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Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to

a 8th list of substances for food contact materials

Question N° EFSA-Q-2003-224, EFSA-Q-2003-189

Adopted on 27 April 2005

SUMMARY

Within the general task of evaluating substances intended for use in materials in contact with food according to Council Directive 89/109/EEC of 21 December 1988 relating to materials and articles intended to come into contact with foodstuffs, the AFC Panel evaluated the following substances.

Ref. No.:	47500
Name of the substance:	N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide
CAS number:	153250-52-3
Classified in list:	3
Restriction:	5 mg/kg food
Ref. No.:	67360 and 47600
Name of the substance:	Mono-n-dodecyltin tris(isooctyl mercaptoacetate) and Di-n- dodecyltin bis(isooctyl mercaptoacetate)
CAS number:	067649-65-4 and 084030-61-5
Classified in list:	3
Restriction:	0.05 mg/kg food (as sum of mono-n-dodecyltin tris(isooctyl mercaptoacetate), di-n- dodecyltin bis(isooctyl mercaptoacetate), mono-dodecyltin trichloride and di-dodecyltin dichloride) expressed as the sum of mono- and di-dodecyltin chloride

KEY WORDS

Food Contact Materials, Plastics, Additives, N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide, REF. No 47500, CAS No 153250-52-3, Mono-n-dodecyltin tris(isooctyl mercaptoacetate) and Di-n- dodecyltin bis(isooctyl mercaptoacetate), REF. No 67360 and 47600, CAS No 067649-65-4 and 084030-61-5

BACKGROUND

According to Article 7 of the Council Directive 89/109/EEC of 21 December 1988 it is necessary to consult the Scientific Committee on Food (SCF) on the risks connected with the migration of substances into food from food contact materials in which they are used. This competence was transferred to the European Food Safety Authority (EFSA) by virtue of the Regulation (EC) 178/2002. The opinion of the EFSA is required before a substance is authorized to be used in food contact materials and be included in a positive list when this is established in the relevant legislation.

TERMS OF REFERENCE

The Commission asks EFSA to carry out risk assessments on:

1.all new substances used in food contact materials before their authorization and inclusion in a positive list;

2.substances which are already authorized in the framework of Council Directive 89/109/EEC but need to be re-evaluated.

ASSESSMENT

Within this general task the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) evaluated the following substances used in food contact materials. The substances examined are listed in ascending order of their Reference Number (REF No.), with their chemical name, Chemical Abstract Number (CAS No.) and classification according to the "SCF list". (Previously the evaluation of substances used in food contact materials was undertaken by the Scientific Committee on Food (SCF)). The definitions of the various SCF lists and the abbreviations used are given in the appendix.

Ref. No.:	**47500**
Name of the substance:	**N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide**
CAS number:	153250-52-3
Document reference:	EFSA/AFC/FCM/225-Rev.IB/47500 of April 2005
General information:	According to the petitioner N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide is used as an additive in polypropylene (PP) homopolymer and copolymers only, with the function of a nucleating agent at maximum level of 0.2%. The finished products containing the additive are for single and repeated use , for all types of foods, in conditions ranging from -20°C / 30days through to 120°C / 5min
Previous evaluations (by SCF or AFC):	None
Available data used for this evaluation:	

Ref. No.:	**47500**
Name of the substance:	**N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide**

Non-toxicity data:

- Identity of the substance
- Intended application of the substance
- Estimated half life at 25°C at different pH
- Specific migration in 10% ethanol, 3% acetic acid and olive oil
- Stability study in 10% ethanol and 3% acetic acid and determination of hydrolysis products

Toxicity data:

- Gene mutation assay in bacteria
- Chromosomal aberration assay in cultured mammalian cells
- Gene mutation assay in cultured mammalian cells
- 28 day oral subacute study
- Literature data on hydrolysis products

Evaluation:

Specific migration of N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide was measured on PP plaques containing 0.2% of the additive in 10% ethanol, 3% acetic acid, and olive oil, for 2 hours at 121°C followed by 10 days at 40°C. In olive oil, migration levels ranged from 0.58 to 0.65 mg/kg. In ethanolic simulant, migration ranged from 0.032 mg/kg to 0.080 mg/kg. Migration was not detected in the 3% acetic acid test solutions at a limit of detection of 0.007 mg/kg. Recovery test demonstrated the absence of hydrolysis in the conditions of the migration test.

