EXPLANATORY STATEMENT

APPLICATION A508

PHYTOSTEROLS DERIVED FROM TALL OILS AS INGREDIENTS IN LOW FAT MILK

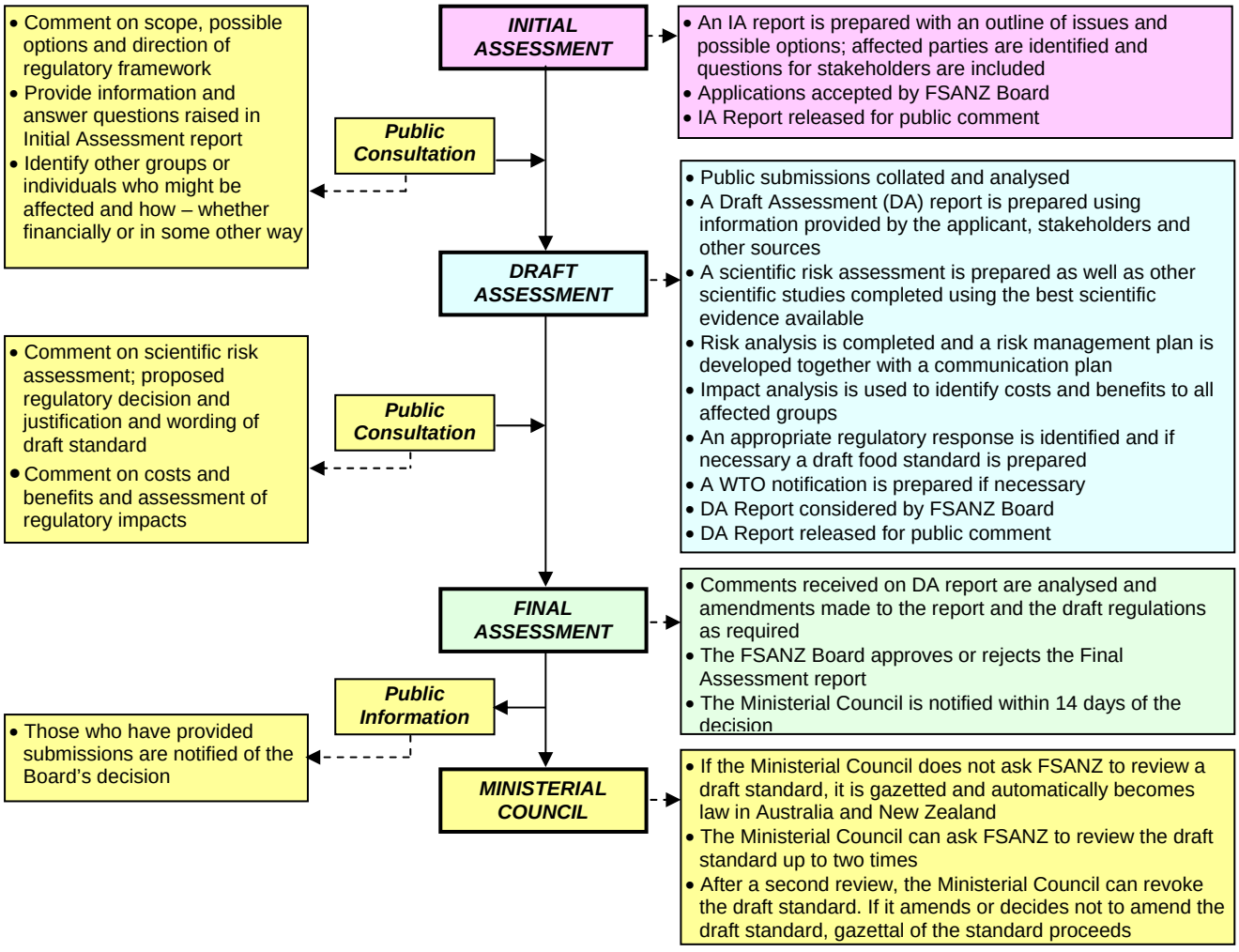
FOOD STANDARDS AUSTRALIA NEW ZEALAND (FSANZ)

FSANZ's role is to protect the health and safety of people in Australia and New Zealand through the maintenance of a safe food supply. FSANZ is a partnership between ten Governments: the Commonwealth; Australian States and Territories; and New Zealand. It is a statutory authority under Commonwealth law and is an independent, expert body.

FSANZ is responsible for developing, varying and reviewing standards and for developing codes of conduct with industry for food available in Australia and New Zealand covering labelling, composition and contaminants. In Australia, FSANZ also develops food standards for food safety, maximum residue limits, primary production and processing and a range of other functions including the coordination of national food surveillance and recall systems, conducting research and assessing policies about imported food.

The FSANZ Board approves new standards or variations to food standards in accordance with policy guidelines set by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) made up of Commonwealth, State and Territory and New Zealand Health Ministers as lead Ministers, with representation from other portfolios. Approved standards are then notified to the Ministerial Council. The Ministerial Council may then request that FSANZ review a proposed or existing standard. If the Ministerial Council does not request that FSANZ review the draft standard, or amends a draft standard, the standard is adopted by reference under the food laws of the Commonwealth, States, Territories and New Zealand. The Ministerial Council can, independently of a notification from FSANZ, request that FSANZ review a standard.

The process for amending the *Australia New Zealand Food Standards Code* (the Code) is prescribed in the *Food Standards Australia New Zealand Act 1991* (FSANZ Act). The diagram below represents the different stages in the process including when periods of public consultation occur. This process varies for matters that are urgent or minor in significance or complexity.



Final Assessment Stage

FSANZ has now completed two stages of the assessment process and held two rounds of public consultation as part of its assessment of this Application. This Final Assessment Report and its recommendations have been approved by the FSANZ Board and notified to the Ministerial Council.

If the Ministerial Council does not request FSANZ to review the draft amendments to the Code, an amendment to the Code is published in the *Commonwealth Gazette* and the *New Zealand Gazette* and adopted by reference and without amendment under Australian State and Territory food law.

In New Zealand, the New Zealand Minister of Health gazettes the food standard under the New Zealand Food Act. Following gazettal, the standard takes effect 28 days later.

Further Information

Further information on this Application and the assessment process should be addressed to the FSANZ Standards Management Officer at one of the following addresses:

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Assessment reports are available for viewing and downloading from the FSANZ website www.foodstandards.gov.au or alternatively paper copies of reports can be requested from FSANZ's Information Officer at info@foodstandards.gov.au including other general enquiries and requests for information.

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Purpose and scope of the Application

Parmalat Australia Ltd has submitted an Application to FSANZ seeking approval for the use of tall oil phytosterols[1] (TOPs) as a novel food ingredient in low-fat milk under Standard 1.5.1 – Novel Foods, in the *Australia New Zealand Food Standards Code* (the Code). Parmalat is specifically seeking to extend the current permissions to allow use of TOPs in low-fat milk.

Standard 1.5.1 requires that novel foods undergo a safety assessment before being permitted in the food supply. If approved, the novel food is listed in the Table to the Standard and must comply with any special conditions of use also listed in the Table.

Efficacy of TOPs

TOPs are added to foods with the intended purpose of lowering cholesterol absorption. The Applicant has submitted efficacy studies including the data and results from clinical studies involving mildly hypercholesterolaemic individuals in a variety of food matrixes, including milk. The available human studies do provide information in relation to the effectiveness of TOPs incorporated into food products to reduce cholesterol absorption. However, there is no specific evaluation of any health claim being considered as part of this Application. Irrespective of whether any statement is considered a health claim, all statements on the label should be true and not mislead consumers.

Technical properties of TOPs

Tall oil phytosterols as well as phytosterols derived from edible vegetable products are comprised of varying ratios of the same four primary phytosterol substances sitosterol, sitostanol, campesterol and campestanol, with varying amounts of minor components such as stigmasterol and brassicasterol. The physiological activity of phytosterol products is due to the presence of these compounds. However, TOPs do not necessarily need to be esterified to improve their solubility as the Applicant has indicated that they can be incorporated into low-fat milks.

Risk assessment

The data support the safety of TOPs in both the target and non-target population at the level of dietary exposure that would be achieved by addition of TOPs to low-fat milk at the levels proposed to be used by the Applicant (0.9g/250 mL serve). The estimated mean dietary exposure to TOPs did not exceed 1.9 g/day in any population group assessed. The 95th percentile dietary exposure for the target population was 4.8 g/day, the majority of which is derived from edible oil spreads. While this level of exposure is higher than that used in the human studies, FSANZ is proposing additional risk management measures to reduce over-consumption of TOP containing low-fat milks. The overall conclusion of the risk assessment is that low-fat milk enriched with TOPs is not associated with any adverse effects.

[1] i.e. phytosterols derived from tall oils

Risk management

In order to ensure appropriate use of TOP-enriched low-fat milk by the target group and to discourage use by the non-target groups, the following risk management measures are proposed:

1. retain the current mandatory advisory statements in Standard 1.5.1;
2. prescribe an additional labelling statement that indicates that there is no additional benefit from consuming greater than 2-3 serves/day; and
3. prescribe additional conditions of use, namely: (i) that low-fat milk must not contain more than 3.6g/litre of free phytosterols (from a tall oil source); (ii) the fat content must not contain more than 1.5g total fat/100g liquid, and (iii) maximum container size is to be specified at 1 litre (i.e. the labelled volume must be no more than 1 litre); and (iv) that foods containing added plant sterols must not be used as ingredients in other foods,

Additional risk management strategies have been proposed by the Applicant. Ongoing monitoring (possibly via a survey) of the use of phytosterols in foods would provide additional reassurance of the effectiveness of the proposed risk management measures.

Other issues raised in public submissions

Other issues raised in the public submissions consisted of comments on the specific requirements and intent of the novel foods standard, specifications and labelling for phytosterols in general, the possibility of inequity for consumers of lower socio-economic groups and the issue of medicalisation of the food supply if TOP-containing products are approved.

Impact analysis of regulatory options

The options identified were to permit or not permit the use of TOPs in low-fat milk, or to permit the use of TOPs generally. The impact analysis shows that the second option (to permit TOPs in low fat milk) satisfies the objectives based on the outcome of the scientific risk assessment and the Regulatory Impact Statement (RIS), taking into account matters raised following the public consultation period.

These matters included the following:

- an assurance of the safety of TOPs;
- the provision of adequate labelling so as to give consumers informed choices for purchases of products containing TOPs;
- advisory statements and conditions of use to manage inappropriate use and over-consumption of products; and
- the provision of benefits to industry and governments, in terms of enhanced market opportunities and trade.

Statement of Reasons

FSANZ agrees to approve the use of TOPs in low-fat milk subject to specified conditions of use, for the following reasons:

- there are no anticipated public health and safety concerns associated with the use of TOPs in low-fat milk when used in conjunction with the risk management measures proposed;

- there is evidence that TOPs when incorporated into low-fat milk can, following consumption, reduce cholesterol absorption in humans;

- the nutrition assessment indicates that TOPs have no significant adverse nutritional effects at the proposed levels of use;

- conditions of use, including an additional labelling statement, are proposed as part of a comprehensive risk management strategy to ensure appropriate use of TOP-enriched low-fat milk by the target consumers, and to discourage use by non-target consumers;

- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and

- the Regulatory Impact Statement indicates that, for the preferred option, namely, to approve the use of TOPs as a novel food ingredient in low-fat milks; the benefits of the proposed amendment outweigh the costs.

The proposed drafting to the Code is shown in **Attachment 1**.

1. Introduction

1.1 Nature of Application

An Application was received from Parmalat Australia Pty Ltd, on 25 June 2003 seeking approval for the use of tall oil phytosterols (TOPs) as novel food ingredients in low-fat milk under Standard 1.5.1 – Novel Foods of the Code. The Application is cost-recovered and designated as a Category 3.

FSANZ has previously received and approved an Application for permission to add TOPs to edible oil spreads and margarines. There are currently no products on the market containing TOPs. TOPs when added to the diet lead to a reduction in plasma cholesterol levels in the target age group, namely, hypercholesterolaemic individuals aged 45-years plus.

