

**Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies  
on a request from the Commission related to a notification from AAC on  
wheat-based maltodextrins pursuant to Article 6, paragraph 11 of  
Directive 2000/13/EC**

**(Request N° EFSA-Q-2006-163)**

**(adopted on 3 May 2007)**

**SUMMARY**

Since wheat is relevant both as a source of epitopes known to induce coeliac disease and as a source of allergens triggering wheat allergy, it is appropriate to investigate wheat products, namely wheat starch hydrolysates, for their potential to induce coeliac disease or trigger wheat allergy.

The applicant provided information on wheat starch hydrolysates, particularly concerning the potential effects of maltodextrins in coeliac disease and wheat allergy. The history of safe use of wheat starch maltodextrin is claimed based on the safe use of wheat starch-based gluten-free diet in coeliac disease. Similar data do not exist on wheat-allergic individuals. Low amounts of residual gluten and peptides were found by mass spectrometry and high-pressure liquid chromatography analysis in wheat starch maltodextrins (0.3-1.4 mg/kg).

A biopsy-controlled clinical study in 27 adult patients with coeliac disease shows no deterioration of coeliac disease after a maltodextrin challenge over 24 weeks. Two challenge studies in 32 wheat allergic individuals examining clinical allergic reactions to maltodextrins are considered by the Panel to be inconclusive regarding the likelihood that the product may trigger an allergic reaction in susceptible individuals.

Wheat-based maltodextrins may contain low levels of proteins and peptides. It is not known at which levels of intake wheat-based maltodextrins would cause allergic reactions in wheat-allergic individuals. Nevertheless, taking into account the scientific information provided and in particular the levels of wheat proteins reported in wheat-based maltodextrins, the Panel considers that it is not very likely that this product will trigger a severe allergic reaction in susceptible individuals.

For coeliac disease, assessment of the evidence provided including a new clinical study indicates that wheat-based maltodextrins are unlikely to cause an adverse reaction in individuals with coeliac disease provided that the (provisional) value of gluten considered by Codex Alimentarius for foods rendered gluten-free is not exceeded.

## **KEY WORDS**

Wheat starch hydrolysates, maltodextrins, coeliac disease, food allergy.

## **BACKGROUND**

In November 2003, the European Parliament and the Council adopted Directive 2003/89/EC<sup>1</sup> amending Directive 2000/13/EC, as regards indication of the ingredients present in foodstuffs.

Annex IIIa of the Directive specifies a list of food ingredients or substances that are known to trigger allergic reactions or intolerances in sensitive individuals for which no labelling exemptions are allowed. Whenever the listed ingredients/substances or their derivatives are used in the production of foodstuffs, they must be labelled.

Article 1, paragraph 11, subparagraph 2 of the Directive establishes a procedure allowing for temporary labelling exemption of derivatives from ingredients listed in Annex IIIa for which it has been scientifically established that it is not possible for them to cause adverse reactions. In accordance with this provision, submissions of requests for temporary labelling exemption were notified to the Commission before 25 August 2004. The Commission, after consultation with the European Food Safety Authority, adopted a list (Directive 2005/26/EC<sup>2</sup>) of those ingredients which are temporarily excluded from Annex IIIa until 25 November 2007, pending the final results of the notified studies.

Consequently, applicants who submitted a dossier in 2004 on the basis of subparagraph 2, resulting in the inclusion of a product in the list of Directive 2005/26/EC, and who are seeking exclusion of that product from Annex IIIa beyond 25 November 2007 will have to submit a request enclosing the final results of the notified scientific studies. Therefore in the context of the permanent labelling exemption procedure, the European Food Safety Authority is asked to provide scientific opinions on the submissions in accordance with the present terms of reference.

## **TERMS OF REFERENCE**

In accordance with Article 29 (1) (a) of Regulation (EC) N° 178/2002, the European Commission requests the European Food Safety Authority to evaluate the scientific data submitted by AAC in the framework of the procedure laid down in Article 6, paragraph 11 of Directive 2000/13/EC. On the basis of that evaluation, EFSA is requested to issue an opinion on the information provided, and particularly to consider the likelihood of adverse reactions triggered in susceptible individuals by the consumption of the following ingredients/substances used under the conditions specified by the applicant: wheat-based maltodextrins.