N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide did not show genotoxic properties in the two *in vitro* mutagenicity tests (gene mutation in bacteria and gene mutation in cultured mammalian cells) according to the experimental conditions. Furthermore, it did not induce chromosomal aberrations *in-vitro.*

N,N'-dicyclohexyl-2,6-naphthalene dicarboxamide was administered, orally to Sprague Dawley rats at dose levels of 40, 200, and 1000 mg/kg bw in a 28-day oral study, performed to the full OECD protocol, followed by a recovery period of 14 days (with a 1000 mg/kg bw group and a control group). Besides some minor haematological effects in female rats receiving 1000 mg/kg bw/day at the end of the treatment period and in males at this dose level at the end of the recovery period, no other effects were observed during the treatment period. A NOAEL of 1000 mg/kg bw is considered for this substance in this study.

Although the 90-day subchronic oral toxicity study requested by the SCF Guidelines is not available, in this case the Panel considered a restriction of 5 mg/kg food appropriate.

This decision is based on the large margin of safety (4 orders

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of magnitude) from the 28-day study, the low solubility in both polar and apolar media and the fact that the expected metabolites cyclohexylamine and 2,6-naphthalene dicarboxylic acid are already evaluated by the SCF. Cyclohexylamine (REF No 45760) is in List 2 with a TDI of 1 mg/kg b.w (SCF, R33) and 2,6-naphthalene dicarboxylic acid (REF No 22360) is in List 3 with a restriction of 5 mg/kg food (SCF, 1999).

Conclusion: Based on the above-mentioned data the substance is classified:
SCF_List: **3**
Restriction: **5 mg/kg food**
Remark for Commission: None
Needed data or information None

References:

Unpublished data submitted by the petitioner, November 2003 and November 2004

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://europa.eu.int/comm/food/fs/sc/scf/reports/scf_reports_33.pdf

SCF Opinion on an additional list of monomers and additives for food contact materials, expressed on 23 September 1999 http://europa.eu.int/comm/food/fs/sc/scf/out41_en.pdf

Ref. No.:	**67360 and 47600**
Name of the substance:	**Mono-n-dodecyltin tris(isooctyl mercaptoacetate) and Di-n-dodecyltin bis(isooctyl mercaptoacetate)**
CAS number:	067649-65-4 and 084030-61-5
Document reference:	*EFSA/AFC/FCM/218-Rev.IIB/67360/47600, March 2005*

General information: According to the petitioner dodecyltin stabilizers used for rigid PVC are mixtures of 50-70% of mono-n-dodecyltin tris(isooctyl mercaptoacetate) and 30-50% di-n- dodecyltin bis(isooctyl mercaptoacetate). Upon processing at 210°C mono-dodecyltin trichloride and di-dodecyltin dichloride are formed.

Previous evaluations (by SCF or AFC): The substances were first evaluated in 1990 (reported in SCF, 1999) and classified in SCF_L2 with t-TDI of 0.4 mg/kg bw (REF No. 67360) and

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Name of the substance:	Mono-n-dodecyltin tris(isooctyl mercaptoacetate) and Di-n-dodecyltin bis(isooctyl mercaptoacetate)

0.2 mg/kg bw (REF No. 47600) based on incomplete toxicity data.

Needed: rat liver UDS with monododecyltin trichloride.

Available data used for this evaluation:

Non-toxicity data:
- data on identity of dodecyltin stabilizers and migration of tin from processed PVC in food simulants
- data on hydrolysis of methyl- butyl- and octyltinthioglycolates in simulted gastric juice

Microbiological data:

Toxicity data:
- gene mutation tests in bacteria with di-dodecyltin-dichloride, mono-dodecyltin trichloride and dodecyltin stabilizer (a 63:36 mixture of REF No. 67360 and REF No. 47600)
- gene mutation assay in mammalian cells with di-dodecyltin-dichloride and mono-dodecyltin trichloride
- chromosomal aberration tests in vitro with di-dodecyltin-dichloride and mono-dodecyltin trichloride
- mouse bone marrow micronucleus test with mono-dodecyltin trichloride
- UDS in rat liver with mono-dodecyltin trichloride
- 90-day oral toxicity studies in rat with dodecyltin stabilizer (a 63:36 mixture of REF No. 67360 and REF No. 47600)
- toxicokinetic and metabolism of REF No. 67360 in rats and rabbits

Evaluation:

Migration of tin in food simulants from PVC containing 1.5 % w/w dodecyltin stabilizers (a mixture 63:36 of REF No. 67360 and REF No. 47600) was measured after 10 days at 40°C and after 2 hours at 70°C. The highest value, determined in fat simulant at 70°C, was 3.8 μg Sn/6 dm^2, equivalent to 3.8 μg Sn/kg food.

