Maisons-Alfort, 15 November 2011

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the evaluation of the initial assessment report by the UK authorities concerning the placing on the market of the novel food ingredient phosphated distarch phosphate

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are made public.

On Monday, 3 October 2011, the Directorate General for Competition, Consumer Affairs and Fraud Control requested that ANSES provide the following expert assessment: evaluation of the initial assessment report by the UK authorities concerning the placing on the market of the novel food ingredient phosphated distarch phosphate.

1. 1. BACKGROUND AND PURPOSE OF THE REQUEST

Phosphated distarch phosphate (PDP) was initially the subject of an application by a different applicant and was evaluated under Request No 2009-SA-0127. That application led to Commission Implementing Decision No 2011/494/EU. This new dossier was submitted at the same time as the previous one and could not therefore benefit from the substantial equivalence procedure.

This Opinion falls within the scope of Regulation (EC) No 258/97 concerning novel foods and novel food ingredients (NI). The product applied for belongs to class 2.1, i.e. a complex novel food ingredient from non-genetically modified sources which has a history of food use in the Community.

According to Table II of Commission Recommendation 97/618/EC, the information required for class 2.1 NIs is as follows:

I. Specification of the NI
II. Effect of the production process applied to the NI
III. History of the organism used as the source of the NI
IX. Anticipated intake/extent of use of the NI
X. Information from previous human exposure to the NI
XI. Nutritional information on the NI
XII. Microbiological information on the NI
XIII. Toxicological information on the NI

2. 2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

The collective expert appraisal was conducted by the Expert Committees (CESs) on Human nutrition (NUT) (the lead CES) and on Additives, flavourings and processing aids (AAAT) – which were consulted by correspondence owing to the short response times imposed – based on initial reports drafted by three rapporteurs.

3. 3. ANALYSIS AND CONCLUSIONS OF THE CES

PDP is a resistant starch obtained through chemical modification. Resistant starch is generally defined as 'the sum of the starch and its degradation products that are not absorbed in the small intestine of healthy individuals. It encompasses four types, with type 4 (RS4) consisting of chemically modified starches, including PDP. The minimum dietary fibre content of the NI, estimated using the AOAC[1] No 991.43 method, is 66%.

PDP is currently included in the list of authorised food additives (E1413), for use *quantum satis*. It is used in soups, sauces, fruit fillings and as a freeze-thaw-stable thickener. The use of PDP for nutritional purposes is a new development necessitating a new application subject to Regulation (EC) No 258/97/EC on novel foods and novel food ingredients.

- Specification of the NI

The NI is an 'ordinary' wheat starch which is esterified and cross-linked with sodium tripolyphosphate and sodium trimetaphosphate. It takes the form of a white or off-white powder.

It is a resistant starch obtained by combining chemical treatments to create phosphate cross links between carbohydrate residues and by esterifying some of the hydroxyl functional groups with phosphate.
The UK authorities report that the applicant describes two different preparations of the NI with total fibre contents of 66% and 76% respectively. The applicant analysed the heavy metal, pesticide and mycotoxin content of the raw material (wheat flour). It did not provide analyses for each batch but the technical data provided show that the NI is produced in accordance with the specifications. According to these data, the preparations contain less than 0.4% residual phosphorus.

The UK authorities consider the information provided by the applicant on the specification of the NI to be adequate.

The two CESs note that the applicant has not provided the resistant starch content measured by a specific official method (i.e. AOAC 2002.02). Moreover, precise information on the degree of esterification and cross-linking of glucose units is essential for the purposes of comparing the NI with the PDPs previously used as an additive for their rheological properties.

They add that the product is not a chemically modified starch derived from high-amylose starch as in the first referral concerning a PDP described as a type 4 resistant starch. In fact, the NI is derived from 'ordinary' wheat starch (containing approx. 25% amylose).

- Effect of the production process applied to the NI

[1] Association of Analytical Chemists

The NI is produced from wheat starch, which is widely used in the agro-food industry. It is treated with sodium tripolyphosphate and sodium trimetaphosphate under alkaline conditions with moderate heating (47°C). The preparation is adjusted to pH 6, and is then dried to produce a final product with 76% fibre, or heat treated to produce a version containing 66% fibre.

The UK authorities asked the applicant to provide information on the stability of the products. The applicant therefore investigated changes in moisture content and total fibre and used infrared spectroscopy to identify changes in the physico-chemical structure of the carbohydrates. These studies found no substantive change in either form of the NI during a 2-5 year storage period.

The UK authorities add that the production of the NI is in accordance with Hazard Analysis Critical Control Point (HACCP) procedures.

