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Safety assessment of the substance Ln 1,4-benzene dicarboxylic acid (with Ln = La, Eu, Gd, Tb) for use in food contact materials

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Abstract

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP Panel) assessed the safety of the additive Ln 1,4-benzene dicarboxylic acid (with Ln = La, Eu, Gd, Tb) for use in food contact materials. It is a family of mixtures combining the four lanthanides lanthanum (La), europium (Eu), gadolinium (Gd) and/or terbium (Tb) in different proportions as their 1,4-benzene dicarboxylate complexes, used as a taggant in plastics for authentication and traceability purposes. The powdered additive, not in nano form, is intended to be used at up to 100 mg/kg in polyethylene, polypropylene and polybutene. Materials and articles made of these plastics are intended for contact with all foods types at up to 4 h/100°C or for long-term storage at ambient temperature. In tests with food simulants, migration of each Ln was below 5 μg/kg. The Panel considered that irrespective of the composition of the lanthanides, these would dissociate completely from the terephthalic acid salt under aqueous conditions. Evaluation of the genotoxicity studies provided on the individual complexes (La, Eu, Gd and Tb) and on their mixture, taken together with data available in the scientific literature, allows ruling out concern for genotoxicity. Consequently, the CEP Panel concluded that the substance Ln 1,4-benzene dicarboxylic acid (with Ln = La, Eu, Gd, Tb) does not raise a safety concern for the consumer under the proposed conditions of use and if the migration of the sum of the four lanthanides in ionic form does not exceed 50 μg/kg food.

Keywords: Ln 1,4-benzene dicarboxylic acid, FCM substance No 1074, food contact materials, safety assessment, Lanthanum, Europium, Gadolinium, Terbium

Requestor: French Competent Authority (Ministère de l'économie des finances et de l'industrie)

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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 French Competent Authority (Ministère de l'économie des finances et de l'industrie), requesting the evaluation of the substance Ln 1,4-Benzene Dicarboxylic acid (with Ln = La, Eu, Gd, Tb), with the FCM substance No 1074. The dossier was submitted by OLNICA, France.

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 Ln 1,4-Benzene Dicarboxylic acid (with Ln = La, Eu, Gd, Tb) to be used in FCM.

Data submitted and used for the evaluation are:

Non-toxicological data and information

- Chemical identity
- Description of manufacturing process of substance/FCM
- Physical and chemical properties
- Intended use
- Existing authorisation(s)
- Migration of the substance
- Residual content of the substance

Toxicological data

- Bacterial gene mutation test
- *In vitro* mammalian cell gene mutation test
- *In vivo* micronucleus assay 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).

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.

[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.

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, Ln 1,4-benzene dicarboxylic acid (terephthalic acid), with the lanthanides (Ln) lanthanum (La), europium (Eu), gadolinium (Gd) and/or terbium (Tb), is a family of isostructural compounds combining the four lanthanides in different proportions. It is intended to be used in polyethylene, polypropylene and polybutene at up to 100 mg/kg, in contact with all food types at up to 4 h/100°C or for long-term storage at ambient temperature.

The additive is intended as a taggant to authenticate raw materials, packaging materials or packaged foods, to aid traceability and security. With the four lanthanides chosen, a large number of permutations of the mixture can be prepared by varying the proportions of each lanthanide.

Terephthalic acid is authorized as a substance No 785 in Regulation (EU) 10/2011 with a specific migration limit of 7.5 mg/kg. No lanthanide compounds have been authorised to date for use in food contact plastics.

3.1. Non-toxicological data

Chemical formula: $Ln_2Ter_3(H_2O)_4$ with Ter = terephthalic acid and with Ln=Lanthanides in all combinations of La, Eu, Gd and Tb.

According to the applicant, the complexes are solid salts formed by reaction of disodium terephthalate with the corresponding lanthanide chloride ($LnCl_3$) followed by precipitation from aqueous solution. The molecular masses range from 842 Da for $La_2(Ter)_3(H_2O)_4$ to 882 Da for $Tb_2(Ter)_3(H_2O)_4$. Purities range from 99.8% to 99.99%. Upon heating, the complexes lose water between 150°C and 200°C and are decomposed above 470°C. In water and 50% ethanol, solubility was determined to be ca. 20 mg/L, in 3% acetic acid ca. 100 mg/L. The additive is used as a fine powder with particles largely in the 10 μm range and is not considered a nano material.

Migration experiments used polybutene; since preliminary tests showed that of the three polymers proposed, it gave rise to the highest migration. $La_2(Ter)_3(H_2O)_4$, $Eu_2(Ter)_3(H_2O)_4$, $Gd_2(Ter)_3(H_2O)_4$ and $Tb_2(Ter)_3(H_2O)_4$ were added to polybutene at 100 mg/kg each. This plastic was tested for migration using the simulants 3% acetic acid, 50% ethanol, 95% ethanol and modified polyphenylene oxide, using conditions of time and temperature that adequately covered the food contact applications that are foreseen. The simulants were analysed for Ln using inductively coupled plasma - optical emission spectrometry (ICP-OES) and inductively coupled plasma-mass spectrometry (ICP-MS). The highest migration value observed was 4.5 μg/kg for La into 3% acetic acid at 10 days/60°C. The Panel considered that irrespective of the composition of the lanthanides, these would dissociate completely from the terephthalic acid salt under aqueous conditions.

According to the applicant, the additive may contain up to 350 mg/kg ytterbium (Yb) and 350 mg/kg lutetium (Lu) as inorganic impurities. Since ytterbium and lutetium are expected to migrate in similar proportions as the lanthanides used, their migration is expected be at only low ng/kg levels.

