SCIENTIFIC OPINION

Scientific Opinion on the safety evaluation of the substance, 1,3-bis(isocyanatomethyl)benzene, CAS No. 3634-83-1 for use in food contact materials[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

This Scientific Opinion, published on 16 August 2012, replaces the earlier version published on 24 July 2012[4]

ABSTRACT

This scientific opinion of EFSA deals with the risk assessment of the monomer 1,3-bis(isocyanatomethyl) benzene, CAS No. 3634-83-1, FCM Substance No 988. In water and gastric fluid simulant, immediate and complete hydrolysis of the substance to 1,3-benzenedimethanamine occurs. The toxicity of 1,3-bis(isocyanatomethyl)benzene was tested in three in vitro genotoxicity tests, with and without metabolic activation and in an in vivo micronucleus assay in rats and was considered as non-genotoxic in vivo. In addition, its hydrolysis product, 1,3-benzenedimethanamine, was tested in two in vitro tests, in the presence and absence of a metabolising system, and one in vivo mouse micronucleus assay. The tests were negative. No concern for genotoxicity in vivo is raised by 1,3-bis(isocyanatomethyl)benzene and its hydrolysis product 1,3-benzenedimethanamine. The CEF Panel concluded that that the use of the substance 1,3-bis(isocyanatomethyl)benzene as co-monomer in the manufacture of a middle layer coating in a multilayer film does not raise safety concern if the migration of its hydrolysis product, 1,3-benzenedimethanamine, does not exceed 0.05 mg/kg food.

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[1] On request from the Ministry for Health, Welfare and Sport, the Netherlands, Question No EFSA-Q-2012-00062 adopted on 5 July 2012.

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[3] Acknowledgement: The European Food Safety Authority wishes to thank the members of the Working Group on Food Contact Materials for the preparation of this scientific opinion: Mona-Lise Binderup, Laurence Castle, Riccardo Crebelli, Roland Franz, Nathalie Gontard, Eugenia Lampi, Jean-Claude Lhuguenot, Maria Rosaria Milana, Karla Pfaff, Fatima Poças, Philippe Saillard, Kettil Svensson and Detlef Wölfle for the support provided to this EFSA scientific opinion.

[4] Corrections were made in the page number of the suggested citation. The changes do not affect the overall conclusions of the opinion. To avoid confusion, the original version of the Opinion has been removed from the website, but it is available on request

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KEY WORDS

1,3-bis(isocyanatomethyl)benzene; m-xylylene diisocyanate; CAS number 3634-83-1; FCM Substance No 988; Food contact materials; Safety assessment; Evaluation.

SUMMARY

Within the general task of evaluating substances intended for use in materials in contact with food according to the 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 foodstuffs, the CEF Panel received a request from a competent Member State Authority for safety evaluation of a substance following a corresponding application from the industry.

The request received and the outcome of the safety evaluation is summarised below:

The Ministry for Health, Welfare and Sport, the Netherlands, requested for evaluation of the monomer 1,3-bis(isocyanatomethyl)benzene with the CAS number 3634-83-1, the European Commission FCM substance No 988, for use as a monomer in the manufacture of a coating on poly(ethylene terephthalate) film. This coating is used as an inner layer in multilayer films, so that no direct contact of the coating with food is foreseen. The dossier was submitted on behalf of the applicant, Toray Advanced Film Co. Ltd, Japan.

In water and gastric fluid simulant, the substance hydrolyses immediately and completely to 1,3-benzenedi- methanamine, which has been evaluated by the SCF in 1991, and it is listed in the Regulation (EU) No 10/2011 under FCM Substance No 421 with an SML = 0.05 mg/kg food.

The toxicity of 1,3-bis(isocyanatomethyl)benzene was tested in three *in vitro* genotoxicity tests, with and without metabolic activation and in an *in vivo* micronucleus assay in rats. The substance induced a clear and concentration related increase in structural but not numerical chromosomal aberrations in cultured mammalian cells, both in the absence and the presence of the metabolic activator. Gene mutation assays in bacteria provided negative results. In the forward *in vitro* mouse lymphoma assay, the test substance did not induce gene mutations at the tk locus. The clastogenic effect observed *in vitro* was not confirmed in an *in vivo* micronucleus assay in rats, but there is no indication that the test substance did reach the bone marrow.

The hydrolysis product, 1,3-benzenedimethanamine, was also tested in two *in vitro* tests, in the presence and absence of a metabolising system, and one *in vivo* mouse micronucleus assay . The tests were negative.

Based on these considerations, no concern for genotoxicity is raised by 1,3-bis(isocyanatomethyl)benzene and its hydrolysis product 1,3-benzenedimethanamine.