They note that the production process of the NI is similar to that of the approved food additive phosphated distarch phosphate (E1413) and take the view that there are appropriate controls in place on the production of the NI to ensure the safety of the final product. Although the applicant did not provide any data examining the stability of the NI in food matrices, the authorities consider the analyses carried out by the applicant to demonstrate the stability of the NI over an extended time period to be adequate.

The two CESs concur with these observations. However, they point out that precise purity criteria for the food additive PDP (E1413) are set out in European legislation[2].

- History of the organism used as a source of the NI

The UK authorities comment on the applicant's observation that wheat has been used and consumed for many years. The applicant highlights that new varieties require a degree of scrutiny before they can be used commercially and notes that although there are few concerns about the safety of wheat *per se*, there are certain sets of the population for whom consumption of wheat is contra-indicated (cf. section on toxicology).

The UK authorities note that the history of consumption of wheat, the source used to produce the NI, is well documented.

Neither CES has any concerns regarding the raw material used.

- Anticipated intake/extent of use

The applicant is proposing to market the NI as a source of dietary fibre and as a replacement for flour in a wide range of foods (including bread, breakfast cereals, pasta, pizza dough, biscuits and cakes) at levels of up to 15% of the weight. It has not specified whether the foods containing the NI will be introduced in a particular geographic area. The applicant used NDNS[3] data to estimate the anticipated daily intake of the NI and residual phosphorus for the different population groups in the EU.

The UK authorities consider that an estimation of intake from these food groups is required to determine the potential level of consumption of phosphated distarch phosphate from all dietary sources.

The applicant amended its selection of food categories in which the NI could be incorporated to mirror those proposed in the previous application. The applicant estimated that mean daily intake of the NI will vary

[2] Commission Directive 2008/84/EC of 27 August 2008 laying down specific purity criteria on food additives other than colours and sweeteners

[3] UK National Diet and Nutrition Surveys

between 4.9 g/person (0.07 g/kg bw) for adult women and 9.0 g/person (0.17 g/kg bw) for male adolescents. On a body weight basis, the highest estimated intake is in young children (mean 0.38 g/kg bw/day, 97.5th percentile 1.09 g/kg bw/day). In practice, it is unlikely that these 'worst case' intakes will be reached, as this would necessitate the incorporation of the NI at the maximum level in all staple foods containing starch.

The UK authorities had previously noted that the anticipated intake of the NI was within the range tolerated in clinical studies (1 g/kg bw/day), with the exception of high-level intake (97.5th percentile) in young children. While there is a degree of conservatism in the calculation of these intake estimates (high intake hypothesis), the potential for high levels of intake by young children requires careful consideration.

The CES NUT agrees with the UK authorities that only potential intake of the NI by young children requires particular consideration. Consumption by this group should thus be monitored.

- Information from previous human exposure to the NI or its source

The applicant notes that the NI is authorised as a food additive within the European Union. Although there are no data quantifying consumption, the previous applicant had noted that the current consumption of the additive E1413 was less than 0.5 g/day at high intake levels in UK adults. The applicant also cites UK Government data which state that average daily starch consumption is 156 g per person, equating to 26.4% of daily energy intake.

The UK authorities acknowledge that the NI is consumed as a food additive in the EU.

The CES NUT concurs with the UK authorities.

- Nutritional information on the NI

The UK authorities comment on three studies which the applicant submitted in its dossier:
- An *in vitro* fermentation study carried out on the NI (containing 76% fibre) comparing production of short-chain fatty acids with a potato-based resistant starch and the results of an earlier (1990) report which looked at a number of different starches. The applicant concludes that the profiles are comparable, although there were some differences in the production of butyrate.
- An *in vivo* study (dating back to the 1970s), in which 12 healthy volunteers were fed 60 g of a maize-based phosphated distarch phosphate over four successive days with no adverse reactions. The applicant carried out a human tolerance study using the NI (76%), in which 10 young adults consumed 30-33 g of a range of resistant starches over a three-week period. The applicant reports the study as showing no adverse reactions associated with consumption of resistant starch other than a mild increase in flatulence. Analysis of the microflora revealed an increase in *Bifidobacteria* (in 4 of the 10 subjects) and in the number of *Bacteroides* following consumption of the NI. This effect is generally considered to be positive.
- The applicant carried out a study to assess the effect of the NI (containing 76% fibre) on the glycaemic and insulinaemic response of healthy individuals and monitored plasma insulin and glucose following consumption of muffins and cereal bars containing the NI. When incorporated into muffins, the NI had a greater effect on postprandial insulinaemia than it did on parallel measurements of glycaemia, while the reduction in glycaemia was greater when the NI was added to cereal bars. The applicant notes that similar matrix effects have been reported with other resistant starches.