Application A508 is seeking to extend the current permissions to allow use of TOPs in low-fat milk.

2. Regulatory Problem

In the Code Standard 1.5.1-Novel Foods requires that non-traditional foods which have features or characteristics that may raise safety concerns undergo a safety assessment before they are offered for retail sale in Australia and New Zealand. Novel foods or novel food ingredients that have been assessed under the Standard, when approved, are listed in the Table to clause 2 of the Standard.

TOPs are considered to be novel foods for the purposes of the Standard 1.5.1 because they are a non-traditional food for which there is insufficient knowledge in the broad community to enable safe use of this food in the form or context in which it is presented.

The current permissions to use TOPs as novel food ingredients was limited to edible oil spreads and margarines primarily due to the availability of safety data using these foods and the lack of relevant scientific information relating to their cholesterol lowering effects in other food matrices.

Application A508 seeks permission to add TOPs to low fat milk, as currently there is no permission in the Code.

3. Objective

The objective of this Application is to establish if the food regulations should be changed to allow the use of TOPs in low-fat milk. Before this food containing TOPs can enter the food supply in Australia and New Zealand, FSANZ must undertake a safety assessment that specifically considers (a) the potential health impact of higher dietary exposure to these compounds on target consumers and (b) the potential effects on non-target consumers. For approval, an amendment to the Code must be agreed by the FSANZ Board, and subsequently be notified to the Australia and New Zealand Food Regulation Ministerial Council. An amendment to the Code may only be gazetted once the Ministerial Council process has been finalised.

In addressing the proposed variation to Standard 1.5.1 to extend the current permissions to allow use of TOPs in low-fat milk as novel food ingredients, FSANZ is required by its legislation to meet three primary objectives in developing and varying food standards that are set out in section 10 of the FSANZ Act. These are:

- the protection of public health and safety;
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food; and
- any written policy guidelines formulated by the Ministerial Council.

4. Background

4.1 Historical background

In 1999, following consultation between FSANZ and Senior Food Officers (SFOs) in each of the Australian States and Territories and New Zealand, it was agreed that phytosterol esters derived from vegetable oils ought to be regarded as novel food ingredients because of the lack of a history of significant consumption by the broad community at the proposed levels of dietary exposure. Non-esterified phytosterols derived from tall oils are also considered to be novel for similar reasons.

In June 2000, FSANZ received an Application (A417) to amend the Code to include TOPs in edible oil spreads as novel foods at a level of 8% w/w. Approval was granted by the Ministerial Council in June 2002. The permissions were limited to edible oil spreads at that time primarily because of a lack of information relating to the safety of phytosterols at the higher levels of exposure in a broader range of foods.

4.2 Nature of tall-oil phytosterols

Phytosterols are found naturally in plants at low levels. TOPs are predominantly a mixture of four phytosterols: sitosterol, sitostanol, campesterol and campestanol, extracted from tall oil soap which is a bi-product of the pulping process used for coniferous trees in North America and Europe. They are then purified in a three-step process. The free phytosterols are structurally related to cholesterol and occur naturally at low levels (up to 0.9%) in common vegetables. TOPs are reported to reduce plasma cholesterol levels. It is claimed by the Applicant that incorporation of additional phytosterols, namely, TOPs into the diet may be an effective way of lowering total and low-density lipoprotein (LDL) cholesterol levels.

4.3 Related Applications

FSANZ is currently considering two other related Applications:

- **A434 from Dairy Farmers**-is seeking to extend the approval for the use of phytosterol esters derived from vegetable oils to a low-fat milk product.
- **A433 from Goodman Fielder Ltd**-is seeking to extend the approval for the use of phytosterol esters derived from vegetable oils to breakfast cereals.

4.4 Additional information requested during assessment

During the assessment period, FSANZ requested the Applicant on 12 September and 27 October 2003 to provide further data and information on the safety, efficacy and proposed risk management options with TOPs in low-fat milk to support the Application. The Applicant supplied this information on 13 October 2003 and 28 November 2003. FSANZ re-commenced assessment of the Application on 5 December 2003.

4.5 International regulations for TOPs and free phytosterols

4.5.1 Codex

There are no Codex standards in relation to TOPs.

4.5.2 Approval in other countries

In the USA, vegetable oil-based spreads containing TOPs at a level up to 12% have self-confirmed Generally Recognised as Safe (GRAS) status.

In the EU the following foods were recently approved (31 March 2004) with added phytosterol/phytostanols either from a tall oil or vegetable oil source:

- yellow fat spreads[2] / salad dressings / milk[3] & yoghurt type products / milk based fruit drinks / soy drinks / cheese type products (<12 g/100 g fat content) / spicy sauces

On 25 November 2003, following an Application from Forbes Medi-Tech, an opinion on the use of TOPs containing a mixture of sterol and stanols of plant origin (tall oil) for use in milk-based beverages (Reducol ^{TM}) was expressed by the European Food Safety Authority (EFSA[4]). The EFSA concluded that Reducol ^{TM} could be approved provided that total phytosterol intakes did not exceed 3g/day and that risk management options were implemented to minimise the likelihood of exceeding 3g/day of phytosterol/phytostanols from a tall oil source. The specifications for TOPs approved by the EFSA were consistent with the current ones for TOPs in the Code under Standard 1.3.4-Identity and Purity and those requested for approval by the Applicant for Application A508.

The European Commission is currently considering approval of Reducol in milks drinks and a final decision is expected in September 2005.

[2] Excluding cooking and frying fats and spreads based on butter or other animal fat
[3] Such as semi-skimmed and skimmed milk type products
[4] The EFSA Journal (2003), 15, 1-12.

5. Relevant Issues

FSANZ has identified and addressed the relevant issues in relation to a broader use of TOPs. These issues include safety, the potential for increased dietary exposure, potential nutritional effects in target and non-target consumers, truth in labelling, and the provision of appropriate consumer information, as well as some other issues raised in public submissions. The risk management measures address the issues identified in the risk assessment.

The following issues are discussed:

- the purpose of the Application and purpose for addition of TOPs;
- technical properties of TOPs;
- the potential for adverse health effects from consumption of higher amounts of phytosterols in target and non-target consumers;
- the potential nutritional effects of phytosterols on absorption of certain fat-soluble vitamins and carotenoids;
- details of the proposed risk management measures and the proposed manner of marketing of phytosterol-containing products; and
- consideration of other important issues raised in public submissions.

5.1 Purpose of the Application and addition of TOPs to low-fat milks

Application A508 is seeking to extend the current permissions to allow use of TOPs in low-fat milk.

TOPs are added to foods with the intended purpose of lowering cholesterol absorption. It is proposed that each low-fat milk product will contain 0.9 g of TOPs/250 mL serving size and will carry labelling statements to indicate that consumption of two to three serves/day is the recommended limit for individual daily consumption and that, further consumption above the recommended levels does not significantly lead to any further reductions in cholesterol absorption (refer to further information below on the labelling of these products in section 5.7 below).

The food matrix may be a determining factor in the efficacy of free sterols and stanols. However, while an assessment of efficacy is not a specific requirement of an assessment under the novel foods standard, truth in labelling is considered relevant to the section 10 objectives of the FSANZ Act. If there is a specific intent to indicate on the label that the consumption of phytosterol-containing low-fat milks will achieve lower cholesterol levels in subjects, then this should be supported by relevant clinical evidence as part of the provision of adequate information relating to food to enable consumers to make informed choices.

In support of this Application to extend the use of TOPs, the Applicant has submitted efficacy studies including the data and results from clinical studies involving mildly hypercholesterolaemic individuals in a variety of food matrixes, including milk[5]. The Applicant has also provided specific detailed marketing information[6] in relation to low-fat milk that are the subject of this Application.

[5] These studies are assessed in Attachment 3.
[6] FSANZ has assessed this as commercially-in-confidence material and as such is not available on the public register

Overall, the available human studies do provide information in relation to the effectiveness of TOPs incorporated into food products to reduce cholesterol absorption.

However, there is no specific evaluation of any health claim being considered as part of this Application. Any application for a health claim for TOPs in the future would need to be considered in the context of Proposal P 293 (Nutrition and Related Health Claims). Irrespective of whether any statement is considered a health claim, all statements on the label should be true and not mislead consumers.

5.2 Technical properties of TOPs

Tall oil phytosterols as well as phytosterols derived from edible vegetable products are comprised of varying ratios of the same four primary phytosterol substances sitosterol, sitostanol, campesterol and campestanol, with varying amounts of minor components such as stigmasterol and brassicasterol. The physiological activity of phytosterol products is due to the presence of these compounds.

Free tall oil phytosterols such as 'Reducol^{TM}' (commercial name of the tall oil phytosterols of Application A508) vary from phytosterol ester products as a result of the constituent phytosterol profile. These variations arise for the following reasons:

1. the source material differs;
2. fatty acid esterification is not used to modify the solubility properties for product application; and
3. hydrogenation processing is not used.

However, tall oil phytosterols do not need to be esterified to improve their solubility as the Applicant has suggested that they can be incorporated into low-fat milks.

A report on the technical properties of TOPs is provided at **Attachment 2.**

5.3 Safety of TOPs

The majority of submissions (**Attachment 6**) raised issues in relation to the safety of phytosterol-containing foods; in particular, the following concerns were raised:

- The potential for long-term effects;
- The potential for oestrogenic activity; and
- The need for sufferers of homozygous sitosterolaemia to restrict their intakes of plant sterols.

A previous consideration of the safety of TOPs as novel food substances was conducted under Application A417. An updated safety assessment on TOPs incorporating some new data submitted from the Applicant is at **Attachment 3**. A consideration of the nutritional effects of TOPs in low-fat milk is considered in Section 5.5 below.

FSANZ's safety assessment concluded that TOPs are poorly absorbed in the body, have low toxicity (which is supported by subchronic studies in animals up to 90-days duration), are not genotoxic and demonstrate no reproductive or developmental toxicity.

The human studies demonstrated that administration of TOPs in the diet at 3.6g/day for a period up to 28 days or at 1.8g/day for an 8-week period was well tolerated and raised no safety concerns. A study with 4g/day of a phytostanol mixture for 8 weeks further supports the safety of TOPs.

In respect of the long-term safety of phytosterols, there have now been a number of human studies addressing the safety and efficacy of phytosterols orally administered to normal and hypercholesterolaemic subjects from both tall oil and vegetable oil sources. The longest study identified in the scientific literature to date used a dose of 1.6g/day (free phytosterols derived from vegetable oils) for a period of one year, and showed no evidence of adverse toxicological effects. However, there is no evidence to suggest that long-term effects would result from continuous use of these products, based on the overall toxicological studies now available in animals and the safety/efficacy studies in humans.

The submission from Queensland Health cited a 1999 Report from the National Heart Foundation (NHF) which raised some concerns in relation to the safety of phytosterols in foods. However, the most recent report (August 2003) from the NHF's Nutrition and Metabolism Advisory Committee suggests that many of the concerns raised in the earlier report on safety of phytosterols have now been addressed. The NHF (2003) Report cites evidence of oestrogenic activity in Rainbow Trout following oral administration of sitosterols; however, they considered that the relevance of these findings for humans was not known. The report also suggests that there is no evidence of safety concerns with short-term consumption of plant sterols and stanols, although it was noted that long-term safety studies have not been conducted.

From the studies evaluated by FSANZ under Application A417 there was no evidence of *in vitro* or *in vivo* oestrogenic activity in rats or human studies. These studies are more relevant to an assessment of any possible oestrogenic effects in humans compared to studies conducted in Rainbow Trout. In addition, a recent evaluation from the EU Scientific Committee on Food (SCF) Final Report (3 October 2002) stated that newly submitted studies provided sufficient reassurance of the absence of endocrine effects via the oral route (SCF, 2002).