3.2. Toxicological data

The four individual complexes (europium-, gadolinium-, lanthanum- and terbium 1,4-benzene dicarboxylate) were tested in water suspension for gene mutation in the bacterial reverse mutation test using *Salmonella* Typhimurium strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* tester strain WP2*uvrA*(pKM101) up to 5,000 μg/plate in the presence and absence of rat liver S9 following the 471 OECD guideline. The plate incorporation method with the 48 h exposure was applied. No

statistically significant increases in revertant colonies were observed with any rare earth salts tested in any *Salmonella* strains at any test conditions.

The mixture of the four individual complexes (25% w/w of each) was tested in the same way using the pre-incubation test in triplicate. No increase in revertants was detected at any concentration.

The four individual complexes were also tested in water suspension for the induction of micronuclei in cultured human HepG2 cells, following the 487 OECD guideline. In the presence or absence of S9 mix following 4-h treatment, the concentrations selected for evaluation were 125, 62.5, 31.25, 15.6 and 7.8 μg/mL. In the absence of S9 mix following 48-h treatment, the concentrations selected for evaluation were 62.5, 31.25, 15.6 and 7.8 μg/mL. Precipitate was observed in all concentrations tested. No increases in the frequency of micronuclei were observed in the cultures treated with the test material in the absence and the presence of S9 mix.

The mixture of the four individual complexes (25% of each) was also tested following the same OECD 487 guideline. In the presence or absence of S9 mix following 4-h treatment, the test concentrations chosen were 250, 125 and 62.5 μg/mL. In the absence of S9 mix following 48-h treatment, the concentrations selected for evaluation were 125, 62.5, 31.25 and 15.6 μg/mL. No increases in the frequency of micronuclei were observed.

These conclusions were reinforced by the results of *in vivo* micronucleus studies available in the scientific literature, demonstrating that the most relevant compound, the lanthanum, was not genotoxic *in vivo* (Damment et al., 2005; Yang et al., 2016).

Negative results were obtained in two independent rodent bone marrow micronucleus tests carried out in the same laboratory. In the first one, groups of male and female CD1 mice were administered single oral doses of lanthanum carbonate up to the maximum tolerated dose (800, 1,250 and 2,000 mg/kg body weight (bw)). In the second one, male Sprague–Dawley rats were given a single intravenous (i.v.) injection of lanthanum chloride at 0.025, 0.05 and 0.1 mg/kg bw (Damment et al., 2005).

Lanthanum nitrate, administered to male and female BABL/C mice by gavage twice with a 24-h interval up to the ½ LD_{50} (183.8, 367.5, 735.0 mg/kg bw in females and 213.8, 427.5, 855.0 mg/kg bw in males) did not increase the frequency of bone marrow micronuclei and chromosomal aberrations (Yang et al., 2016).

Overall the evaluation of the studies provided on the individual complexes (lanthanum, europium, gadolinium and terbium) and on their mixture, along with the data available in the scientific literature (Damment et al., 2005 and Yang et al., 2016), makes it possible to rule out concern for genotoxicity.

Concerning the two impurities that were identified (Yb and Lu), the Panel considered data from literature about their background levels in drinking water (Reimann et al., 2010) suitable for human consumption. The migration potential at low ng/kg levels that was identified for these two impurities did not give rise to concern and therefore no further data were requested on these two elements.

4. Discussion

It was noted that the application requests use of the additive only in three types of polyolefin. Considering the chemical characteristics of the Ln elements themselves and of their 1,4-benzene dicarboxylate complexes, no undesirable interactions with plastics (including but not limited to polyolefins) leading to formation and possible migration of undesirable reaction and transformation products, are to be expected. Therefore, if a specific migration limit were to be established for this additive, then the Panel would not consider it necessary to restrict the use of the additive to only those three polyolefin types indicated in the request.

The migration of the substance Ln 1,4-benzene dicarboxylic acid (with Ln = La, Eu, Gd, Tb) is clearly below the solubility of the material and the Panel assumes dissociation to the ions. Consequently, the Ln ions may be evaluated as such and, based on the data available on genotoxicity, there would be no safety concern provided their migration into food does not exceed 50 μg/kg. Due to the limited information on the toxicity of the four lanthanides and the possibility that they could have an additive effect, the Panel considered that the migration limit should apply for the individual lanthanides, when used alone or in any combination.

This group limit would also apply to other uses of the four lanthanides, provided that, if migration were to occur, they were present in food/simulants as dissociated ions. However, the data provided do not enable a statement on safety if other Ln substances used did not dissociate into ions, but were present in food/simulants as different species.

5. Conclusions

Based on the above-mentioned data, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) concluded that the substance Ln 1,4-benzene dicarboxylic acid (with Ln = La, Eu, Gd, Tb) does not raise a safety concern for the consumer under the proposed conditions of use and if the migration of the sum of the four lanthanides in ionic form does not exceed 50 μg/kg food.

Documentation provided to EFSA

1) Dossier "Ln 1,4-Benzene Dicarboxylic acid (with Ln = La, Eu, Gd, Tb)". February, 2016. Submitted by Olnica, France.
2) Additional data to the Dossier "Ln 1,4-Benzene Dicarboxylic acid (with Ln = La, Eu, Gd, Tb)". April, 2018. Submitted by Olnica, France.

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Abbreviations

bw	body weight
CEP Panel	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
FCM	food contact materials
ICP-MS	inductively coupled plasma-mass spectrometry
ICP-OES	inductively coupled plasma-optical emission spectrometry
i.v.	intravenous
LD_{50}	lethal dose, median
SCF	Scientific Committee on Food