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SCIENTIFIC OPINION

Scientific Opinion on the safety of "Methyl Vinyl Ether-Maleic Anhydride Copolymer" (chewing gum base ingredient) as a Novel Food ingredient[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

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ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the safety of "methyl vinyl ether-maleic anhydride copolymer (Gantrez SF)" as a novel food ingredient in the context of Regulation (EC) No 258/97. The novel food ingredient Gantrez SF is an anhydrous copolymer formed by the reaction of methyl vinyl ether (MVE) and maleic anhydride (MAN) under appropriate conditions. The Panel considers that the information provided on the specifications, stability and production process do not raise safety concerns. An estimated daily intake (EDI) for Gantrez SF associated with its use in chewing gum may be calculated based on the maximum concentration (2 %) of Gantrez SF in finished chewing gum, and on the level at which chewing gum is consumed. Based on data from the United Kingdom, a high intake estimate of 280 mg Gantrez SF per day was derived. The Panel notes that the NOAEL of 1.8 and 2.1 g/kg bw per day Gantrez SF for male and female rats, respectively, which was derived from a 90-day subchronic toxicity study, is about 500-fold above this conservative intake estimate. The Panel has no safety concerns regarding genotoxicity and the low molecular weight components. The Panel concludes that the novel food ingredient, methyl vinyl ether-maleic anhydride copolymer (Gantrez SF), is safe under the proposed uses and use levels.

KEY WORDS

chewing gum, Gantrez SF, copolymer, methyl vinyl ether, maleic anhydride, dilauroyl peroxide

[1] On request from the European Commission, Question No EFSA-Q-2012-00653, adopted on 10 October 2013.

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the safety of "methyl vinyl ether-maleic anhydride copolymer" (Gantrez SF, chewing gum base ingredient) as a novel food ingredient in the context of Regulation (EC) No 258/97, taking into account the comments and objections of a scientific nature raised by Member States.

The novel food ingredient, Gantrez SF, is an anhydrous copolymer formed by the reaction of methyl vinyl ether (MVE) and maleic anhydride (MAN) under appropriate conditions. Dilauroyl peroxide (LP) is used to initiate the reaction. Depending on the reaction conditions, the process results in one of two end product types, referred to as type A or type B polymers. The two variants differ in their molecular weights and therefore viscosities. As with many high molecular weight polymers that may be subject to oxidation damage in storage or in use, butyl hydroxytoluene (BHT) is added to type B polymers as an antioxidant. The Panel considers that the information provided on the specifications, stability and production process do not raise safety concerns.

An estimated daily intake (EDI) for Gantrez SF associated with its use in chewing gum may be calculated based on its maximum concentration (2 %) in chewing gum and an estimated intake of 14 g chewing gum per day for high consumers. No data have been provided on the amount of Gantrez SF that may be released from the chewing gum upon consumption. In the absence of such data, it is assumed that Gantrez SF would be fully ingested. The applicant used chewing gum consumption data from the United States National Association of Chewing Gum Manufacturers, which indicate a mean chewing gum consumption level among all individuals who chew gum of 0.7 grams per day, and of 1.3 grams of gum per day for consumers at the 90th percentile. This covers long-term consumption (i.e. taken from three- or four-week food consumption diaries. Based on this information, the estimated daily intake for Gantrez SF, when present at levels up to 2 % in finished chewing gum, is calculated to be 26 mg per person per day for high consumers. However, in a previous EFSA opinion a value of 14 g per day was calculated for European high consumers of chewing gum, which was based on the 95th percentile of United Kingdom adolescent consumers. This would correspond to an intake of 280 mg Gantrez SF per day.

Taking into account the negative results from an Ames test and a mouse micronucleus assay (although both tests were not fully in accordance with the respective current OECD Guidelines), and the chemical structure of copolymer, the Panel has no concerns related to genotoxicity.

The applicant provided two 90-day rat studies. One study was not performed according to the current standard and it was unclear whether the test material 'Gantrez Resin Salt' corresponds to the novel food ingredient. Therefore, the Panel considers that this study is of limited value for the risk assessment. Another 90-day rat study was performed with the novel food ingredient and in compliance with GLP standards and OECD Guideline 408. Gantrez SF was administered to groups of 20 male and 20 female CRL:CD(SD) rats at dietary concentrations of 1, 2.5 or 5 %. The NDA Panel noted a higher incidence of skeletal muscle degeneration (minimal grade) and thymus epithelial hyperplasia (minimal grade) in male animals of the high dose group, when compared with the control group. On request of the Panel, the applicant provided additional histopathological examinations of skeletal muscle tissue and thymus for all rats of the mid and low dose groups. Skeletal muscle degeneration was identified in male and female animals of all groups with a similar incidence rate (i.e. max. 20 %), except for high-dose males (i.e. 60 %), where the incidence was considerably higher than the percentage observed in historical controls (i.e. 21.8 %). Thymus epithelial hyperplasia was identified in male and female animals of all groups, including the control group, with a higher incidence than usually observed in historical controls. Considering the high background incidence of thymus epithelial hyperplasia in this study, the Panel is of the opinion that the higher incidence observed in high dose males was not test material-related. On the basis of the results, the NDA Panel concludes that the mid dose administered, i.e. 2.5 % Gantrez SF in the diet, equivalent to

approximately 1.8 and 2.1 g/kg bw per day for male and female rats, respectively, represents the NOAEL in this study.

