SCIENTIFIC OPINION

Scientific Opinion on the safety evaluation of the substance, 5-chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1), CAS No. 55965-84-9, as a biocide for processing coatings and paper and boards [1]

EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

This scientific opinion of EFSA deals with the risk assessment of the biocide 5-chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1), with CAS No. 55965-84-9, REF. No. 43730 for which the CEF Panel concluded that there is no safety concern for the consumer if the maximum residual amount in the finished products does not exceed 25 µg/dm² and the use of the mixture does not result in an anti-microbial effect at the surface of the polymer or on the food itself.

KEY WORDS

5-Chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1); CAS number 55965-84-9; Ref. No. 43730; Biocide; Coatings; Paper and boards; Safety assessment; Evaluation.

1 On request from the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, Question No EFSA-Q-2009-00515 adopted by written procedure on 5 March 2010.

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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 Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, requested the evaluation of the substance 5-chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1), with the CAS number 55965-84-9 and the European Commission reference number (REF. No.) 43730, as a biocide intended to be used as a preservative in water-based polymer dispersions used to make coatings, as a preservative in water-based formulations of paper making chemicals and as a slimicide in process water for paper manufacturing at the maximum use levels of 30, 15 and 2 mg/l respectively. The final products are intended to be used for contact with all kinds of foodstuffs without restrictions of time and temperature. The dossier was submitted by the applicant, THOR GmbH, Germany.

The CEF Panel concluded that there is no safety concern for the consumer if the maximum residual amount of the substance in the finished products does not exceed 25 µg/dm². Its use should not result in an anti-microbial effect at the surface of the polymer or on the food itself.

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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 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food[4].

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, the EFSA received an application from the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, requesting the evaluation of the substance 5-chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1), with the CAS number 55965-84-9 and the European Commission reference number (REF. No.) 43730.

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:

1. new substances intended to be used in food contact materials before their authorisation and inclusion in a positive list;
2. substances which are already authorised in the framework of Regulation (EC) No. 1935/2004 but need to be re-evaluated.

[4] This Regulation replaces Directive 89/109/EEC of 21 December 1988, OJ L 40, 11.2.1989, P.38.

ASSESSMENT

1. Introduction

The European Food Safety Authority was asked by the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, to evaluate the safety of the substance 5-chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1), with the CAS number 55965-84-9 and the REF. No. 43730. The request has been registered in the EFSA's register of received questions under the number EFSA-Q-2009-00515. The dossier was submitted by the applicant, THOR GmbH, Germany.

Since in the past the evaluation of substances used in food contact materials was undertaken by the Scientific Committee on Food (SCF), the same system of classification into a "SCF list" is retained for uniformity purposes. The definitions of the various SCF lists and the abbreviations used are given in the APPENDIX A.

2. General information

According to the applicant, the substance under evaluation is a biocide intended to be used as a preservative in water-based polymer dispersions used to make coatings, as a preservative in water-based formulations of paper making chemicals and as a slimicide in process water for paper manufacturing at the maximum use levels of 30, 15 and 2 mg/l respectively. It is a process mixture of 5-chloro-2-methyl-2H-isothiazol-3-one (CIT) and 2-methyl-2H-isothiazol-3-one (MIT) obtained directly from the reaction in the production process in the ratio CIT/MIT 3:1. The final products are intended to be used for contact with all kinds of foodstuffs without restrictions of time and temperature.

The mixture as such has not been evaluated by the SCF or EFSA in the past. However, one of the constituents, 2-methyl-2H-isothiazol-3-one (MIT) with the Ref. No. 66755, was assessed by the Scientific Committee of Food (SCF) in 1992 (EC, 1992) and by EFSA in 2007 (EFSA, 2007). In the latest evaluation, EFSA classified MIT in the SCF_List 3 with the restriction 0.5 mg/kg food and "only to be used in aqueous polymer dispersions and emulsions and at concentrations which do not result in an anti-microbial effect at the surface of the polymer or on the food itself".

