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FOOD STANDARDS AGENCY

Mr Andreas Klepsch
European Commission
By email

27 April 2009 Reference: NFU 580

INITIAL OPINION: PHOSPHATED DISTARCH PHOSPHATE AS A FOOD INGREDIENT

Dear Mr Klepsch,

On 23 August 2005 the UK Competent Authority accepted an application from National Starch Food Innovation for Phosphated Distarch Phosphate as a novel food ingredient, in accordance with Article 4 of regulation (EC) 258/97. The Advisory Committee on Novel Foods and Processes (ACNFP) reviewed this application and their opinion is attached.

In view of the ACNFP's opinion, the UK Competent Authority considers phosphated distarch phosphate meets the criteria for acceptance of a novel food defined in Article 3(1) of regulation 258/97 subject to the labelling requirement described below.

I am copying this letter and the ACNFP's opinion to the applicant.

Yours sincerely,

(By e-mail only)
Dr Chris Jones
For the UK Competent Authority

cc Julie Scott National Starch

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR PHOSPHATED DISTARCH PHOSPHATE AS A FOOD INGREDIENT

Applicant: **National Starch Food Innovation**

Responsible Person: **Julie Scott**

EC Classification: **2.1**

Background

1. An application was submitted by National Starch for the authorisation of phosphated distarch phosphate as a novel food ingredient in a range of low moisture food products.

2. Phosphated distarch phosphate (PDP) is a chemically modified resistant starch derived from high amylose maize starch. Resistant starch (RS) is commonly defined as "the sum of starch and products of starch degradation not absorbed in the small intestine of healthy individuals". RS is divided into four types and PDP is classified as a type 4 resistant starch (RS4). This classification covers chemically modified starches, which are the most resistant forms of modified starch. The novel ingredient contains a minimum of 70% dietary fibre (as measured by the AOAC method) and not more than 0.4% residual phosphorus, which is covalently bound to the starch molecules.

3. PDP is currently listed as an approved food additive (E1413)[1] for use *quantum satis*[2]. This approval applies only to its use for technological purposes and E1413 is currently used in products such as soups, sauces, gravies and fruit fillings as a freeze-thaw-stable thickener. The use of PDP for nutritional purposes is a new development and is therefore subject to the Novel Food Regulation (EC) 258/97.

4. This application for authorisation of PDP was prepared pursuant to Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. PDP has been classified as a complex novel food ingredient from a non-GM source having a history of food use in the community (class 2.1).

I. Specification of the novel ingredient (NI)

Application dossier p 5-10 and Annexes A, B and C

5. The novel ingredient (NI) is a variety of phosphated distarch phosphate (PDP) and is referred to in the application dossier as "RS4-fibre*" (See also Section XI below). PDP is a chemically modified starch obtained by a combination of

[1] European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners (as amended)

[2] maximum level not specified, in accordance with good manufacturing practice at a level not higher than it is necessary to achieve the intended purpose

chemical treatments that result in phosphate bridges between the carbohydrate molecules and substitution of a proportion of the hydroxyl groups with phosphate. PDP is a permitted food additive (E1413) that is defined as "starch having undergone a combination of treatments as described for monostarch phosphate[3] and for distarch phosphate[4]". The NI meets the purity criteria for E1413, including the limit of 0.4% residual phosphorus, and is produced from specific varieties of high amylose maize.

6. The chemical and physical specifications for the NI are given in the application dossier. The applicant has reported chemical and microbiological analysis of 5 batches of the NI[5], which were found to contain: dietary fibre (≥70%), starch (7-14%), water (10-14%), fat (0.8%), proteins (0.8%) and residual (covalently bound) phosphorus (≤ 0.4%).

7. The presence of lead, nitrates and a range of mycotoxins was not detected in any of the 20 batches of the NI produced in 2004, at the respective limits of detection of the methods used.

8. The applicant has indicated that the NI and its raw material will be monitored on a quarterly basis for pesticide residues, heavy metals, mycotoxins, nitrosamines and microbiological contaminants. Annex C shows the results obtained with such analyses on one batch of the NI produced in 2005. The applicant states that these results illustrate the typical levels of these compounds in the NI and all were found to be within the limits set out in the specification.