The UK authorities report the applicant's view that the NI behaves no differently from other types of naturally occurring resistant starch (RS1 & RS2) and resistant starch formed by cooking (RS3).

The UK authorities take the view that the points raised in their consideration of the earlier application apply directly to this NI, i.e.:
- *The conclusions of a review article that the regular consumption of high levels (>30 g/day) of resistant starch may give rise to gastrointestinal intolerance. The applicant emphasises only the lack of available data*

and not the specific safety concerns raised in the review. It also points out that the unpublished report by Pieters et al. (1971) shows that there is no intolerance to resistant starch when this is consumed in relatively large quantities. The UK authorities agree that the human study by Pieters et al. (1971) shows that the consumption of up to 60 g of the NI per day would not give rise to GI intolerance in healthy adults. However, they question whether this can be extrapolated to other population groups such as children, in whom gut microflora is still developing and does not have an adult composition until the age of about 11 or 12. Also, it is known that children are more sensitive than adults to the laxative effects of other poorly absorbed ingredients such as polyols.

- *Moreover, the UK authorities add that discussions are ongoing at international level regarding the definition of 'fibre'. The current recommendations by the Food Standards Agency (FSA), according to which resistant starch is included in the definition of fibre, propose that the quantification of dietary fibre should be carried out using AOAC methodology. However, the FSA currently recommends that for the purpose of regulating nutrition claims, the term 'fibre' should mean 'non starch polysaccharides' and should exclude chemically modified resistant starch. This means that food manufacturers in the UK could include the contribution of the NI in the declared fibre content for nutrition labelling purposes, but could not refer to 'fibre' in the context of dietary or health claims. Until health claims are harmonised at EU level, products marketed in other EU Member States will have to comply with the relevant national rules concerning nutrition and health claims*.

The CES NUT notes that the UK authorities have already discussed in a previous request the risk of digestive intolerance in the case of a regular intake higher than 30 g of resistant starch per day, even though the applicant claims that there is no intolerance up to a dose of 60 g per day of the NI in healthy adults. The UK authorities are concerned about the risk of digestive discomfort in children, in whom microflora does not become stable until the age of about 11 or 12 and who are more sensitive (laxative effects) than adults to the effects of poorly absorbed polyols.
The CES NUT agrees with the UK authorities but refutes the argument that the evidence of heightened sensitivity to polyol in children implies that the NI might produce laxative effects in them. The laxative effects observed in connection with polyols are osmotic in nature, which is not the case for chemically modified starches, which have a much higher molecular weight (degree of polymerisation of about 12, as opposed to 1 or 2 for polyols). No evidence has been provided of the presence of free-glucose and/or disaccharides (of glucose) in the faeces of infants. Moreover, the physiopathological hypothesis of unstable microflora in children is at odds with data contained in the scientific literature, which show that microflora has almost stabilised by the age of 1-2 years (Palmer et al. 2007).
Moreover the committee has no problem, in principle, in accepting that a type 4 resistant starch is a dietary fibre if at least one of the beneficial physiological effects of fibres is produced following consumption of this resistant starch, in accordance with the definition of dietary fibre adopted by the Codex Alimentarius in 2009.

It also notes that estimated phosphorus intake is on average 40 to 80 mg/day, with an intake of 256 mg/day at the 97.5th percentile in male adolescents, as compared with ANC[4] ranging between 360 and 830 mg/day in France, a European consumption rate estimated between 1000 and 2000 mg/day and a tolerance threshold suggested by EFSA of 3000 mg/day (3200 mg/day according to the Expert Group on Vitamins and Minerals). However, it cannot be ruled out that the phosphorus released and absorbed following the fermentation of the resistant starch in the colon may contribute to an excessive phosphorus intake and may thus have adverse effects on bone metabolism.

- Microbiological information on the novel food

The production of the NI does not involve the use of microorganisms and the manufacturing process is controlled through HACCP procedures.

[4] "Apports nutritionnels conseillés" (ANC) are the French equivalent of the Population Reference Intakes (PRI)

The microbiological purity of the NI is defined in the specification, which sets maximum counts for undesirable organisms. The applicant provided the results for both NI products (five separate batches), whose values are within the specified limits.

The UK authorities consider that the manufacturing process does not give rise to any microbiological concerns. Evidence of the absence of pathogenic microorganisms is required in order to comply with the specifications of the NI.

***The two CES agree with the UK authorities' conclusions**.*

- Toxicological information on the NI

The UK authorities state that according to the applicant the NI is a chemically modified starch authorised as a food additive in the EU. The many studies reported are similar to those reported in the previous application and are not reproduced in the UK authorities' assessment. These studies were chronic and subchronic toxicity studies on reproduction and mutagenicity in animals, mainly rats. The results of these studies do not indicate any undesirable toxicological results.

