# 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 4th list of substances for food contact materials

# (Question N° EFSA-Q-2003-210, EFSA-Q-2003-223, EFSA-Q-2003-187, EFSA-Q-2003-202, EFSA-Q-2003-203)

# adopted on 26 May 2004 by written procedure


## 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.

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| Ref. No.: | 13317 |
| Name of the substance: | N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide |
| CAS number: | 132459-54-2 |
| Classified in list: | 3 |
| Restriction: | 0.05 mg/kg food |

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| Ref. No.: | 25540 |
| Name of the substance: | Trimellitic acid |
| CAS number: | 528-44-9 |
| Classified in list: | 3 |
| Restriction: | 5 mg/kg food |

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| Ref. No.: | 25550 |
| Name of the substance: | Trimellitic anhydride |
| CAS number: | 552-30-7 |
| Classified in list: | 3 |
| Restriction: | 5 mg/kg food, expressed as trimellitic acid |

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| Ref. No.: | 66930 |
| Name of the substance: | Methylsilsesquioxane |
| CAS number: | 68554-70-1 |
| Classified in list: | 3 |
| Restriction: | Residual monomer in methylsilsesquioxane: < 1 mg methyltrimethoxysilane/kg of methylsilsesquioxane |

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| Ref. No.: | 86432 |

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| Name of the substance: | Silver-containing glass (Silver-magnesium-calcium-phosphate-borate) |
| CAS number: | - |
| Classified in list: | 3 |
| Restriction: | Group restriction of 0.05 mg Ag/kg food |
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| Ref. No.: | 86434 |
| Name of the substance: | Silver sodium hydrogen zirconium phosphate |
| CAS number: | - |
| Classified in list: | 3 |
| Restriction: | Group restriction of 0.05 mg Ag/kg food |

**KEY WORDS**
Food Contact Materials, Plastics, Monomers, Additives, N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide, REF. No 13317, CAS No 132459-54-2, Trimellitic acid, REF. No 25540, CAS No 528-44-9, Trimellitic anhydride, REF. No 25550, CAS No 552-30-7, Methylsilsesquioxane, REF. No 66930, CAS No 68554-70-1, Silver-containing glass (Silver-magnesium-calcium-phosphate-borate), REF. No 86432, Silver sodium hydrogen zirconium phosphate, REF. No 86434.

**BACKGROUND**
According to Article 3(3) 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 authorised 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 authorisation and inclusion in a positive list;

2. substances which are already authorised 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) (re)evaluated three substances used as additives 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.

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| **Ref. No.:** | **13317** |
| **Name of the substance:** | **N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide** |
| CAS number: | 132459-54-2 |
| Document reference: | EFSA/AFC/FCM/135-Rev.IB/13317 |

**General information:**

According to the petitioner, N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide (purity > 98.1%) is a co-monomer (used up to 4%) in polyester articles [poly(ethylene terephthalate), poly(butylene terephthalate)], to provide UV shielding properties.

**Previous evaluations (by SCF or AFC):**

The substance was first evaluated in 2002 (SCF 2002) and it was classified in List 7

The non-toxicity data included:

- data on identity, purity, chemical and physico-chemical behaviour, use and authorisation
- an estimation of migration by a worst case calculation
- data on residual content of the substance of the polymer, with a properly described method

The substance is used as a co-monomer for polyesters (polymeric additives, PET and PBT). It is used at up to 4 % in the final article (usually 1 %) and gives strong UV shielding properties. No reaction nor degradation products in food are expected. The maximum possible migration was calculated to be 15 µg/kg of food by determining the residual amount of the substance in the plastic, and assuming a 100 % migration, which is a very severe assumption. In the HPLC-UV chromatogram of the extracts supplied with the data of the first evaluation, an unidentified compound, in an unknown proportion, was detected, which justified the request for additional information. This will be discussed below.