In respect of individuals with the rare inherited lipid storage disorder known as sitosterolaemia characterised by excessive absorption of phytosterols (20% compared with approximately 5% in normal individuals) from the previous FSANZ evaluation under Application A417 it was cited that by 1996, 26 cases had been identified worldwide. People with this condition are under regular medical supervision and must maintain a diet free of phytosterols. However, given the rarity of this disease and the need for individual suffers to be under regular medical supervision, a specific warning on the label for this at-risk group appeared unnecessary.

5.4 Dietary Exposure Assessment

A dietary exposure assessment was undertaken to determine the impact of allowing TOPs to be added to low-fat milk. The assessment took into account the existing permission under Standard 1.5.1 to add TOPs to edible oil spreads (the 'baseline' scenario) as well as the proposed addition of TOPs to milks (the 'milk only' scenario) and a combination of these products (the 'milk plus baseline' scenario).

In each scenario, addition of phytosterols at a level equivalent to 0.9 g free phytosterols per serve was assumed and it was further assumed that all edible oil spreads and low fat milks contained added free phytosterols. Intrinsic levels of phytosterols in foods were not taken into consideration.

Assuming that consumers maintain their existing eating patterns, estimated mean dietary exposure, (expressed as free phytosterols), did not exceed 1.9 g per day in any population group assessed under any of the scenarios considered. At the 95th percentile of exposure, no population group assessed exceeded 4.8 g free phytosterols per day for any of the scenarios modeled. The analysis shows that, for the target population group in particular, edible oil spreads contribute more to dietary exposure to added TOPs (78-84% of exposure) than low fat milks, according to the available data on food consumption patterns.

A detailed report on the potential dietary exposure to TOPs is provided at **Attachment 4.**

5.5 Nutritional issues associated with TOPs

Submissions raised concerns in relation to the loss of fat soluble vitamins, carotenoids and other fat soluble phytochemicals following consumption of TOPs, nutritional concerns in relation to consumption by non-target groups and the lack of evidence that consumers will consume extra fruit and/or vegetables to make up for the loss of carotenoids.

There were no significant reductions in β-carotene levels following administration of TOPs at levels ranging from 0.9 to 3.6 g/day for 30-days. However, reductions in α-carotene (23%) was observed at the highest levels of administration of TOPs (3.6g/day) compared to controls. However, the significance of these reductions is unclear, as there is currently no evidence that this would be a significant public health and safety issue particularly as significant reductions in vitamin A following administration of TOPs were not observed.

A separate nutrition report was not undertaken for Application A508, as the report for Applications A433 and A434 (**Attachment 5)** covered the broader nutritional issues associated with the use of TOPs in low-fat milk due to the following reasons:

- the nutrition report was more comprehensive than previous studies submitted for Application A417 in evaluating the effects of phytosterols on a larger number of carotenoids (other than alpha and beta-carotene) and fat-soluble vitamins via new studies undertaken by the CSIRO evaluating specific nutritional parameters following high doses of phytosterols; and

- the levels used in the CSIRO studies of 6.6g free phytosterols/day exceeded the mean and 95th % exposure for consumers in the target group exposed to TOPs in low-fat milk for any population group assessed.

It was concluded from the nutrition report that although reductions in β-carotene were observed following consumption of phytosterol ester-containing foods derived from a vegetable oil source (10.7 g/day phytosterol esters/day which is equivalent to approximately 6.6 g free phytosterols/day), that this will not lead to public health and safety concerns from a nutritional perspective. Other published studies assessed in the nutrition report also suggested that intake of phytosterol esters at high levels (up to approximately 9 g/day) is not associated with adverse effects arising from a reduction in some carotenoids.

The fact that no reductions were observed in β-carotene with TOP administration may reflect subtle differences in design of the study undertaken with TOPs compared to those studies performed by the CSIRO using phytosterol esters. However, the effects of TOP consumption above 4.0 g/day on nutritional parameters, or over the long-term, have not been extensively researched, although many of the individual phytosterol/stanol components are common with phytosterol esters derived from vegetable oils. Overall the conclusions from the Nutrition report (**Attachment 5**) were supportive of TOPs addition in low-fat milks.

5.6 Risk characterisation of TOPs

The data support the safety of TOPs in both the target and non-target population[7] at the level of intake that would be achieved by addition of TOPs to low-fat milk (this category includes no-fat milk) at the levels proposed to be used by the Applicant (0.9g/250 mL serve).

The estimated mean dietary exposure to TOPs did not exceed 1.9 g/day in any population group assessed. This included the scenario of the target population being exposed to TOPs from edible oils and margarines and additional TOPs from low-fat milks. The highest potential exposure by age group (consumers aged 40-65 years at the 95th percentile exposure level) was 4.8 g/day from edible oils, margarines and low-fat milks. This is the target group to which the products will be marketed.

However, it is likely that the dietary modelling overestimates the consumption of TOPs for the following reasons:

- the dietary modelling assumes that all foods within a category contain TOPs at the proposed levels, i.e., consumers purchase only TOP-enriched foods;

- the addition of phytosterols to low fat milks as well as to edible oil spreads results in only a slight increase in predicted mean phytosterols exposure compared to baseline exposure; an increase of 0.2 g/day for all Australians and 0.1 g/day for all New Zealanders. These findings reflect both the greater number of serves of edible oil spreads consumed on average and the much larger number of consumers of edible oil spreads than of low fat milk in the milk + edible oil spreads scenario;

- consumption of foods are actual amounts as recorded in the National Nutrition Surveys (NNSs), as opposed to suggested serve sizes that appear on product labels of foods containing phytosterols. This assumes that consumers will not significantly change their eating habits of the foods containing the phytosterols, but follow existing patterns of use; and that consumers are product loyal, and would always consume the products with added phytosterols; and that

- the data used for modelling is a 24-hour record, which overestimates food consumption for high consumers (the use of multiple day records tends to significantly reduce predicted high consumer exposure).

These assumptions are likely to lead to a conservative estimate for phytosterol dietary exposure for high consumers.

[7] The target population refers to male and female subjects aged over 45 years with elevated cholesterol levels

There were no significant reductions in β-carotene levels following administration of TOPs at levels ranging from 0.9 to 3.6 g/day for 30-days; however, reductions in α-carotene (23%) was observed at the highest levels of administration of TOPs (3.6g/day) compared to controls. No significant reductions in vitamin A were observed.

The nutrition report which specifically assessed studies on phytosterol esters from a vegetable oil source, suggested that reductions in β-carotene levels of approximately 20-25% occurred at doses of approximately 10.7 g/day phytosterol-esters (6.6g free phytosterols/day). However, this is still considered safe from a nutritional perspective as these reductions are still within a broad natural range and there was no measurable effect on retinol or vitamin A levels.

The safety of non-target groups, namely, infants, children, pregnant and lactating women has not been specifically demonstrated in these studies on TOPs and whilst FSANZ considers that there will be no specific concerns at the anticipated low doses, it is not appropriate that these products should be consumed by these groups.

High-consumers (95^{th} %) of edible oils and margarines and low-fat milks have a dietary exposure of between 3.5 and 4.8 g/day for all population groups assessed with the target population having the highest exposure at 4.8 g/day. The available data does not indicate any cause for concern regarding the safety of TOPs at these dose levels; however, the highest dose level of TOPs tested was 3.6 g/day. The new studies on phytosterol esters derived from vegetable oils at 10.7g/day (equivalent to 6.6 g free phytosterols/day) provide some supporting data in this regard. The potential for adverse health effects (including nutritional effects) is considered to be very small, however, risk management strategies should be considered to ensure appropriate use of TOPs in the target group, and to discourage use in the non-target groups.

5.7 Risk management options for TOPs

5.7.1 Risk management issues previously raised

The assessment of previous phytosterol applications had identified a discrepancy between the broad nature of the foods for which approval was sought, and the stated intention of the applicants to target these foods to a particular section of the market i.e. consumers over 40 years with concerns about plasma cholesterol levels. Product descriptions such as low-fat milk and low-fat yoghurt are very broad and may include products that are generally not restricted to a specific population group.

FSANZ considers that phytosterol-enriched foods should be marketed as part of a healthy food choice. Consumers who are concerned about their cardiovascular health are then more likely to make food choices that are consistent with the current public health messages regarding the nutritional benefits of a low-fat, high-fibre diet including multiple daily servings of fruits and vegetables. Certain foods such as those with limited salt (sodium) and sugar content are also compatible with public perceptions of a ‘healthy’ food profile, especially in relation to dietary risks for obesity and cardiovascular disease. For these reasons, phytosterol enrichment of foods that are already associated with healthy eating habits provides a more consistent health message.

With regard to non-target consumers, consumption of phytosterol enriched products by children and pregnant women is presently considered unnecessary. However, casual consumption by individuals other than those in the target group is considered more likely when phytosterols are added to staple foods such as milk, or to foods that are generally available to a broad range of consumers, such as with yoghurts.

Labelling can assist consumers to use phytosterol-enriched foods appropriately, as part of a healthy food choice. In addition, the availability of a broader range of phytosterol-enriched foods may require some additional advisory statements that would apply to all such foods.

5.7.2 Risk management options considered for A508

FSANZ considers that there are minimal, if any, potential risks to consumers of the target group from the use of TOPs in low-fat milk. However, a number of strategies can be employed to achieve the goals of permitting broader choice in the range of phytosterol-enriched products available to interested consumers, whilst at the same time discouraging consumption by children and pregnant or lactating women, thus minimising the likelihood that non-target groups would become regular consumers. The risk management measures proposed in this assessment also aim to address the issue of appropriate consumption by the target group.

These measures included:

- prescribing of maximum limits in the Code for TOPs in low-fat milks;
- specifying a maximum container size;
- an additional labelling statement and other conditions of use to avoid possible over-consumption of TOPs; and
- consideration of the marketing and other strategies proposed by the Applicant to confine exposure to the target population.

5.7.3 Additional information sought from the Applicant on the risk management issues

In light of these issues and in order to clarify the main messages to the specific target group on the label in relation to cholesterol reduction, and to ascertain Parmalat's position on strategies for non-target consumers, FSANZ sought additional information from the Applicant on the following:

1. Specific information as to how these products would be promoted to the identified target consumers, and how the message in relation to achieving an effective daily intake of TOPs would be presented, given that one serve of food per day may not deliver an effective amount for average consumers.

2. The risk management strategy proposed in relation consumption by pregnant women and children as a result of inadvertent use of a phytosterol-containing product in the absence of any specialist dietary advice for this population group.

3. Information on how the effectiveness of the milk products is to be ensured, and hence the truthfulness of the proposed labelling statement regarding the reduction in cholesterol absorption.

FSANZ met with the Applicant on 22 September 2003 to discuss these questions and received letters in response to the above questions on 13 October 2003 and 28 November 2003.

The Applicant submitted information on the proposed labelling and packaging of low-fat milks, which highlighted the following information on the label of a 1-litre carton of low-fat milk:

- there was clear advice on the label that a minimum level of consumption was required (e.g., two 250 mL serves at 0.9g) for a cholesterol-lowering effect;
- the intent stated on the label was that consumption above the recommended two serves/day does not significantly improve effect. This statement on the label also serves to confine consumption to a maximum daily amount;
- the label indicated that the product is not recommended for infants, children, pregnant or lactating women except on medical advice; and that;
- a healthy lifestyle should be maintained.

In respect of the promotion of the products to the target groups, Parmalat submitted survey data from Roy Morgan Brand Planner[8] indicating that 74% of 1 litre milk purchases are from households with no children compared to 13% with one child in the home, 9% with 2 children, and 3% with 3 or more children. This suggested that the majority of purchases of 1 litre milk would be in households without children and that the proposed marketing of these products confined to 1 Litre cartons would be expected to further confine exposure to specific target groups.

Other strategies proposed by the Applicant are as follows:

- a consumer information line will be established to assist consumers with advice on purchasing and consumption of phytosterol-containing foods;
- advertising will be specific for the target audience; and
- educational material will be distributed to medical and diet related professionals.

