ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOOD REGULATION TO EXTEND THE USE OF PHYTOSTEROL ESTERS

Applicant	**Unilever**
Responsible Person	**Carlo Bulkmans**
EC Classification	**2.1**

Background

1. Unilever has submitted an application to extend the use of phytosterol esters (PS) as a novel food ingredient. This is the third application made by this applicant for this novel ingredient; following its authorisation for use in yellow fat spreads in 2000[1] and an extension of use to 'milk type' and 'yoghurt type' products[2] in 2003.
2. This application relates to the scope of the original authorisation in 'yellow fat spreads' (margarines). Although the definition of yellow fat spreads is broad[3], the original application was assessed on the basis that that the spreads would not be used in cooking (frying or baking)[4]. This application is to extend the use of spreads for such purposes, and to permit the addition of PS to liquid vegetable fat based emulsions (so called 'liquid margarines'), which are outside the scope of 'yellow fat spreads', but are widely used for cooking and baking.
3. In their 2002 opinion[5] the Scientific Committee on Food (SCF) did not derive a formal acceptable daily intake (ADI) for PS but they noted that blood levels of carotenoids, especially beta-carotene, can be reduced after consumption of 3g phytosterols or stanols and that there was no evidence indicating additional benefit at intakes of greater than 3g. The SCF advised that, as a precaution, intake of plant sterols and stanols should not exceed 3g/day and that their

[1] Commission Decision 24 July 2000 authorising the placing on the market of yellow fat spreads with added phytosterol esters as novel food ingredients under Regulation (EC) No 258/97 of the European Parliament and of the Council (2000/500/EC)

[2] Commission Decision of 31 March 2004 authorising the placing on the market of milk type products and yoghurt type products with added phytosterol esters novel food ingredients under Regulation (EC) No 258/97 of the European Parliament and of the Council (2004/335/EC)

[3] EC Regulation N°2991/94 defines a yellow fat spread as products that must remain solid at 20°C, be suitable for use as a spread and have a fat content of not less than 10% but less than 90%. The fat content must be at least two-thirds of the dry matter (whey powder, caseinates, etc., but excluding salt).

[4] Refer to text on page 5 of the 2000 SCF report on the safety assessment of phytosterol esters in yellow fat spreads http://ec.europa.eu/food/fs/sc/scf/out56_en.pdf and 2004 authorisations for ADM (2004/333/EC) Pharmaconsult (2004/334/EC) and Teriaka (2004/336/EC)

[5] http://ec.europa.eu/food/fs/sc/scf/out143_en.pdf

consumption should be part of a healthy diet that is rich in fruit and vegetables, to counteract any potential deleterious effects on blood cholesterol levels.

4. The approach used in this application follows other requests for the extension of use of novel foods by referring to previous safety assessments. The application therefore focuses on two issues; the likely effect of additional food uses on estimated intake and the potential formation of phytosterol oxidation products during cooking or baking. The applicant addresses the former point by providing a detailed intake assessment, coupled with the presentation of an extensive post market monitoring survey that estimates current consumption of phytosterol and phytostanols from all fortified products which are on the market in five EU Member States. For the second point, the applicant has carried out studies on phytosterol oxide products and has also presented a number of newly published safety studies on the safety of phytosterols *per se.*

5. This application is to extend the scope of the original approval for yellow fat spreads to enable their use for cooking and baking. This use is referred to in the application dossier as **'PS-Spreads for CB'**. The applicant also requests approval of use in liquid vegetable fat based emulsions (referred to in the application dossier as **'PS-Liquids for CB'**).

I Specification of the Novel Ingredient (NI)

6. No changes have been made to the product that was considered in the previous applications[6].

II Effect of the production process applied to the NI

7. No changes have been made to the product that was considered in the previous applications[6].

III History of the organism used as the source of the NI

8. No changes have been made to the product that was considered in the previous applications.[6]

Discussion I-III *The Committee accepted that the specification, source and production process used novel ingredient did not differ from that seen in previous applications and did not comment on these sections of the application.*

IX Anticipated intake and extent of use of the NI

Dossier p.20-32

9. A description of the typical composition of PS-Spreads and PS-Liquids for CB is given in Table I.1.2. of the Dossier. Both product categories contain proteins, varying levels of emulsifiers, stabilisers salt and vitamins with a PS level,

[6] http://www.food.gov.uk/multimedia/pdfs/unilever.pdf

described in terms of free plant sterols, of 7.5g/100g (equivalent to 12.5g sterol esters).