***Discussion**: The Committee was satisfied with the information provided by the applicant on the specification of the NI and accepted that the compositional data show that it is reliably produced within the defined specification.*

II. Effect of the production process applied to the novel food

Application dossier p.12-18, Annexes D and E

9. The starting material for the production of the NI is a starch slurry mixture derived from high amylose maize grains. The normal level of amylose in commercial sources of starches is 17-25%, with the rest being amylopectin. The maize grains are obtained from two proprietary maize hybrids specifically grown for the applicant. The applicant has indicated that new hybrids may be used in the future if they have improved agronomic characteristics. The supplied seeds are tested from their production stage to their final delivery into the plants to ensure the absence of genetically modified material, using the procedures described in Annex D. The maize grains contain high amylose starch granules which are not broken down at boiling temperature (154 to 171°C). This makes them less susceptible to be digested by amylase in the human small intestine and they are therefore an appropriate source of starch for the NI.

[3] i.e. esterified with ortho-phosphoric acid, or sodium or potassium ortho-phosphate or sodium tripolyphosphate.
[4] i.e. cross-linked with sodium trimetaphosphate or phosphorus oxychloride.
[5] The dossier mistakenly refers to 3 batches; the table on p.9 is mistakenly numbered IX.1-1 and has the wrong title.

10. **Process** - The high amylose maize grains are milled together using corn wet milling to obtain a high amylose starch slurry. This is then mixed with a re-slurry of high amylose starch in water to obtain the starting material for the production of the NI. A combination of chemical treatments to induce specific degrees of esterification and cross-linking is then applied to this unmodified starch material to reduce its digestibility and obtain the NI. As noted above, the production of the NI and its chemical characteristics meet the EU specification for the food additive E1413

11. The applicant has stated that any impurities resulting from the production process will be detected through microbiological and mycotoxin testing (see paragraphs 9 and 33).

12. Stability testing has not been carried out on the NI but the applicant has given a typical shelf-life of 720 days for PDP which coincides with the standard best before date for starch (24 months from the date of manufacture), set by the European Starch Industry in 1997. The applicant has not provided any data examining stability in the intended food matrices.

13. The production of the NI is in accordance with Hazard Analysis Critical Control Point (HACCP) procedures.

***Discussion**: The Committee noted that the production process of the NI is similar to that of the approved food additive phosphated distarch phosphate (E1413). Members accepted that there were appropriate controls in place on the production of the NI to ensure the safety of the final product.*

III. History of the organism used as a source of the novel food

Application dossier p.16-18

14. Two maize hybrids are currently used to produce the unmodified high amylose starch slurry, which is the source of the NI.

15. The applicant highlighted that traditional (unmodified) starches derived from maize are currently used for the production the food additive PDP (E1413). The applicant has not confirmed whether the hybrids of high amylose maize used for the production of the NI are the same as those used in the production of E1413.

***Discussion**: The Committee noted that there is a substantial history of consumption of maize, the source used to produce the NI.*

IX. Anticipated intake/extent of use of the novel food

Application dossier p.19-25, Annex F

16. The applicant is proposing to market the NI as a replacement for part of the digestible unmodified starch provided by food ingredients such as flour in low moisture food products. The applicant has not specified whether the introduction of the foods containing the NI will be restricted geographically.

17. The Committee highlighted a number of concerns arising from the estimated intake of the NI arising from the range of uses described in the application dossier.

Based on the original proposals, it was estimated that high level intake (97.5th centile) in adults would exceed 1 g/kg bw/day, which was the highest dose tested in the human tolerance study that was submitted as part of the toxicological data set (see section XII below). Intake in children, expressed on a body weight basis, would be still higher. The Committee therefore requested that the applicant review their proposed use categories and levels of incorporation. The applicant subsequently provided a refined list of proposed uses. The following table lists the revised levels of incorporation of the NI in different food categories and the corresponding levels of added phosphorus:

Proposed food uses and use levels for PDP and the corresponding levels of added phosphorus

Food Category	Proposed Food Uses	Maximum Use Level (%)	Added Phosphorus (1) (%)
Cereals and Cereal Products (including bakery products)	Batters and breading	15	0.06
	Biscuits (sweet)	15	0.06
	Cakes and Muffins	15	0.06
	Pizza Dough	15	0.06
	Breakfast / nutritional / energy bars	15	0.06
Crisps and Savoury Snacks	Savoury biscuits, crackers and non-extruded snacks	15	0.06
Pasta and noodles	Canned pasta	15	0.06
	Pasta contained in ready meals	15	0.06

(1) PDP contains 0.4% of residual (covalently bound) phosphorus

18. Based on these proposed use levels, the applicant has estimated the anticipated daily intake of the NI and its residual (bound) phosphorus for different population groups, using data from UK National Diet and Nutrition Surveys (NDNS). These surveys covered young children aged 1.5 to 4.5 (1992-93), young people aged 4 to 18 (1997) and adults aged 16 to 64 (2000-01). The applicant has provided separate estimates for the whole population group, including those not consuming any products in which the NI is proposed for use ("all-person intake") and for individuals who consume food products in which the use of the NI is under consideration ("all-users intake"). In practice, the two sets of figures are very similar as between 86% and 99% of each population group consume one or more of the food products in which the NI is proposed for use.

