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Safety assessment of the substance (triethanolamine-perchlorate, sodium salt) dimer, 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 the substance (triethanolamine-perchlorate, sodium salt) dimer, FCM substance No 1080, intended to be used as a thermal stabiliser at up to 0.15% w/w in rigid poly(vinyl chloride) (PVC) for repeated use bottles in contact with water. No thermal degradation of the substance is expected during the manufacture of the PVC articles. In water, the substance fully dissociates into triethanolamine, sodium (cations) and perchlorate. Therefore, migration would lead to exposure to triethanolamine and perchlorate and not to the substance itself. Specific migration of perchlorate, ethanolamine, diethanolamine and triethanolamine was tested under repeated use conditions covering the requested uses. After the second and third contacts, perchlorate was detected at ca. 0.3 μg/kg food. Ethanolamine, diethanolamine and triethanolamine were not detected in any of the three contacts at an estimated limit of detection of 0.03 mg/kg food. The available *in vitro* studies on the substance confirmed the lack of concern for genotoxicity, as anticipated by the dissociation of the substance into authorised non-genotoxic substances. Therefore, the CEP Panel concluded that the substance is not of safety concern for the consumer if used, under the condition requested by the applicant, as an additive at up to 0.15% w/w in rigid PVC for repeated use bottles intended for contact with water. Additionally, the migration of triethanolamine and perchlorate should not exceed the specific migration limits (SMLs) of 50 μg/kg food and 2 μg/kg food, respectively, set in the Regulation (EU) 10/2011. This evaluation also covers acidic foods such as fruit juices that can reasonably be foreseen to be in contact.

Keywords: CAS number 156157-97-0, FCM substance No 1080, Stabiliser, rigid PVC, water, food contact materials, safety assessment

Requestor: Ministero della Salute, Italy

Question number: EFSA-Q-2017-00444

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*This opinion was first adopted on 5 February 2020, as reflected in the minutes of the 12th plenary meeting of the CEP Panel (available online: http://www.efsa.europa.eu/sites/default/files/event/2020/12th-plenary-meeting-cep-panel-minutes.pdf). However, the adopted version was withdrawn prior to publication and the current version was adopted on 29 April 2020.

Panel members: José Manuel Barat Baviera, Claudia Bolognesi, Andrew Chesson, Pier Sandro Cocconcelli, Riccardo Crebelli, David Michael Gott, Konrad Grob, Claude Lambré, Evgenia Lampi, Marcel Mengelers, Alicja Mortensen, Gilles Rivière, Vittorio Silano, Inger-Lise Steffensen, Christina Tlustos, Henk Van Loveren, Laurence Vernis, and Holger Zorn.

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.

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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 di(m-2,2′,2″-nitrilotris(ethanol)-diperchlorato)dinatrium, with the CAS number 156157-97-0 and the FCM substance No 1080. The dossier was submitted by Reagens S.p.A.

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 di(*m*-2,2′,2″-nitrilotris(ethanol)-diperchlorato)dinatrium to be used in plastic food contact materials.

Additional information was provided by the applicant during the assessment process in response to the requests from EFSA sent on 18 October 2017 and 28 May 2018. During the pre-notification, sent on 26 February 2020, the applicant commented and provided additional revised data (see Documentation provided to EFSA).

Following the request for additional data sent by EFSA on 28 May 2018, the applicant requested a clarification teleconference, which was held on 5 September 2018. Following the submission of the data, EFSA requested a clarification teleconference, which was held on 4 April 2019.

Data submitted and used for the evaluation are:

Non-toxicological data and information

- Chemical identity
- Manufacturing process of the substance and of the FCM article
- Physical and chemical properties
- Intended uses
- Existing authorisation(s)
- Migration of the substance and screening of its potential reaction products

Toxicological data

- Bacterial reverse mutation test
- *In vitro* mammalian chromosome aberration 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).