The Panel notes that the NOAEL of the 90-day rat study is about 500-fold more than the conservatively estimated intake of Gantrez SF of 280 mg/day for high consumers of chewing gum. Furthermore, the Panel notes that the novel ingredient would usually not, but may rarely, be swallowed.

The maximum consumption of 14 g chewing gum per day also forms the basis for calculations of the amount of low molecular weight components (less than 1000 Da), which are potentially released from the gum during the act of chewing. Since there are no data on the release of low molecular weight compounds during chewing the Panel must assume that all such materials, e.g. residual MAN, MVE, methanol, acetaldehyde, LP and BHT, are released at the maximum values indicated in the specification. The estimated maximum intake of 70 µg/day of MAN is considered negligible in relation to the tolerable daily intake of 0.5 mg/kg bw. Regarding the other monomer, MVE, the Panel considers that there is no safety concern with respect to genotoxicity. In accordance with relevant EFSA Guidance for the evaluation of monomers used in the production of high-molecular weight polymers to be used in food contact materials, no additional toxicological data are required considering the estimated maximum intake of 42 µg/day MVE.

The Threshold of Toxicological Concern (TTC) concept has been applied in the safety evaluation of residual levels of LP, which is used as a synthesis initiator in the production process of Gantrez SF. There is no concern with regard to genotoxicity of this substance. The estimated maximum intake of LP of 4.2 µg/day is well below the threshold value for Cramer class I substances, and thus does not raise safety concerns. The estimated maximum intakes of methanol of 140 µg/day and acetaldehyde of 140 µg/day are considered low in relation to the intake from natural sources, and do not pose a health risk at the levels set in the specification.

Addition of the antioxidant BHT to Gantrez SF, as indicated in the specification, is in accordance with EU legislation on food additives.

The Panel concludes that the novel food ingredient "Methyl Vinyl Ether-Maleic Anhydride Copolymer" (Gantrez SF, chewing gum base ingredient) is safe under the proposed uses and use levels.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

On 30 June 2008, the company Reading Scientific Services Ltd. (United Kingdom) submitted a request under Article 4 of the Novel Food Regulation (EC) N° 258/97 to place on the market "Methyl Vinyl Ether-Maleic Anhydride Copolymer" (chewing gum base ingredient) as a novel food ingredient.

On 14 July 2011, the competent authorities of the Netherlands forwarded to the Commission their initial assessment report, which came to the conclusion that "Methyl Vinyl Ether-Maleic Anhydride Copolymer"—(chewing gum base ingredient) may be placed on the market.

On 18 August 2011, the Commission forwarded the initial assessment report to the other Member States. Several of the Member States submitted comments or raised objections.

The concerns of a scientific nature raised by the Member States can be summarised as follows:

- There are no validation data for the analytical methods applied to characterise the novel ingredient. Nor have any test reports been provided for the results. It would appear that the analyses were carried out in the test facilities of the actual manufacturer, International Speciality Products (ISP). There is no indication as to whether these facilities are accredited to carry out these analyses, or whether another recognised quality control system was applied.

- There is no information on quality management and product stability.

- For the safety assessment of food contact materials, toxicological information is required on substances with a molecular weight of < 1000 Da that are transferred from food contact material, and the subsequent quantities consumed. A similar approach has been used in the safety assessment of a novel chewing gum base (EFSA NDA Panel, 2011) i.e. a measure of the low molecular weight compounds that migrate from the novel ingredient into the mouth. In this application, no analysis has been made of the release of the monomers (methyl vinyl ether and maleic anhydride) from the chewing gum, for example studies on release under simulated chewing conditions. In the absence of such information, it must be assumed that they are completely released; a maximum of 70 µg maleic anhydride and 140 µg methyl vinyl ether could thus be consumed from 14 g chewing gum. An estimated maximum intake of 70 µg maleic anhydride from chewing gum would be well below the tolerable daily intake of 0.5 mg/kg body weight expressed as maleic acid (6th SCF report, 1978; Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food). However, for methyl vinyl ether, this level of possible intake would require a 90-day study on rodents, genotoxicity studies and studies to show that no bioaccumulation occurs.

- Although batch testing showed levels lower than 100 ppm, an intake estimate for residual maleic anhydride and methyl vinyl ether should be based on the limits given by the specification (250 and 500 ppm, respectively).

- Considering research papers presented by the applicant showing that use of the copolymer in dental products has a significant effect on bacterial growth in the mouth, potential effects of this copolymer on human gut flora should be investigated.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Food Safety Authority is asked to carry out the additional assessment for "Methyl Vinyl Ether-Maleic Anhydride Copolymer" (chewing gum base ingredient) as a novel food ingredient in the context of Regulation (EC) N° 258/97.