19. The applicant has estimated that the mean daily intake of the NI will vary 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 teenagers and high level daily intake will vary between 14.2 g/person (0.22 g/kg bw) for adult women to 25.3 g/person (0.53 g/kg bw) for male teenagers. On a body weight basis, the highest estimated intake is in young children (mean 0.38 g/kg bw/day, high level 1.09 g/kg bw/day). In practice, it is unlikely that these "worst case" intakes will be reached as it would necessitate the incorporation of the NI at the maximum level in all staple "starchy" foods. The applicant notes that

the current consumption of PDP from its use as a food additive, E1413, is less than 0.5 g/day (see paragraph 25 below).

20. The applicant also notes that the addition of the NI as partial replacement for unmodified starches will contribute to an increase in dietary fibre consumption which is currently estimated in the UK at 12 to 14 g/day.

21. The estimated mean daily intake of added phosphorus varies between 17.7 mg/person for adult women and 36 mg/person for male teenagers and the high level (97.5th percentile) daily intake will vary between 56 mg/person for adult women to 101 mg/person for male teenagers.

22. The applicant has not identified any population groups that might be at higher risk, for which a separate analysis would be required (see paragraph 40 below).The applicant has not included background sources of resistant starch, other modified starches or phosphorus in the intake assessment. The applicant has however mentioned that the Expert Group on Vitamins and Minerals (EVM) established a guidance level for the use of phosphorus in supplements at 250 mg/day (Application dossier, p 31, para. 3). The increase in phosphate consumption as a result of the consumption of the NI will be generally well within this guidance level. The applicant also pointed out that the NI would provide a less concentrated source of phosphate than food supplements and therefore its impact would be unlikely to be as high.

***Discussion**: The Committee noted that the estimated intake of the NI was within the range tolerated in clinical studies (1 g/kg bw/day), with the exception of high level intake in small children. While there is a degree of conservatism in the calculation of these intake estimates, the potential for high levels of intake by young children requires careful consideration (see section XI below).*

X. Information from previous human exposure to the novel food or its source

Application dossier p.26-27, Annexes H and I

23. The NI is derived from high amylose starch slurry. The applicant estimates that British adults consume 150g of unmodified starches per day, which represents 24% of their daily energy.

24. As mentioned in paragraph 4, the NI meets the specification for the food additive E1413, which is currently used as a freeze-thaw-stable thickener in a range of food products at a levels around 3%. The applicant has provided additional information showing the estimated intake of E1413 from these foods is up to 450 mg/day for a high level adult British, which is considerably lower than the intakes resulting from the proposes uses as a food ingredient (Annex I).

25. Although the NI is not proposed for use in baby foods, the applicant notes that, on the advice of the Scientific Committee on Food, EU legislation permits the use of up to 5% (50 g/kg) of various modified starches, including PDP, as technological additives in weaning foods for infants and young children. If used at this level, consumption of a 200g jar of baby food would result in the intake of 10 g of PDP. For a 10kg infant, this is equivalent to 1 g/kg bodyweight.

26. The applicant has highlighted that a modified resistant starch type 4 (RS4) containing 70 to 80% dietary fibre and derived from wheat, potatoes and high amylose maize is currently marketed as an ingredient for use in low moisture food products, outside the EU. The applicant has also listed examples of "low carb" food products (pitta bread, cookies, pancake mix, pasta, rolls, muffins, breads, pretzels) containing modified resistant starch, which have been sold in the United States and Canada, since 2003 (Annex H). The majority of these products contain modified starch derived from wheat (pasta, rolls, breads, pretzels, pitta breads). The applicant has also stated that RS4 starches have been used in Australia as food ingredients in products with 2.9% to 5.6% dietary fibre, since 1994. They have also been used in Japan since 1995 in food products with 2% to 6% dietary fibre (Application dossier, p.17, para. 3). In all cases, the RS4 ingredient was not produced by the applicant, who is therefore unlikely to be aware of any record of adverse reactions attributed to the consumption of resistant starch by individuals or sub-groups of the population. Also, there is no information on which to base a detailed comparison between the composition of the applicant's product and these existing ingredients.