5.7.4 Current labelling information for consumers

Submissions raised concerns over the use of TOPs, particularly, in non-target groups (e.g. children and pregnant women) and use by individuals already prescribed cholesterol-lowering medication by a medical practitioner.

These concerns have also been raised in previous Applications and are addressed below.

Currently labelling requirements (1-3 below) are as follows for TOPs in edible oils and spreads:

[8] January to December 2001 (Australian data)

1. A statement to the effect that the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables.

For a food for which there is a clear intention to market its beneficial effects, consuming the food as part of a healthy diet is an important dietary message. While there is evidence that TOPs can lead to lower plasma cholesterol by reducing the absorption of cholesterol from the diet, phytosterols are ineffective in preventing the elevation of plasma cholesterol that is a consequence of the ingestion of saturated fatty acids.

This requirement is justified under the third of the section 10 objectives of FSANZ, namely, the prevention of misleading or deceptive conduct, and is consistent with the policy on mandatory advisory statements developed during the review of the Code. It is also consistent with the second section 10 objectives of FSANZ, namely, the provision of adequate information relating to food to enable consumers to make informed choices.

2. A statement to the effect that the product is not recommended for infants, children, and pregnant or lactating women unless under medical supervision.

For specific groups in the population (e.g. children, pregnant and lactating women) it may be inappropriate and unnecessary to reduce cholesterol in these groups without consulting a medical practitioner who could conduct a thorough clinical evaluation to determine the needs. Therefore, a clear statement on the label should indicate that this novel food ingredient is inappropriate for these population groups. The above requirement is justified under the first section 10 objective of the FSANZ, namely, the protection of public health and safety.

Another group is individuals with the rare inherited lipid storage disorder known as sitosterolaemia, which is characterised by excessive absorption of phytosterols (20% compared with approximately 5% in normal individuals). This disorder leads to premature atherosclerosis and by 1996, 26 cases had been identified worldwide. People with this condition are under regular medical supervision and must maintain a diet free of phytosterols. Given the rarity of this disease and the need for individual suffers to be under regular medical supervision, a specific warning on the label for this at-risk group seems unnecessary.

3. A statement to the effect that consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

While the use of phytosterol-enriched spreads may assist in the reduction of plasma cholesterol, its use should not be considered a substitute for cholesterol-lowering medication unless advised by a medical practitioner. The above requirement is justified under the first section 10 objectives of FSANZ, namely, the protection of public health and safety.

5.7.5 Proposed labelling information for consumers

In order to ensure that the target groups receive the appropriate amount of phytosterols in order to achieve the desired effects, and has adequate information to make an informed choice, the following labelling option is proposed in addition to the above current labelling requirements:

Consuming greater than 3 serves per day of products containing plant sterols provides no additional benefit.

This will serve to limit over-consumption of TOPs and is consistent with the data that demonstrates the safety of phytosterols for high consumers within the target group. It will also provide a consistent message for consumers of all phytosterol-containing foods.

5.7.6 Conditions of use

In order to ensure appropriate use of phytosterols in the target group and discourage use in the non-target group, the following conditions of use are proposed:

Foods containing added plant sterols must not be used as ingredients in other foods.

Low-fat milk must not contain more than 3.6 g/litre of free phytosterols (from a tall oil source) and the fat content must not contain more than 1.5 g total fat/100 g liquid

The maximum container size is to be specified at 1 litre.

This will limit over-consumption by prescribing a maximum limit consistent with available safety studies and a maximum container size, be consistent with recent dietary guidelines in relation to healthy food choices (to consume products low in saturated fats) and prohibit the use of TOP enriched foods in mixed foods, other than those specified, will limit the ability of manufacturers to extend the product range beyond the products now under assessment.

5.7.7 Recent international surveys on the consumption of phytosterol-containing foods

As part of the European Commission's decision to allow Unilever to place 'yellow fat spread with added phytosterols' on the market they were obliged to collect data to assess the extent to which the product was reaching its target market. In 2001, Unilever undertook post launch monitoring. The study was undertaken using independent market research companies in The Netherlands, UK, France, Germany and Belgium. The results from about 2000 households are as follows (SCF):

- 75-95% of purchasers were over 45 years old
- 66-90% of regular purchaser came from 1-2 person households
- 62-82% of all people purchasing the product came from 1-2 person households.
- 79-91% of household purchasing the products had no children
- 87-96% of regular purchasers had no children living at home

With the exception of Germany, intake estimated for one person households were similar to those of two to four person households, indicating that the product was predominantly used by one person per household. Actual intakes of the product by the target population of 15-18g/day were lower than the 20-30 g/day predicted. Users of Unilever margarines were also consuming other plant stanol ester products (spread and non spread products).

As part of an on-going surveillance of novel food use in food in Australia and New Zealand, a survey of phytosterol use in food in 3-5 years time may provide useful information with regard to the effectiveness of the proposed risk management measures.

5.7.8 Summary of proposed risk management strategies

In conclusion, in order to manage any possible associated risk from additional consumption the following risk management options are proposed:

Retain the current mandatory advisory statements in Standard 1.5.1.

Prescribe an additional labelling statement that consuming greater than 3 serves per day of products containing plant sterols provides no additional benefit.

Prescribe additional conditions of use (as described above).

5.8 Other issues raised in public submissions (first round)

5.8.1 Issue 1

The AFGC considers that FSANZ has erred in not making a decision at the time of initial assessment to determine whether the application warrants a variation to a regulatory measure.

5.8.1.1 Evaluation

The AFGC are not taking account of the context of section 13 which is the Initial stage - the assessment that FSANZ is required to make is a preliminary one only, and is therefore limited by those circumstances. Thus whether a variation is warranted can only be assessed within that limited and restricted circumstance.

5.8.2 Issue 2

The AFGC disputes that efficacy in relation to labelling statements has anything to do with a safety assessment under Standard 1.5.1-Novel Foods as there is no requirement for provision of efficacy data.

5.8.2.1 Evaluation

FSANZ agrees that this has nothing to do with a safety assessment *per se* under the provisions of Standard 1.5.1. However, there is a broader issue of provision of adequate information to consumers under the requirements in the FSANZ Act on how the effectiveness of TOP containing milk products is to be ensured, and hence the truthfulness of the proposed labelling statement regarding the reductions in cholesterol absorption observed in studies in humans.

The dietary modelling undertaken by FSANZ suggests a significant potential for intake by the target group below the level reported to provide a benefit for average consumers where no change is made to dietary habits. Therefore, FSANZ has required that the Applicant provided data to support the labelling statements that reductions in cholesterol absorption can be achieved by appropriate use of both TOPs containing low-fat milk.

5.8.3 Issue 3

AFGC considers that conditions of use are an essential part of fulfilling the requirements of being a novel food.

5.8.3.1 Evaluation

Specific conditions of use will be required to use TOPs in low-fat milk as detailed in Section 5.7, which addresses this comment.

However, the AFGC submission does not adequately take into account the whole of standard 1.5.1. Taken as a whole, Standard 1.5.1 makes clear that the imposition of restrictions or conditions is not a necessary prerequisite to a food being considered novel. Clause 2 of 1.5.1 provides:

> A novel food must not be sold by way of retail sale as a food or for use as a food ingredient unless it is listed in column 1 of the Table to this clause and complies with the conditions of use, **if any**, specified in column 2 (emphasis added).

The words 'if any' clearly leave open that a novel food may be sold in the manner contemplated in the clause without any condition or restriction whatsoever. That must include any condition or restriction relating to safety. This permits, in FSANZ's view, the sale of a novel food without any conditions or restrictions whatsoever. It is self-evident that the absence of public health and safety concerns, and consequent absence of restrictions upon use cannot prevent a food from being regarded as a novel food.

5.8.4 Issue 4

NZFSA and Food Technology Association of Victoria considered that approval for phytosterol-containing foods should all be addressed at one time rather than approving an increasing number of product categories on a case-by-case basis.

5.8.4.1 Evaluation

The intent of Standard 1.5.1 is prohibition on the sale of novel foods and novel food ingredients unless they are listed in the Table to clause 2. This was a policy issue decided during formulation of the standard in order that an appropriate and adequate risk-based safety assessment could be undertaken before approval was granted. This policy is also consistent with other international regulatory bodies approach to assessment of novel foods.

5.8.5 Issue 5

The editorial note in Standard 1.5.1 and clause 2 (1) of Standard 2.4.2 require review and revision as it is unclear what the situation is with the use of phytosterols and phytosterol esters in the same products (Food Technology Association of Victoria).

5.8.5.1 Evaluation

The requirements of the editorial note and Clause 2 (1) of Standard 2.4.2 is that no mixing of phytosterol esters and TOPs are permitted. They both have separate specifications in order to alleviate manufacturers mixing the two ingredients leading to the possibility of higher doses of phytosterols for consumers.

5.8.6 Issue 6

Request consideration of specifications accepted by other regulatory agencies to be included as part of this application and also requested FSANZ to review the current specifications to include both the free sterol and ester forms. Questioned the need for minimum limits of sterols (Unilever).

5.8.6.1 Evaluation

As there are currently numerous specifications approved and products currently being considered for approval in the EU, it is too early to give consideration to specifications from other regulatory agencies.

The minimum limits relates to the issue of truth in labelling and ensures that TOPs are efficacious. Additionally, the Applicant has indicated that the current specifications for TOPs in edible oil a spread is appropriate for use of TOPs in low-fat and no-fat milk products.

5.8.7 Issue 7

Suggest that consideration is given to a common labelling format for multiple foods containing phytosterols (Unilever).

5.8.7.1 Evaluation

FSANZ is currently giving strong consideration to labelling that provides meaningful information to consumers and is always conscious of international labelling considerations. Refer to section 5.7 above.

5.8.8 Issue 8

FSANZ needs to use previous information on the labelling costing study following the introduction of mandatory nutrition labelling to determine the impact on target groups consumers (Nestle Australia Ltd).

5.8.8.1 Evaluation

The results of the original costing study undertaken by Peat Marwick was contentious and its validity was questioned by another study commissioned by FSANZ and undertaken by the Allen Consulting Group. As the costing concerned the change over costs from old to new labels the original costing studies would be of limited relevance to the introduction of a new product in which the design and printing of a label would represent part of the normal development costs.

Parmalat has already considered the issue of the impacts of labelling on the target groups and have presented evidence of labelling of TOPs in low-fat milks to FSANZ.

5.8.9 Issue 9

The cost of phytosterol-containing foods is high and raises issues of inequity for some consumers (e.g. from lower socio-economic groups). (Queensland Health)

5.8.9.1 Evaluation

Cost is always an issue with lower socio-economic groups because of competing demands on their resources. However, FSANZ does not have a role in determining the price of food. This is a commercial decision on the part of the manufacturer and is subject to the influence of the marketplace. The higher prices for products containing phytosterols reflect the costs of researching and developing products initially, the high costs of extracting the phytosterols, together with production and marketing costs. If consumers are unwilling to pay the price set the product may not be established in the market place.

5.8.10 Issue 10

The Environmental Health Unit of Queensland Health expressed concerns that a broader approval for phytosterols equates to the food supply becoming a vehicle for the delivery of a therapeutic agent not required by the whole population.

5.8.10.1 Evaluation

Phytosterol esters derived from vegetable oils and TOPs are already approved novel foods for use in edible oil spreads and margarines under Standard 1.5.1 in the Code. Although they occur naturally in foods such as legumes and nuts at low levels, they are regarded as novel food ingredients when used in amounts some 5-10 fold higher than normal consumption would provide.

Several identified risk factors for major diseases such as cardiovascular disease and stroke can be correlated in varying degrees with the diet. Of these, obesity, high blood cholesterol, and high blood pressure have been at the forefront of public health messages over an extended period. In Australia and New Zealand, government and non-government organisations like the National Heart Foundation as well as clinicians, nutritionists, dieticians and other health professionals have reinforced the link between dietary and lifestyle choices and improved general health.