EFSA is asked to carry out the additional assessment and to consider the elements of a scientific nature in the comments raised by the other Member States.

ASSESSMENT

In accordance with Commission Recommendation 97/618/EC, the ingredient "Methyl Vinyl Ether-Maleic Anhydride Copolymer" (Gantrez SF, chewing gum base ingredient) is allocated to Class 1.2, i.e. foods or food ingredients that are 'pure chemicals or simple mixtures which are not obtained from plants, animals or microorganisms that have been genetically modified. The source of the NF has no history of food use in the Community'. The assessment of the safety of this novel food ingredient (NF) is based on data supplied in the original application, the initial assessment by the competent authority of the Netherlands, the concerns and objections of the other Member States, and the responses of the applicant. The data are required to comply with the information required for novel foods of Class 1.2, i.e. structured schemes I, II, III, IX, XI, XII and XIII of Commission Recommendation 97/618/EC. In the text, these structured schemes are listed 1 to 7. Gantrez SF is intended by the applicant to be added to chewing gum, with a view to making the gum easier to remove from a variety of surfaces. This assessment only concerns risk that might be associated with consumption, and is not an assessment of Gantrez SF with regard to any claimed beneficial effects.

1. Specification of the Novel Food (NF)

Gantrez SF is an anhydrous copolymer of methyl vinyl ether (MVE) and maleic anhydride (MAN). Its structural formula is:

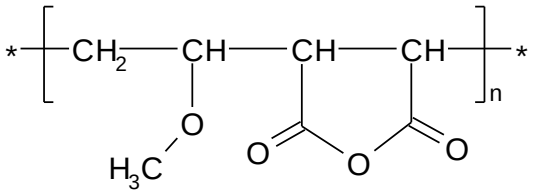

Figure 1: Structural formula of methyl vinyl ether-maleic anhydride

The applicant specifies two variants, Types A and B, that differ in their molecular weights and therefore viscosities. Gantrez SF polymers with specific viscosities less than 3.5 are considered Type A polymers, while those with specific viscosities greater than 3.5 are considered Type B.

Both types of product can be used as chewing gum ingredients and have to meet the specification presented in Table 1. As with many high molecular weight polymers that may be subject to oxidation damage in storage or in use, butyl hydroxytoluene (BHT) is added to type B polymers as an antioxidant.

Table 1: Specification for 'Methyl Vinyl Ether-Maleic Anhydride Copolymer' (chewing gum base ingredient), as proposed by the applicant

Test	Limit	Test method
Identification Test	Matches Standard	By IR, MP 1125W & Gantrez AN Reference
Visual	free-flowing, white to off-white powder	
Purity	≥ 99.5 %, corrected for water	
Residual MVE (ppm)[(a)]	Not more than 150 ppm	By GC, 1642W
Residual MAN (ppm)[(b)]	Not more than 250 ppm	By HPLC, MP 1633W
Acetaldehyde (ppm)	Not more than 500 ppm	MP-880W

Methanol (ppm)	Not more than 500 ppm	1642W
Dilauroyl Peroxide (ppm)	Not more than 15 ppm	1684W
Specific Viscosity (1 % MEK)	2-10	MP 1115
BHT (ppm, from batch records)	< 120 ppm	-
% Total Water	Not more than 2.0	By oven transfer/Karl Fisher MP-732
Heavy Metals (tin, lead, mercury, cadmium, bismuth, silver, arsenic, copper, antimony, molybdenum, in total)	Not more than 10 ppm	By ICP, MP-1494
Total Aerobic Plate Count (CFU/g)	< 500	Q200, USP, Ch 61
Mould/Yeast (CFU/g)	< 500	Q200, USP, Ch 61
Staphylococcus aureus (CFU/g)	Negative to test	Q200, USP, Ch 61
Pseudomonas aeruginosa (CFU/g)	Negative to test	Q200, USP, Ch 61
Salmonella (CFU/g)	Negative to test	Q200, USP, Ch 61
Escherichia coli (CFU/g)	Negative to test	Q200, USP, Ch 61

(a): Methyl vinyl ether (MVE) is quantified by gas chromatography (Ashland GC, Method 1642W). The limit of detection in Gantrez SF polymer is 50 ppm.
(b): Residual maleic anhydride (MAN) is reported as maleic acid (MAA) due to the conditions of the analytical test method. For calculation purposes MAA is convertible to MAN by subtracting one mole of water i.e. MAN is 84.7 % of the weight of MAA.

Table 2 shows data for six production batches and one pilot batch (PPTOX) used for toxicological studies. Batches 158, 62, 163 and 140 were of Type B (average molecular weights of 9.02 to 13.4 x 10^6 g per mol), while batches 27, 2 and PPTOX were of Type A (2.48 to 2.88 x 10^6 g per mol average molecular weights). In some cases, molecular weight distributions by gel permeation chromatography coupled with multi angle laser light scatterings (GPC/MALLS) and refractive index (RI) detectors have been provided.