27. The applicant has referred to various scientific reports (JECFA (1974d), IOM (1997), EVM (2003) and COT (2004b)) and has concluded that phosphorus derived from the NI will not be toxic for human consumption at the proposed level of incorporation.

***Discussion**: The Committee accepted that there was evidence that the NI had been consumed as a food additive in the EU, and that other types of chemically modified starch were used as food ingredients outside the EU.*

XI. Nutritional information on the novel food

Application dossier p.28-31, Annex G

28. The NI is intended for use in a range of foods where it would replace part of the digestible unmodified starch provided by ingredients such as flour. A 1963 study in rats showed that the NI was nutritionally equivalent to raw unmodified starch (Application dossier, p.29 para. 1). However, this finding is of limited relevance as unmodified starches are rarely consumed in an uncooked form and are almost fully digested in foods after cooking.

29. The applicant proposes that the principal use of the NI would be as a source of dietary fibre. The applicant has explained that due its high amylose content (>70%) the NI will be able to resist digestion and will therefore retain its physical structure as it passes through the GI tract, whilst unmodified starch is rapidly digested. The applicant has provided data showing that only 8% of the uncooked NI is digested when submitted to "Englyst Digestion" (controlled enzymic hydrolysis with pancreatic amylase and amyloglucosidase at 37°C). This rises to 20% when the NI is cooked. The equivalent figures for unmodified maize starch are 85% (uncooked) and 95% (cooked). The applicant concludes that the NI is able to withstand cooking and commercial food processing techniques without losing its dietary fibre content.

30. In response to questions from the Committee concerning the effect of the NI in diabetics, the applicant commissioned an *in vivo* study which demonstrated that

the presence of the NI at levels up to 27% in biscuits did not alter the glycaemic response.

31. The applicant also commissioned an *in vitro* fermentability study, comparing the NI with a number of resistant starches in a human gut model. This study was designed to provide additional information to the Committee on potential gastrointestinal intolerance to the NI. The results showed that the starches were all fermented in a similar manner, although there were minor differences in bacterial numbers at the end of the fermentation.

***Discussion**:*

A recent review article (Nugent, 2005)[6] investigated the health properties attributed to the consumption of resistant starch. This review summarises reports in the literature that indicate that the regular consumption of high levels (>30 g/day) of resistant starch may give rise to intolerance. The applicant suggests that this review points to an absence of available data, rather than specific safety concerns and that the unpublished study by Pieters et al (1971) (see paragraph 37(g) below) offers reassurance that there is no intolerance of resistant starch when consumed in relatively high quantities.

Members agreed that the human study by Pieters et al., (1971) provided reassurance that the consumption of up to 60g of the NI per day would not give rise to GI intolerance in healthy adults, but questioned whether this conclusion could be extended 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.

Members noted that there are ongoing discussions at international level regarding the definition of 'fibre' independent of this application. The current advice from the Food Standards Agency (FSA) is that the quantification of dietary fibre (for nutrition labelling purposes) should be carried out using AOAC methodology, a method that includes resistant starch in the definition of fibre. However, the FSA currently advises that, for the purpose of health claims, the term "fibre" means non starch polysaccharides and excludes chemically modified resistant starch.

In practical terms 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 have to comply with the relevant national rules concerning nutrition and health claims.

[6] Nugent, A.P. 2005. Health properties of resistant starch. Nutr Bull BNF 30:27-54.

XII. Microbiological information on the novel food

Application dossier p.32, annex A

32. The production of the NI does not involve the use of microorganisms and the manufacturing process is controlled through HACCP procedures (see paragraph 13 above).

33. The microbiological purity of the NI has been defined in its specification, which sets limits for a number of undesirable organisms. The applicant provided a summary of the analytical results obtained on a large number of batches of the base high amylose starch produced in 2004 (prior to chemical processing) for all the microbiological parameters listed in the specification of the NI. These results are all within the specified limits. Similar data have been provided for one batch of the final product.