The pursuit of a ‘healthy diet’ is now promoted in many countries. These messages were formulated in the early 1980’s and, in Britain, were documented in a report of the National Advisory Committee on Nutrition Education (NACNE, 1983). This publication sought to establish the nature of a healthy diet in practical terms and proposed nutritional guidelines based on accumulated information. The proposed guidelines included recommendations for changes in the profile of energy and nutrient intake in the typical diet over both the short and long term. Specifically, this entailed reductions in total and saturated fat, salt and sugar intake, together with a concomitant increase in fibre intake. Over time, similar dietary recommendations have prevailed in broad nutritional health policy development.

In response to nutritional messages concerning the health benefits of reducing obesity in the population as a whole, and subsequent changing consumer attitudes particularly with respect to processed foods, the food industry has engaged in continuous development of new food products that reflect the changing market conditions. Consumers also have readily demonstrated the extent to which they can alter traditional eating habits in their widespread acceptance and consumption of low or reduced fat foods, even where staple foods in the Australian and New Zealand diet, such as dairy products, are targeted.

Despite the obvious market success and broad availability of fat-modified foods, they are not suitable for all consumer groups. For example, low-fat milk is not recommended for children because of the requirement for a full complement of dietary fats necessary for growth and development. Similarly, low or no-fat versions of many foods are not selected by many consumers, on the basis of personal choice. In general, consumers have adapted well to the co-existence of numerous product variations that cater to individual dietary requirements. In this regard, mandatory labelling, in combination with manufacturer's information provided on packages, are significant communication tools to assist consumers to make an informed choice with respect to their food purchases.

Foods with added TOPs are intended for a specific group of consumers for whom they offer a potential benefit in terms of reducing the absorption of dietary cholesterol. At the same time, consumption of these foods may interfere with the bioavailability of some carotenoids and they therefore offer no advantages to individuals who are not primarily interested in lowering LDL cholesterol. These purchasing criteria are not significantly different from those that can be applied to other more specialised foods targeted to particular sections of the public. In addition, because of the costs associated with production, phytosterol enriched foods are more expensive to purchase compared with the non-enriched counterparts, providing a potent commercial barrier to general consumption. Restricting package sizes of phytosterol enriched foods further reduces their appeal to entire households.

These combined marketing features of phytosterol enriched products places them in a similar retail position to reduced fat products which do not provide benefits to all consumers and whose unsuitability to certain subgroups within the population is managed through appropriate labelling. With phytosterol enriched spreads already on the market for several years, consumers who are sufficiently motivated to purchase these products have demonstrated that their use of them is likely to be informed and appropriate, and therefore restriction to broadening the choice of products is unwarranted.

5.9 Issues raised in public submissions (second round)

At Final Assessment the following issues were identified from submissions received in the second round of public consultation.

5.9.1 Health, safety and nutritional issues

5.9.1.1 Issue 1

- Concerns about whether approval of additional phytosterol-containing foods is the most appropriate strategy to lower cholesterol levels in the general population, the potential medicalisation of the food supply and that the statement to limit consumption of phytosterol enriched milk products to 2-3 serves/day implies a therapeutic dose.

(Queensland Health, Tasmanian Department of Health, Public Health Association of Australia, WA Department of Health).

Evaluation

The broader public health policy of how to effectively reduce cholesterol levels in humans and the subsequent costs and benefits of each individual measure (albeit by dietary intervention measures alone) cannot be decided by FSANZ in this Application. Consumption of phytosterol-containing foods is essentially just one measure whereby consumers can effectively reduce cholesterol.

A minimum number of servings for phytosterol enriched foods represents the appropriate amounts required to achieve the optimal cholesterol lowering effect (as determined in multiple studies) and to convey to consumers the important message that unlimited consumption will not increase this effect. This information assists consumers who choose phytosterol-enriched foods to take full advantage of the potential benefits without incurring unnecessary expense.

The statement to limit consumption to 3 serves/day is intended to convey a specific message to the consumer that is not necessary to over-consume these products in order to gain further benefits. It is also not meant to imply a therapeutic dose, but rather, that the product will lower cholesterol in the target groups if used appropriately.

5.9.1.2 Issue 2

Many submissions in favour of maintaining the restriction on the use of plant sterols to currently approved edible oil spreads express concerns relating to the effects of phytosterols on the levels of β-carotene. Queensland Health, the Tasmanian Department of Health and Human Services and the Public Health Association of Australia suggest that there is evidence that a reduction in β-carotene levels may be associated with chronic diseases.

In particular, the following questions were asked:

- What is considered the broad 'natural range' of plasma beta-carotene levels?
- Has FSANZ considered the studies that have associated lower serum beta-carotene levels with a range of chronic disease?

Evaluation

It should also be noted that in the pivotal study in humans where TOPs were administered in a milk matrix up to levels of 3.6g/day for 30 days that no reductions in β-carotene levels were observed. Whilst this may reflect differences in design of the study undertaken with TOPs compared to those studies performed by the CSIRO using phytosterol esters it also indicates the variability in measurements of specific parameters in these studies.

At the present time, the totality of evidence does not support the view that a potential reduction in serum β-carotene levels following phytosterol intake from vegetable oil sources could be considered a health risk. FSANZ has considered a number of published studies provided by submitters on β-carotene levels in patients with diabetes.

In general, the studies do not report a direct causal relationship between low serum β-carotene and diabetes. Type II diabetes is a chronic disease in which a host of metabolic disturbances are manifest. In addition, the studies generally do not assess confounding dietary factors, accommodate for serum cholesterol levels or account for other significant risk factors such as obesity, a sedentary lifestyle, consumption of alcohol or smoking.

The result of a large number of variables impacting on levels of β-carotene is a broad natural range. This is reflected in nutritional data from the United States in the National Health and Nutrition Examination Survey (NHANES III)[9] published in 1999 using a pool of over 22,000 individuals. Although the data reflect United States levels, they are indicative of the range that would at least be expected in the Australian and New Zealand populations, on the basis of a reasonable expectation that consumption of fruits and vegetables is higher in New Zealand/Australia than in the United States.

For all individuals (ages 4 to 71+), serum β-carotene levels ranged from 3.0 μg/dL at the lowest (1st percentile) level, to 82.6 μg/dL at the highest (99th percentile) level. The mean serum level was identified at 18.9 μg/dL. The data also show that for adults in the target age range (over 40 years of age), the difference in serum β-carotene levels between the 1st percentile and the 5th percentile is almost 100% (i.e. a doubling overall). Therefore, even for consumers of phytosterol-enriched foods already down at 5th percentile level for serum β-carotene, a decrease of 20-25% would be relatively insignificant and not place them outside of the existing broad natural range.

5.9.1.3 Issue 3

- There is still paucity of trials that consider the long-term safety of these products. (Queensland Health, Department of Health Western Australia, Public Health Association of Australia, Tasmanian Department of Health)

Evaluation

This issue was addressed at Draft Assessment in Section 5.3. FSANZ considers that there is no evidence to suggest that long-term effects would result from continuous use of these products, based on the overall toxicological studies now available in animals and the safety/efficacy studies in humans.

The conclusions from the safety assessment were that the safety of TOPs has been established up to an including 3.6g/day, although additional studies on phytosterol-esters derived from vegetable oils provide support on the safety of phytosterols up to higher levels of 6.6g/day. To date, FSANZ has not cited studies, which demonstrated adverse effects up to these levels in the diet.

5.9.1.4 Issue 4

- Exposure estimates for phytosterols are based on out-of-date dietary data, raising concerns over their validity. (Queensland Health, Tasmanian Department of Health, Public Health Association of Australia)

[9] Institute of Medicine (2000). *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, page 448-449

Evaluation

FSANZ is aware of the lapse of time since the previous National Nutrition Surveys and of the need to generate new survey data that documents the changes that may have occurred in the eating patterns of consumers over the last decade. However, when considering the foods encompassed by the current phytosterol applications (namely breakfast cereal, low-fat milk and low-fat yoghurt) FSANZ considers that minimal change is likely to have occurred since the mid 1990's in terms of consumption of these foods, as they were already established, staple foods in both New Zealand and Australia. The data and information provided by the previous NNSs in this case is likely to be appropriate and valid for current times. Where necessary FSANZ looks for additional data on consumption or market sales/volumes for new foods, however for the purpose of this application it was not necessary.

5.9.1.5 Issue 5

- Dietary modelling for adolescents has not been carried out and the DAA recommends this be considered. Adolescents are increasingly being diagnosed with hypercholesterolemia and are a group most likely to consume large quantities of the foods for which A508 applies (breakfast cereals, low fat milk and low fat yoghurt).

Evaluation

Application A508 is only permitting TOPs in low-fat milks not breakfast cereal or low-fat yoghurts. However, the dietary exposure assessment performed for A 508 included potential exposure for adolescents via the modelling performed on the whole population (2 years + for Australia and 15 years + for NZ) and in the 16-44 year age group for females in both countries. Due to the conservative estimates, FSANZ is confident that the present modelling covers adolescents.

5.9.2 Use of phytosterol-containing products

5.9.2.1 Issue 1

- It was questioned what evidence is available that consumers who purchase phytosterol-containing products have demonstrated that their use is likely to be informed and appropriate? (Queensland Health and Tasmanian Department of Health)

Evaluation

FSANZ has no specific evidence on this point, other than the results of the post launch monitoring conducted in 2001 of 2000 households by Unilever using independent market research companies in Netherlands, UK, France, Germany and Belgium. Actual intakes of yellow fat spreads by the target population of 15-18g/day were lower than the 20-30 g/day predicted which suggested that those consumers were using the products appropriately. However, FSANZ has suggested that as part of an on-going surveillance of novel food use in food in Australia and New Zealand, a survey of phytosterol use in food in 3-5 years time may provide useful information with regard to the effectiveness of use of the products and the proposed risk management measures.

5.9.2.2 Issue 2

- The AFGC considers that, since FSANZ has required efficacy studies from the Applicant that FSANZ should specifically permit lowering of cholesterol claims on products containing TOPs, either as part of this Application or as part of the Health Claims Standard when it is developed, without the need for a further Application.

Evaluation

This was addressed at Draft Assessment. There is no specific evaluation of any health claim being considered as part of this Application. Any application for a health claim for TOPs in the future would need to be considered in the context of PP 293 (Health Claims). Irrespective of whether any statement is considered a health claim, all statements on the label should be true and not mislead consumers.

5.9.2.3 Issue 3

- The words '*recommended daily intake*' could easily be confused with Recommended Dietary Intake (RDI), which applies to nutrients, and therefore should not be allowed. (Public Health Association of Australia)

Evaluation

This does not apply to Application A 508 but was part of messages on the labels for Application A 434. However, the term recommended daily intake was not mandated but was there to convey to consumers to consume a minimum serve in order to achieve appropriate reductions in cholesterol levels.

5.9.3 Clarification of the appropriate serves/day of phytosterol-containing foods.

- FSANZ needs to clarify why the recommended level of consumption is three serves/day.

- The statement that there is no additional benefit in consuming greater than 2-3 serves/day of TOPs is **inconsistent** with the other phytosterol Applications (Nestle Australia Ltd and Dairy Australia).

Evaluation

The main message proposed in the labelling formats provided by the industry (although not mandated in the current labelling requirements of Standard 1.2.3) to FSANZ for TOPs or phytosterol esters is to convey to consumers that between 2-3 serves/day of any phytosterol containing products is the most appropriate range of consumption. For phytosterol ester-containing foods consumption of 3 serves per day is desirable, from a choice of cereal, yoghurt, spread or milk; whereas, TOPs can achieve efficacy in low fat milks at a minimum level of 2 serves/day, although 3 serves/day is more desirable in achieving further reductions in LDL and total cholesterol.

FSANZ has cited clear evidence from the industry sectors that they intend to use these messages on the label of products. Therefore, in the case of TOP-containing foods it will be two serves of the product as a minimum requirement but a consumer still does not need to consume greater than 3 serves.