Table 2: Analysis for Compliance with Specification on six production batches and one pilot batch.

Test	**Batch No**						
	158 Type B	**62 Type B**	**163 Type B**	**140 Type B**	**27 Type A**	**2 Type A**	**PPTOX * Type A**
Appearance	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder
Heavy Metals, each (ppm)	< 1	< 1	< 1	< 1	< 1	< 1	<1
Residual MVE (ppm)	< 100	< 100	< 100	< 100	< 100	< 100	Not detected
Residual MAN (ppm)	< 50	73	<50	96	238	91	85
Acetaldehyde (ppm)	<100	<100	<100	<100	<100	<100	84
Specific Viscosity	6.00	5.49	9.01	5.34	2.38	3.11	3.3
% Total Water	0.230	0.283	0.510	0.977	1.1	1.99	0.89

Total Aerobic Plate Count (CFU/g)	<10	<10	<10	<10	<10	<10	<10
Mould/Yeast (CFU/g)	<10	<10	<10	<10	<10	<10	<10
Staphylococcus aureus (CFU/g)	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Pseudomonas aeruginosa (CFU/g)	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Salmonella (CFU/g)	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
E. coli (CFU/g)	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.

*The material used for the 90-day toxicology study is identified in the study report as "Lot No. PPTOX"
n. d. = not detected

Originally, the applicant specified a limit of 500 ppm for the monomer MVE. On the basis of the data provided for seven batches, and following discussion with the Panel, the applicant reduced the limit for MVE to 150 ppm (Table 1).

One Member State noted that no information is provided on quality management or product stability. The applicant responded that the stability of all lots of Gantrez SF was in full accordance with the ISP Sales Specification acceptance criteria throughout the thirty-six month retest period.

The Panel considers that the information provided on the composition, specifications and stability of the NF do not raise safety concerns.

2. Effect of the production process applied to the NF

International Speciality Products (ISP) has ISO 9001 accreditation and the appropriate certification has been provided to the Panel.

Polymers are formed by the reaction of MVE and MAN under appropriate conditions. Dilauroyl peroxide (LP) is used to initiate the reaction.

Specifications for the three starting materials, including minimum purity values, have been provided. Depending on the reaction conditions, the process results in type A or type B polymers. In the production of type B, which is more viscous than type A, the substance BHT is added as an antioxidant. MVE is produced by ISP. All other raw materials are purchased. MVE, MAN and LP are commercial grade; the BHT is food grade.

The Panel considers that the production process is sufficiently described by the applicant. The production process comprises conventional separation techniques, and does not raise safety concerns.

3. History of the organism used as a source

Not applicable.

4. Anticipated intake/extent of use of the NF

An estimated daily intake (EDI) for Gantrez SF associated with its use in chewing gum may be calculated based on the maximum concentration (2 %) of Gantrez SF in finished chewing gum, and of the level at which chewing gum is typically consumed. In the absence of data on the amount of Gantrez SF that is released in the act of chewing the gum, it is assumed that all Gantrez SF present in a piece of chewing gum would be ingested. This assumption considerably overestimates actual dietary exposure to Gantrez SF as a significant portion of the Gantrez SF would remain trapped in the

chewing gum base, in order to function as intended after chewing gum is discarded. . More importantly, no measure has been made of the amount of low molecular weight substances (less than 1000 Da) that may migrate from Gantrez SF into the mouth.

The applicant's intake estimate used chewing gum consumption data from the United States National Association of Chewing Gum Manufacturers (2004). These data indicate that the mean chewing gum consumption level among all individuals who chew gum is 0.7 grams per day, with consumers at the 90th percentile chewing 1.3 grams of gum per day. This covers long-term consumption (i.e., estimated from three- or four-week food consumption diaries. Based on this information, the EDI for Gantrez SF, when present at levels up to 2 % in finished chewing gum, is calculated to be 26 mg/day for a high consumer.

However, a value of 14 g per day was previously calculated for European high consumers of chewing gum (EFSA NDA Panel, 2011), which was based on the 95th percentile of UK adolescent consumers. This would correspond to an EDI of 280 mg Gantrez SF per day.

5. Information from previous exposure to the NF or its source

According to the applicant, a fully hydrated form of the NF has been used in toothpaste for decades. Typical quantities are reported to be around 2 % of the toothpaste product.

6. Nutritional information on the NF

The Panel notes that the novel food is a synthetic gum base, which has no nutritional value. The Panel considers that the consumption of the NF is not nutritionally disadvantageous.

7. Microbiological information on the NF

Microbiological limits are set in the product specification (Table 1). The Panel has no concerns with regard to the microbiological safety of the novel food.

8. Toxicological information on the NF

8.1. Genotoxicity

In bacterial reverse mutation tests (Ames test) using the plate incorporation method and *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, the acid form of Gantrez SF showed no mutagenicity at dose levels of 100 to 5 000 µg/plate, in the absence or presence of a metabolic activation system (S9) (Lawlor, 1992). This study was performed in compliance with GLP-regulations but, with regard to the tester strains, not according to current OECD Guideline 471.