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).

Non-toxicity data:

- Data on identity
- Data on physical and chemical properties
- Data on intended use and authorisation
- Data on residual content or use level
- Data on calculation of worst case migration

Microbiological data:

- Spectrum of activity
- Minimum Inhibitory Concentrations
- Lack of antimicrobial activity on the surface of the final article

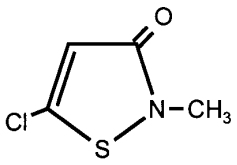
Toxicity data:

- Bacterial gene mutation test
- *In vitro* mammalian cell gene mutation test
- *In vitro* mammalian chromosome aberration test
- Mouse bone marrow micronucleus test
- Rat liver unscheduled DNA synthesis (UDS)
- 90-day oral toxicity study in dogs
- 2-year chronic toxicity/carcinogenicity study in rats
- Reproduction/developmental toxicity studies in rats
- Sensitization study in guinea pigs
- Absorption, distribution, metabolism and excretion (ADME) studies in rats

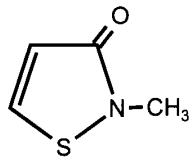
4. Evaluation

4.1. Non-toxicological data

Structural and molecular formula:



5-Chloro-2-methyl-2H-isothiazol-3-one



2-Methyl-2H-isothiazol-3-one

The specific migration of CIT/MIT from paper or coating into food or food simulants was not determined experimentally, but it was calculated on the basis of the residual amount, when the mixture is used at the maximum intended use level, assuming 100 % migration into food in a worst case scenario (worst case migration):

- The use of CIT/MIT mixture as a preservative in water-based polymer dispersions for manufacturing of coatings at the maximum use level of 30 mg/l would result in a residual amount of the mixture in the dry coating of 24 µg/dm^2. The total transfer of CIT/MIT can then be calculated equal to 144 µg/kg food.
- The use of CIT/MIT mixture as a preservative in water-based formulations of paper making chemicals at the maximum use level of 15 mg/l would result in a residual amount of the mixture in the paper of 0.24µg/dm^2. The total transfer of CIT/MIT was calculated to be 1.4 µg/kg food.
- The use of CIT/MIT mixture as a slimicide in the process water for paper manufacturing was calculated to result in a potential transfer of the residual amount of less than 1 µg/kg food.

4.2. Microbiological data

The mixture has antimicrobial activity against a wide range of spoilage bacteria, moulds and yeasts with minimum inhibitory concentrations ranging from 2-20 mg/l. It has been demonstrated that coated papers made from dispersions containing up to 30 mg CIT/MIT/l do not have antimicrobial activity in the inhibition test with *Bacillus subtilis* and *Aspergillus niger* spores.

No cases of resistance arising during the use of CIT/MIT in the process have been reported. Therefore, in the light of the current knowledge and considering the proposed use, there is no basis for concern for induction of antimicrobial resistance during the use of CIT/MIT in the manufacturing process.

4.3. Toxicological data

The biocide gave positive results in genotoxicity tests *in vitro* in bacteria and in mammalian cells, both at gene and chromosome level. No significant genotoxicity was observed *in vivo* in mouse bone marrow and rat liver after oral administration up to the maximum tolerated dose. The genotoxic activity of the biocide *in vitro* can be related to the reactivity of the N-S bond of the isothiazolidone ring with nucleophilic targets, including the amino groups of DNA bases. On the other hand *in vivo* metabolism leads to extensive ring opening, with cleavage of the N-S bond and loss of reactivity toward nucleophiles. Therefore, the biocide is considered as non-genotoxic *in vivo*. The lack of genotoxicity *in vivo* is also confirmed by the negative results obtained in a 2-year oncogenicity study in rats.