10. **Intake estimation**. The applicant has used three different approaches to estimate the intake of PS (as plant *sterols*) from PS-Spreads and PS-Liquids for CB using three distinct data sets from the UK National Diet and Nutrition Survey (NDNS), the Dutch food survey (DNFCS),and The European Food Safety Authority's (EFSA) comprehensive data base.

11. As this application was submitted to the UK competent authority the dossier focusses on the methodology employed for estimating intakes using the UK data. The use of Dutch and EFSA data is briefly summarised in the dossier but is presented in detail in Appendices F and G of the Dossier.

12. The applicant's intake estimates, for all three data sets, are comprehensively presented in the Dossier p23–30 and summarised in the table below. The applicant has focussed on consumption by the target group (adults >45 years old) but has also looked at potential consumption in non-target groups, specifically young children and women of child bearing age, as these were the population groups who were identified as being most susceptible to reductions in blood carotenoid levels).

13. These intake estimates indicate that high level consumption (at the 95 percentile) can exceed 3g/day and, in theory, there could be consumption in each of the non-target groups. The applicant notes that the intake assessments are conservative, most notably because it is assumed that all margarine and liquid vegetable based emulsions that are consumed contain PS and all margarines and liquid vegetable based emulsions used in baked and cooked foods also contain PS.

	Plant sterol intakes, based on total margarine intake (all users)								
	Netherlands			UK			EFSA		
	Age	Median	95%ile	Age	Mean	95%ile	Age	Mean	95%ile
Infants	na	na	na	na	na	na	0-11m	0.0.2	0.0.4
Toddlers	2-6	0.8-1.0*	1.5-2.0	1-3	0.7	1.4	1-3	0.2-0.7	0.6-1.6
Children	7-13	1.0-1.4	2.9-3.7	4-10	1.0	2.1	3-9	0.2-1.0	0.5-3.4
Adolescents	14-18	0.9-1.4	2.9-4.7	11-18	1.0	2.4	10-17	0.4-1.1	0.9-3.4
Adults	19-30	1.1-1.7	3.4-5.4	19-44	1.2	2.9	na	na	na
Female Adults	19-50	1.1	3.4	19-44	1.1	2.5	na	na	na
Adults	31-69	1.1-1.8	3.4-5.0	45+	1.4	3.2	18-64	0.6-1.7	1.4-6.4
Elderly	na	na	na	na			65-74	0.3-2.5	0.5-7.1

na = data not available for this population group
*Data on The Netherlands toddlers aged 2-6 are presented as mean intakes rather than median intakes. Therefore, the Netherlands 'toddlers' include children aged 2-6 to keep these data separate from other the Netherlands data which are presented as medians.

Discussion *The Committee accepted that the use of the three data sets provided an extensive estimation of intake but it was concerned that the applicant had not investigated the level of uncertainty that exists for each of the data sets. The Committee sought to address this question by assessing the level of uncertainty using guidance produced by EFSA in 2006[7]. This qualitative assessment, tabulated below, offered sufficient reassurance to the Committee that the intake estimates were reasonable and, as far as the data allowed, accurate.*

Qualitative evaluation of the impact of uncertainties on the exposure assessment of Phytosterol esters				
	Direction of impact			
Sources of Uncertainty	***UK[1]***	***Dutch[2]***	***EFSA[3]***	***PLM[4]***
Known under-reporting in dietary surveys	-	-	-	*na*
All products in a given category are assumed to contain the novel ingredient at the highest proposed level of incorporation	+	+	+	*na*
Lack of information on background intake from other dietary sources	-	-	-	-
High level consumption recorded in the period of the survey may not be sustained in the longer term	+	+	+	*na*
High level exposure is summed across multiple food categories, but the same individual is unlikely to be a high level consumer in more than one or two food categories	*na*	+	+	*na*
Consumption of foods in the proposed categories may not be equally distributed across the EU	+/-	+/-	*na*	+/-
Certain age-groups within individual countries	*na*	*na*	+/-	*na*

