

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

PHOSPHATED DISTARCH PHOSPHATE

ISSUE

An application has been submitted to the UK Competent Authority for authorisation of phosphated distarch phosphate, a type of modified starch, as a novel food ingredient. The Committee is asked to advise whether the available data provide an adequate basis for a safety assessment, and if it recommends authorisation of this novel ingredient.

Background

1. An application has been submitted by National Starch for the authorisation of a phosphated distarch phosphate as a novel food ingredient in a range of low moisture food products. The UK Competent Authority accepted the application on 23 August 2005. In accordance with Article 6(3) of Regulation (EC) No 258/97, the UK has 3 months to prepare an initial assessment report on the above application. The European Commission will then circulate this initial assessment to the Competent Authorities in the other Member States for comment.
2. The application dossier, including nine annexes, is attached as Appendix 1. A number of sections in Appendix 1 contain commercially sensitive details of the production process. In addition, Annex E is confidential in its entirety.
3. Phosphated distarch phosphate (PDP) is a chemically modified resistant starch derived from high amylose maize starch. Resistant starches (RS) are defined as “the sum of starch and products of starch degradation not absorbed in the small intestine of healthy individuals”. They are divided into four types (Appendix 1, p.2, para. 5). PDP is classified as a resistant starch type 4 (RS4) because it is obtained by cross-linking with chemicals. This novel ingredient contains a minimum of 70% dietary fibre and not more than 0.4% residual phosphorus which is covalently bound to the starch molecules.
4. The same modified starch is currently listed as an approved food additive (E1413)¹ for use at *quantum satis*² (Appendix 1, p.3, para. 3). This approval applies only to the use of PDP for technological purposes. The use of PDP for other purposes is a new development and is therefore subject to the Novel Food

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

Regulation (EC) 258/97. E1413 is currently used in products such as soups, sauces, gravies and fruit fillings as a freeze-thaw-stable thickener.

5. 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). The requirements for a submission for this class are as follows:

I	Specification of the NF	X	<i>VIII</i>	<i>Ability to survive in and colonise the human gut</i>	-
II	Effect of the production process applied to the NF	X	IX	Anticipated intake/extent of use of the NF	X
III	History of the organism used as the source of the NF	X	X	Information from previous human exposure to the NF or its source	X
<i>IV</i>	<i>Effect of the genetic modification on the properties of the host organism</i>	-	XI	Nutritional information on the NF	X
<i>V</i>	<i>Genetic stability of the GMO</i>	-	XII	Microbiological information on the NF	X
<i>VI</i>	<i>Specificity of expression of novel genetic material</i>	-	XIII	Toxicological information on the NF	X
<i>VII</i>	<i>Transfer of genetic material from GM microorganisms</i>	-			

The information presented in the dossier is structured accordingly and is considered below under these schemes.

6. The Committee will wish to note that the application dossier was published on the Agency's website for a 21-day public consultation, on 31 August 2005. Any comments received will be tabled at the meeting.

I. Specification of the novel ingredient (NI)

Appendix 1 p 5-10, Annexes A, B and C

7. The novel ingredient (NI) is a variety of phosphated distarch phosphate (PDP) and is referred to in the application dossier as "RS4-fibre*". PDP is a chemically modified starch obtained by a combination of chemical treatments that results 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 used for its thickening properties and is defined as "starch having undergone a combination of treatments as described for monostarch phosphate³ and for distarch phosphate⁴". The NI meets the purity criteria for

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.

E1413, including the limit of 0.4% residual phosphate, and is produced from specific varieties of high amylose maize under conditions that optimise its nutritional qualities.