The toxicity data included:

- a gene-mutation assay in bacteria,
- a chromosomal aberration test in cultured mammalian cells,
- a gene-mutation assay in cultured mammalian cells,
- a micronucleus assay
- a 28-day oral study in male and female rats (Sprague Dawley).

In the chromosome aberration assay, the incidence of cells with numerical aberrant chromosomes increased significantly (up to 11 fold) and it was dose-dependent in both 48-hour continuous treatment and in the pulse treatment when S9 mix was added.

However, in a bone marrow micronucleus test with the substance, the rate of micronuclei was in the same range than negative controls and the PCE/NCE ratio was significantly affected only in males at the 24h sampling time, indicating that the substance did reach the target organ.

| Ref. No.: | 13317 |
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| Name of the substance: | N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide |

From these *in vitro* and *in vivo* assays, it was concluded that the substance has no genotoxic potency.
In an acute oral toxicity study, the $LD_{50}$ was greater than 2000-mg/kg b.w. N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide was administered, via the diet, to Sprague-Dawley rats, at different doses (dose range: 0 to 1000 mg/kg b.w.) for 28 days. A 14-day recovery period experiment was performed for control and high dose. No examined parameter was significantly modified. The NOEL is 1000 mg/kg b.w., based on the highest dose tested.

The first evaluation concluded that the data available were consistent with a migration limit 50 ppb. However, since concerns had been expressed about the identity of the unknown compound co-eluted with the substance in the HPLC chromatogram, and its possible toxicity, it was decided to request in first instance information on the nature, quantity and migration of the co-eluted compound. Depending on its identity, additional toxicological data on this compound may later be required. The substance was therefore classified in list 7.

**Available data used for this evaluation:**

Non-toxicity data:
- New data on purity, with identification of impurities, and estimation of their possible migration
- Adequate information about the unknown peak

**Evaluation:**

The purity of the co-monomer has been completely re-investigated, using modern analytical methods (HPLC-UV and HPLC-MS), which allowed a convincing identification of the impurities. The new results are:
the co-eluted peak is no longer detected, and a likely explanation for this has been given.
Four impurities of the co-monomer were identified, accounting for a total of 1.9 % (purity of the substance > 98.1%). These impurities become covalently bound to the polyester, and were not detected in a polyester made from the co-monomer (detection limits 2-10 mg/kg).
The information package needed for safety assessment has thus been completed. The impurities of the substance are of no concern anymore, for the following reasons:
(i) they have the same functional groups as the parent monomer, and become covalently bound to the polymer (the impurities are indeed not detected in the polymer),
(ii) their migration into food could be predicted to be well below 1 µg/kg food simulant and
(iii) their chemical similarity with the parent compound suggested a similar *in vivo* behaviour

**Conclusion:**

Based on the above data the substance is classified:

**SCF_List: 3**

| Ref. No.: | 13317 |
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| **Name of the substance:** | **N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide** |

**Restriction:** **0.05 mg/kg food**

Remark for Commission: FRF is applicable
N,N'-Bis[4-(ethoxycarbonyl)phenyl]-1,4,5,8-naphthalenetetracarboxydiimide
(> 98.1 %) is requested as a co-monomer (max. 4 %) for polyesters (like PET, PBT).

Needed data or information: None

**References:**
- Unpublished data submitted by the petitioner
- Opinion of the Scientific Committee on Food on the 19th additional list of monomers and additives for food contact materials expressed on September 2002
  http://europa.eu.int/comm/food/fs/sc/scf/out141_en.pdf

| Ref. No.: | 25540 |
|---|---|
| **Name of the substance:** | **Trimellitic acid** |

CAS number: 528-44-9

Document reference: SDS EFSA/AFC/FCM/84-Rev.1A/25540

**General information:** According to the petitioner Trimellitic anhydride (TMA) is used as monomer in epoxy resins for coatings and in polyamidimide. Polyamidimide is used as an anchoring agent for PTFE dispersion polymers on various substrates. The finished products are used in high temperature applications (backing and cooking). TMA modified coatings are applied in coatings and lining of cans and utensils; conditions of contact will vary from long term storage at room temperature to sterilization.
Trimellitic acid is the remaining acid after hydrolysis of trimellitic anhydride.