[7] http://www.efsa.europa.eu/en/efsajournal/pub/438.htm

may be not be included in dietary surveys				
Certain population groups within individual countries may be under-represented in dietary surveys	+/-	+/-	+/-	+/-
Fortified and non-fortified foods are assumed to be consumed in comparable amounts	+/-	+/-	+/-	*na*
Post launch monitoring surveys are based on point of sale and/or household purchasing patterns and do not necessarily reflect individual consumption patterns	*na*	*na*	*na*	+/-

1: National Diet and Nutrition Survey
2: Data from Dutch National Food Consumption Survey
3 Data from EFSA Comprehensive Database,
4: Unilever post launch monitoring data.
na: not applicable

X Information from Previous Human Exposure

Dossier p33-42

14. The applicant highlighted the current approvals for phytosterol products (Table X.1.2-1), and also notes that, while products containing PS require authorisation under the novel food regulation, this is not the case for products containing phytostanol esters[8] for which the use of yellow fat spreads in cooking and baking is encouraged by the manufacturers.

15. Plant sterols occur naturally in a number of foods (vegetable oil, seeds etc.) and typical consumption can be around 200-300mg/day. (Dossier Table X.1.4-1). Intake in vegetarians is reported to be higher, often in the range 500-1000mg/day.

16. **Post launch monitoring (PLM).** The applicant also describes a large scale post launch monitoring programme that they have commissioned to assess and quantify current consumption of PS. The applicant highlights that these data, which are based on actual purchasing patterns, give a more accurate measure of intake than the theoretical assessment carried out on each of the authorised products in the manner described in Section IX, which is likely to result in overly conservative estimates.

17. The applicant has used detailed quantitative market research to estimate the levels of consumption of a range of products with added phytosterol and phytostanol esters in five EU Member States (UK, Germany, France, Belgium and the Netherlands')**.** This study, carried out throughout 2011, used relatively large consumer panels (5,000–30,000 per country) and households used a barcode reader at home to continually log the food that they purchased. This PLM study assumes that all the products purchased were consumed and that no additional products were purchased and consumed outside the home. The households that purchased products with added phytosterol and/or phytostanol

[8] The active ingredient in Benecol®

esters (available products are detailed in the Dossier Table X.2.1-1), ranged from 4700 households in the UK to 646 in the Netherlands. The results of this study are detailed below.

Phytosterol and phytostanol consumption per household (g/day)			
	Mean	**Median**	**95%ile**
UK	0.86	0.22	2.53
The Netherlands	0.82	0.26	3.70
France	0.35	0.12	1.06
Germany	0.40	0.16	1.53
Belgium	0.76	0.26	2.96

18. The applicant suggests that the median figures are the most valid measurement as most households consumed low levels of fortified products, although high level consumption is significantly higher, ranging from 1.06g/day to 3.70g day per *household*. The applicant has broken down the figures further, according to household size, with a separate category for households with children less than 5 years old. These results, which are shown in the following table, indicate that two-member households consume the highest levels of fortified products, followed (in many countries) by 1 and 3 member households.

Mean daily phytosterol and phytostanol consumption per household (g/day), Differentiated per household size					
	UK	**NL**	**FR**	**DE**	**BE**
All households	0.86	0.82	0.35	0.40	0.76
1 member HHs	0.75	0.53	0.28	0.34	0.67
2 member HHs	1.09	1.09	0.42	0.46	0.88
3 member HHs	0.63	0.79	0.41	0.45	0.78
4 member HH	0.71	0.65	0.28	0.28	0.56
5+ member HH	0.50	0.43	0.18	0.26	0.50
Households with children <5 years	0.36	0.20	0.14	0.41	0.45

19. The applicant notes that 2-member households consume more than the national averages and this is because they are more likely to be composed of individuals aged 45 years or older (the target population). Consumption levels in Germany show the least variation, which may indicate that consumption of fortified products is largely being restricted to single individuals within a household.