In a mouse micronucleus assay in compliance with GLP, the acid form of Gantrez SF was administered by gavage at levels of 1 250, 2 500, and 5 000 mg/kg bw to groups of 5 male and 5 female ICR mice (Murli, 1992). The animals were euthanised 24, 48 or 72 hours after dosing, and bone marrow was extracted for analysis; only 1 000 polychromatic erythrocytes (PCEs) were counted as compared to 2 000 PCEs required by current OECD Guideline 474. A statistically significant reduction in the ratio of polychromatic to normochromatic erythrocytes (PCE:NCE ratio) was observed in males of the high dose group (72 hours after treatment), which indicates exposure to the test material. Non-significant reductions were noted in females of the high and intermediate dose groups (24 and 48 hours after treatment). Gantrez SF did not induce significant increases in the number of PCEs with micronuclei, while the positive control (cyclophosphamide) induced significant increases in both sexes.

The Panel notes that the studies date from before publication of the current OECD Guidelines and are not fully in accordance with them. Considering the structure of the NF, the Panel has no safety concerns related to genotoxicity.

8.2. *In vitro* and animal studies

8.2.1. Absorption, distribution, metabolism and excretion (ADME)

Absorption, distribution and excretion was studied after oral administration (gavage) of a single dose of ^{14}C-labelled Gantrez Resin Salt (Gantrez AN-169) to two male and two female rats housed individually in metabolism cages (Nelson, 1962). During the 3-day post-dosage period, samples of urine, faeces and CO_2 were collected from each animal for radioanalysis at 12-hour intervals. After 3 days, the animals were sacrificed and samples of liver, heart, kidney, hind limb muscle, abdominal fat, and lungs were collected for radioanalysis.

An average of 95.2 % ± 10 % of the dose was recovered in the faeces, urine and CO_2 throughout the 3-day post-dosage period. Of the recovered radioactivity, an average of 97.7 % was found in the faeces within 12 hours and an additional 2.0 % during the remaining 60 hours of the study, showing that over 99.7 % of the radioactivity remained unabsorbed. Approximately 0.1 % was found in the urine indicating some degree of absorption. Up to 0.3 % appeared in the exhaled CO_2, indicating that part of the absorbed material is metabolised to CO_2. No significant radioactivity was found in any of the selected body tissues. The Panel notes that the study was not performed according to the current standards (e.g. OECD guidelines), and some weaknesses in the conduct of the experiment, but the results suggest that the copolymer was not absorbed systemically to a significant degree in rats.

8.2.2. Subchronic toxicity

In a 90-day feeding study, 'Gantrez Resin Salt' was administered to groups of 15 male and 15 female rats at dietary concentrations of 0, 0.5 or 3 % (Scala, 1993). The study included observations of appearance and behaviour, determination of body weight and food consumption, blood and urine analyses, macroscopic observations at autopsies, as well as weight determinations and histopathological examinations of selected organs. No relevant differences in relation to the control group were observed. However, it is unclear whether the test material corresponds to the product intended to be marketed. Furthermore, the study was not performed according to the current standard, in particular regarding the number of analysed parameters. Therefore, the Panel considers that this study is of limited value for the risk assessment.

The applicant provided an additional 90-day study (Eapen, 2009), which was carried out in compliance with GLP regulations and OECD Guideline 408. Gantrez SF (a batch called "PPTOX", Table 2) was administered to groups of 20 male and 20 female CRL:CD(SD) rats for approximately 90 days at dietary concentrations of 1, 2.5 or 5 %. The control group received a standard rodent diet.

There was no mortality during the test period and no clinical signs were observed which could be attributed to consumption of the test substance. While food consumption was comparable in all groups, water consumption was higher in the high dose group, reaching statistical significance at several time points. Mean body weights and total body weight gains in the dose groups were comparable to the control group, but slight (not significant) decreases were notable in high dose males. No relevant differences between groups were observed in Functional Observation Battery (FOB) and motor activity tests in week 12 of the study using 10 animals/sex. Ophthalmic examinations of all animals during week 12 revealed no test substance-related findings.

Haematology and clinical chemistry analyses in weeks 1, 6 and 13, and urinalysis in week 13 (on 10 animals/sex) showed a number of significant differences in relation to the controls. Regarding haematology, males of the high dose group showed significantly lower absolute (and relative) reticulocyte and neutrophil counts in week 13, and the haematocrit value was significantly higher in week 6. In clinical chemistry analyses, total protein was significantly lower in high dose males in week 13. Total bilirubin was significantly lower in males of all dose groups in week 6 (showing no relation to dose); similar but non-significant differences were also seen in week 13. Blood urea nitrogen (BUN) was significantly lower in high dose males in week 13, and non-significantly lower in week 6. A significantly lower BUN was also observed in high dose females in week 6. Globulin was

lower in high dose females in weeks 6 and 13, and in mid dose females in week 6. The albumin/globulin (A/G) ratio was significantly higher in high dose females in week 6, and a non-significant trend was notable in week 13. Significantly lower serum mineral concentrations were observed: calcium in high dose males (weeks 1, 6 and 13) and in high dose females (week 1); phosphorous in high dose males (weeks 1, 6 and 13), mid dose males (week 1 and 6), low dose males (week 6) and high dose females (week 6); chloride in high and low dose females (week 6); potassium in high and low dose males (week 6) and high and mid dose females (week 6). Urinalysis showed a significantly lower urine pH value in high dose males (non-significantly lower in the mid and low dose group). According to the applicant, the changes were either not treatment-related or minimal and not associated with any histopathological findings. However, the Panel is of the opinion that no satisfactory explanation has been provided for a number of effects, which largely occurred at the high dose level.