The available set of toxicity data comprises oral repeated-dose toxicity studies (90-day study in dogs and a chronic toxicity study in rats) and a two-generation reproductive toxicity study in rats. From these studies, the lowest NOAEL (2 mg/kg bw/day) was established in the chronic toxicity study in rats, based on histopathological alterations of stomach mucosa. These lesions can be related to the irritating and corrosive properties of the biocide. The mixture was also recently re-evaluated by the Scientific Committee on Consumer Safety (SCCS, 2009) who considered a NOAEL of 2.8 mg active ingredient/kg bw/day based on the results from a two-generation reproductive oral study in the rat.

ADME studies show that the biocide is rapidly absorbed when given by the oral route, and eliminated by urine and faeces after extensive metabolic transformation, mainly consisting in glutathione conjugation and opening of the isothiazolidone ring. Based on the results of ADME studies, and in consideration of the low log Po/w, no potential of accumulation in man is expected.

The Panel noted that in sensitisation tests in guinea pigs the biocide elicited discrete and moderate erythema and oedema when applied dermally at 0.025% and above. Dermal sensitisation of this substance is well known and was recently re-evaluated by the Scientific Committee on Consumer Safety (SCCS) which considered a threshold for induction of sensitisation of 0.75 µg active ingredient/cm² skin (EC, 2009), as determined in a local lymph node assay. The Panel noted that paper/board is a dry matrix from which the substance would not easily diffuse to the skin and that the contact between the skin and a food contact material is typically not prolonged. Even by considering total mass transfer of the residual amount of 25 µg/dm² from the paper to the skin, the aforementioned threshold would not be reached. The Panel also considered that when the substance is present at 25 µg/dm^2, in case of migration of the substance into food, the low dose exposure resulting from this migration will not result in systemic toxicity. This exposure is also unlikely to result in sensitization given the limited ability of this route to elicit sensitization reactions.

Based on the intended use, the data on the worst case migration potential, the microbiological data and the lowest NOAEL from the repeat dose toxicity study, the Panel considers a restriction of the maximum residual amount in the finished products up to 25µg/dm² would be appropriate.

CONCLUSIONS

The CEF Panel after having considered the above-mentioned data proposes that the substance 5-chloro-2-methyl-2H-isothiazol-3-one, mixture with 2-methyl-2H-isothiazol-3-one (3:1) be classified in the SCF_List 3 with a restriction of the maximum residual amount in the finished products up to 25 µg/dm². The use of the mixture should not result in an anti-microbial effect at the surface of the polymer or on the food itself.

As a remark addressed to the Commission, the Panel noted that analytical methods were provided for the determination of the substance (CIT/MIT) only in paper and board and for MIT in coatings.

DOCUMENTATION PROVIDED TO EFSA

Dossier referenced: CIT/MIT (3:1); Dated: March 2009. Submitted by Thor GmbH, Germany.

REFERENCES

EC (European Commission), 1992. Scientific Committee on Food (SCF) Reports, 33rd Series, Opinions expressed until 3 May 1992, first report on certain additives used in the manufacture of plastic materials intended to come into contact with foodstuffs; http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_33.pdf.

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.

EFSA (European Food Safety Authority), 2007. 16th list of substances for food contact materials - Scientific Opinion of the Panel on food additives, flavourings, processing aids and materials in contact with food (AFC); the EFSA Journal (2007) 555-563, 1-31; http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178652695290.htm.

EC (European Commission), 2009. Opinion of the Scientific Committee on Consumer Safety (SCCS) on the mixture of 5-chloro-2-methylisothiazolin-3(2H)-one and 2-methylisothiazolin-3(2H)-one adopted at its 5th plenary meeting of 8 December 2009; http://ec.europa.eu/health/ph_risk/risk_en.htm.

Appendices

APPENDIX A

DEFINITION OF THE SCF LISTS

The classification into a SCF_List is a tool used for tackling authorisation dossiers and does not prejudice the management decisions that will be taken on the basis of the scientific opinions of the CEF Panel and in the framework of the applicable legislation.