20. **Other PLM studies.** The applicant has also summarised PLM findings from 3 other reports. An EFSA study published in 2008 reviewed published and unpublished consumer and market research information and a meta-analysis of published literature found that more than half the consumers of phytosterols belonged to the intended target population. Of these, 1-4% were identified as having consumption in excess of 3/g day. The same report noted low level consumption amongst children (8% of children less than 5 years) and that the market share for products with added PS was less than 10%. The applicant notes that this latter point reinforces their view that the assumptions used in prospective intake assessments are conservative.

21. In 2012, EFSA's opinion on the use of stigmasterol-rich plant sterols as a food additive noted that the average daily intake of phytosterols from all sources was 2770mg/day in adults. A survey of phytosterol intakes in preschool children in Belgium identified 21% of 2.5 to 7 year olds as consumers (mean intake 0.7g/day, range 0.01g-2.1g/day).

22. The applicant concluded that their own PLM data reinforce the findings of other market research, indicating that long-term consumption levels are more likely to be insufficient to achieve cholesterol lowering effect rather than at, or beyond, the recommended 1.5g-3g/day range.

Discussion *The Committee noted that that average consumption levels reported in the 2012 EFSA opinion and levels and the applicants' PLM data, which estimated consumption by household, indicated that the de facto upper limit of 3g is not exceeded.*

XI Nutritional Information on the Novel Food

Dossier p43-48

23. The applicant notes that phytosterols have been approved for use as novel foods since 2000, there have been no changes to the specification since the original authorisation and that there are a number of approved health claims which relate the consumption of phytosterols to cholesterol lowering effects.

24. The applicant also provides a commentary on the use of cooking and baking fats in the diet and notes that PS-Spreads for CB and PS-Liquids for CB could be used as a replacement for other similar products in the diet which are currently used for the same purpose, including products with added phytostanols.

Discussion *The Committee's assessment focuses on safety and labelling and does not address any nutrition or health benefits that may be claimed for the novel ingredient or for foods that contain it. Nutrition or health claims may only be made if they are specifically authorised under EU Regulation (EC) No 1924/2006.*

XII Microbiological Information

Dossier p49

25. No changes have been made to the product that was considered in the previous applications[6].

Discussion *The Committee accepted that data provided in previous applications demonstrated that there was adequate provision to ensure that the phytosterol esters would not contain significant quantities of pathogenic or spoilage microorganisms*

XIII Toxicological Information

Dossier p50-66

26. The safety of phytosterols *per se* has been assessed in the previous applications[6]. However, given the proposed uses that are described in this application the applicant has assessed the safety of any phytosterol oxidation products (POPs) which may be produced during cooking or baking.

27. The applicant initially assessed the stability of phytosterols by repeatedly heating 25g of a 70% fat PS-Spread and analysing the sterol content and profile. The applicant concluded that no significant decomposition or oxidation of the phytosterols was seen (Dossier Table XIII.2.1-1).

28. In order to evaluate the effect of frying and baking on the oxidation of phytosterols, samples were taken of a number of PS-Spread for CB products after frying and baking using a number of different scenarios, including cooking with beef steak (Dossier, pp52-53). These analyses, particularly those using end of shelf life products, showed significantly higher levels of POP than are seen in vegetable oils (up to 76mg/100g compared with 26mg/100g in sunflower oil) and the applicant notes that these differences are not significant (same order of magnitude) or unexpected given the differences in the levels of phytosterols seen in oils when compared to phytosterol fortified products.

29. A sample of PS-Spreads for CB was also tested in a worst case scenario by heating the product to 180°C and holding for 15 minutes. Analysis of this product showed similar levels of POPs to the maximum seen in the previous analyses and the applicant concluded that these studies indicate that the profile of POPs is similar to that in existing vegetable oils and that the levels are of the same order of magnitude to those seen in vegetable oil.

30. The applicant has also assessed the safety of POPs in a range of toxicity studies carried out on a plant sterol oxide concentrate (POC) containing 30% POPs. This test material, which consists largely of POPs and oxidised phytosterols, contains significantly higher POPs than would be present in any commercial product (see Dossier Table XIII.3.1-2 for composition).