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<sup>1</sup> Directive 2003/89/EC of the European Parliament and of the Council amending Directive 2000/13/EC as regards indication of the ingredients present in foodstuffs. OJ L 308. 25.11.2003, p. 15.

<sup>2</sup> Commission Directive 2005/26/EC of 21 March 2005 establishing a list of food ingredients or substances provisionally excluded from Annex IIIa of Directive 2000/13/EC of the European Parliament and of the Council. OJ L 75, 22.03.2005, p. 33-34.

## ASSESSMENT

Since wheat is relevant both as a source of epitopes known to elicit coeliac disease and as a source of allergens eliciting wheat allergy (NDA, 2004a), it is appropriate to investigate wheat products, namely wheat starch hydrolysates for their potential to induce coeliac disease or wheat allergy.

In 2004, the Panel issued an Opinion of a notification submitted by AAC to the European Commission pursuant to article 6, paragraph 11 of Directive 2000/131/EC as amended by the Directive 2003/89/EC, for temporary exemption from labelling (NDA, 2004b).

Under the framework of permanent exemption from labelling, the present Opinion is based on assessment of an updated dossier from AAC which contains additional information on dietary exposure to gluten from wheat starch hydrolysates, on immunochemical and HPLC analysis of products and new clinical studies into coeliac disease and into wheat allergy.

### **1. Manufacturing process**

Different purification steps, in particular the active carbon treatment, remove proteins and other nitrogen-containing compounds. The preparation process of wheat starch hydrolysates includes isolation, conversion, purification, preservation and blending. The applicant also states that good manufacturing process protocols are followed and that particular attention should be given to avoid gluten contamination during the manufacturing process.

### **2. Characterisation of the product**

Maltodextrins are a purified concentrated mixture of saccharide polymers obtained by the partial hydrolysis of edible starch. Maltodextrin powders and granules are soluble or dispersible in water. Maltodextrins are used for confectionery, sauces and soups, and for dietetic foods.

#### **2.1 Exposure estimation**

A new study analysing dietary exposure to gluten from wheat starch hydrolysates has been conducted by TNO Nutrition and Food Research and provided by the applicant. Main sources of exposure were soft drinks, dairy desserts, yoghurt drinks, candy and canned food, soups and savoury sauces. This study was designed to collect data from The Netherlands, Italy and Ireland (representative sample of Dutch population including children, Italian students living in the district of Rome, Irish adults aged 18-64 years) based on food consumption data from these countries and on gluten content in maltodextrins from wheat starch hydrolysates of 20-40 mg per kg (mass spectrometry). According to the applicant, exposure to gluten from maltodextrin was less than 1 mg per day for 95% of the adult Dutch men. All other population subgroups had lower exposure.

### **3. Evidence of non-allergenicity**

#### **3.1 History of non-allergenicity of the product**

An extensive literature review has provided information on wheat protein analysis and effects of wheat on coeliac disease and wheat allergy. The review has not identified papers on wheat starch hydrolysates.

In a study on coeliac disease, wheat starch-based gluten-free diet was compared to naturally gluten-free diet in 76 adult patients with coeliac disease (Collin *et al.*, 2004). The authors showed gluten contamination up to the level of 200 mg/kg of diet in both dietary groups. The long-term mucosal recovery of the patients was good in both groups. By this and other studies it has been shown that wheat starch-derived gluten-free products still containing trace amounts of gluten are safe for children and adults with coeliac disease. The authors came to the conclusion that a gluten threshold of 100 mg/kg of food “can safely be set”. Although the paper is not directly devoted to the use of maltodextrins in coeliac disease, the evidence given is relevant to the application.

