabbit and a sensitisation study in guinea pig (negative) were provided, but these studies are not required for the evaluation of a substance for use in FCM. The toxicity studies in the rat did not show any adverse effects at or below the level of the NOAEL (15 mg/kg bw/day) from the 90 day repeated dose oral toxicity study.

3.2.2.3 Accumulation in man

BEPD has a log Po/w of 2.2 at 25°C, where a log Po/w value below 3 is considered sufficient evidence for the lack of accumulative potential in the mammalian body. BEPD is therefore not expected to accumulate in humans.

3.2.3 Concluding remarks on toxicity

An bacterial reverse mutation test in 4 strains and an in vitro gene mutation assay with mouse lymphoma L5178Y cells were both negative. A 5^{th} bacterial test strain as currently required in OECD TG 471 was not studied, but the substance is not an oxidising agent nor a hydrazine, and is not expected to be able to induce crosslinks. The two studies available are thus considered sufficient to conclude that BEPD is not inducing gene mutations. An in vitro chromosomal aberration assay in CHO cells was positive, but since the in vivo

micronucleus test was negative, overall, BEPD is considered to be a non-genotoxic substance.

Based upon the log Po/w <3, the substance is considered to be not accumulative in humans. In a repeated dose 90-day oral toxicity study in rats, a NOAEL of 15 mg/kg bw/day was derived. Additional toxicity studies available (prenatal developmental, subacute and acute toxicity in rats) did not report adverse effects below this dose level. A NOAEL of 15 mg/kg bw/day is sufficient to allow an SML of 5 mg/kg food, as the highest SML that can be set with the data available.

4. Conclusions

Based on the data submitted, the CBVV concluded that the substance 2-butyl-2-ethyl-1,3-propanediol does not raise a safety concern for the consumer under the intended and tested conditions of use as a monomer in the preparation of polyester resins that are subsequently used to manufacture coatings for metallic substrates. To CBVV's opinion, the substance can be included in part A of the Annex to the Commodities Act Regulation on packaging and consumer articles as follows:

Chapter	Section	Subsection
X. Coatings	3. Dispersions of macromolecular substances in water	a. monomers

CAS No	Name	SML mg/kg	Restrictions and specifications
115-84-4	2-Butyl-2-ethyl-1,3-propanediol	5	

In Dutch:

Hoofdstuk	Paragraaf	Subparagraaf
X. Deklagen	3. Dispersies van macromoleculaire stoffen in water	a. monomeren

CAS Nr	Naam	SML mg/kg	Restricties en specificaties
115-84-4	2-Butyl-2-ethyl-1,3-propaandiol	5	

Documentation provided to CBVV

1) Initial dossier. December 2019. Submitted by Exponent International Limited, on behalf of Synthomer Specialty Additives.

2) Additional data. June 2021. Submitted by Exponent International Limited, on behalf of Synthomer Specialty Additives.
3) Additional data. September 2022. Submitted by Exponent International Limited, on behalf of Synthomer Specialty Additives.

References

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2021. Note for Guidance for the preparation of an application for the safety assessment of a substance to be used in plastic Food Contact Materials (update 2021). EFSA Journal 2008, 6(7):21r, 41 pp. https://doi.org/10.2903/j.efsa.2008.21r

EFSA Scientific Committee, 2011. Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379, 69 pp. https://doi.org/10.2903/j.efsa.2011.2379

European Commission, 2001. Guidelines of the Scientific Committee on Food for the presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out82_en.pdf

Abbreviations

$BMDL_{10}$	benchmark dose at 10% response rate (lower bound confidence limit)
bw	body weight
CAS	chemical abstracts service
EFSA	European Food Safety Authority
FCM	food contact materials
NIAS	non-intentionally added substances
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
Po/w	n-octanol/water partition coefficient
SCF	Scientific Committee on Food
SML	specific migration limit
TG	test guideline