List 0	Substances, e.g. foods, which may be used in the production of plastic materials and articles, e.g. food ingredients and certain substances known from the intermediate metabolism in man and for which an ADI needs not being established for this purpose.
List 1	Substances, e.g. food additives, for which an ADI (=Acceptable Daily Intake), a t-ADI (=temporary ADI), a MTDI (=Maximum Tolerable Daily Intake), a PMTDI (=Provisional Maximum Tolerable Daily Intake), a PTWI (=Provisional Tolerable Weekly Intake) or the classification "acceptable" has been established by this Committee or by JECFA.
List 2	Substances for which this Committee has established a TDI or a t-TDI.
List 3	Substances for which an ADI or a TDI could not be established, but where the present use could be accepted. Some of these substances are self-limiting because of their organoleptic properties or are volatile and therefore unlikely to be present in the finished product. For other substances with very low migration, a TDI has not been set but the maximum level to be used in any packaging material or a specific limit of migration is stated. This is because the available toxicological data would give a TDI, which allows that a specific limit of migration or a composition limit could be fixed at levels very much higher than the maximum likely intakes arising from present uses of the additive. Depending on the available toxicological studies a restriction of migration into food of 0.05 mg/kg of food (3 mutagenicity studies only) or 5 mg/kg of food (3 mutagenicity studies plus 90-day oral toxicity study and data to demonstrate the absence of potential for bio-accumulation in man) may be allocated.
List 4	**(for monomers)**
4A	Substances for which an ADI or TDI could not be established, but which could be used if the substance migrating into foods or in food simulants is not detectable by an agreed sensitive method.
4B	Substances for which an ADI or TDI could not be established, but which could be used if the levels of monomer residues in materials and articles intended to come into contact with foodstuffs are reduced as much as possible.
List 4	**(for additives)**

Substances for which an ADI or TDI could not be established, but which could be used if the substance migrating into foods or in food simulants is not detectable by an agreed sensitive method.

List 5 Substances that should not be used.

List 6 Substances for which there exist suspicions about their toxicity and for which data are lacking or are insufficient.

The allocation of substances to this list is mainly based upon similarity of structure with that of chemical substances already evaluated or known to have functional groups that indicate carcinogenic or other severe toxic properties.

6A Substances suspected to have carcinogenic properties. These substances should not be detectable in foods or in food simulants by an appropriate sensitive method for each substance.

6B Substances suspected to have toxic properties (other than carcinogenic). Restrictions may be indicated.

List 7 Substances for which some toxicological data exist, but for which an ADI or a TDI could not be established. The required additional information should be furnished.

List 8 Substances for which no or only scanty and inadequate data were available.

List 9 Substances and groups of substances which could not be evaluated due to lack of specifications (substances) or to lack of adequate description (groups of substances).

Groups of substances should be replaced, where possible, by individual substances actually in use. Polymers for which the data on identity specified in "SCF Guidelines" are not available.

List W "Waiting list". Substances not yet included in the Community lists, as they should be considered "new" substances, i.e. substances never approved at national level. These substances cannot be included in the Community lists, lacking the data requested by the Committee.

APPENDIX B

TERMS USED RELEVANT TO MIGRATION:

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

ABBREVIATIONS

AFC	Scientific Panel on additives, flavourings, processing aids and materials in contact with food
ADME	Absorption, distribution, metabolism, and excretion
bw	body weight
CAS	Chemical abstracts service
CEF	Scientific Panel on food contact materials, enzymes, flavourings and processing aids
CIT	5-chloro-2-methyl-2H-isothiazol-3-one
DNA	Deoxyribonucleic acid
EC	European Commission
EFSA	European Food Safety Authority
FCM	Food Contact Material(s)
MIT	2-methyl-2H-isothiazol-3-one
NOAEL	No observed adverse effect level
Po/w	Octanol/water partition coefficient
REF No	Reference Number
SCF	Scientific Committee on food
UDS	Unscheduled DNA synthesis