8. The chemical and physical specifications for the NI are given in Table I.8.1-1, along with the method of analysis used (Appendix 1, p.8). The applicant has reported chemical and microbiological analysis of 5 batches of the NI (Appendix 1, p9⁵), which were found to contain: dietary fibre ($\geq 70\%$), starch (7-14%), water (10-14%), fat (0.8%), proteins (0.8%) and residual phosphorus ($\leq 0.4\%$). Members should note that the level of residual phosphorus represents the level of phosphorus covalently bound to the starch molecules (Appendix 1, p10, para. 1).
9. 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 (Appendix 1, Annex B).
10. 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 of Appendix 1 provides 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 found in the NI for these compounds and these were to be within those described in the specification. The Secretariat noted that this batch number did not correspond with any of the 20 batches used to test for lead, nutrition and mycotoxins. The applicant has advised that this is because these are examples of their quarterly standard surveillance testing and the tests are therefore not done for every product but are representative for a finished product typical of the site of manufacture.
11. The applicant is intending to market the NI using one of the following names: RS4-fibre modified starch or RS4 PDP or Novelose® 480H.

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

Appendix 1 p.12-18 [some information is CONFIDENTIAL], Annex D and Annex E [CONFIDENTIAL]

12. 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 proprietary maize hybrids specifically grown for the applicant. The applicant has specified 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. Annex D of Appendix 1 gives details of the procedures used by the applicant for this purpose. 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.

⁵ The dossier mistakenly refers to 3 batches; the table on p.9 is mistakenly numbered IX.1-1 and has the wrong title.

13. **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 with 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 (Appendix 1, p.2, para. 1). A diagram of the manufacturing process for the NI has been provided (Appendix 1, p.14, fig. II.3.1). Most of the information given on this diagram is confidential.
14. The applicant has stated that any impurities resulting from the production process will be detected through microbiological and mycotoxin testings (see paragraphs 10 and 35).
15. 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 European Starch Industry standard best before date of 24 months, set in 1997. The applicant has not provided any data examining stability in the intended food matrices.
16. The production of the NI is in accordance with Hazard Analysis Critical Control Point (HACCP) procedures (Appendix 1, Annex E [CONFIDENTIAL]).

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

Appendix 1 p.16-18

17. Two natural hybrids of regular maize are currently used to produce the unmodified high amylose starch slurry, which is the source of the NI. The precise characterisation of the maize used by the applicant has been kept confidential for commercial reasons. The applicant has not provided any information to show that the maize hybrids used have any detrimental effect on human health.
18. The applicant has 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.

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

Appendix 1 p.19-25, Annex F

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

20. The table below provides a summary of the levels of incorporation of the NI in the proposed food categories and the corresponding “use levels” of phosphorus:

Summary of the proposed food uses and use levels for PDP and the corresponding use levels for phosphorus			
Food Category	Proposed Food-Uses	PDP	Added Phosphorus (1)
		Maximum Use-Level (%)	(%)
Cereals and Cereal Products (including bakery products)	Biscuits (sweet)	12	0.05
	Crackers	10	0.04
	Cakes and Muffins	20	0.08
	Pasta	20	0.08
	Pizza Dough	20	0.08
	Ready-to-Eat Breakfast Cereals	20	0.08
	Tortillas	20	0.08
	Bread products made with white flour	20	0.08
Crisps and Savoury Snacks	Pretzels	35	0.14

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

21. Based on these proposed use levels, the applicant has used data from the following UK National Diet and Nutrition Surveys (NDNS) of 1992-93 for children aged 1.5 to 4.5, 1997 for young people aged 4 to 18 and 2000-01 for adults aged 16 to 64 to estimate the anticipated daily intake of the NI and its residual (bound) phosphorus for the different population groups, in the EU (Appendix 1, Annex F). The applicant has provided separate estimates for the whole population, 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 more than 97% of the population consume one or more of the food products in which the NI is proposed for use. The estimated mean and maximum (97.5 percentile) daily intake of the NI vary between the different surveyed population groups. A summary of the estimated intake values is provided in tables IX.2.1-1 and IX.2.1-3, respectively, shown below:

Table IX.2.1-1 Summary of the Estimated Daily Intake of PDP from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)											
Population Group	Age Group (Years)	% User	Actual number of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (g)	Percentile (g)			Mean (g)	Percentile (g)		
					90	95	97.5		90	95	97.5
Children	1½ - 4½	98.6	1625	14.4	24.2	27.7	31.6	14.5	24.2	27.7	31.6
Young People	4-10	99.6	834	26.1	39.4	46.0	49.7	26.2	39.6	46.0	49.9
Female Teenager	11-18	97.8	436	26.0	40.7	46.5	54.2	26.1	40.7	46.6	54.2
Male Teenager	11-18	99.5	414	34.5	55.1	59.5	69.3	34.5	55.1	59.5	69.3
Female Adults	16-64	93.2	893	22.0	36.6	42.6	49.7	22.3	37.0	42.8	49.7
Male Adults	16-64	94.3	722	31.9	54.7	62.8	71.6	32.4	55.3	63.4	72.2

Table IX.2.1-3 Summary of the Estimated Daily Intake of Phosphorus from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)											
Population Group	Age Group (Years)	% User	Actual Number of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (mg)	Percentile (mg)			Mean (mg)	Percentile (mg)		
					90	95	97.5		90	95	97.5
Children	1½ - 4½	98.6	1625	57.8	96.7	110.7	126.4	58.0	96.7	110.7	126.4
Young People	4-10	99.6	834	104.4	157.6	184.2	198.7	104.6	158.5	184.2	199.5
Female Teenager	11-18	97.8	436	104.0	162.7	186.1	216.9	104.4	163.0	186.5	216.9
Male Teenager	11-18	99.5	414	138.0	220.2	237.8	277.2	138.0	220.2	237.8	277.2
Female Adults	16-64	93.2	893	88.1	146.2	170.4	198.7	89.3	148.0	171.2	198.7
Male Adults	16-64	94.3	722	127.4	218.9	251.4	286.3	129.5	221.1	253.7	288.7

22. The applicant has estimated that the mean daily intake of the NI will vary between 14.5g/person for children to 34.5g/person⁶ for male teenagers and the maximum daily intake will vary between 31.6g/person for children to 72.2g/person for male adults. The applicant has explained that the highest level exposure to the NI, which is reached by male adults, will be equivalent to a daily consumption of 60g dietary fibre. 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 (as E1413) is less than 0.5g/day (see paragraph 28 below).

23. 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 14g/day. The Secretariat wishes to highlight to members a recent review article referenced by the applicant that investigates health properties attributed to the consumption of resistant starch. This review by Nugent (2005) attached at Appendix 2 summarises reports in the literature (also in appendix 2) indicating that high levels (>30g/day) of resistant starch consumed on a regular basis may give rise to intolerance (p.47, last paragraph). The applicant suggests that this review points to an absence of available data, rather than specific safety concerns and that the study by Pieters *et al* (1971) [See below, para. 37(g)] offers reassurance that there is no intolerance of resistant starch when consumed at relatively high quantities.

⁶ Not 32.4g/person as stated on p.23 of the dossier

24. In terms of residual phosphorus present in the NI, the applicant has concluded that the mean daily intake of added phosphorus will vary between 58 mg/person for children to 138 mg/person⁷ for male teenagers and the maximum (97.5th percentile) daily intake will vary between 126.4 mg/person for children to 288.7 mg/person for male adults.
25. The applicant has highlighted that estimated daily intakes for the NI and its residual phosphorus were found to be lower in females than in males. The applicant has not identified any population groups that might be at higher risk, for which a separate analysis would be required, according to the SCF guidelines (see paragraph 40).
26. Members should note that 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 phosphate in supplements at 250 mg/day (Appendix 1, p 31, para. 3). The increase in phosphate consumption as a result of the consumption of the NI via the proposed food uses will be generally equivalent to this guidance level. They were also of the view 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.