***Discussion**: Members accepted that the production process did not give cause for microbiological concern, and that the compliance with the specification would require the NI to be demonstrably free from pathogenic micro-organisms.*

XIII. Toxicological information on the novel food

Application dossier p.33-55, Appendix 3

34. PDP is one of a group of chemically modified starches authorised as food additives in the EU. The former EC Scientific Committee for Food advised on the safety of modified starches[7] and concluded that PDP could be regarded as fully acceptable and commented "because these modified starches also contribute to the energy balance of the diet, the Committee considered it unnecessary to establish individual ADIs provided technological usage remained at present-day levels". The SCF did not publish details of the use levels but, as indicated above, the estimated intake of the NI is up to 50 times higher than the estimated intake resulting from current food additive uses in the UK.

35. The applicant has reviewed a series of toxicological studies carried out on PDP and other modified starches[8] and on related phosphorus-containing compounds intended for use as food additives.

36. **Modified starches**. A summary of the toxicological studies on modified starches reviewed by the applicant is provided in table XIII.2.9-1 of the dossier.

    a) Absorption, Distribution, Metabolism and Excretion (ADME)

    When absorbed, a small amount of the NI (8%) is digested to glucose in the small intestine wall and then absorbed. The rest of the NI (92%) is, like other complex carbohydrates that survive passage to the lower bowel, fermented by bacteria of the large intestine producing short chain fatty acids (SCFA) such as acetate, propionate and butyrate and gases such as carbon dioxide, hydrogen

[7] The SCF considered the safety of modified starches in 1976, and 1981. In 1997 the SCF reiterated their earlier position on the safety of modified starches in a report concerning the use of certain food additives in infant formulae, follow-on foods ,and weaning foods.

[8] The applicant notes that many of these studies, most of which date from the 1960s and 1970s, were carried out on products not derived from maize starch and not using the same reaction processes as the NI.

and methane. These SCFA and a small amount of the gases are then absorbed through the large intestine walls. A small amount of the unfermented NI is excreted in the faeces along with the majority of the gases created during the NI fermentation in the large intestine.

b) Acute studies

No acute oral toxicity studies are available for PDP. In two acute studies on a related type of modified starch, distarch phosphate (Hodge, 1954, 1956), no histological abnormalities were reported in the livers and kidneys of the animals tested (mice, rats, guinea pigs, rabbits and cats). These tests gave high LD-50 values of between 7 and 35 g/kg bw depending on the species.

In a 10-day nutritional assay (Khon and Kay, 1963a), no abnormal behavioural reactions and no difference in weight gains were observed in rats fed with PDP compared with distarch phosphate.

c) Subchronic studies

The applicant has referred to seven subchronic studies carried out on PDP between 1963 and 1973. The results obtained in these studies are summarised below:

Species	**Duration**	**Dose level (% of diet or g/kg bw)**	**Principal findings**	**References**
1. Miniature Pigs	25 days	5.6% PDP or distarch phosphate 5.4% unmodified starch (controls)	- Normal growth - Composition of blood, serum, organ weights, carcass and liver were comparable between treated and control animals	Anderson et al, 1973
2. Rats	7 days + 3days	0, 25 or 50% maize modified starch for 7 days additional 4% cellulose for 3 more days	- Slightly reduced body weight in dose related manner - increase of faecal dry matter, no diarrhoea - increase of caecal size, but without histological abnormalities - no adverse effect from cellulose	De Groot and Spanjers, 1970
3. Rats	8 weeks	0, 25 or 50% maize modified starch containing 0.3% phosphate	- no effect on body weight or faeces production - no diarrhoea - at 50% test level: high faecal water content - at 25% test level: slight increase in caecal weight in male rats	De Groot and Spanjers, 1970 (Follow up study)

Species	Duration	Dose level (% of diet or g/kg bw)	Principal findings	References
4. Rats	60 days	10% rising to 35% PDP from maize	- weight gain constantly reduced in female rats - natural deaths (4 treated and 2 controls) unrelated to treatment - lower kidney weights for male and female and lower liver weights for male = unrelated to treatment - no histopathological alterations on altered organ weights	Khon et al, 1964
5. Rats	90 days	0.2,1 or 5 % unmodified starch, control phosphate starch or PDP	- no adverse effects on body weight gain, food consumption, food utilisation, survival, behavioural patterns, haematological and urinalysis results, gross and microscopic pathological endpoints, organ weights and ratios related to test substance - the few deaths were not related to treatment	Khon et al, 1964
6. Rats	90 days	0, 5, 15, 45 % of 2 types of distarch phosphate (0.085% esterified and 0.128% esterified phosphate)	- no abnormalities on general appearance, behaviour, mortality, food consumption, haematology, serum, urinalysis, caecal weights, stool consistency (no diarrhoea), gross and histopathology	Til et al, 1970
7. Dogs	90 days	50, 250, 1,250 mg PDP/kg body weight/day	- no adverse effect reported on body and organ weights, food consumption, mortality, haematology, urinalysis, liver function, gross and microscopic pathologic findings - 1 death – not treatment related	Cervenka and Kay, 1963