**Previous evaluations (by SCF or AFC):** The substance was first evaluated by SCF in 1998 and classified in List 7. Needed data: 90-day oral study.

**Available data used for this evaluation:**

Non-toxicity data: -

Microbiological data: -

Toxicity data: Data on 90-day oral study

**Evaluation:** Specific migration of trimellitic acid into water, 3% acetic acid, 8, 15 or 50% ethanol, n-heptane, olive oil or HB307 and iso-octane at a range of time/temperature conditions has been determined. The test samples were trimellitic anhydride-based epoxy powder coatings on support and

| Ref. No.: | 25540 |
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| Name of the substance: | Trimellitic acid |

polyamidimide resin on support. The finished coatings were investigated at temperatures up to 121°C. Maximum migration found in water after 2 hours at 121˚C is 1.6 mg/kg into food.
Analytical data concerning the residual content of trimellitic anhydride in polyamidimide coatings were provided. Residual content was determined as trimellitic acid and was found to be less than 0.5 µg/dm² in a typical PTFE coating, resulting in a maximum migration of 0.003 mg/kg food.

Trimellitic acid has low oral toxicity.
Short-term toxicity: In a 30-day gavage study in rats trimellitic acid caused diarrhoea at the highest dose-level of 1000 mg/kg b.w. Macroscopy revealed watery contents of caecum and distention of the caecum at this dose level. One male and one female animal on 300 and 100 mg/kg b.w. showed also watery caecal contents but no distention was seen. No microscopical abnormalities were observed.

Mutagenicity studies performed with trimellitic anhydride and carried out according to the guidelines, are negative.
Based on the data given above a factor 2000 can be calculated between the slight effect level in the 30-day study and the estimate for maximum daily oral exposure of man (~0.05 mg/kg b.w.).
Oral administration of trimellitic acid to rats by dietary administration for a period of 90 consecutive days at dose levels of up to 20000 mg/kg food resulted in treatment-related changes in both sexes that received 20000 mg/kg food and in females treated with 5000 mg/kg food. No such changes were detected in males treated with 5000 mg/kg food or in either sex treated with 1000 mg/kg food and for this reason the "No Observed Effect Level" (NOEL) was considered to be 5000 mg/kg food for males and 1000 mg/kg food for females.
The treatment-related effects detected in females treated with 5000 mg/kg food were confined to a minor caecal change detected histologically. The occurence of this change is not considered to be indicative of an adverse health effect so the NOAEL is taken as 5000 mg/kg food for both sexes, equivalent to around 400 mg/kg b.w./day

**Conclusion:** Based on the above-mentioned data the substance is classified:
**SCF_List:** **3**
**Restriction:** **5 mg/kg of food**
Remark for Commission: Group restriction together with the trimellitic anhydride REF No 25550
Needed data or information: None

**References:**


- Unpublished data submitted by the petitioner.
- Opinion of the Scientific Committee on Food on an additional list on monomers and additives for food contact materials (Adopted at the 111th SCF meeting) (18-19 March 1998) http://europa.eu.int/comm/food/fs/sc/scf/out10_en.pdf

| **Ref. No.:** | **25550** |
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| **Name of the substance:** | **Trimellitic anhydride** |
| CAS number: | 552-30-7 |
| Document reference: | EFSA/AFC/FCM/85-Rev.IA/25550 |

**General information:** According to the petitioner Trimellitic anhydride (TMA) is used as monomer in epoxy resins for coatings and in polyamidimide. Polyamidimide is used as an anchoring agent for PTFE dispersion polymers on various substrates. The finished products are used in high temperature applications (backing and cooking). TMA modified coatings are applied in coatings and lining of cans and utensils; conditions of contact will vary from long term storage at room temperature to sterilization.
Trimellitic acid is the remaining acid after hydrolysis of trimellitic anhydride.