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

Appendix 1 p.26-27, Annexes H and I

27. The NI is derived from high amylose starch slurry. The applicant has stated that British adults are consuming 150g of unmodified starches per day and this represents 24% of their daily energy.
28. 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 food products such as frozen gravies, frozen savoury sauces, frozen white sauces, frozen fruit fillings, prepared soups, dry soup mixes and condensed soups, at a levels around 3% (Appendix 1, p.2). 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, considerably lower than the intakes resulting from the proposed uses as a food ingredient (Appendix 1, Annex I).
29. Although the applicant does not propose the use of the NI in baby foods, the applicant notes that, on the advice of the Scientific Committee on Food, EU legislation permits the use of up to 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 (current food additive uses of PDP are described above in paragraph 28).
30. The applicant has highlighted that a modified resistant starch type 4 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

⁷ Not 129.5 mg/person as stated on p.24 of the dossier

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 (Appendix 1, Annex H). The majority of these products contains modified starch derived from wheat (pasta, rolls, breads, pretzels, pitta breads). The applicant has also stated that resistant starches of type 4 (RS4) 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 (Appendix 1, p.17, para. 3). In all cases, the ingredient used was not produced by the applicant who is therefore unlikely to be aware of any record of adverse reaction attributed to the consumption of resistant starch by individuals or sub-groups of the population. There is however no information on which to base a detailed comparison between the composition of the applicant’s product and these existing ingredients. The applicant has referred to different 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.

XI. Nutritional information on the novel food

Appendix 1 p.28-31, Annex G

31. The NI will replace part of the digestible unmodified starch provided by food ingredient such as flour in foods. A 1963 study in rats showed that the NI was nutritionally equivalent to uncooked unmodified starch (Appendix 1, p.29 para. 1). The Secretariat notes that whilst equivalence with uncooked starches may be established, these products are rarely consumed in an uncooked form and unmodified starches are fully digested in final products after cooking.
32. The principal purpose of the NI is 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 a graph showing that 8% of uncooked and 20% of cooked NI are digested when submitted to “Englyst Digestion” (controlled enzymic hydrolysis with pancreatic amylase and amyloglucosidase at 37°C), whilst 85% of uncooked and 95% of cooked unmodified maize starch are digested (Appendix 1, fig. XI.1-1). The applicant is of the opinion that this highlights that the NI is able to withstand cooking and commercial food processing techniques without losing its dietary fibre content.

XII. Microbiological information on the novel food

Appendix 1 p.32, annex A

33. The production of the NI does not involve the use of microorganisms and the manufacturing process is controlled through HACCP procedures (see paragraph 16 above).
34. The microbiological purity of the NI has been defined in its specification (Appendix 1, p.8, table I.8.1-1) which sets limits for a number of undesirable organisms. A summary of the analytical results obtained on a large number of batches of the base high amylose starch produced in 2004 (prior to any chemical processing) for

all the microbiological parameters listed in the specification of the NI is provided in Annex A of Appendix 1. The applicant has stated that these are all within the specified limits. Similar data have been provided for one batch of the final product (see paragraph 10).

XIII. Toxicological information on the novel food

Appendix 1 p.33-55, Appendix 3

35. 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 in 1976 and 1981. In its latter opinion (Appendix 3), the SCF 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 in 1981 but, as indicated above, the estimated intake of the NI is about two orders of magnitude higher than the estimated intake resulting from current food additive uses in the UK.
36. The applicant has evaluated the toxicological risks of the NI by reviewing a series of toxicological studies carried out on modified starches including PDP and related phosphorus-containing compounds intended for use as food additives. Reports of these studies, most of which date from the 1960s and 1970s, are available from the Secretariat.
37. **Modified starches.** A summary of the toxicological studies on modified starches reviewed by the applicant is provided in table XIII.2.9-1 (Appendix 1, p.40). Members should note that, as stated by the applicant, not all the tested starches were derived from maize starch or produced using the same reaction process as the NI.

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

The applicant refers to *in vitro* digestibility study on starches pre-cooked by drum drying which indicates that the digestibility of PDP seems lower compared to unmodified starch. But *in vivo* study shows that the digestibility of PDP is similar compared to unmodified starch. This study does not specify whether the unmodified starch is cooked. The applicant reiterates that the NI is more resistant to digestion than unmodified maize starch, due to its high amylose content (see paragraph 32 above). 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 as mineral sources (orthophosphate or pyrophosphate).