Macroscopic examinations of all animals at necropsy revealed no abnormalities attributable to the test material. Organ weight determinations showed a significantly higher mean adrenal gland weight in relation to body weight in males of the high dose group (0.012 vs. 0.011 g/100 g bw). The difference was small and the mean value was within the historical control reference range, according to the applicant. No histopathological changes were identified in this organ. The Panel considers that this finding is not toxicologically relevant.

Microscopic examinations of selected organs and tissues of all animals in the control and high dose group identified a number of changes. The Panel noted a higher incidence of skeletal muscle degeneration (minimal grade) and thymus epithelial hyperplasia (minimal grade) in male animals of the high dose group when compared with the control group. On request of the Panel, the applicant provided additional histopathological examinations of skeletal muscle tissue and thymus from all rats of the mid and low dose groups. Skeletal muscle degeneration was identified in male and female animals of all groups with a similar incidence rate (i.e. max 20 %; 2 and 4 animals in the low and mid-dose male groups, respectively; 1 and 4 animals in the low and mid-dose female groups) except for high-dose males (12 animals, i.e. 60 %). According to the historical control data, this finding occurred with an incidence rate of c. 21.8 % and 13.4 % in male and female Crl:CD(SD) rats, respectively. Thus, for high dose males the incidence is considerably higher than the percentage observed in the historical controls. Thymus epithelial hyperplasia was identified in male and female animals of all groups (3, 3, 3 and 7 males in the control, low, mid and high dose group, respectively; 9, 5, 11 and 9 females, respectively). According to the historical control data, this finding occurred with an incidence rate of 3.1 % and 5.4 % in male and female Crl:CD(SD) rats, respectively. No explanation for the high background incidence in this study (15 % in females of the control group and 45 % in males of the control group) was provided by the applicant. Considering the high background incidence of thymus epithelial hyperplasia in this study, the Panel is of the opinion that the higher incidence observed in high dose males is not test material-related.

Considering the effect of the highest dose on skeletal muscles, the Panel considers that the mid dose administered, i.e. 2.5 % Gantrez SF in the diet, equivalent to approximately 1.8 and 2.1 g/kg bw per day for males and females, respectively, represents the NOAEL in this study.

8.2.3. Low molecular weight components

8.2.3.1. Processing aids and additives

Considering the maximum acetaldehyde level of 500 mg/kg Gantrez SF, as set in the specification, which corresponds to a level of 10 mg/kg in chewing gum, and a high chewing gum consumption of 14 g/day, a maximum intake of 140 µg acetaldehyde per day is estimated. The International Agency for Research on Cancer (IARC) has classified acetaldehyde in combination with alcoholic beverages as 'carcinogenic to humans (Group 1)' (EFSA ANS Panel, 2010; IARC, 2009; Secretan et al., 2009). However, the Panel notes that the evaluation by IARC was mainly based on experimental data obtained from animals after inhalation exposure, and on human epidemiological data considering

polymorphisms of the enzymes involved in ethanol metabolism. In the single available carcinogenicity study, in which the animals were orally exposed to acetaldehyde, the effects were not dose-related and no clear conclusion could be drawn. Considering that acetaldehyde occurs naturally in many fruits and vegetables and other food categories, for example up to 132 mg/kg in orange juice and up to 10 mg/kg in bread, and that it can occur endogenously in blood plasma, the Panel considers that an additional intake of 140 µg resulting from consumption of chewing gum containing Gantrez SF would be negligible and not of safety concern.

The specification limits the level of methanol, which may be present as a contaminant in the starting material MVE, to 500 mg/kg Gantrez SF, which corresponds to 10 mg/kg in chewing gum. The high intake scenario would thus be 140 µg/day methanol. Methanol may be used as an extraction solvent in the production of foodstuffs and food ingredients with a maximum residue limit in the extracted foodstuff or food ingredient of 10 mg/kg (Directive 2009/32/EC[4]). Methanol also occurs naturally in foodstuffs (VCF database[5]). The methanol concentration in fruit juices ranges from 1-640 mg/L with an average of 140 mg/L (IPCS, 1997; Lund et al., 1981). The Panel considers that a possible additional intake of methanol from chewing gum containing Gantrez SF is thus not of safety concern.