**Previous evaluations (by SCF or AFC):** The substance was first evaluated by SCF in 1998 and classified in List 7. Needed data: 90-day oral study.

**Available data used for this evaluation:**

Non-toxicity data: -

Microbiological data:

Toxicity data: Data on 90 day oral study with trimellitic acid

**Evaluation:** Trimellitic anhydride hydrolyses within ten minutes by stirring with water at 27 - 30°C to trimellitic acid.
Migration of trimellitic anhydride has been determined by means of trimellitic acid.
Specific migration of trimellitic acid into water, 3% acetic acid, 8, 15 or 50% ethanol, n-heptane, olive oil or HB307 and iso-octane at a range of time/temperature conditions has been determined. The test samples were trimellitic anhydride-based epoxy powder coatings on support and polyamidimide resin on support. The finished coatings were investigated at temperatures up to 121°C. Maximum migration found in water after 2 hours at 121˚C is 1.6 mg/kg into food.
Analytical data concerning the residual content of trimellitic anhydride in polyamidimide coatings were provided. Residual content was determined as trimellitic acid and was found to be less than 0.5 µg/dm² in a typical PTFE coating, resulting in a maximum migration of 0.003 mg/kg food.
Due to the rapid hydrolysis Trimellitic anhydride is not expected to be a migrant. It is therefore considered justified to use the toxicological data on trimellitic acid for the evaluation of trimellitic anhydride in this context.
Oral administration of trimellitic acid to rats by dietary administration for a period of 90 consecutive days at dose levels of up to 20000 mg/kg food resulted in treatment-related changes in both sexes that received 20000 mg/kg food and in females treated with 5000 mg/kg food. No such changes were detected in males treated with 5000 mg/kg food or in either sex treated with 1000 mg/kg food and for this reason the “No Observed Effect

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| **Name of the substance:** | **Trimellitic anhydride** |

Level" (NOEL) was considered to be 5000 mg/kg food for males and 1000 mg/kg food for females.
The treatment-related effects detected in females treated with 5000 mg/kg food were confined to a minor caecal change detected histologically. The occurrence of this change is not considered to be indicative of an adverse health effect so the NOAEL is taken as 5000 mg/kg food for both sexes, equivalent to around 400 mg/kg b.w./day.

**Conclusion:** Based on the above-mentioned data the substance is classified:
**SCF_List:** **3**
**Restriction:** **5 mg/kg of food, expressed as trimellitic acid**
Remark for Commission: Group restriction together with the trimellitic acid REF No 25540
Needed data or information: None

**References:**
- Unpublished data submitted by the petitioner.
- Opinion of the Scientific Committee on Food on an additional list on monomers and additives for food contact materials (Adopted at the 111th SCF meeting) (18-19 March 1998) http://europa.eu.int/comm/food/fs/sc/scf/out10_en.pdf

| Ref. No.: | 66930 |
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| **Name of the substance:** | **Methylsilsesquioxane** |

CAS number: 68554-70-1
Document reference: SDS EFSA/AFC/FCM/155-Rev.IIIA/66930 of March 2004

**General information:** According to the petitioner methylsilsesquioxane is used as a release and anti-blocking agent during the manufacturing and processing of polyolefins and PET resins and films for food packaging materials. The proportion of the additive in the plastic is 0.5%, not homogeneously distributed but all added to the outer layer of the film.

**Previous evaluations (by SCF or AFC):** The substance has been evaluated in 2001. Since only irrelevant toxicity data were available, mutagenicity data on the monomer (methyltrimethoxysilane) were requested, according to the guidelines. The substance was therefore listed in SCF_List 7. New information was supplied in 2003.