The applicant has provided a diagram illustrating the metabolism of PDP in the human digestive tract (Appendix 1, p.35, fig XIII.2.1-1). 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 carbohydrate 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 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 7,000 and 35,000 mg/kg bw/day 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 being fed with PDP compared with distarch phosphate.

c) Subchronic studies

The applicant has referred to seven subchronic studies carried out on PDP between 1964 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)
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

Species	Duration	Dose level (% of diet or g/kg bw)	Principal findings	References
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 refers to a 104-week chronic study on rats using PDP at 0, 5, 10 and 30% (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 30% 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 which concluded that these findings were peculiar for the rat and had little relevance for the safety assessment of modified starches for man (Appendix 3).

e) Developmental and reproductive studies

The applicant presented a 3-generation reproduction study on rats fed 10% of various modified starches. 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 generation were not affected by modified starch consumption, except for F₁

parent male (increased filled caecum weight) and for F₃b females (increased spleen weight). No pathological changes were observed. It was concluded that none of the tested modified starches, which included PDP derived from maize, were 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 short-term studies using one unmodified potato starch and five chemically modified starches including PDP from maize (Pieters *et al*, 1971). Ten volunteers completed this 6-week-trial. Each week, they consumed 60g/day of one particular starch on 4 consecutive days. The summary report of this study indicates that no adverse effects were reported, the frequency of faeces or faecal water and lactic acid were not affected and the modified starches were well tolerated.

38. **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.

39. 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 adults). The 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.

40. Summaries of the toxicological studies chosen by the applicant are provided in tables XIII.3.2-1, XIII.3.3-1, XIII.3.4-1, XIII.3.5-1 and XIII.3.6-1 Appendix 1. p.42-49). Conclusions where applicable are based on opinions from Agency toxicologists.

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

The ADME of the NI has been described under paragraph 37(a) above. The applicant has indicated that phosphorus is absorbed through the small intestine walls to the human bloodstream. The phosphorus blood level is regulated by the parathyroid hormone (PTH) and appears as a constituent of phospholipids or as inorganic phosphate. The kidney plays a major role in regulating the retention and excretion of plasma phosphorus. The majority (80%) of phosphorus 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 (Appendix 1, 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 (Appendix 1, 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.

d) Chronic studies

Eight chronic oral studies carried out on phosphorus containing compounds have been provided in Table XIII.3.4-1 (Appendix 1, p.46-47). They demonstrated decreased growth rates, pelvic nephrocalcinosis, increased rate of bone turnover, increased parathyroid hormone levels and kidney damage at intake levels of up to 5g/kg bw/day.

e) Developmental and reproductive studies

Details of seven developmental and reproductive studies are presented in Table XIII.3.5-1 (Appendix 1, p.46-47). They 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 in Table XIII.3.6-1 (Appendix 1, p.49). No positive results were found in any of the 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 hypercalcaemia (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 the Bernstein and Newton study (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 3,008 mg/day of phosphorus supplemented on top of a standard diet containing 1,700 mg phosphorus/day, appeared to show similar incidences of diarrhoea and few effects on bone resorption or bone turnover (Grimm et al 2001).

Allergenicity and labelling

Appendix 1 p.30 and p.55

41. The applicant states that the NI has no allergenic potential but has not provided any data to support this statement. The Secretariat notes that 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. Also, maize-derived ingredients are not covered by EU rules on allergy labelling, unlike those derived from e.g. wheat. It therefore seems unlikely that the product presents any allergy risk to consumers.
42. The applicant intends to label the NI as "gluten-free", in accordance with the Codex Alimentarius definition of the term. EU legislation on food labelling allows the use of "gluten free" labelling on foods (other than those derived from wheat) that contain a maximum of 20ppm of gluten, allowing for the presence of low levels of wheat via adventitious contamination during the production process. The use of the term "gluten-free" on the final food is therefore subject to the production conditions and relevant tests on the final food in which the NI is being used. 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.
43. The applicant will advise food manufacturers intending to use the NI to label food products as follows:
- RS4-fibre*- on the front label
 - * modified starch (PDP) – in the ingredient listing

Response to public consultation

44. In line with standard practice for the assessment of novel food dossiers, the original request from National Starch was published on the Food Standards Agency's website for public comment with a deadline of 19 September. Any comments received will be provided to Members on the day of the ACNFP meeting.