This would ensure that consumers reach a minimum level for either tall oils (e.g. in low-fat milks) or phytosterol esters (from a vegetable oil source) containing products (e.g. yoghurts) whilst the message on the label (a mandatory requirement under Standard 1.2.3) is that >3 serves/day will not be any more beneficial in lowering total or LDL cholesterol levels. This is consistent with international legislation and labelling requirements and will also alleviate any concerns in relation to reductions of β-carotene levels as discussed extensively in the Nutrition Report. The FSANZ assessment considers these levels are safe and efficacious and will effectively limit over consumption of phytosterol-containing products by the target groups.

In conclusion, the inconsistency in the key messages between Application A508 in respect of the statement suggesting that there is no additional benefit by consuming greater than 2-3 serves/day, compared to the other Applications (A434 and A433) is noted, and reflected minor differences in the efficacy data between studies provided in support of Application A508 compared to the breakfast cereal Application A433.

FSANZ has amended the proposed risk management strategy in Section 5.7 for A508 to up to 3 serves/day of TOP-containing low-fat milks as not providing any additional benefits in order to be consistent with phytosterol ester containing product messages and to provide greater clarity for consumers.

5.9.4 Labelling of phytosterol-containing foods

5.9.4.1 Issue 1

The NZFSA suggests that clause 2 of Standard 1.5.1 is amended as follows, in order that consumers can avoid the potential for over-consumption (via mixing of tall oils and esters containing products):

- Tall oil phytosterols are labelled as ‘plant sterols’ (tall oil phytosterols)’ and;
- Phytosterol esters are labelled as ‘plant sterols’ (phytosterol esters)’

Evaluation

The proposed mandatory labelling statement that there is no additional benefit in consuming greater than 3 serves/day of phytosterol-containing products should ensure that consumers would have sufficient information in order not to over consume either TOP or phytosterol-ester-containing products.

5.9.4.2 Issue 2

- Consideration should be given to a common labelling similar to that under consideration in the EU whereby producers of these types of products work to a similar wording and format to facilitate consumer choice and understanding (Unilever).

Evaluation

The main differences of the EU labelling requirements compared to the proposed drafting for A 508 relates to the following:

- The EU has advice on the label that the product is to be used as part of a healthy diet, including regular consumption of fruit and vegetables to help maintain carotenoid levels. This differs from the proposed FSANZ labelling requirements in which advice is to consume as part of a diet low in saturated fats and high in fruit and vegetables (i.e., there is no mention of regular consumption of fruit and vegetables to help maintain carotenoid levels).

- The EU designates 'plant sterol', 'plant sterol', 'plant stanol' or 'plant stanol ester' rather than the proposed FSANZ drafting as either 'tall oil phytosterols' or 'plant sterols'.

However, overall FSANZ considers that the intent of the proposed draft standard for A 508 is relatively consistent with the EU labelling of foods and ingredients with added phytosterols, phytosterol esters, phytostanols and/or phytostanol esters (EC No 608/2004) of 31 March 2004.

5.9.6 Specific comments on the draft standard

5.9.6.1 Issue 1

- The maximum level of 3.6g/L is overly prescriptive and inconsistent with the requirements of other phytosterol-containing foods (e.g. phytosterol esters added to breakfast cereals. It is recommended that **'no more than 3.6 g/L'** be prescribed, compared to the current words in the drafting: 'where the total phytosterol (from a tall oil source) added is 3.6g/L of milk'. (Nestle Australia, Dairy Australia, AFGC).

Evaluation

FSANZ agrees with this and has changed the drafting accordingly.

5.9.6.2 Issue 2

- By restricting container size and level of phytosterols in the proposed drafting it is not possible for manufacturers to offer consumers flexible formats to suit their particular requirements – for example if consumers wanted to get 0.8g of phytosterols in a smaller serving size, it is not possible to meet this consumer need with the current drafted regulation (Unilever).

Evaluation

Restriction of the container size was part of an overall risk management strategy to focus purchase of TOP containing low-fat milks to the target group, as data had suggested that this would avoid purchases from non-target groups such as children.

5.9.6.3 Issue 3

- AFGC recommends the drafting to be changed to allow for capacity in I L containers of a little over 1 Litre (to allow for headspace in packages) to the following:

Supplied in a package, the nominal capacity of which is no more than 1 Litre.

Evaluation

The drafting has been amended with new words to allow for small variations in container sizes.

5.9.6.4 Issue 4

- The term 'low-fat milk' is not otherwise defined in the Code. This should be rectified prior to this Proposal being finalised (FTA Association of Victoria).

Evaluation

It is correct that low-fat claims are not defined in the Code. However, these claims are covered in Australia under the Code of Practice on Nutrient Claims in Food Labels and in Advertisements (CoPoNC) where a liquid food must not contain more than 1.5 g total fat per 100 g of liquid food. This maximum level is consistent with the maximum fat level proposed in the current drafting for low-fat milks in clause 5 of Standard 2.5.1 (**Attachment 1**) for TOP-containing milk.

FSANZ is also looking at the issue of low-fat claims in Proposal P293 - Nutrition, Health and Related Claims where it is being suggested that CoPoNC criteria for 'low fat' claims be retained.

In addition, CoPoNC does not apply to foods imported into Australia and is not recognised in New Zealand. In NZ 'low fat' claims are managed by reference to the general provisions in the *New Zealand Fair Trading Act* 1986, which require that any representations regarding the labelling of food must not be false or misleading. Previous to December 2002, they were managed under the *New Zealand Food Regulations* 1984.

Therefore, FSANZ sees no further need to define low fat any further in relation to use in TOP-containing low-fat milks.

5.9.6.5 Issue 5

- In the Draft Variations, clause 5 requires that TOPs when used in milk should be supplied in a package which is no more than 1 litre capacity. This means that TOPs will be supplied in smaller packs, i.e. 200, 250, 500 mL capacities which in turn are pack sizes consumed by children. (FTA Association of Victoria).

Evaluation

The Applicant has informed FSANZ in writing (16 July 2004) that TOPs in low-fat milks will be sold in 1 Litre gable top packs only and that there is currently no proposal to sell them in smaller container sizes. However, should this occur in the future, FSANZ considers that there are adequate mandatory labelling requirements in place indicating that these products are not recommended for children.

6. Regulatory Options

6.1 Option 1 – prohibit the use of TOPs in low-fat milks

This option maintains the status quo by not including these foods in the Table to clause 2 of Standard 1.5.1, thereby retaining the current limitations on the use of TOPs to edible oil spreads only.

6.2 Option 2 – approve the use of TOPs in low-fat milks

This option will result in an amendment to the Code to permit the sale and use of TOPs at specified levels in low-fat milks.

6.3 Option 3 – approve the general use of TOPs

This option will result in an amendment to the Code to permit the use of TOPs as ingredients in any food to a maximum permitted level.

7. Impact Analysis

7.1 Affected parties

- consumers, especially target groups such as adults over 45 years of age with health concerns about high serum cholesterol and non-target groups such as pregnant and lactating women and children;
- dietitians and allied health professionals providing dietary advice to consumers;
- the manufacturing and retail sectors of the food industry; and
- Government generally, where a regulatory decision may impact on trade or WTO obligations, and State, Territory and New Zealand enforcement agencies.

7.2 Impact Analysis

In the course of developing food regulatory measures suitable for adoption in Australia and New Zealand, FSANZ is required to consider the impact of all options on all sectors of the community, including consumers, the food industry and governments in both countries. The regulatory impact assessment identifies and evaluates, though is not limited to, the costs and benefits of the proposed regulation, including the likely health, economic and social impacts.

The following assessment of the costs and benefits of the three regulatory options identified so far is based on an assessment of the information supplied by the applicant, knowledge of previous considerations relating to the use of phytosterols in the food supply and public submissions.

7.2.1 Option 1

There is a potential cost to consumers with this option in terms of the lack of availability and choice of TOPs-enriched milk products. Similarly, there is an identifiable cost to the food industry in terms of a loss of product range and marketing opportunities. There would be no immediate impact on government. There are no benefits to consumers or government.

7.2.2 Option 2

7.2.2.1 Impact on Consumers and the Community

There is a reported benefit to consumers from consuming TOPs in milk products, leading to a reduction in their blood cholesterol. The community would also benefit from any improvement in health status. The evidence also shows that consumption of TOPs under specified conditions, which equate to normal and informed use by consumers, is safe.

A cost to consumers would be the lack of choice of phytosterols in full fat milk products. This disadvantages consumers who may be 'brand loyal' and prefer to purchase a full-milk product for taste etc. rather than a low-fat product.

Another cost would be that a wider range of foods containing added phytosterols may lead to over consumption of phytosterol-containing foods.

7.2.2.2 Impact on Industry

This option would provide an alternative novel food ingredient and would increase market opportunities for other manufactures of low-fat milk beverages. There may be some impact of the labelling requirements for some manufacturers in terms of costs associated with labelling.

7.2.2.3 Impact on Government

In the short-term, this option would not have a material impact on the enforcement activities of the State, Territory and New Zealand Governments.

However, it would have an impact on the resources required to provide dietary advice to consumers from organisations within governments charged with this role.

In the long-term, governments may benefit in terms of health expenditure from lower blood cholesterol in the community associated with the normal and informed use of TOPs in low-fat milks, although the extent of this benefit cannot be measured at present.

7.3 Option 3

This option was not considered appropriate due to the possible expansion of phytosterols in a range of foods that would effectively expose non-target consumers to phytosterol-containing foods. This option overall received no strong support from public submissions.

7.4 Evaluation

Option 1 would not allow TOPs as an ingredient in low-fat milks. This option cannot be justified on the basis of public health and safety. It also imposes costs on consumers of loss of choice of new products where their safety has been established.

Option 2 allows TOPs in low-fat milks, which by virtue of the data submitted, have been shown to be safe. Option 2 does not subject consumers, the community or governments to other costs.

Overall, **Option 2** is preferred because of the two options it most clearly achieves the objectives of this assessment: providing a reasonable assurance of the safety of consuming TOPs products, providing information to consumers that will contribute to the safe consumption of TOPs and provides a fair trading aspect to allow manufacturers and businesses a new source of phytosterols for inclusion in low-fat milks.

8. Consultation

FSANZ conducted an Initial Assessment on A508 and public comments on the application were called for from the period 13 August to 24 September 2003. A total of 13 submissions were received at Initial Assessment and are summarised in **Attachment 6.**

A second round of public consultation was called for from the period 26 May to 21 July 2004. A total of 13 submissions were received at Draft Assessment and are summarised in **Attachment 6.**

The Initial Assessment Report sought early input from the general community on a range of issues concerning the availability of a low-fat milk containing TOPs. Comment was also invited on a broader permission for food products containing phytosterols than is currently permitted in the food supply in Australia and New Zealand. These comments have been addressed in the Draft and Final Assessment Report.

All individuals, groups or organisations who made a submission in relation to this application were included on a mailing list to receive further FSANZ documents pertaining to this application.

FSANZ sought public comment to assist with assessment of the application on the following:

- scientific aspects of the application, in particular, any information relevant to the safety assessment;

- information that would assist in an assessment of the appropriateness and effectiveness of current labelling statements on edible spreads containing phytosterol esters derived from vegetable oils and/or phytosterols derived from tall oils;

- parties that might be affected by having this application approved or rejected;

- potential costs and benefits to consumers, industry and government.

8.1 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

There are not any relevant international standards, namely a Codex standard for TOPs. Amending the Code to allow TOPs as novel food ingredients may have a liberalising effect on international trade via removal of the prohibition on the sale of these novel food ingredients. Therefore, this matter was not notified to the WTO as either a TBT or SPS issue.

9. Conclusions

The conclusions from the draft assessment are as follows:

- there are no anticipated public health and safety concerns associated with the use of TOPs in low-fat milk when used in conjunction with the risk management measures proposed;
- there is evidence that TOPs when incorporated into low-fat milk can, following consumption, reduce cholesterol absorption in humans;
- the nutrition assessment indicates that TOPs have no significant adverse nutritional effects at the proposed levels of use;
- conditions of use, including an additional labelling statement, are proposed as part of a comprehensive risk management strategy to ensure appropriate use of TOP-enriched low-fat milk by the target consumers, and to discourage use by non-target consumers;
- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and
- the Regulatory Impact Statement indicates that, for the preferred option, namely, to approve the use of TOPs as a novel food ingredient in low-fat milks; the benefits of the proposed amendment outweigh the costs.