**Available data used for this evaluation:**

Non-toxicity data:
- Intended use of the substance and details about use in outer layers of films
- Residual monomer amount in polymeric additive
- Calculated worst case migration data for monomer

Microbiological data:

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| **Ref. No.:** | **66930** |
| **Name of the substance:** | **Methylsilsesquioxane** |

Toxicity data:
- Bacterial reverse mutation assays
- *In vitro* mammalian cell gene mutation test
- *In vitro* mammalian chromososme aberration test
- *In vivo* mouse micronucleus test

**Evaluation:**

The substance is a polymeric additive with a MW > $1.7 \times 10^{10}$ D; the fraction with MW<1000 D is <0.4%. Residual methyltrimethoxysilane monomer was not detected in the polymeric additive at a level of $0.1 \pm 0.07$ mg /kg polymeric additive. Assuming 100% migration of the potentially residual monomer methyltrimethoxysilane from a plastic film containing 0.5% methylsilsesquioxane, the worst case migration, as it was calculated by the petitioner for the conventional ratio of 6 $dm^2$ per 1 kg of food, was less than 0.55 ng/kg of food.
Taking into account the very low potential residual amount of the methyltrimethoxysilane in the final product and the resulting worst case migration, specifications for residual monomer in the polymeric additive can be set at 1 mg methyltrimethoxysilane /kg methylsilsesquioxane.

According to SCF Guidelines the genotoxicity of the monomer was tested. The monomer (methyltrimethoxysilane) was tested under *in vitro* conditions in an Ames test, a mouse lymphoma assay, and in a CHO cells chromosome aberration assay. The Ames test was negative. The monomer was mutagenic at the TK-locus of mouse lymphoma L5178Y cells and clastogenic in the chromosome aberration test with CHO cells; positive results were only obtained in the presence of S9-mix.
An *in vivo* mouse micronucleus test has been performed. The monomer does not induce micronuclei in the polychromatic erythrocytes of treated mice despite the evidence of toxicity to bone marrow cells. From this study it is assessed that genotoxic potential observed *in vitro* with S9 mix is not expressed *in vivo*.

**Conclusion:**

Based on the above mentioned data the substance is classified:

**SCF_List:** **3**

**Restriction:** **Residual monomer in methylsilsesquioxane: < 1 mg methyltrimethoxysilane /kg of methylsilsesquioxane**

Remark for Commission: None

Needed data or information: None

**References:**


- Opinion of the Scientific Committee on Food on the 15th additional list of monomers and additives for food contact materials (13 December 2001) http://europa.eu.int/comm/food/fs/sc/scf/out114_en.pdf
- Unpublished data submitted by the petitioner.

| **Ref. No.:** | **86432** |
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| **Name of the substance:** | **Silver-containing glass (Silver-magnesium-calcium-phosphate-borate)** |

CAS number: -
Document reference: SDS CS/PM/4063-Rev.0G/86432 of March 2004

**General information:** According to the petitioner is intended for use as an antimicrobial additive in all kinds of polyolefins

**Previous evaluations (by SCF or AFC):**

**Available data used for this evaluation:**

Non-toxicity data:
- data on specification,
- data on use
- data on specific migration of $Ag^+$ from LDPE into 3 % acetic acid, 15 % ethanol, and olive oil
- data on residual content in the polymer

Microbiological data:
- data on intended microbiological function,
- data on spectrum of microbial activity,
- data on level of activity (minimum inhibitory concentrations, dose response), consequences of use,
- data on possible interaction with food constituents,
- data on efficacy

Toxicity data:
- gene mutation in bacteria
- in vitro mammalian cell gene mutation test
- in vitro mammalian chromosome aberration test
- limited 90-day oral rat study with a Ag-containing Zeolite not identical with the compound requested
- review on silver toxicity

**Evaluation:** The substance is used up to 0.3 % in the finished product corresponding to 0.0073 % active $Ag^+$. Migration was measured after 10 days/40°C. The highest value was determined into 3 % acetic acid at 44 µg/kg.
Well-described analytical methods for the determination of Ag in the migration solutions and in the polymer are provided.
Inconsistent data on the detection limit in the simulants are given.
The Panel noted that due to the nature of the substance the only ion that might migrate in toxicologically relevant quantities is silver
The release of silver ions into solutions not containing substantial amounts of organic materials such as proteins or peptides can exert a considerable antimicrobial effect given an appropriate time/concentration exposure to the microorganisms.
Virtually all microorganisms that might be expected to be present in a food environment will be sensitive to silver ions so that the problem of selecting populations that are resistant to silver ions appears unlikely. With regard to