Consumer access and choice

45. The Secretariat has considered the issues of access and choice in relation to the NI. If authorised, the NI would be available for use in products across the UK and subsequently in other EU Member States. In practical terms, access to products containing the NI could be limited by a high price or by limited geographic distribution, which are both driven by commercial considerations that cannot be predicted at this stage.

46. It is envisaged that the introduction of products containing the NI will increase existing consumer choice and will not affect access to existing foods that do not contain this ingredient. The consumer would be aware of the presence of the NI through the ingredient list and, most likely, through special marketing that highlights its contribution to the nutrient composition of the foods.

COMMITTEE ACTION REQUIRED

47. The Committee is asked to consider whether the available data are adequate to determine whether the NI complies with the criteria for acceptance under the novel food regulation, namely:

- It does not present a danger to the consumer
- It does not mislead the consumer
- It is not nutritionally disadvantageous compared with foods which it might replace.

48. If so, the Committee is asked whether it is content to recommend approval for this NI to be used in the proposed food products.

49. If not, the Committee is invited to identify what further data should be provided.

**Secretariat
September 2005**

Appendices attached:

Appendix 1: Application for the approval of phosphated distarch phosphate

- Annex A** US Manufacturer Product – Typical of the site of Manufacture: Microbiological Testing
- Annex B** US Manufactured Product – typical of the site of Manufacture: Mycotoxin Testing
- Annex C** EEX 6612 Certificate of Analysis: Example Pesticide, Heavy Metal, Mycotoxin, Nitrosamines, and Microbiological Testing
- Annex D** Non-GM Status of National Starch Food-Grade Starches True Trace™ Program
- Annex E** Hazard Analysis Summary Table (HACCP) **[Confidential]**
- Annex F** Estimated Daily Intake of RS4 fibre by the UK Population and Corresponding Intakes of Phosphorus from Proposed Food-Uses in the EU
- Annex G** AOAC Official Method 991.43 Total, Soluble, and Insoluble Dietary Fibre in Foods
- Annex H** Examples of Food Products Containing PDP as a Source of Dietary Fibre from the US and Canada
- Annex I** Estimated daily intake of modified starches from existing food-uses by the UK population

Appendix 2: Nugent, A.P. 2005. Health properties of resistant starch. *Nutr Bull BNF* 30:27-54

Heijnen ML, Van Amelsvoort JMM, Deurenberg P et al. (1996) Neither raw nor retrograded resistant starch lowers fasting serum cholesterol concentrations in healthy normolipidaemic subjects. *American Journal of Clinical Nutrition* 64: 312–18. 35–43. [cited in Nugent AP (2005) paper]

Van Munster IP, de Boer HM, Jansen MC, et al. Effect of resistant starch on breath-hydrogen and methane excretion in healthy volunteers. *Am J Clin Nutr* 1994; 59:626-30. [cited in Heijnen ML (1996) paper, ref 42]

Heijnen ML, Deurenberg P, van Amelsvoort JMM, Beyen AC. Replacement of digestible by resistant starch lowers diet-induced thermogenesis in healthy men. *Br J Nutr* 1995; 73:423-32. [cited in Heijnen ML (1996) paper, ref 43]

Appendix 3: Second report of the Scientific Committee for Food on modified starches (opinion expressed 12 June 1981)

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Application for the approval of phosphated distarch phosphate.

This document has been published on the Food Standards Agency website at:

<http://www.food.gov.uk/science/ouradvisors/novelfood/assess/>

**Secretariat
September 2005**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

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

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**Secretariat
September 2005**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Second report of the Scientific Committee for Food on modified starches (opinion expressed 12 June 1981).

This document is available on the European Commission website at:

http://europa.eu.int/comm/food/fs/sc/scf/reports/scf_reports_13.pdf

**Secretariat
September 2005**