ATTACHMENTS

1. Draft variations to the *Australia New Zealand Food Standards Code*
2. Food Technology Report
3. Safety Assessment of Tall Oil Non-Esterified Phytosterols (TOPs)
4. Dietary Exposure Assessment Report
5. Nutrition Assessment Report for Application A433 – Phytosterol esters in breakfast cereal bars and Application A434 – Phytosterol esters in low-fat milk and low-fat yoghurt
6. Summary of Submissions received

Attachment 1

Draft Variations to the *Australia New Zealand Food Standards Code*

To commence: On gazettal

[1] ***Standard 1.2.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Food regulated in Standard 2.4.2 containing tall oil phytosterols	Statements to the effect that – 1. the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; and 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

substituting –

Foods containing added tall oil phytosterols	Statements to the effect that - 1. the product should be consumed as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication; and 4. foods containing added plant sterols do not provide additional benefits when consumed in excess of three serves per day.

[2] ***Standard 1.5.1*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Tall oil phytosterols	The requirements in clause 2 of Standard 1.2.3. The name 'tall oil phytosterols' or 'plant sterols' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to food - (1) according to Standards 1.3.4 and 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food.

substituting –

Tall oil phytosterols	The requirements in clause 2 of Standard 1.2.3. The name 'tall oil phytosterols' or 'plant sterols' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to edible oil spreads – (1) according to Standard 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food. May only be added to milk in accordance with Standard 2.5.1. Foods to which tall oil phytosterols have been added may not be used as ingredients in other foods.

[3] ***Standard 2.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting after the Editorial note to clause 4 –*

6 Tall oil phytosterols

Tall oil phytosterols may only be added to milk –

(a) that contains no more than 1.5 g/100 g milkfat; and
(b) that is supplied in a package, the labelled volume of which is no more than 1 litre; and
(c) where the total phytosterol (from a tall oil source) added is no more than 3.6 g/litre of milk.

Attachment 2

FOOD TECHNOLOGY REPORT

A508 – PHYTOSTEROLS DERIVED FROM TALL OILS AS INGREDIENTS IN LOW FAT LIQUID MILK

Introduction

Phytosterols (plant sterols) belong to a group of plant compounds that are found in a variety of foods in the human diet. The tall oil non-esterified phytosterols are sourced from tall soap, a by-product that is formed in the pulping process of coniferous trees [1].

Tall oil phytosterols as well as phytosterols derived from edible vegetable products are comprised of varying ratios of the same four primary phytosterol substances sitosterol, sitostanol, campesterol and campestanol, with varying amounts of minor components such as stigmasterol and brassicasterol. The physiological activity of phytosterol products is due to the presence of these compounds[1].

Free tall oil phytosterols such as 'Reducol^{TM}' (commercial name of the tall oil phytosterols of this Application) vary from phytosterol ester products as a result of the constituent phytosterol profile. These variations arise for the following reasons:

1. the source material differs;
2. fatty acid esterification is not used to modify the solubility properties for product application; and
3. hydrogenation processing is not used.

Structure of plant sterols and stanols

Plant sterols have a role in plants similar to that of cholesterol in mammals, e.g. forming cell membrane structures. The sterol ring is common to all sterols, with differences in the side chain accounting for different properties in sterol compounds. Phytosterols fall into one of three categories: 4-desmethylsterols (no methyl groups); 4-monomethylsterols (one methyl group) and 4,4-dimethylsterols (two methyl groups). The most common plant sterols are β-sitosterol, campesterol and stigmasterol and structurally these are very similar to cholesterol, belonging to the class of 4-desmethylsterols (Fig. 1)[1].

Plant stanols are hydrogenation products of the respective plant sterols, e.g. campestanol/campesterol and sitostanol/sitosterol, and are found in nature at very low levels. Stanols have no double bonds in the sterol ring and belong to the group of 4-desmethylsterols (Fig. 1).

All plant sterols and stanols are closely related in structure to cholesterol. The main difference is the presence of a methyl or ethyl group in their side chains (again see Fig. 1).

Solubility

Free phytosterols or stanols in free form; exhibit limited lipid solubility. Some manufacturers elect to esterify them with fatty acids from edible oils. The solubility of free sterols in oil is around two percent, but the solubility of sterol esters in oil exceeds twenty per cent.

The esterification of phytosterols improves their solubility in oil and facilitates their incorporation into certain foods. However, esterification does not materially affect the physiological properties of the phytosterol components. Once ingested, the esters are rapidly cleaved by endogenous lipases, releasing the free phytosterols that are then able to interact with cholesterol absorption[6].

On a molar basis, free and esterified phytosterols exhibit similar physiological activity. This equivalence means the extensive safety and efficacy data for esterified phytosterol forms is directly and appropriately applicable to non-esterified forms. Difference in molecular weight of phytosterols needs to be taken into account when assessing safety and efficacy i.e. 1.6 grams esters is approximately equivalent to 1.0 grams of free phytosterols[2].

Phytosterol esters are fat soluble, and the main reason for esterification is to allow incorporation into fatty foods such as margarines. The Applicant has advised FSANZ that tall oil non-esterified phytosterols are able to blend with non-fat matrices, although details of this specific process remain intellectual property of the company. The free phytosterols are therefore able to be incorporated into non-fat foods such as low-fat and non-fat milks as requested in the Application.

Stability

Phytosterols and their fatty acid esters are basically very stable compounds and experience only limited damage during oil processing [3]. Only under specific conditions, such as high temperatures (>100 °C) in the presence of air, may some oxidation of phytosterols occur, in the same way as for cholesterol [4]. Phytosterols are mono-unsaturated compounds (double bond in the B-ring), which are much more stable than the mono-unsaturated fatty acids (e.g. oleic acid), because of steric hindrance by the ring structure. Therefore even under severe conditions, such as during deep frying, sterol oxidation products are only formed at ppm concentrations [5].

The Applicant states that there are some losses (approximately 5-10%) of the tall oil phytosterols content with heating at high temperatures (100˚C) for several hours, which appear to be as the result of oxidation.

Production methods

Tall oil soap is the lipid layer skimmed off when wood chips are digested at pH 14 and 50˚C, to free wood fibres. Phytosterols are extracted directly from the tall oil soap and purified in a three-step process.

1. The first step is a solvent extraction of the tall oil soap. Organic solvents, water and tall oil soap are mixed while heating in stainless steel reactors. The mixture is allowed to separate into distinct aqueous and organic phases. The organic phase contains extracted organic materials, and 15-25% sterols, which is used in the next step of the process.

2. The second step consists of a complexation-washing process that removes the bulk of the organic material. The extract from Step 1 is mixed while heating with a solvent, and complexing agent. The sterols rapidly bind to the agent, which are then separated from the solvent phase by centrifugation. Next, the complexing agent is dissolved from the crude complex by heating in water. The water is removed and the resulting material contains 60-75% sterols, that are referred to as crude sterols.

3. Crude sterols are dissolved in alcohol at elevated temperature. The temperature of the mixture is reduced to allow for crystallisation of the sterols. The crystals are recovered and then dried. The mixture is assayed for the content of sterols. If the desired purity is not achieved, then the mixture is re-crystallised.

Legislation

Recent tall oil phytosterol FDA GRAS notifications (where the FDA raised no questions) are:

- GRN 000039 (2000) – Tall oil phytosterols – for use in vegetable oil spread.
- GRN 000112 (2002) – Phytosterols from vegetable oils or tall oil – for use in spreads, various dairy products (including milks, ice-cream, cream cheese), snack bars, various dressings and various breads and rolls.

CONCLUSIONS

Tall oil phytosterols are sourced as a by-product from pulping of coniferous trees. The ratio of primary phytosterol substances and minor compounds of tall oil phytosterols is different to that of other oils and this in turn determines physiological activity. The major limitation to this point, on the wider use of phytosterols and stanols, has been their limited solubility in food matrices and consequently this has affected the efficacy with which they could be blended into foods.

However, tall oil phytosterols do not need to be esterified to improve their solubility as the Applicant has suggested that they are able to be incorporated into the non-fat food media of this Application, namely low-fat and non-fat milks.

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1. 'Phytosterol Esters (Plant Sterol And Stanol Esters)'. The Institute of Food Science & Technology UK, Information Statement, June 2000.

2. Lea, L. (July 2002) Phytosterol-Esters: Use in a Range of Food Products Volume 1 of 3. Unilever UK document D02-018 (application to the UK Food Standards Agency to include phytosterol esters to 'milk' and 'yoghurt' type products).

3. Ferrari R.A., Esteves W., Mukherjee K.D. and Schulte, E., 1997, 'Alterations of sterols and steryl esters in vegetable oils during industrial refining'. Journal of Agricultural and Food Chemistry, 45, 4753-4757.

4. Yanishlieva-Maslarova, N.V. and Marinova, E.M., 1985, 'Autoxidation of sitosterol in lipid systems of different unsaturation degree'. Journal of The American Oil Chemists Society, 62, 622.

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6. Expert Panel Statement, 'Determination of the GRAS status of Tall Oil derived Phytosterols Used as an Ingredient of Vegetable Oil-Based Spreads'.

Other relevant references

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Colebank, S. (31/3/03) The Rising Stock of Sterols & Stanols.
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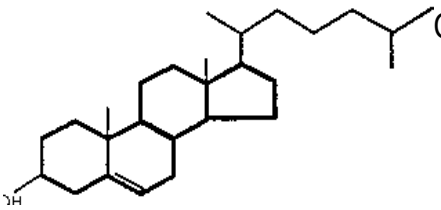
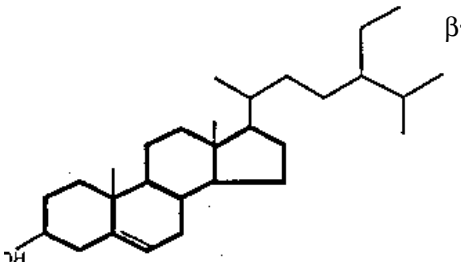
European Commission, Scientific Committee on Food. General view of the Scientific Committee on Food on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on ß-carotene. SCF/CS/NF/DOS/20 ADD 1 Final (3 October 2002).

Figure 1. Structure of cholesterol and some common phytosterols and phytostanols (taken from Reference 1).

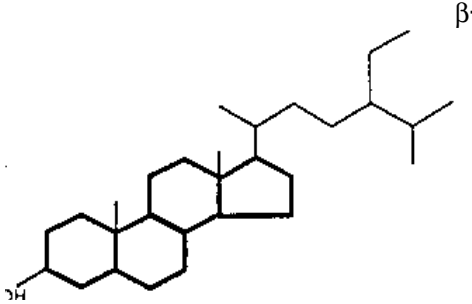
Cholesterol



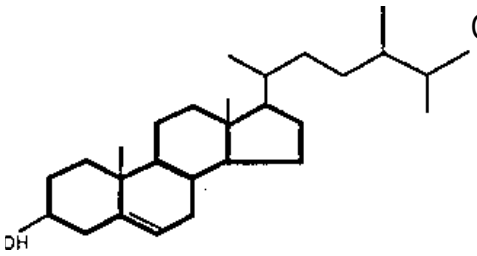
β-Sitosterol



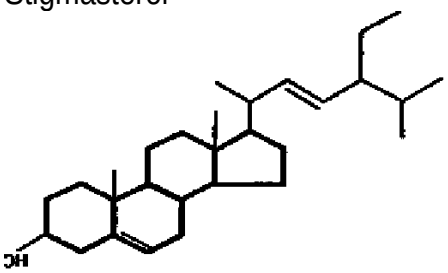
β-Sitostanol



Campesterol



Stigmasterol



Attachment 3

SAFETY ASSESSMENT OF TALL OIL NON-ESTERIFIED PHYTOSTEROLS (TOPS)

The safety of TOPs were reviewed under Application A417 following a previous application from Novartis Pty Ltd. A summary of the safety assessment is included below. Additional studies submitted on the safety and efficacy in humans by Parmalat for A508 has also been included in the safety assessment below.