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| Name of the substance: | Silver-containing glass (Silver-magnesium-calcium-phosphate-borate) |

the selection of mutants resistant to silver in sensitive populations no evidence exists that such mutants have arisen during the use of silver compounds for decades in water treatment or for medical purposes even though silver-resistant strains of bacteria have been isolated from environments such as silver mines and photographic film waste water. However this does not appear to be a problem in those food environments where Silver-containing glass (Silver-magnesium-calcium-phosphate-borate) would be used.

The minimum inhibitory concentrations have been determined in terms of the concentration of the biocide substance. It would be much more useful if the MIC was determined in concentration of silver ions for particular test microorganisms in defined media e.g. phosphate buffer. Then the efficacy of the biocide could be measured in terms of its ability to release concentrations of silver ions at levels required to inactivate foodborne spoilage or pathogenic microorganisms.

Some of the data supplied have been derived from poorly designed experiments e.g. efficacy of the biocide in diluted milk and sponging the side of a piece of pork in contact with the biocide.

Silver-containing glass (Silver-magnesium-calcium-phosphate-borate) was not mutagenic in three *in vitro* genotoxicity test systems, however it is not clear from the study reports to what extent silver was released into culture media.

In a limited 90-day oral rat study with an Ag- and Zn-containing Zeolite (not identical with the compound applied for) even at the lowest dose of 1,25 % in the diet compound-related effects were observed. From this study it is not clear to what extent silver was bioavailable and may have interacted with zinc to produce toxic effects.

The AFC panel also took note of the WHO "Guidelines for drinking-water quality". According to these Guidelines a total lifetime oral intake of about 10 g of silver (equal to 0.39 mg/person/day) can be considered on the basis of epidemiological and pharmacokinetic knowledge as the human NOAEL. To maintain the bacteriological quality of drinking water, levels of silver up to 0.1 mg/l, could be tolerated without risk to health. On the basis of a daily intake of 2 l of drinking water this concentration is equal to a daily silver intake of 0.2 mg/person and gives a total dose over 70 years of half the human NOAEL (WHO 1996).

Based on the data above, a Restriction of 0.05 mg/kg of food (as silver) for the substance would limit intake to less than 12.5 % of the human NOAEL

**Conclusion:** Based on the above reasoning, the substance is classified*:*

**SCF_List:** **3**

**Restriction:** **Group restriction of 0.05 mg Ag/kg of food.**

Remark for Commission: It is a surface biocide

Needed data or information: None

**References:**

- Unpublished data submitted by the petitioner
- World Health Organization (1996). Guidelines for drinking-water quality.

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| **Ref. No.:** | **86432** |
| **Name of the substance:** | **Silver-containing glass (Silver-magnesium-calcium-phosphate-borate)** |

Second edition

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| **Ref. No.:** | **86434** |
| **Name of the substance:** | **Silver sodium hydrogen zirconium phosphate** |

CAS number:

Document reference: SDS CS /PM/3382-Rev.IVI/86434 of March 2004

**General information:** According to the petitioner Silver sodium hydrogen zirconium phosphate is intended for use as a biocide in all polymeric food contact materials to protect the surface of finished articles from microbial contamination during use. The active antimicrobial components are $Ag^+$ ions released through ion exchange mechanisms by monovalent cations in any aqueous environment. Silver compounds have a long history of use in the control of bacterial and fungal contamination in water treatment and in specific medical applications. Silver ions act through a non-specific mechanism after diffusing into the microorganism by binding to cellular proteins and nucleic acids.

**Previous evaluations (by SCF or AFC):** The substance was first evaluated in 2000 (SCF, 2000) and classified in SCF_List 7 based on inadequate non-toxicity data.