d) Chronic studies

The applicant referred to a 104-week chronic study on rats fed PDP at 0, 5, 10 and 30% in the diet (Knecht-Van Eekelen *et al.,* 1971). The main observations were that the spleen weights of male rats significantly decreased and the spleen and kidney weights of female rats significantly increased, when consuming the highest dose of test material. It was reported that these differences in organ weight were not associated with any gross pathological findings. No effect on caecal weights was observed and no carcinogenic effect was found. The test and control animals showed some randomly distributed non-neoplastic lesions, except for a kidney abnormality with hyperplasia of the renal papillary and pelvic epithelium with calcified patches of underlying tissues.

The report of this study indicates that test animals fed the 30% diet showed a slightly higher incidence of nephrocalcinosis and hyperplasia of the pelvic epithelium. Reports of pelvic nephrocalcinosis associated with consumption of PDP and other modified starches were considered in detail by the SCF in its 1981 opinion (paragraph 35, above), which concluded that these findings were peculiar for the rat and had little relevance for the safety assessment of modified starches for man.

e) Developmental and reproductive studies

The applicant presented a 3-generation reproduction study on rats fed 10% of various modified starches, including PDP derived from maize. No adverse effect were observed on the appearance, behaviour, body weights, fertility, litter size, resorption quotient, pup weights and mortality. The caecal and organ weights of most of the generations were not affected by modified starch consumption, except for F_1 parent male (increased filled caecum weight) and for F_3b females (increased spleen weight). No pathological changes were observed. It was concluded that none of these modified starches was associated with reproductive effects.

f) Mutagenicity and genotoxicity studies

No data are currently available on mutagenicity or genotoxicity of unmodified or modified starches.

Although not relevant for the safety assessment of the NI, the applicant has referred to a study from Chambers and Grand (1937, 1939) which indicated that sarcomas, melanoma and carcinomas completely regressed in rats and mice after being injected with starch granules.

g) Human studies

The applicant has referred to a summary report of unpublished human digestibility studies using one unmodified potato starch and five chemically modified starches, including PDP from maize (Pieters *et al*, 1971[9]). Ten volunteers completed this 6-week-trial in which they consumed 60g/day of one particular starch on 4 consecutive days each week. The summary report of this study indicates that no adverse effects were reported, the frequency of faeces, faecal water and lactic acid were not affected and the modified starches were well tolerated.

37. **Phosphorus-containing compounds**. The safety of added phosphate in food has been evaluated in the context of food additives by JECFA in 1982, which advised that the Maximum Tolerable Daily Intake of phosphorus from all sources was 70 mg per kg bodyweight. This level of intake would be equivalent to 1050 g of the NI per day for a 60kg adult, or 350 g/day for a 20kg child, assuming this was the only source of phosphorus in the diet.

38. In 2003, the UK Expert Group on Vitamins and Minerals advised on the levels of various minerals in food supplements and established a guidance limit of 250 mg of phosphorus per day, taking into account the background intake of phosphorus from food (mean intake = 1260 mg/day, 97.5th centile = 2110 mg/day, for British

[9] Pieters, J.J.L.; van Staveren, W.A.; Brinkhuis, B.G.A.M. 1971. Unpublished Report No. R3433 by Central Instituut voor Voedingsonderzoek. (Provided as part of the application dossier)

adults). The UK Committee on Toxicity concluded in 2004 that there are insufficient data to substantiate earlier concerns that high intake of phosphate might be associated with a bone-weakening effect.