[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/are 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 'di(*m*-2,2′,2′′-nitrilotris(ethanol)-diperchlorato)dinatrium', renamed by the Panel 'triethanolamine-perchlorate, sodium salt) dimer' for being listed in the Union list, is intended to be used as a thermal stabiliser at up to 0.15% w/w to manufacture rigid poly(vinyl chloride) (PVC). Final articles are repeated use bottles, e.g. used for sports, and intended only for contact with water.[2]

The substance has not been evaluated by the SCF or EFSA in the past. However, triethanolamine (FCM No 793) and sodium perchlorate (FCM No 822 for perchloric acid salts) that constitute the substance are both authorised to be used in plastics (Regulation (EU) 10/2011[3]). Triethanolamine has a specific migration limit (SML) of 50 μg/kg food expressed as the sum of triethanolamine and its hydrochloride expressed as triethanolamine. Perchloric acid, salts has a SML of 2 μg/kg food (Regulation (EU) 2018/83[4]). The CEP Panel acknowledged that the previous SML for perchloric acid, salts was lowered from 50 to 2 μg/kg food by the European Commission in 2018, applying an allocation factor of 10% (due to other sources of exposure) to the tolerable dietary intake (TDI) of 0.3 μg/kg body weight (bw) per day set for perchlorate by the EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel, 2014).

3.1. Non-toxicological data

3.1.1. Identity of the substance[5]

Chemical formula: C12H30N2O14Cl2Na2

Molecular mass: 543 Da

CAS number: 156157-97-0

The substance, (triethanolamine-perchlorate, sodium salt) dimer, is a complex consisting of two molecules, each, of triethanolamine (CAS number 102-71-6) and sodium perchlorate (CAS number 7601-89).

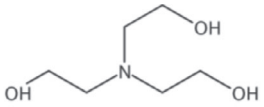
[2] Technical dossier/Consolidated version_010917/Appendix B/Section 3 and Technical Annexes Ref 3.2, 3.4., 3.5; Technical dossier/Additional data April 2018/Answer to EFSA letter 18-10-2017, 20180322; Technical dossier/Additional data March 2020/Answer integration to EFSA letter 17-03-2020 20200329.

[3] Regulation (EU) No 10/2011 of the European Commission of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1–89.

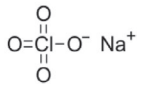
[4] Regulation (EU) No 2018/831 the European Commission of 5 June 2018 amending Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0831&from=EN.

[5] Technical dossier/Consolidated version_010917/Appendix B/Section 1 and Annexes Ref 1.1.1., 1.1.2. and 1.1.7.

Triethanolamine



Sodium perchlorate



3.1.2. Physical and chemical properties[6]

The substance is highly soluble in water (between 2.5 and 5 kg/L), and soluble in ethanol, acetone (> 1 g/L). The log $P_{o/w}$ is 0.68. In water, the substance fully dissociates into triethanolamine, sodium (cations) and perchlorate. Therefore, migration would lead to exposure to triethanolamine and perchlorate, and not to the intact substance itself.

The substance is thermally stable up to 270°C, which is above the maximum processing temperature of rigid PVC (commonly up to about 200°C). Therefore, no thermal degradation of the substance is expected during the manufacture of rigid PVC articles. According to the applicant, the substance acts as a stabiliser and reduces thermal degradation of the polymer during processing of PVC. The exact mechanism of action is not known, but the applicant postulates that the substance forms complexes with allylic sites and so prevents them from propagating into conjugated double bonds in the polymer chain.

3.1.3. Specific migration[7]

Migration was modelled from a rigid PVC made with 0.08% w/w of the substance. At the conservative conditions assumed, the modelled migration of the substance (expressed as perchlorate) exceeded the revised SML of 2 μg/kg food. However, the Panel noted that migration modelling for ionic substances of this type has not been validated. Moreover, for repeated use bottles, the use in contact with foods other than water, such as acidic fruit juices, can reasonably be foreseen. Therefore, specific migration of perchlorate, ethanolamine, diethanolamine and triethanolamine was tested using 3% acetic acid (covering contact with water as well as acidic foods) for 24 h at 40°C under repeated use conditions. The PVC samples contained the substance at the maximum intended use level of 0.15% w/w.[8] The simulant was analysed by liquid chromatography coupled with mass spectrometry (LC–MS/MS (QTOF)). In the first contact, perchlorate migrated at 18 μg/kg food. After the second and third contacts, it was detected at ca. 0.3 μg/kg food, below the limit of quantification (LoQ) of 1 μg/kg food, hence below the SML of 2 μg/kg food. Ethanolamine, diethanolamine and triethanolamine were not detected to migrate in any of the three contacts at an estimated limit of detection of 0.03 mg/kg food. Therefore, the migration of triethanolamine, if any, is expected to comply with the SML of 0.05 mg/kg food.