Extensive hydrolysis of tin mercaptide stabilizers in simulated gastric juice was demonstrated.

REF No. 67360 and REF No. 47600 (as 63:36 mixture) and the chlorinated derivatives mono-dodecyltin trichloride (MDTC) and di-dodecyltin dichloride (DDTC) were not mutagenic in bacterial reversion tests, with and without exogenous metabolic activation. Negative results were also obtained with MDTC and DDTC in gene mutation assays in mammalian cells and in tests for induction of gene conversion in yeast. Cytogenetic tests with human lymphocytes showed a direct clastogenic activity for MDTC; negative results were obtained with DDTC. *In vivo*, oral administration of MDTC to mice up to doses producing overt toxicity and bone marrow depression did not induce micronuclei in polychromatic

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erythrocytes. Negative results were also obtained in the liver UDS assay in rats treated orally with MDTC at the maximum recommended dose. Considering that REF No. 67360 and 47600 are converted into MDCT and DDTC during curing of PVC, and that tin mercaptide stabilizers undergo extensive hydrolysis in gastric juice, on the basis of experimental data available for MDTC and DDTC it is concluded that REF No. 67360 and REF No. 47600 do not pose genotoxic risk.

A 90-day oral toxicity study in rats with dodecyltin stabilizers (REF No.67360:REF No.47600 at 63:36) administered at 0, 60, 600 or 6000 mg/kg of diet, showed no effect at the dose of 600 mg/kg in the diet, including no effect on thymus or lymph node weights or histopathology, normally an indicator for immune effects of organotin compounds. A NOAEL of 60 mg/kg bw/day is derived. ADME studies with MDTC in rats and rabbits showed low intestinal absortion after oral administration, with rapid elimination via the feces of the compound largely unmodified.
The subchronic studies available for REF 67360 and REF 47600 did not address immunotoxicity in great detail. However, neither thymus or lymph node weights nor histology were adversely affected at dose levels up to 555 mg/kg bw. This strongly indicates that these subsatnces are far less potent immunotoxicant than those substances covered by the group TDI for Sn of 0.1 µg/kg bw set for other organotin compounds. As immunotoxicity, the critical effect for organotin compounds (SCTEE, 2003), requires investigation by special studies, it is not completely assessed by the available oral 90-day toxicity study in the rat. Therefore, solely on the basis of the results of the available genotoxicity studies, mono-n-dodecyltin tris(isooctyl mercaptoacetate) (REF No. 67360) and di-n- dodecyltin bis(isooctyl mercaptoacetate) (REF No. 47600) are classified in the SCF List 3 with a restriction of 50 µg/kg of food.

Conclusion: Based on the above-mentioned data the substance is classified:

SCF_List: **SCF_list: 3**

Restriction: 0.05 mg/kg food (as sum of mono-n-dodecyltin tris(isooctyl mercaptoacetate), di-n- dodecyltin bis(isooctyl mercaptoacetate), mono-dodecyltin trichloride and di-dodecyltin dichloride) expressed as the sum of mono- and di-dodecyltin chloride

Remark for Commission: None

Needed data or information None

References:

Unpublished data submitted by the petitioner on 3/12/2002 and 26/03/2004

SCF (Scientific Committee for Food), 1999. In "Compilation of the evaluations of the Scientific Committee for Food on certain monomers and additives used in the manufacture of plastic materials intended to come into contact with foodstuffs until the 21 March 1997". 42nd Series of Reports of the Scientific Committee for Food. Office of Official

Ref. No.:	**67360 and 47600**
Name of the substance:	**Mono-n-dodecyltin tris(isooctyl mercaptoacetate) and Di-n-dodecyltin bis(isooctyl mercaptoacetate)**

Publications of the European Communities, Luxembourg, 1999. http://europa.eu.int/comm/food/fs/sc/scf/reports/scf_reports_42.pdf

Scientific Committee on Toxicity, Ecotoxicity and the Environment (2003) Opinion on the non-food aspects of "Assessmnet of the risk to health and the environment posed by the use of organostannic compounds (Excluding use as a biocide in antifouling paints) and a description of the economic profile of the industry" http://europa.eu.int/comm/health/ph_risk/committees/sct/documents/out188_en.pdf

SCIENTIFIC PANEL MEMBERS

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LIST OF ABBREVIATIONS:

UDS: Unscheduled DNA synthesis

APPENDIX

DEFINITION OF THE SCF LISTS

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 need not be 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.