Needed :

- migration data from plastic containing the additive, into buffers (simulants) containing sodium ions
- depending on these results, information on whether or not these migration levels could exert a preservative effect on foodstuffs.

The substance was re-evaluated in 2001 (SCF, 2001) and again classified in SCF_List 7 because of lack of evidence that the substance did not have any preservative effect on the food. Microbiological data have now been submitted.

**Available data used for this evaluation:**

Non-toxicity data:
- Demonstration of not detectable (<4 ppb) migration of Zr and Ag into food simulants under worse-case conditions of reflux
- Demonstration of < 23 ppb migration into aqueous buffers containing sodium ions
- Calculation of < 2 ppb migration into foodstuffs for typical applications

Microbiological data:
- data on intended microbiological function,
- data on spectrum of microbial activity,
- data on level of activity (minimum inhibitory concentrations, dose response),
- consequences of use,
- data on possible interaction with food constituents,
- data on efficacy

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|---|---|
| Name of the substance: | Silver sodium hydrogen zirconium phosphate |

Toxicity data:
- 2 gene mutation assays in bacteria (performed with two samples of the test substance (3.8% silver) and (10% silver)
- gene mutation assay in cultured mammalian cells
- *In vivo* mouse micronucleus test
- 13-week oral rat study

**Evaluation:**

Test data were provided for silver migration from LDPE containing 1.8% of the additive. Buffered sodium salt solutions were used and these were 40mM sodium acetate at pH 5, 50mM sodium phosphate at pH 7, and 35mM sodium borate at pH 9. The test conditions were immersion for 10 days at 40ºC. The migration of silver was 20 ppb, 22 ppb and < 15 ppb into the three buffers, respectively, calculated using the conventional mass/area ratio of 1 kg/6dm$^2$.

Worst-case estimates of migration expected in two typical food applications - use of the additive in a chopping board or conveyor belt with contact conditions of 30 min at 20ºC, and for a food container used to store food in a refrigerator for 2 days at 10ºC. The migration expected was calculated from the highest results seen for migration into buffers for 10 days at 40ºC (< 23 μg/6 dm$^2$) using the activation energy and diffusion model of Piringer et al (Brandsch, Mercea and Piringer, 2000). Migration to the food was estimated to be < 2 μg/6 dm$^2$.

The petitioner has demonstrated that silver ions generated in a number of ways have antimicrobial activity against a wide range of Gram-positive and negative bacteria and fungi. Silver sodium hydrogen zirconium phosphate can be incorporated into food contact materials. In an aqueous environment monovalent cations enter the inorganic compound and release silver ions. In the experiments reported both Silver sodium hydrogen zirconium phosphate and silver nitrate have been used to generate silver ions to study their effect on microorganisms that might be foodborne. In general, MICs derived from the use of Silver sodium hydrogen zirconium phosphate powder in agar are in the range of 6.3 – 12.5 mg $Ag^+$/kg, on the basis of 10% silver in the Silver sodium hydrogen zirconium phosphate, and 0.4 – 0.7 mg $Ag^+$/kg generated via silver nitrate.

With regard to the selection of mutants resistant to silver in sensitive populations no evidence exists that such mutants have arisen during the use of silver compounds for decades in water treatment or for medical purposes even though silver-resistant strains of bacteria have been isolated from environments such as silver mines and photographic film waste water. However this does not appear to be a problem in those food environments where Silver sodium hydrogen zirconium phosphate would be used.

