

SCIENTIFIC OPINION

Scientific Opinion on the safety evaluation of the substance, 2,4-diamino-6-hydroxypyrimidine, CAS No. 56-06-4, for use in food contact materials¹

EFSA Panel on food contact materials, enzymes,
flavourings and processing aids (CEF)^{2,3}

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ABSTRACT

This scientific opinion of EFSA deals with the risk assessment of the additive 2,4-diamino-6-hydroxypyrimidine, CAS No. 56-06-4, REF. No. 46330 for which the CEF Panel concluded that there is no safety concern for the consumer if the substance is used only in rigid poly(vinyl chloride) (PVC) in contact with non-acidic and non-alcoholic aqueous food and its migration is up to 5 mg/kg food.

KEY WORDS

2,4-Diamino-6-hydroxypyrimidine; CAS number 56-06-4; Ref. No. 46330; Food contact materials; Safety assessment; Evaluation.

1 On request from the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, Question No EFSA-Q-2009-00681 adopted on 26 November 2009.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on food contact materials for the preparation of this opinion: Mona-Lise Binderup, Laurence Castle, Riccardo Crebelli, Roland Franz, Nathalie Gontard, Eugenia Lampi, Jean-Claude Lhuguenot, Maria Rosaria Milana, Karla Pfaff, Kjetil Svensson and Detlef Wölfle for the support provided to this EFSA scientific output. M.-L. Binderup declared an interest as the evaluation of the toxicological studies on the substance was done by her Institute DTU under contract with EFSA. She presented the evaluation results and another member of the WG was appointed as rapporteur to present the draft opinion to the Panel.

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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 for evaluation of the additive 2,4-diamino-6-hydroxypyrimidine with the CAS number 56-06-4 and the European Commission reference number (REF. No.) 46330, for use as heat stabilizer in poly(vinyl chloride) (PVC) material at a maximum content of 0.18% (w/w) for contact with aqueous food at room temperature for a long period and in some applications, at any condition of time and temperature. The dossier was submitted by the applicant, Sun Ace Kakoh (Pte.) Ltd, Singapore.

The CEF Panel concluded that there is no safety concern for the consumer if the substance is used only in rigid PVC in contact with non-acidic and non-alcoholic aqueous food and the migration of the substance is up to 5 mg/kg food.

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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 food⁴.

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 additive 2,4-diamino-6-hydroxypyrimidine with the CAS number 56-06-4 and the European Commission reference number (REF. No.) 46330.

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 2,4-diamino-6-hydroxypyrimidine with a CAS number 56-06-4 and a REF. No. 46330. The request has been registered in the EFSA's register of received questions under the number EFSA-Q-2009-00681. The dossier was submitted by the applicant, Sun Ace Kakoh (Pte.) Ltd, Singapore.

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 2,4-diamino-6-hydroxypyrimidine is intended to be used as heat stabilizer in poly(vinyl chloride) (PVC) material at a maximum content of 0.18% w/w for contact with non-acetic and non-alcoholic aqueous food at room temperature for a long period. In some applications, any condition of time and temperature may be applied.

The substance has not been evaluated by the SCF or EFSA in the past.

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:

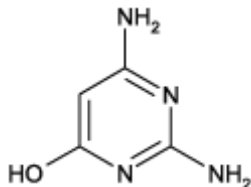
- Data on identity
- Data on physical and chemical properties
- Data on intended use and authorisation
- Data on migration of the substance

Toxicity data:

- Bacteria gene mutation test
- In vitro mammalian cell gene mutation test
- In vitro mammalian chromosome aberration test
- 90-day oral toxicity study in rats

4. Evaluation

4.1. Non-toxicological data



Structural formula:

Molecular formula: CH₆N₄O

2,4-Diamino-6-hydroxypyrimidine does not hydrolyse in aqueous foods and is thermally stable up to 260 °C. The substance is soluble in water with a Log Po/w (20°C) ≤ -1.

Specific migration from a rigid PVC test sample with the substance at the maximum intended use level was determined into water which is appropriate in this case for non-acidic aqueous food. The test conditions were 10 days at 40°C. The surface to volume ratio was 6 dm²/l. Under these conditions, the specific migration was 75 µg/kg.

The residual content of the substance from the PVC test sample was determined by extraction into methanol to be 0.13 % w/w versus a nominal content of 0.18% w/w.

4.2. Toxicological data

2,4-Diamino-6-hydroxypyrimidine was tested for genotoxic potential in the three recommended mutagenicity tests. The genotoxicity tests were performed according to current OECD guidelines and in compliance with GLP. The test substance did not induce gene mutation in bacteria and in mammalian cells. It did not induce chromosomal aberrations in human peripheral blood lymphocytes. Therefore the substance is considered as non-genotoxic.