According to the specifications, residues of the substance dilauroyl peroxide (LP) may be present in the end product at levels of maximum 15 mg/kg. LP was reported not to be genotoxic in the Ames test and in a mammalian cell test (Merck, 2011), but the toxicological database is limited. The Panel has therefore applied the concept of Threshold of Toxicological Concern (TTC) (EFSA SC, 2012) in the evaluation of this substance. LP falls into Cramer class I based on a bioinformatics-supported structural analysis (Toxtree, version 2.6.0[6]). The maximum daily intake of LP that would result from consumption of 14 g chewing gum is 4.2 µg, corresponding to 0.06 µg/kg bw per day for a 70 kg person. This is well below the TTC for Cramer class I substances (30 µg/kg bw per day).

The addition of BHT to Gantrez SF (type B) as an antioxidant at an amount of 100 mg/kg as described by the applicant will lead to a level of 2 mg/kg in the chewing gum. The addition of this substance to chewing gum as a food additive is permitted, subject to a limit of 400 mg/kg (gallates, BHT and BHA, individually or in combination) (Directive No 95/2/EC[7]).

8.2.3.2. Maleic anhydride (MAN)

MAN appears on the list of authorised monomers and other starting substances which may be intentionally used in the manufacture of plastic layers in plastic materials and articles intended to come into contact with food (Commission Regulation (EU) No 10/2011[8]). A specific migration limit of 30 mg/kg food, as well as a tolerable daily intake (TDI) of 0.5 mg/kg bw (group TDI), both expressed as maleic acid, were derived for this substance (SCF, 1986). The estimated maximum intake of 70 µg MAN, which would result from consumption of 14 g chewing gum, would thus be considerably lower than the TDI of 35 mg for a person of 70 kg body weight.

MAN has been shown to exert weak sensitising capacity, predominantly in occupational settings. Thresholds below which there is no risk of sensitisation have not been established. The Panel considers that the low amount of MAN which may be released from the novel food at a similar amount as another chewing gum ingredient (EFSA NDA Panel, 2011) is unlikely to have clinically relevant consequences.

[4] Directive 2009/32/EC of the European Parliament and of the Council on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients. OJ L 141, 6 June 2009, pp. 3-9.
[5] VCF Volatile Compounds in Food : database. Nijssen, LM, van Ingen-Visscher, CA, Donders, JJH eds, TNO, 1963-2008.
[6] Available from: http://sourceforge.net/projects/toxtree
[7] European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners. OJ L 61, 18.3.1995, pp 53.
[8] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, OJ L 12, 15.1.2011, pp. 1-89.

8.2.3.3. Methyl vinyl ether (MVE)

No specific migration limit and no TDI have been derived for MVE. Originally, the applicant specified a limit of 500 ppm for MVE monomers. On the basis of the data provided for seven batches, and following discussion with the Panel, the applicant reduced the limit for MVE to 150 ppm. Anticipating a consumption of 14 g chewing gum per day, the estimated maximum daily intake of MVE would be 42 µg. According to EFSA Guidance for the safety assessment of a substance to be used in food contact materials (EFSA, 2008), for substances with a migration into food at concentrations of below 50 µg/kg food the potential for exposure is low, and substances can be used if they are considered to lack genotoxic potential and bioaccumulation. The Panel notes that this conservative default value for exposure is currently being re-examined by the CEF Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) (Engel et al., 2012).

Methyl vinyl ether was the subject of bacterial reverse mutation assay (Ames) tests in various strains, with or without metabolic activation. Results were all negative, which indicates that MVE is not mutagenic in the Ames assay (Araki at al., 1994; IUCLID, 2000; JETOC, 2000). An *in vivo* micronucleus test was conducted on male and female mice by inhalation at doses of 0, 5 000 and 25 000 ppm (0, 12, 60 mg/L). Some of the male animals of the high dose (25 000 ppm) group had a significantly increased number of cells with micronuclei. In a similar study, MVE did not produce a clastogenic effect following inhalation of 25 000 ppm (60 mg/L) (IUCLID, 2000).

The Panel considers that MVE is not of concern with respect to genotoxicity because the molecule has no structural alerts (Ashby and Tennant, 1988), Ames tests were negative, and *in vivo* micronucleus tests by inhalation exposure at very high doses showed no reproducible clastogenic effects.

Following a concern expressed by a Member State with regards to the safety of MVE, the applicant provided additional toxicological information obtained through a literature review, comprising data on acute oral and inhalation toxicity, as well as subacute (28-day) and developmental toxicity studies in rats, both using inhalation exposure. Since inhalation exposure is generally not appropriate for the safety assessment of food, the Panel considers that these data are not relevant for the evaluation.

The Panel considers that the estimated exposure of 42 µg is based on a highly conservative assumption, i.e. daily consumption of 14 g chewing gum and the intake of 100 % of the maximum specification limit for MVE. In the absence of genotoxicity concerns, the Panel considers that MVE under the proposed use and use levels is not of safety concern.

The Panel considers that the applicant has presented sufficient evidence to support the view that the residual levels of the low molecular weight components expected to be present in Gantrez SF are not of safety concern under the proposed uses and use levels.