3.1.4. Screening of migrating reaction products related to the substance[9]

To address the possible migration of reaction products resulting from the use of the substance in the rigid PVC, a non-targeted comparative analysis was performed in simulants after contact with rigid PVC samples made with and without the substance. Gas chromatography coupled with mass spectrometry (GC–MS) was used for screening non-polar and polar substances in 3% acetic acid after 3 successive migration contacts for 24h at 40°C. No peak attributed to the use of the substance was found from any of the three contacts at a LoQ of ca. 0.01 mg/kg. Headspace GC–MS analysis was used for screening volatiles in both water and 3% acetic acid after 3 successive migration contacts for 24 h at 40°C. No difference from the PVC without the substance was found in each of the three contacts at the LoQ of ca. 0.01 mg/kg.

[6] Technical dossier/Consolidated version_010917/Appendix B/Section 2 and Annexes Ref 2.1.2, 2.1.4, 2.1.5, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.6, 2.2.7, 3.2, 3.3; Technical dossier/Additional data April 2018/Answer to EFSA letter 18-10-2017, 20180322, Annex B_Inorg. Chem., 1994, 33 (10), pp 2137–2141 and Annex C_Mechanism of TEAP 20180316.

[7] Technical dossier/Consolidated version_010917/Appendix B/Section 5.1 and Annex Ref 5.1; Technical dossier/Additional data March 2019/Answer integration to EFSA letter 28-05-2018 20190312, 2098_FPM_FDC_18_2 and 2098_FPM_FDC_18_3.

[8] Technical dossier/Additional data March 2020/Answer integration to EFSA letter 17-03-2020 20200329.

[9] Technical dossier/Consolidated version_010917/Appendix B/Section 5.3; Technical dossier/Additional data March 2019/Answer integration to EFSA letter 28-05-2018 20190312, 2098_FPM_FDC_18_1 and 2098_FPM_FDC_18_2.

3.2. Toxicological data

The applicant submitted two *in vitro* genotoxicity assays on the substance.

3.2.1. Bacterial reverse mutation test[10]

The substance (purity 98%) was tested in a bacterial reversion assay (Ames test) performed according to the OECD Test Guideline 471 (1997) and good laboratory practice (GLP). The substance was dissolved in deionised water and tested in *Salmonella* Typhimurium strains TA97a, TA98, TA100, TA102, TA1535, in the presence and absence of metabolic activation by liver S9 from Aroclor 1254 induced rats. Two separate experiments were performed using triplicate plates. In the first experiment, five doses of the test item (50, 150, 500, 1,500 and 5,000 μg/plate) were tested using the plate incorporation method. In the repeat experiment, three doses (1,250, 2,500 and 5,000 μg/plate) were tested by using the pre-incubation procedure. In both experiments, no reproducible and/or dose-related increases in revertant colony numbers were observed, neither in the presence nor in the absence of exogenous metabolic activation. No signs of toxicity to bacteria, or precipitation of the test item, were observed at any dose.

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

3.2.2. *In vitro* mammalian chromosome aberration test[11]