Another study submitted concerns wheat allergy in children and adults (Moneret-Vautrin *et al.*, 2003). Most of the paper is not directly relevant to the use of wheat starch hydrolysates in wheat allergy. However, provocation tests using 1 mg-19.99 g of wheat protein have been used as part of the diagnostic procedure. 80% of allergic children reacted to less than 2 g, 40% to less than 1 g of wheat protein. However, 6% (two out of 32) of the children reacted to less than 10 mg of protein. It is not made clear how the figures reported for wheat proteins relate to the quantities of wheat flour used for provocation tests, even if the authors consider protein content of wheat flour to be 12% by weight (as cited by the applicant). The results given cannot be used as dose-response information with general validity. The authors’ conclusion that “threshold doses of wheat flour in wheat flour allergic individuals were globally higher than those considered risk levels for coeliac disease, seeming to indicate that a wheat starch-based diet could be safe for allergic patients” is not sufficiently based on the evidence presented. A further study has been carried out recently in 37 adult patients with wheat allergy by Scibilia *et al.* (2006). By double-blind placebo-controlled food challenge (DBPCFC), the lowest provocation dose was 0.1 g of raw and cooked wheat flour. 27% of the subjects had a provocation dose ≤ 1.6 g. The papers by Moneret-Vautrin *et al.* (2003) and Scibilia *et al.* (2006) have only indirect relevance to the application, since the protein content of the eliciting dose of wheat flour was not determined.

By history, non-allergenicity of wheat starch hydrolysates is assumed by the applicant. Based on the literature review submitted no adverse reactions have been reported to wheat starch hydrolysates in coeliac disease or wheat allergy. However, the evidence provided is indirect and under-reporting of allergic reactions may have occurred.

### **3.2 Laboratory-based tests**

Further evidence was provided using R5 enzyme-linked immunosorbent assay (ELISA) specific for the gluten/gliadin epitope QQFP. While in starches up to 279.3 mg/kg of gluten were found, there was no detected gluten level higher than 3.1 mg/kg (limit of detection, LOD) in maltodextrin samples in the years 2005-2006 (15-33 samples per year). One out of four previous (2004) maltodextrin samples was positive for gluten content at LOD of 4.5 mg/kg. Therefore the conclusion that the gluten/gliadin epitope QQFP was absent in most wheat starch hydrolysates with the exception of one maltodextrin sample is justified.

A large and exhaustive body of previous evidence on quantitative and qualitative protein and peptide content of wheat starch hydrolysates was provided. Twenty-one samples (14 wheat glucose syrups, 3 crystalline dextrose, 4 maltodextrins) were studied by a highly refined methodology based on a detailed purification scheme and different applications of mass spectrometry. The limit of detection for gliadin was 1 mg/kg. The recovery of gliadin by the

method was 86%. It was found that all samples contained some level of residual intact gliadin as well as peptides arising from degradation of gluten in the range of 1-40 mg/kg. Protein composition was slightly variable. It was observed that specific peptides from well-defined regions of gliadins and glutenins were relatively resistant to hydrolysis as indicated by a summary table on 21 single samples. By high-pressure liquid chromatography (HPLC) the applicant showed that protein concentrations ranged from 0.3 to 1.4 mg/kg.

IgE-binding was found by ELISA in 5 out of 32 sera from wheat-allergic patients with 1 out of 2 maltodextrin preparations (antigen-coated plates (ACP) ELISA). These five sera also showed strong IgE-binding to different native wheat protein fractions (gluten, gliadin, albumins and globulins, lipid transfer protein). The authors assume that this reactivity does not reflect the *in vivo* potential of maltodextrin products to induce an allergic reaction in these patients.

### 3.3 *Clinical studies*

#### 3.3.1 *Coeliac disease*

A new DBPCFC was provided by the applicant involving 90 adult patients with a biopsy-based diagnosis of coeliac disease. Patients were challenged with either wheat starch-based maltodextrin (n = 30), glucose syrup (n = 30) or placebo (n = 30) daily for 24 weeks. Patients with refractory coeliac disease or with dietary transgressions had been excluded. Assessment was accomplished by clinical evaluation, dietary and laboratory analyses, telephone assessment and initially and ultimately a small intestinal biopsy. Differences between baseline and end of study were indicated by delta values. Daily ingestion of wheat starch-based maltodextrin did not have any deleterious effect on the small bowel mucosa. Differences in small intestinal villous height by crypt depth ratio and density of intraepithelial lymphocytes were not statistically significant. The same was observed for gastrointestinal symptoms, quality of life and laboratory parameters.