8.2.4. Potential effects of the copolymer on human gut flora

One Member State raised concern about potential effects of the NF on human gut flora. According to the applicant, this may be a misunderstanding since in its application in dental products the polymer does not have any effect on bacteria; it is rather used as an inert substrate for other products which have an antibacterial effect (e.g. Triclosan) and acts as a 'bioadhesive' to cause the active ingredient to adhere to the mouth.

Considering the nature of the NF and the intended use, the Panel does not expect an impact of the NF on human gut flora.

DISCUSSION

The Panel has no concerns with the specification of Gantrez SF as proposed by the applicant. Analytical data have confirmed that the novel food ingredient conforms to the specification. The description of the manufacturing process is considered sufficient.

Gantrez SF is intended to be used as a novel food ingredient in chewing gum at a maximum concentration of 2 %. In a previous safety assessment of a chewing gum base (EFSA, 2011), high consumption of chewing gum was estimated to be 14 g per day (teenagers in the UK, 95th percentile). The potential maximum consumption of Gantrez SF might thus be 0.28 g/day, corresponding to 4 mg Gantrez SF/kg bw per day for a 70 kg person.

Based on the toxicological data, the Panel concludes that there are no safety concerns related to genotoxicity. The NOAEL for Gantrez SF in a 90-day toxicity study in rats was approximately 1.8 and 2.1 g/kg bw per day for males and females, respectively. This is about 500-fold more than the anticipated intake for high consumers of chewing gum. Furthermore, the Panel notes that the novel food ingredient would usually not, but may rarely, be swallowed.

The maximum consumption of 14 g chewing gum per day also forms the basis for calculations of the amount of low molecular weight components (less than 1000 Da) which are potentially released from the gum during the act of chewing. Since there are no data on the release of low molecular weight compounds during chewing, the Panel assumes that all such materials, for example residual MAN, MVE, methanol, acetaldehyde, LP and BHT, are released at the maximum values indicated in the specification.

The estimated maximum intake of 70 µg/day of the monomer MAN is considered negligible in relation to the TDI of 0.5 mg/kg bw. Regarding the other monomer, MVE, the Panel considers that there is no safety concern with respect to genotoxicity. In accordance with relevant EFSA Guidance for the evaluation of monomers used in the production of high-molecular weight polymers to be used in food contact materials, no additional toxicological data are required considering the estimated maximum intake of 42 µg/day MVE.

The TTC concept has been applied in the safety evaluation of residual levels of LP, which is used as a synthesis initiator in the production process of Gantrez SF. There is no concern with regard to genotoxicity of this substance. The estimated maximum intake of LP of 4.2 µg/day is well below the threshold value for Cramer class I substances, and thus does not raise safety concerns. The estimated maximum intakes of 140 µg/day methanol and 140 µg/day acetaldehyde are considered low in relation to intake from natural sources, and do not pose a health risk at the levels given in the specification. Addition of the antioxidant BHT to Gantrez SF, as indicated in the specification, is in accordance with EU legislation on food additives.

CONCLUSIONS

The Panel concludes that the novel food ingredient, Methyl Vinyl Ether-Maleic Anhydride Copolymer (Gantrez SF, chewing gum base ingredient), is safe under the proposed uses and use levels.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier “Gantrez SF” received on 05/06/2012. Submitted by Reading Scientific Services Ltd. on behalf of International Speciality Products, Ashland. Additional data were provided on 08/03/2013, 28/05/2013 and 28/08/2013.

2. Letter from the European Commission to the European Food Safety Authority with the request for an opinion on the safety of a 'Methyl Vinyl Ether-Maleic Anhydride Copolymer' (chewing gum base ingredient). Brussels, dated 12/06/2012.

3. Initial assessment report carried out by the Netherlands “Methyl Vinyl Ether-Maleic Anhydride Copolymer” (chewing gum base ingredient) as a novel food ingredient, Initial assessment under Article 4 of Regulation (EC) No 258/97.

4. Member States’ comments and objections.

5. Response by the applicant to the initial assessment report and the Member States' comments and objections.

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ABBREVIATIONS

bw	Body weight
BHT	butyl hydroxytoluene
CEF Panel	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CFU	Colony-forming unit
EDI	Estimated daily intake
FOB	Functional Observation Battery
GLP	Good Laboratory Practice
GPC/MALLS	Gel permeation chromatography coupled with multi angle laser light scatterings
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Database
kDa	kiloDaltons
LP	Dilauroyl peroxide
MAA	Maleic acid
MAN	Maleic anhydride
MVE	Methyl Vinyl Ether
NCE	Normochromatic erythrocyte
NDA Panel	Panel on Dietetic Products, Nutrition and Allergies
NF(I)	Novel Food (Ingredient)
NOAEL	No Observed-Adverse-Effect Level
OECD	Organisation for Economic Co-operation and Development
PCE	Polychromatic erythrocyte
RI	Refractive index
SCF	Scientific Committee on Food
TDI	Tolerable daily intake
TTC	Threshold of Toxicological Concern
VCF	Volatile Compounds in Food