39. Members considered a comment from a dietician who works with patients who have serious renal disease. This comment noted that the level of phosphorus in the NI (which equates to 101mg of phosphorus/day in high level teenage males, equivalent to 295mg phosphate) may have an adverse effect in individuals with serious renal disease who have to control their phosphorus consumption. The applicant's preliminary response to this concern noted that the upper intakes estimates of phosphorus were conservative overestimates and it would be unlikely that dialysis patients would achieve this level of intake of phosphorus from the novel ingredient. However the applicant subsequently highlighted that dietician's concerns were based on European guidelines[10] which had been incorrectly quoted. The guidelines referred to "phosphorus" rather than "phosphate" which, following application of the appropriate conversion factor indicated that the recommended intake of phosphate was in the range 3100 – 4300 mg day.

a) Absorption, Distribution, Metabolism and Excretion (ADME)

A study in rats indicates that the distribution and excretion of radiolabelled phosphorus (32P) does not differ when administered orally as a modified starch (monostarch phosphate) or in mineral form (orthophosphate or pyrophosphate). The applicant has indicated that phosphorus is absorbed through the small intestine walls to the human bloodstream. The phosphorus appears in blood as a constituent of phospholipids or as inorganic phosphate and the level in blood is regulated by parathyroid hormone (PTH). The kidney plays a major role in regulating the retention and excretion of plasma phosphorus. The majority (80%) of phosphorus in the body is stored in the skeleton, whilst the remainder stays in soft tissues and extracellular fluid. Phosphorus is excreted in the urine.

b) Acute studies

The applicant has stated that the results obtained for nine acute studies on various animal species using phosphorus containing compounds which were carried out in 1950, 1957 and 1975 (Application dossier, p.42, Table XIII.3.2-1) indicate that phosphorus is not particularly toxic. These studies produced LD-50 values of between 1,300 and 4,600 mg/kg bw.

c) Subchronic studies

The applicant has provided a list of ten sub-chronic studies have been carried out on phosphorus-containing compounds (Application dossier, p.43-45, Table XIII.3.3-1). Intakes in these studies ranged from 0.1 g/kg bw/day to 5g/kg bw/day. In higher dose groups, kidney damage or increased kidney weights were commonly found. Decreased weights and pelvic nephrocalcinosis were also seen but these doses are well in excess of those anticipated in the human diet.

[10] Guidelines available at : http://www.edtnaerca.org/pages/education/jrc/2003/1.php

d) Chronic studies

Eight chronic oral studies carried out on phosphorus containing compounds, listed in Table XIII.3.4-1 (Application dossier, p.44). These studies demonstrated decreased growth rates, pelvic nephrocalcinosis, increased rate of bone turnover, increased parathyroid hormone levels and kidney damage. (Range of doses from 0.05 – 5% of diet, dependent on the chemical source of phosphorus tested)

e) Developmental and reproductive studies

Details of seven developmental and reproductive studies are presented in Table XIII.3.5-1 (Application dossier, p.46-47). These studies showed no toxicological effects at levels of 128 to 465 mg/kg bw in various species. These doses were administered orally on days 6-15 of gestation.

f) Mutagenicity and genotoxicity studies

The applicant has referred to a total of five *in vitro* and *in vivo* mutagenicity / genotoxicity tests on phosphorus containing compounds (Application dossier, p.49 Table XIII.3.6-1). No positive results were found in any of these studies.

g) Human studies

The applicant has provided nine human studies involving the oral administration of phosphate. The administered doses ranged from 750 mg/day for 7 days to 9.9 g/day for 2 years. Many of these studies, especially those with a high dose, were carried out on patients with osteoporosis or idiopathic hypercalcuria (kidney stone formation) and therefore it is possible that these people have calcium and phosphate imbalances that may make them more tolerant of high doses of phosphates. Clinical blood chemistry and urinalysis were carried out in most of the studies and any subjective side effects reported by the subjects were noted. In one study (Bernstein and Newton, 1966), the rate of recurrence of renal calculi was reported to be reduced by the administration of sodium phosphate. The main side effect of phosphate consumption was the occurrence of diarrhoea in many subjects.

Studies carried out on healthy subjects with doses of 3g/day of phosphorus supplemented on top of a standard diet containing 1.7g phosphorus/day, appeared to show similar incidences of diarrhoea and few effects on bone resorption or bone turnover (Grimm et al 2001).

Discussion: *The Committee accepted that the toxicological data provided by the applicant provided adequate reassurance that the NI was not toxic. The human study by Pieters et al., (1971) provided reassurance that the proposed uses of the NI would not give rise to GI intolerance in healthy adults but the Committee questioned whether these results were applicable to high level consumption in young children (See section XI above).*

Concerning the public comment about phosphorus levels and patients undergoing renal dialysis, the Committee accepted that reference to the correct figures in the European guidelines did not give any cause for concern and there was no requirement for special labelling to alert such individuals to the phosphorous content of the NI.