The substance (purity 98%) was tested in an *in vitro* chromosome aberration assay in Chinese hamster V79 cells performed according to the OECD Test Guideline 473 (1997) and GLP. The substance dissolved in deionised water, was tested in two separate experiments with and without metabolic activation. In Experiment I, the exposure period was 4 h with and without metabolic activation. In Experiment II, the exposure period was 4 h with S9 mix and 18 h and 28 h without S9 mix. Cells were harvested and fixed 18 h (Exp. I and II) and 28h (exp. II) after start of treatment with the test item. Five concentrations in the dose range 86–2,770 were tested. Based on the toxicity elicited by treatment (evaluated as reduction of cell number), the following concentrations were selected for scoring of chromosomal aberrations: 346, 692 and 1,385 μg/mL (exp. I, 4 h treatment with and without S9 and harvest at 18 h; exp. II, 18 h continuous treatment without S9); 2,770 μg/mL (exp. II, 28 h continuous treatment without S9); 692, 1,385 and 2,770 μg/mL (exp. II, 4 h treatment with S9 and harvest at 28 h). In each experimental group, two parallel cultures were set up, and 100 metaphases per culture were scored for structural chromosome aberrations. In both experiments, in the absence and in the presence of S9 mix, no statistically significant and/or reproducible and dose related increase in the number of cells carrying structural chromosome aberrations and polyploidy was observed.

Although in line with OECD guideline at the time when the study was performed, the Panel noted that the number of scored metaphases (200 per dose) was lower than that recommended (300) in the last revision of the guideline with the purpose to increase the statistical power of the test (OECD TG 473, 2014). The Panel acknowledged this limitation but considered that the study was adequately performed and valid, and the clearly negative results obtained as reliable. The Panel concluded that the substance was not clastogenic and did not induce polyploidy in cultured Chinese hamster cells under the conditions used in this study.

Therefore, the Panel concluded that the available *in vitro* genotoxicity studies on the substance confirmed the lack of concern for genotoxicity, as anticipated by the complete dissociation of the substance into triethanolamine and perchlorate (as perchloric acid, salts) derivatives, previously evaluated as not genotoxic and authorised with SMLs of 0.05 and 0.002 mg/kg food, respectively.

4. Conclusions

Based on the above-mentioned data, the CEP Panel concluded that the substance '(triethanolamine-perchlorate, sodium salt) dimer' is not of safety concern for the consumer if used, under the condition requested by the applicant, as additive at up to 0.15% w/w in rigid PVC for repeated use bottles

[10] Technical dossier/Consolidated version_010917/Appendix B/Section 8.1.1 and Annex Ref 8.1.1; Technical dossier/Additional data April 2018/Answer to EFSA letter 18-10-2017, 20180322, Annex A_RG15-35_XRD_cert-17-19feb2018 and Annex B_Inorg. Chem., 1994, 33 (10), pp 2137–2141.

[11] Technical dossier/Consolidated version_010917/Appendix B/Section 8.1.3 and Annex Ref 8.1.3; Technical dossier/Additional data April 2018/Answer to EFSA letter 18-10-2017, 20180322, Annex A_RG15-35_XRD_cert-17-19feb2018 and Annex B_Inorg. Chem., 1994, 33 (10), pp. 2137–2141.

intended for contact with water. Additionally, the migration of triethanolamine and perchlorate should not exceed the SMLs of 50 μg/kg food and 2 μg/kg food, respectively, set in the Regulation (EU) 10/2011. This evaluation also covers acidic foods such as fruit juices that can reasonably be foreseen to be in contact.

Documentation provided to EFSA

1) Initial dossier. May 2017. Submitted by Reagens S.p.A.
2) Additional data. April 2018. Submitted by Reagens S.p.A.
3) Additional data. March 2019. Submitted by Reagens S.p.A.
4) Additional data received during Pre-notification. March 2020. Submitted by Reagens S.p.A.

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EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2014. Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables. EFSA Journal 2014;12(10):3869, 117 pp. https://doi.org/10.2903/j.efsa.2014.3869

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

bw	body weight
CAS	Chemical Abstracts Service
CEP	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
CONTAM	EFSA Panel on Contaminants in the Food Chain
FCM	food contact materials
GC–MS	gas chromatography coupled with mass spectrometry
GLP	good laboratory practice
LC–MS/MS (QTOF)	liquid chromatography coupled with mass spectrometry using hybrid quadrupole time of flight
LoQ	limit of quantification
OECD	Organisation for Economic Co-operation and Development
PVC	poly(vinyl chloride)
$P_{o/w}$	octanol/water partition coefficient
SCF	Scientific Committee on Food
SML	specific migration limit
TDI	tolerable dietary intake
w/w	weight per weight