There were eight drop-outs, seven due to abdominal symptoms, one to non-compliance. None of those patients developed villous atrophy. Three of those drop-outs belonged to the maltodextrin group, three to the placebo group, and two to the glucose syrup group.

Minor dietary lapses were observed in six out of 90 patients. One of those patients belonged to the maltodextrin group, one to the placebo group. Eighty-six out of 90 patients (including drop-outs) consented to a final biopsy and full evaluation. It is concluded by the applicant that there was no adverse effect of the maltodextrin preparation used over a 24-week challenge in 27 fully evaluated adult Finnish coeliac patients.

#### 3.3.2 *Wheat allergy*

A new clinical study was provided by the applicant. Thirty-six patients were enrolled, and 32 completed the study. This included 22 children aged 2-12 years old and ten female adults aged 22-54 years. Diagnosis of wheat allergy was based on DBPCFC using raw wheat flour in 23 patients, in three highly allergic patients diagnosis was based on application on the lips and in six patients diagnosis was based “on the fact that the patients did not pass the trial of reintroduction”. Symptoms were atopic dermatitis, angioedema, urticaria, growth failure, diarrhoea and abdominal pain. For the clinical study, a powdered orange-flavoured soft drink containing maltodextrin syrup was used containing 0.1 mg wheat protein in 34.6 g powdered soft drink. Sucrose was used for placebo.

Differences in skin prick test results were difficult to evaluate due to a positive reaction in a negative control and due to the small numerical differences in diameters compared with reactions in positive controls.

Two challenge studies were provided by the applicant using a maltodextrin preparation: a DBPCFC was conducted in 17 patients with three doses at 30-minute intervals. The total challenge dose was 1.35 g (containing 0.05 mg of cereal proteins) for children and 2.7 g (containing 0.1 mg of cereal proteins) for adults. Two patients had symptoms (pollakisuria, atopic dermatitis) after maltodextrin and two (abdominal pain, vomiting, atopic dermatitis) after placebo. A second challenge was done at home over a 20-day period. In a blind manner the maltodextrin product and placebo were consumed consecutively for 10 days in 17 patients. One patient showed symptoms (pruritus, atopic dermatitis) after maltodextrin and five (pruritus, rhinitis, cough, diarrhoea, urticaria, abdominal pain, atopic dermatitis, vomiting) after placebo. With the limitation that only one maltodextrin product was tested and only children over two years of age were included in the study for ethical reasons, there was no statistically significant clinical reactivity to maltodextrins over placebo shown in the study presented.

The Panel considers that these challenge studies are inconclusive regarding the likelihood that the product may trigger an allergic reaction in susceptible individuals.

## **CONCLUSIONS**

1. Wheat-based maltodextrins may contain low levels of proteins and peptides. It is not known at which levels of intake wheat-based maltodextrins would cause allergic reactions in wheat-allergic individuals. Nevertheless, taking into account the scientific information provided and in particular the levels of wheat proteins reported in wheat-based maltodextrins, the Panel considers that it is not very likely that this product will trigger a severe allergic reaction in susceptible individuals.

2. For coeliac disease, assessment of the evidence produced including a new clinical study indicates that wheat-based maltodextrins are unlikely to cause an adverse reaction in individuals with coeliac disease provided that the (provisional) value of gluten considered by Codex Alimentarius for foods rendered gluten-free is not exceeded.

## **DOCUMENTATION PROVIDED TO EFSA**

Dossier submitted by the “Association des Amidonneries de Céréales de l’Union Européenne” (AAC) to the European Commission pursuant to Article 6, paragraph 11 of Directive 2000/13/EC as amended by Directive 2003/89/EC on 31 August 2006.

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