The CEF Panel concluded that that the use of the substance 1,3-bis(isocyanatomethyl)benzene as co-monomer in the manufacture of an middle layer coating in a multilayer film does not raise safety concern if the migration of its hydrolysis product, 1,3-benzenedimethanamine, does not exceed 0.05 mg/kg food.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE LEGISLATION

Before a substance is authorised to be used in food contact materials and is included in a positive list EFSA´s opinion on its safety is required. This procedure has been established in Articles 8 and 9 of the Regulation (EC) No. 1935/2004[5] 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 in their turn transmit the applications to the EFSA for their evaluation. The application is supported by a technical dossier submitted by the industry following the SCF guidelines for the "presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation" (EC, 2001).

In this case, EFSA received an application from the Ministry for Health, Welfare and Sport, the Netherlands, requesting the evaluation of the monomer 1,3-bis(isocyanatomethyl)benzene with the CAS number 3634-83-1 and the FCM Substance No 988.

TERMS OF REFERENCE AS PROVIDED BY THE LEGISLATION

The EFSA is required by Article 10 of Regulation (EC) No. 1935/2004 of the European Parliament and of the Council on materials and articles intended to come into contact with food to carry out risk assessments on the risks originating from the migration of substances from food contact materials into food and deliver a scientific opinion on:

new substances intended to be used in food contact materials before their authorisation and inclusion in a positive list;

substances which are already authorised in the framework of Regulation (EC) No. 1935/2004 but need to be re-evaluated.

5 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;

ASSESSMENT

1. Introduction

The European Food Safety Authority was asked by the Ministry for Health Welfare and Sport, the Netherlands, to evaluate the safety of 1,3-bis(isocyanatomethyl)benzene with a CAS number 3634-83-1, a FCM substance No 988. The request has been registered in the EFSA's register of received questions under the number EFSA-Q-2012-00062. The dossier was submitted on behalf of the applicant, Toray Advanced Film Co. Ltd, Japan.

2. General information

According to the applicant, the substance 1,3-bis(isocyanatomethyl)benzene is used as a monomer in the manufacture of a coating on poly(ethylene terephthalate) polymer film. This coating, with a thickness of up to 1 µm, is used as a middle layer of multilayer films, so that no direct contact of the coating with food is foreseen. The finished multilayer film is intended to come into contact with all types of foods under long term storage conditions at room temperature including a possible preceding heat treatment such as sterilisation for up to 30 minutes at 130°C.

The substance itself has not been evaluated by EFSA in the past. Its hydrolysis product, 1,3-benzenedimethanamine (m-XDA), has been evaluated by the SCF (1991) and is listed in the Regulation (EU) No 10/2011[6] under FCM Substance no 421 with an SML = 0.05 mg/kg food.

3. Data available in the dossier used for this evaluation

The studies submitted for evaluation followed the SCF guidelines for the presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation (EC, 2001).

3.1. Non-toxicity data:

- Data on identity
- Data on physical and chemical properties
- Data on intended use and authorisation
- Data on migration and hydrolysis of the substance
- Data on residual content of the substance
- Data on identification, quantification and migration of oligomers and reaction products

3.2. Toxicity data:

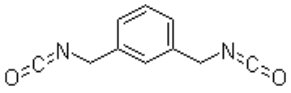
- Bacteria gene mutation test
- *In vitro* mammalian cell gene mutation test
- *In vitro* mammalian chromosome aberration test
- *In vivo* rat bone marrow micronucleus test.
- data on genotoxicity assays performed with the hydrolysis substance were also available from OECD SIDS on 1,3-bis(aminomethyl)benzene Id 1477-55-0 Dated 28.06.2001.

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

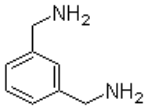
4. Evaluation

4.1. Non-toxicological data

Chemical formulae: $C_{10}H_8N_2O_2$

Chemical structure: 

The substance 1,3-bis(isocyanatomethyl)benzene or m-xylylene diisocyanate (m-XDI) with CAS no. 3634-83-1 is an individual substance with a molecular weight 188.19 g/mol. The substance has an estimated log Po/w = 3 and is therefore lipophilic. Due to the chemical nature of isocyanates, the substance is highly reactive with water to form 1,3-benzenedimethanamine (m-xylylenediamine, m-XDA) listed in EU Regulation No 10/2011 with a SML = 0.05 mg/kg food.

Chemical structure of the hydrolysis product, 1,3-benzenedimethanamine : 

The petitioner has carried out kinetical hydrolysis studies using water, saliva and gastric fluid simulant at 37°C up to 4 hours. In water and gastric fluid simulant, immediate and complete hydrolysis was observed. In saliva, hydrolysis was completed after 4 hours.

Specific and overall migration testing was performed. Additionally, the presence of oligomers and reaction products was analysed by LC-MS in the overall migration solution.

As a test sample the coating was applied onto a PET film and brought, as a worst case, into direct contact with food simulants for 2 hours at 100ºC followed by 10 days at 60ºC.