2,4-Diamino-6-hydroxypyrimidine was tested in a 90-day oral toxicity study in Wistar rats at dose levels of 200, 800 and 1600 mg/kg bw/day.

There were no pre-terminal deaths in any of the study groups. Mild to severe and dose related salivation was observed in all the substance treated groups.

There was no treatment related changes in body weight gain and mean food intake.

Ophthalmological examination of all animals did not reveal any eye abnormalities at the end of treatment and recovery periods.

Haematological examination revealed that mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were significantly increased in the two high-dose groups and in the high-dose recovery group of both sexes. Several other differences in haematological parameters were recorded between the treated and control groups but the findings were inconsistent and/or within the physiological range.

Clinical chemistry examination revealed significant increase in plasma cholesterol in the high dose groups of both sexes. Several differences in other clinical chemistry parameters were recorded

between the treatment and the control groups but the findings were inconsistent, within physiological range or did not show any dose dependency.

Macroscopic examination revealed no lesions of pathological significance. The absolute weights of liver, kidney and spleen were significantly increased in the mid- and high-dose males and the high-dose females. The significantly increased relative weights of kidney, liver and spleen were recorded only in the high-dose males. The lack of any histopathological changes in the kidneys, liver and spleen indicate that the increases in the absolute weights recorded in the mid- and the high-dose male groups and in the high-dose female group as well as the increases in the relative weights of these organs in the high-dose male group could be due to an adaptive response to the test substance.

The decreases in absolute weights of the ovaries in the low- and mid-dose groups, in the absolute heart weight in the low-dose group or in the relative weights of the ovaries and the heart in all treated groups, and of the thymus in the high-dose group were recorded in females only, were not accompanied by histopathological changes, and the dose response was not apparent and therefore could be considered incidental findings.

No treatment related changes were observed in home cage and handling observations of neurobehavioral observations. In open field observation significantly reduced rearing count was observed in male rats from the high-dose group (week 5) and in the high-dose recovery group (week 1 and 3) and in females from the low dose group (week 1), from the mid-dose group (week 1 and 3) and the high-dose group (week 10, 14, 16) as compared to the controls.

In the Functional Observation Battery, significant reduction was observed in motor activity of the high-dose groups and hind limb foot splay of the mid-dose male group.

Changes observed in the approach response, touch response, click response and tail-pinch response of high dose treated rats could be considered as treatment related.

The test substance seems to have neurotoxic potential based on the clinical observation and results of the neurobehavioral tests where changes were observed in the approach response, touch response, click response, tail pinch response, as well as more severe salivation and a reduced motor activity in the high-dose group. Although, the salivation is transient and could be due to administration by gavage it cannot be excluded that the dose related salivation observed in all treatment groups is related to neurotoxicity, giving a LOAEL value of 200 mg/kg/bw for this 90-day study. By application of an uncertainty factor of 3, a NOAEL of 70 mg/kg bw can be derived.

Considering the structure and the Log Po/w value, the substance does not raise concerns for accumulation in man.

CONCLUSIONS

The CEF Panel after having considered the above-mentioned data proposes that the substance 2,4-diamino-6-hydroxypyrimidine be classified in the SCF_List 3 with a restriction of 5 mg/kg food and only to be used in rigid PVC in contact with non-acidic and non-alcoholic aqueous food.

DOCUMENTATION PROVIDED TO EFSA

Dossier dated 5 May 2009. Submitted by the applicant Sun Ace Kakoh (Pte.) Ltd, Singapore.

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

APPENDICES

1. APPENDIX A

DEFINITION OF THE SCF LISTS

The classification into a SCF_List is a tool used for tackling authorisation dossiers and do 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 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.

2. 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 simulant

ABBREVIATIONS

AFC	Scientific Panel on additives, flavourings, processing aids and materials in contact with food
bw	body weight
CAS	Chemical abstracts service
CEF	Scientific Panel on food contact materials, enzymes, flavourings and processing aids
EC	European Commission
EFSA	European food safety authority
FCM	Food Contact Material(s)
GLP	Good laboratory practice
LOAEL	Lowest observed adverse effect level
MCH	Mean corpuscular volume
MCV	Mean corpuscular haemoglobin
NOAEL	No observed adverse effect level
OECD	Organisation for economic co-operation and development
Po/w	Octanol/water partition coefficient
PVC	Poly(vinyl chloride)
REF No	Reference Number
SCF	Scientific Committee on food
w/w	Weight by weight