31. The POC was tested in a number of *in vitro* gene mutation assays (Dossier p56-58). A bacterial mutation assay showed no significant increases in revertant

colonies and, while one part of a chromosome aberration assay led to an increase in polyploidy and endoreduplicated cells, this was not seen in a separate experiment with a longer incubation. A separate micronucleus assay was carried out to clarify this discrepancy and did not highlight any evidence of aneuploidy. The applicant concluded the POC did not exhibit mutagenic activity nor did it display clastogenic properties or chromosomal aberrations.

32. A 90 day sub-chronic study was carried out in accordance with OECD guidelines in which animals were fed a control diet with or without added phytosterol esters and test animals were given phytosterol esters supplemented with up to 1.6% POC. No major effects of POC treatments were seen in lower dose groups. Small changes were seen in the certain clinical chemistry parameters in the high dose groups, but these were not regarded to be a cause for concern. Similarly, other changes in clinical parameters were considered to be minor and no treatment-related macroscopic findings were seen at seen at necropsy. A recent human study demonstrated that that, over a 4 week period, daily consumption of phytosterol and phytostanols did not lead to an increase in plasma POP concentrations.

33. Based on the findings of the sub-chronic study the applicant regards the No-Observed Effect Level (NOEL) to be 0.6% POC, which is equivalent to 128 and 144 mg/kg body weight for male and female rats respectively. Taking the lower figure the applicant calculates the margin of safety for humans to be 400 and 131 in adults and children.

34. **Toxicological studies – summary.** The applicant accepts that recent scientific reviews by EFSA (2012) and the Joint FAO/WHO Expert Committee on Food Additives (2008) do not disagree with the SCF's 2002 review which resulted in a *de facto* limit of 3g/day for phytosterols and stanols (see above). While the proposed extension of use could result in a total intake that exceeds this figure the applicant regards this scenario to be unlikely because post-market data indicate that high levels of consumption are not likely to occur across the population for a sustained period. The applicant has, nevertheless, summarised a number of clinical studies that have been published which support the safe use of phytosterols and stanols at levels in excess of 3g/day. These are tabulated in Table XIII 4.2.1 p63 – 65.

Discussion *The Committee was content that the safety of phytosterols per se had already been demonstrated and the proposed changes in use were unlikely to result in sustained consumption beyond 3g/day. The Committee asked the applicant to clarify estimate the likely increase in POP consumption if consumers rely solely on using PS-Spreads and PS-Liquids for cooking and baking. The applicant used NDNS data to estimate the likely level of intake and these indicated that, if PS-Spreads were used for spreading, this would lead to a dietary increase POPs of 2.7mg/day*

(P95 6.6mg/day) compared with unfortified margarine. Using PS-Spreads for cooking and baking would lead to a dietary increase of POP's of 3.0mg/day (P95 8.4mg/day) compared with unfortified margarine. The Committee accepted that the net increase of POPs was not significantly different to the existing uses of phytosterols and did not present a safety concern

Allergenicity and Labelling

35. No changes have been made to the previous application[6]. Phytosterol esters from refined soya oil are specifically exempted from allergen labelling requirements.[9]

36. There are mandatory labelling requirements for all foods and food ingredients with added plant sterols, plant sterol esters, plant stanols and/or plant stanol esters. These requirements are set out in Commission Regulation (EC) Nº 608/2004 and provide appropriate risk management measures for all sources of added phytosterols and stanols.

Discussion *The Committee agreed that phytosterol esters are not an allergenic risk and noted that all products with added phytosterol esters will be labelled in compliance with specific EU labelling requirements.*

Overall Discussion

The Committee concluded that the applicant had provided sufficient scientific data to demonstrate that extending the use phytosterol esters of did not give cause for concern. The Committee also noted that the data provided by the applicant to estimate the current and new intake of phytosterols provided adequate reassurance that consumption would not exceed 3g/day.

The Committee was also reassured that, while PS-Spreads for CB and PS-Liquids for CB would lead to an increase in the level of POP's the net increase was not significantly higher than was seen when comparing consumption of phytosterol fortified margarine with an unfortified variant.

Conclusion

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by the applicant that the extended range of uses for the novel ingredient (phytosterol esters) is acceptable.

Secretariat
February 2014

9 Commission directive 2007/68/EC