Allergenicity and labelling

Application dossier p.30 and p.55

40. The applicant states that the NI has no allergenic potential although it has not provided any data to support this statement. The product specification allows up to 0.8% protein, which can be assumed to be derived from the starting material, maize starch. However, maize is not a common allergenic food and is only a rare cause of occupational allergy. Maize-derived ingredients are not covered by EU rules on allergy labelling, unlike those derived from e.g. wheat.

41. The applicant intends to label the NI as "gluten-free", There is no specific EU legislation that permits the use of "gluten free" labelling on foods. The applicant intends to label the NI as "gluten-free", referring to the Codex Alimentarius definition of the term. This definition, based on a draft standard[11], states that a maximum of 20ppm of gluten is permitted, allowing for the presence of low levels of gluten via adventitious contamination during the production process.

42. The applicant proposed that food manufacturers intending to use the NI would use the name "resistant modified (maize) starch" to describe the product. In response to the Committee's concerns about intolerance, the applicant initially proposed that any food that would be directly marketed at young children, and would provide more than 15g of the NI in one portion, should carry a warning to the effect that the product "may cause increased laxation in small children". However following concerns from the Committee that young children could also eat products not specifically marketed at their age group, the applicant subsequently indicated that labelling would apply to all products containing greater than 10% of the NI.

Discussion

The Committee accepted the applicant's view that, as an ingredient obtained from maize, it is unlikely that the product presented any greater allergy risk to consumers than the source material

The Committee noted the applicant's proposal to use of the term "gluten-free" on the final food as being subject to the production conditions and relevant tests on the final food in which the NI is being used. Members also noted that, in practice many of the foods that would contain the NI will also contain wheat flour, in which case the presence or absence of gluten in the NI is of little or no relevance.

The Committee noted that the use of a name such as "resistant modified (maize) starch" would be appropriate for the NI and would be in line with EU food labelling regulations The Committee did not accept the applicant's proposal that use of an advisory statement should be restricted to products that were solely marketed at children and contained more than 15g of the NI per portion. The Committee noted that the applicant had supplied data showing that the NI would not give rise to intolerance at these levels, but these were adult studies, and the applicant had not provided a justification that the results were equally applicable to children who have a less developed gut flora and are more sensitive to poorly absorbed ingredients (See XI Discussion above). In the absence of evidence of the doses that might be tolerated

[11] See Draft Revised Standard for Gluten Free Foods : Alinorm 07/30/26 November 2006

by children, the Committee considered that the applicant's revised proposal for labelling of products containing greater than 10% of the NI was also unsatisfactory.

Given that many of the food categories would be attractive to children, the Committee noted that it should be possible for the applicant to gain ethical approval to carry out a limited and non-invasive study to determine the level at which consumption of the NI by children gives rise to intolerance. Until these data were available it was prudent to require an advisory statement on all foods containing the NI. This statement should clearly indicate that consumption of the NI may cause laxative effects in small children. The Committee also suggested that the applicant consider the provision of additional 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 manufacture's careline.

Overall discussion

The Committee noted that the NI was an authorised food additive and, on this basis, accepted that the it was unlikely to give rise to any toxicological concerns. However, Members expressed concern that use as an additive was at levels significantly lower than that proposed in this application. The Committee was concerned that the data provided to demonstrate that the NI would not give rise to gastrointestinal intolerance at the proposed levels of consumption applied solely to adults, but that a number of the proposed food categories would clearly be consumed also by children.

Whilst the Committee accepted that the dietary intake estimates provided an overestimate of the likely levels of consumption, they noted that as a chemically modified starch, the NI was unlikely to be fermented by gut bacteria in the same manner other resistant starches. By comparison with other forms of resistant starch, it seems likely that a higher proportion of RS4 (chemically modified) starch would reach the large intestine, as a result of its lower digestibility, and it is also possible that its influence on bacterial fermentation would extend further along the colon. This makes it difficult to predict the consequences of consumption with confidence in all groups of consumers. In view of this, and mindful that unexplained digestive disturbances in children are an increasingly common cause for concern among parents and physicians, the Committee concluded that all food containing the NI should carry an accompanying advisory statement for children.

CONCLUSION

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by the applicant, National Starch, that the range of uses for the novel ingredient (Phosphated Distarch Phosphate) is acceptable subject to the labelling requirement described above.

April 2009