The UK authorities confirm that the toxicological data provided by the applicant show that the NI is not toxic. The human study conducted by Pieters et al. (1971) reveals that the proposed use of the NI would not increase gastrointestinal intolerance in healthy adults, but the UK committee questions whether these results are applicable to high-level consumption in young children.

***The CES AAAT agrees with the conclusions of the UK authorities**.*

- Allergenicity and labelling

According to the UK authorities, the applicant accepts that wheat is known to make a significant contribution to adverse reactions to food and acknowledges that the NI will have to be labelled in accordance with EU requirements. The applicant considers that the NI would not contribute any greater risk to wheat-intolerant consumers than other commercially available wheat starch already used in the food industry.

The applicant acknowledges that the concerns raised by the UK authorities regarding consumption by children in the previous assessment also apply to their NI and therefore proposes that the possible laxative effect in young children should be indicated on the label.

The UK authorities concur with the applicant's view that an ingredient obtained from wheat will not present any greater allergy risk to consumers than wheat itself and that it must be labelled in accordance with EU legislation.

They note that use of the term 'resistant modified (wheat) starch' would be appropriate for the NI and would be in line with EU food labelling regulations.

During the previous assessment, the UK authorities had taken the view that the statement concerning possible gastrointestinal intolerance was adequate, whilst adding that it 'should clearly indicate that consumption of the NI may cause laxative effects in young children'. The UK authorities note that EFSA did not, however, include this request in its opinion. In spite of disagreeing with this position, the UK authorities agreed to amend their suggested statement to 'may cause altered bowel habits'. Moreover, since the foods concerned are very attractive to children, it should be possible for an applicant to obtain approval from an ethical committee to carry out a non-invasive study in children to determine the level at which consumption of the NI by children gives rise to intolerance. However, until these data are available it is prudent to require an advisory statement on all foods containing the NI.

In line with the previous application, the UK authorities are of the opinion that the applicant should provide supplementary information to ensure that the consumer is fully informed as to the nature of the NI. This could be achieved via a reference to a website and a manufacturer's careline.

The two CESs agree with the UK authorities.

- Conclusions

The UK authorities conclude that the recommendations made during the assessment of the previous PDP also apply to this product. The NI is an authorised additive and, on this basis, the above-mentioned authorities consider that it is unlikely to give rise to any toxicological concerns. However, the levels of consumption will be significantly higher than for an additive and foods likely to contain the NI will be widely consumed by children, even though adults are the main target group.

The UK authorities add that, as a chemically modified starch, the NI is not fermented by gut bacteria in the same way as other classes of resistant starch. As a result of its lower digestibility, it is likely that a larger quantity of RS4 starch will reach the colon, where it will be fermented. This makes it difficult to predict the consequences of consumption in all groups of consumers, in particular young children. The UK authorities therefore conclude that all foods containing the NI should carry an accompanying advisory statement for children.

The two CESs do not accept the UK authorities' statement that the NI would not be fermented by gut bacteria in the same manner as other classes of resistant starch. In fact, it cannot be said that following consumption of the NI a larger quantity of type 4 resistant starch will reach the colon, where it will be fermented. Sources of types 2 and 3 resistant starches may actually contain as much resistant starch as the NI. The CES NUT also takes the view that the applicant should indicate the esterification rate of the NI. It would also be desirable for the applicant to refer only to scientific literature on experiments carried out using chemically modified starches that are very similar to the NI, in other words, those with the same chemical modifications and the same substitution (esterification and cross-linking) rates, since chemically modified starches have very diverse physico-chemical properties.

Moreover, this NI differs from the NI concerned in the previous assessment (Request 2009-SA-0127) and in the European Commission Implementing Decision of 5 August 2011, since it is derived from a different starch (wheat rather than maize), but above all because the NI dealt with in the previous assessment was derived from a high-amylose starch, unlike the NI concerned here.

The few studies available on the consumption of exclusively type 4 resistant starch in the form of the NI have not revealed any adverse effects. The two CESs therefore agree with the UK authorities' positive opinion as regards placing this NI on the market with the proposed advisory label ('may cause altered bowel habits'), including for consumption by children. However, the CES NUT regrets the lack of information on the actual chemical composition of the NI in relation to phosphated distarch phosphate consumed as an additive.

4. 4. CONCLUSION AND RECOMMENDATIONS OF THE AGENCY

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusions of the CESs on Human nutrition and on Additives, flavourings and processing aids.

Director General

Marc MORTUREUX

KEYWORDS

modified starch, children, novel ingredient, resistant starch, phosphate, phosphorus.

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