Tests for the determination of the specific migration of the hydrolysis product, m-XDA, were carried out only into 3% acetic acid, which can be considered as worst case food simulant, because under acidic conditions m-XDA will be protonated and readily dissolved. m-XDA was not detected at a detection limit of 10 µg/kg food. This value is in agreement with the result of the determination of the residual content of the parent substance which was not detected in the test sample, at a detection limit of 0.15 µg/6 dm².

Overall migration in 3% acetic acid, 10% ethanol, 95% ethanol and olive oil, at 100°C for 30 min, followed by 10 days at 60°C was up to 0.6 mg/dm².

In the migration solutions obtained from the overall migration test, migrating oligomers and reaction products were investigated by LC-MS. Only two chemical compounds were identified containing the substance moiety. In these investigations, free isocyanate groups could not be detected at an estimated detection limit of 0.15 µg/kg food. This can be explained by the rapidly occurring hydrolysis of the isocyanate group into the free amine. Free amine containing oligomers were estimated to migrate up to 23 µg/kg food. Since the real application foresees a further polymer layer on top of the coating, migration into foods will be even lower.

4.2. Toxicological data

Despite its immediate and complete hydrolysis in water and gastric fluid simulant, the substance itself has been tested in three in vitro genotoxicity tests, with and without metabolic activation. In the bacterial reversion mutation assay, using the Salmonella typhimurium strains TA98, TA100, TA1535, TA1538 and TA1537, and in Escherichia coli tester strain WP2uvrA, the test substance did not induce gene mutations. In the forward mutation test, using mouse lymphoma L5178Y cells, the test substance did not induce gene mutations at the tk locus. The substance induced a clear and concentration related increase in structural but not numerical chromosomal aberrations in Chinese hamster lung fibroblasts (CHL/IU) cells, both in the absence and the presence of S9 mix.

The clastogenic effect observed in vitro was not confirmed in an in vivo micronucleus assay in rats, but there is no indication that the test substance did reach the bone marrow.

Genotoxicity data on the hydrolysis product from an OECD report are mentioned below. The substance 1,3-benzenedimethanamine has also been tested for reverse mutation in Salmonella typhimurium and Escherichia coli. The tests were negative, both in the presence and absence of a metabolising system.

A first in vitro mammalian cytogenetics study on 1,3-benzenedimethanamine in Chinese hamster cells (CHL/IU was conducted and gave negative results. A second in vitro mammalian cytogenetics assay was conducted in CHO cells. In the second assay, although there was a statistically significant increase in chromosomal aberrations in the presence of S9 there was no dose-response relationship and therefore the increase was considered not substance related. 1,3-Benzenedimethanaminewas not clastogenic under the conditions of the two tests.

A mouse micronucleus assay was undertaken on 1,3-benzenedimethanamine. The animals received 750 mg/kg b.w. orally by gavage. Higher doses resulted in significant mortality. The chemical was non genotoxic in this test.

Given the above data on the substance itself and on its hydrolysis product, no concern for genotoxicity is raised by 1,3-bis(isocyanatomethyl)benzene and its hydrolysis product 1,3-benzenedimethanamine.

CONCLUSIONS

After having considered the above mentioned data, the CEF Panel concluded that the use of the substance 1,3-bis(isocyanatomethyl)benzene as co-monomer in the manufacture of an middle layer coating in a multilayer film does not raise safety concern if the migration of its hydrolysis product, 1,3-benzenedimethanamine does not exceed 0.05 mg/kg food.

DOCUMENTATION PROVIDED TO EFSA

Dossier referenced: AR 11-1290/SIT . Dated: December 2011. Submitted by Toray Advanced Film Co. Ltd, Japan.

REFERENCES

EC (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 its authorisation; http://ec.europa.eu/food/fs/sc/scf/out82_en.pdf.

SCF (Scientific Committee for Food) (1991) Reports of the Scientific Committee for Food (30th Series); http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_30.pdf

OECD SIDS on 1,3-bis(aminomethyl)benzene Id 1477-55-0 Dated 28.06.2001.

GLOSSARY AND ABBREVIATIONS

Overall migration: The sum of the amounts of volatile and non volatile substances, except water, released from a food contact material or article into food or food simulant

Specific migration: The amount of a specific substance released from a food contact material or article into food or food stimulant

CAS	Chemical Abstracts Service
CEF	Scientific Panel on food contact materials, enzymes, flavourings and processing aids
CHL/IU	Chinese hamster lung cell line
CHO cells	Chinese hamster ovary cells
EC	European Commission
EFSA	European Food Safety Authority
FCM	Food Contact Msterials
OECD	Organisation for Economic Co-operation and Development
PET	Poly(ethylene terephthalate)
REF No	Reference Number
SCF	Scientific Committee on Food
SIDS	Screening Information Data Set
SML	Specific Migration Limit