The overgrowth by silver resistant microbes of the surfaces of Silver sodium hydrogen zirconium phosphate-containing food contact materials is not expected to be a problem because of the non-specific nature of the inactivation and the multiplicity of targets in the microorganisms provides a general sensitivity of microorganism to silver ions.

| Ref. No.: | 86434 |
|---|---|
| Name of the substance: | Silver sodium hydrogen zirconium phosphate |

The antimicrobial activity of Silver sodium hydrogen zirconium phosphate can be demonstrated against microbes in phosphate buffer, phosphate buffer plus 0.2% tryptic soy broth and minimal medium plus 0.1% yeast extract. However the addition of further organic materials increases the MICs considerably and therefore the effectiveness of the Silver sodium hydrogen zirconium phosphate in reducing the viability of microbes in such materials. In real foods the presence of Silver sodium hydrogen zirconium phosphate at levels well in excess of the MIC has no effect on microbes e.g. in milk, and in a film wrap has no effect on the rate of growth of introduced bacterial pathogens or indigenous spoilage organisms on the surface of chicken. Thus the antimicrobial effect can only be seen in the absence of food and food particles.
The antimicrobial activity is retained through at least two cleaning procedures with chlorine dioxide and three procedures designed to simulate a 6-stage cleaning protocol used in a meat processing plant. This system for generating silver ions is thus fairly robust.
No evidence is provided of efficacy under "in use" conditions i.e. to demonstrate that the use of Silver sodium hydrogen zirconium phosphate in food contact materials improves the hygienic state of manufacturing plant and domestic food preparation areas over and above that of general cleaning procedures, although the laboratory experiments reported suggest that might be the case.

Silver sodium hydrogen zirconium phosphate was not mutagenic in two bacterial mutagenicity assays, where it elicited moderate toxicity to tester strains.
In a mammalian gene mutation assay, borderline increments, in mutation frequencies, with no relation to dose, were observed in experiments without metabolic activation; negative results were observed in the presence of S9.
Clearly negative results were obtained in the mouse bone marrow micronucleus test after administration of the test substance at doses which produced distinct bone marrow toxicity.
Data on chromosomal aberration in vitro were not available but are considered not necessary in view of the results of the *in vivo* micronucleus test.
Based on these results, the substance is evaluated as non genotoxic.
In a 13 week oral subchronic toxicity study in the rat, a NOAEL of 30 mg/kg b.w. was observed.

The AFC Panel also took note of the WHO "Guidelines for drinking-water quality". According to these Guidelines a total lifetime oral intake of about 10 g of silver (equal to 0.39 mg/day/person) can be considered on the basis of epidemiological and pharmacokinetic knowledge as the human NOAEL. To maintain the bacteriological quality of drinking water, levels of silver up to 0.1 mg/l, could be tolerated without risk to health. On the basis of a daily intake of 2 l of drinking water this concentration is equal to a daily silver intake of 0.2 mg/person and gives a

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| Name of the substance: | Silver sodium hydrogen zirconium phosphate |

total dose over 70 years of half the human NOAEL (WHO 1996).

Based on the data above, a Restriction of 0.05 mg/kg of food (as silver) for the substance would limit intake to less than 12.5 % of the human NOAEL

**Conclusion:** Based on the above-mentioned data the substance is classified:
**SCF_List:** **3**
**Restriction:** **Group restriction of 0.05 mg Ag/kg of food.**
Remark for Commission: It is a surface biocide
Needed data or information: None

**References:**


- World Health Organization (1996). Guidelines for drinking-water quality. Second edition
- Opinion of the Scientific Committee on Food on the 10th additional list of monomers and additives for food contact materials (adopted by the SCF on 22/6/2000) http://europa.eu.int/comm/food/fs/sc/scf/out62_en.pdf
- Opinion of the Scientific Committee on Food on the 12th additional list of monomers and additives for food contact materials (adopted on 28 February 2001) http://europa.eu.int/comm/food/fs/sc/scf/out84_en.pdf
- J. Brandsch, P. Mercea and O. Piringer, Modelling of additive diffusion in polyolefins, in 'Food Packaging', S. Risch (editor), ACS Symposium Series No.753, 2000
- Unpublished data submitted by the petitioner.




## List of abbreviations:

QMA = maximum permitted quantity of the substance in the finished material or article expressed as mg per 6 $dm^2$ of the surface in contact with foodstuffs
SM = Specific migration
SML = Specific migration limit
MIC = Minimum inhibitory concentration

## 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.