Summary of the safety assessment for TOPs in Application A417

Absorption, Distribution, Metabolism and Excretion (ADME)

Studies on ADME were reviewed under Application A410-Phytosterol esters derived from vegetable oils and were considered appropriate for the assessment of tall oil non-esterified phytosterols (TOPs), as these studies covered the specifications of the individual phytosterol components.

The major sterols and sterol esters derived from vegetable oils were tested in rats *in vivo* to compare their uptake, tissue distribution, metabolism and excretion with those of cholesterol and cholesterol esters. The summary is as follows:

- The rats adequately tolerated dosing with the sterols sitosterol, sitostanol, stigmasterol, campesterol, and campestanol, and also sitosterol-esters. Sitosterol, sitostanol, stigmasterol and campestanol, in addition to the linoleate ester of sitosterol, were poorly absorbed (between 1.2 and 5% of dose in females, and 0.5 - 1.9% in males), whereas a greater proportion of campesterol and cholesterol were absorbed (12 - 27% in females, 24% cholesterol absorbed in males).

- Sterols were found in tissues at low concentrations. Sitosterol and sitostanol were found in the adrenals, ovary and stomach at low concentrations, campestanol in the adrenals, ovaries and intestinal epithelia, and campesterol in the adrenals, spleen, intestinal epithelia, ovaries, liver and bone marrow.

- The greater proportion of each of the phytosterols investigated was eliminated in the faeces, as both the free sterol and sterol esters, suggesting that some esterification of sterols occurs in the gut *in vivo*. A minor faecal metabolite was observed in various studies, but this was not characterised and may have been an oxidation product, although from *in vivo* or *ex vivo* storage was not clear.

Sub-chronic Studies

In a 13-week subchronic study in rats, there was no evidence of toxicity following treatment with TOPs in the diet of rats up to doses of 5%. The No Observed Effect Level (NOEL) was 4161 mg/kg bw/day in male rats.

Chronic Studies

No chronic studies or carcinogenicity studies were submitted.

Developmental study

A published paper of a developmental/teratology study where rats received up to 5% plant *stanol esters* in the diet for a gestation period of 21 days demonstrated no teratological potential.

Reproduction studies

A 2 generation reproduction study in rats dosed with up to 5% phytosterols in the diet (as a mixture of sterols and sterol-esters at up to 8.0 %) equivalent to up to 4.4 g/kg/day, for 10 weeks prior to mating, then throughout gestation, lactation and weaning, found no significant effect on clinical, growth or reproductive parameters in either the F_0 or F_1 generations.

A published paper of a 2 generation reproduction study in rats dosed up to 4.38% plant *stanol esters* for 10-weeks prior to mating, then throughout gestation, lactation and weaning found no significant effect on clinical or reproductive parameters in either F0, F1 or F2 generations. A treatment related decrease in bodyweights in male and female pups of the F0 and F1 generation was observed at the highest dose of 4.38%. However, this decrease in bodyweight was attributed to the lack of absorption of phytosterols and the resulting reduction in the caloric value of the test diet compared to controls.

Genotoxicity studies

TOPs were found to be negative in a battery of bacterial and mammalian genotoxicity test systems at doses in vivo up to 2000 mg/kg bw and concentrations in vitro up to 1200 μg/ml. These suggest that TOPs are non-genotoxic both with and without metabolic activation.

Other animal studies

A study was conducted to evaluate the oestrogenic potential of TOPs. Doses of up to 5000 mg/kg/day for four consecutive days to immature female rats did not lead to an increase in absolute uterine weight or in the uterine weight/terminal body weight compared to normal controls (significant increases were noted in the positive control groups). There were significant reductions in bodyweight gains at 2500 and 5000 mg/day.

<u>In vitro oestrogenic potential</u>

Two *in vitro* studies on the oestrogenic potential of phytosterols were performed, using binding to rat uterine cytosol oestrogen receptors and binding to and activation of human oestrogen receptor in yeast cells. These studies used phytosterols at up to 100 and 129 μM, with no binding evident in either test system. Positive controls (β-estradiol) performed as expected in these assays.

<u>In vivo oestrogenic potential</u>

A series of studies were conducted to examine the uterotrophic potential of the dietary sterols, using various sterols and their mixtures in rats by gavage. The end point determined was the wet weight of uterus.

Phytosterols, phytosterol esters, cholesterol and cholesteryl palmitate were all found to be negative in this assay system at doses of up to 500 mg/kg/day for 3 days. Positive controls coumestrol and β-estradiol both gave positive responses (increased uterine weights) at doses of 20 and 0.4 mg/kg/day respectively.

Efficacy Studies in animals

These studies, while primarily efficacy studies, do provide some limited information on the toxicity of TOPs. A short-term (10-day) study in rats was submitted. In this study, TOPs at up to 1% w/w in diet (1000 mg/kg bw/day) were well tolerated by rats with no reduction in growth rates.

A number of subchronic efficacy studies were submitted in mice, hamsters and rabbits. In these studies TOPs at up to 2% w/w in the diet were well tolerated (representing doses of up to 3340 mg/kg bw/day in males) for a period of up to 20 weeks. There appeared to be no significant clinical findings (although the studies did not specifically state this or present clinical data), effects on bodyweights or food intakes and growth. Histopathological analysis (albeit limited) was unremarkable even at the highest doses.

An assessment by FSANZ of the efficacy of treatment with TOPs on reductions in cholesterol was not undertaken, although the Applicant has presented numerous published and unpublished studies in which the efficacy of oral doses of TOPs in reducing blood cholesterol has been demonstrated in animals.

Human Studies

The Applicant supplied original data on available studies in humans on TOPs. The phytosterols were administered in four forms, vegetable oil, margarine, milk and a cereal based nutritional bar. Two of the studies were for a period of 10 days in normal and hypercholesterolaemic subjects at 1.5g/day (medium was vegetable oil), one 30-day study in normal subjects with phytosterol-containing table spreads at 1.5g/day, a 28-day study in normal subjects with phytosterol-containing milk at 0.9, 1.8 and 3.6g/day and an 8-week study in hypercholesterolaemic subjects with phytosterol-containing snack bars at 1.8g/day.

Total plasma cholesterol was reduced by 5-7% and low density lipoprotein (LDL) by 5-14% at a dosage of 1.5g/day with a vegetable oil matrix (10-days); 9% and 14% respectively with margarine at 1.5g/day (30-days); 4% and 3% with a cereal bar at 1.8g/day (8-weeks) and; 9% and 13% respectively with a full-milk (3.6%) based beverage at 3.6 g/day (4-weeks).

The studies demonstrated that in normal healthy human subjects and in subjects with hypercholesteraemia, doses of TOPs up to a level of 1.5 g/day over a 10-day period were well tolerated. In the third study, subjects tolerated doses of TOPs up to a level of 1.5g/day over a period of 30 days.

In the fourth 28-day study at 0.9, 1.8 and 3.6g/day, clinical signs and symptoms were not confined to a specific sex and were generally considered unrelated to treatment as there was no dose response and there was no significant difference between treatment groups.

There were no differences between treatment groups in weight post treatment, blood pressure, pulse rate, blood chemistry and haematology parameters or urinalysis other than isolated increases in platelet counts, eosinophils, red blood cell count, haemoglobin and haematocrit during treatment, although no dose-response relationship was evident.

Vitamin A and E and alpha and beta-carotene levels were compared at the start of treatment and at week 4 post-treatment. Reductions were noted in vitamin A levels post-treatment at doses of 0.9, 1.8 and 3.6g/day (10%, 12% and 9% respectively).

However, this lacked a dose-response and there were no other significant differences between treatment groups between day 0 and week 4 post-treatment with respect to either the change or the relative change in vitamin A levels. There were no significant differences between groups with respect to vitamin E levels.

There were no significant differences between treatment groups at day 0 or 4-weeks post-treatment in either alpha or beta-carotene levels. A significant ($p<0.01$) reduction in subjects dosed at 3.6g/day in mean alpha-carotene levels was observed between day 0 and week 4 (23% reduction) compared to placebo values. It was concluded that human subjects tolerated doses of TOPs in a milk-based beverage up to a level of 3.6g/day over a period of 28 days.

In the fifth study, although there were some reports of adverse symptoms, these were also reported in the placebo group. It was concluded that human subjects tolerated doses of TOPs in a cereal based nutritional bar up to a level of 1.8g/day over a period of 8-weeks.

International reviews of the safety of phytosterols

In April 2000, the Scientific Committee on Food (SCF) of the EU concluded that addition of phytosterol esters derived from vegetable oils in yellow fat spreads, as a novel food was safe at levels up to 8% free phytosterols/100g provided the phytosterol profile was as follows: 30-65% β-sitosterol, 10-40% campesterol, 6-30% stigmasterol and a total of 5% other phytosterols.

Since that time further applications for use in novel foods enriched with non-esterified phytosterols and also containing some phytostanols (bakery products, snack products, meat products, margarine, soft cheese, yoghurt or fruit-based milk drinks) have been submitted for approval and the SCF recently expressed an opinion on the safety of non-esterified phytosterols (SCF, March 2003).

They concluded that, provided that intakes of phytosterol enriched foods did not exceed 3g/day then the use of phytosterols in the above specific foods were safe provided the phytosterol/stanol profile was as follows: up to 80% β-sitosterol, 15% β-sitostanol, 40% campesterol, 5% campestanol, 30% stigmasterol, 3% brassicasterol and 3 % other phytosterols.

Additional studies in humans submitted by Parmalat

The Applicant supplied published papers on TOPs administered in three forms, margarine and shortening, edible oils, full milk (3%) and chocolate to both normal and hypercholesterolaemic subjects (**Table 1**).

The studies in edible oils and chocolate demonstrated that reductions in mean total and LDL cholesterol could be achieved at doses of 1.7 g/day (edible oils) or 1.8 g/day (chocolate) over a 30 day period; however, an independent assessment of whether any adverse clinical effects, changes in clinical chemistry parameters and/or urinalysis was not possible, as the data was not presented in the paper. These studies essentially concentrated on the efficacy of TOPs rather than an assessment of the safety of TOPs.

However, the study by Pritchard and Beer (2000**)** in full milk suggested that human subjects tolerated doses of TOPs mixture in a full milk-based beverage up to a level of 3.6 g/day over a period of 28 days without significant adverse effects being experienced by subjects, other than reductions in alpha-carotene levels observed at the highest dose used. No reductions in β-carotene levels were observed.

A study by Plant and Mensink (1998) in margarine and shortening suggested that subjects tolerated plant stanol esters up to a dose of 6.8 g/day (4 g free phytostanols), without any evidence of adverse clinical effects or effect on blood haematology/chemistry parameters, although the data presented was not as comprehensive as the Pritchard and Beer (2000) study.

A recent published study submitted by Parmalat with low-fat food items (bread, meat products, jam and yoghurt) with incorporated TOPs at doses of 0.91 to 4.17g/day for 15-weeks suggested that a reduction of total cholesterol of 8% and LDL of 13% could be achieved. However, as the percentage of fat in these low-fat foods was not stated in the study, FSANZ cannot verify what exact percentage of fat (referred to by the Authors as low-fat) would achieve the above reductions[10]. This is also supported by another study with a low-fat containing margarine derived from a tall oil source, which achieved reductions in total cholesterol of 10.6% and LDL of 13.7%[11].

Overall conclusions of the safety assessment

The available animal studies on TOPs mixtures indicate that these substances are poorly absorbed from the gastrointestinal tract and excretion is via the faeces (entero-hepatic cycling). They have low toxicity are not genotoxic and demonstrate no reproductive or developmental toxicity.

No evidence of adverse effects were noted following administration of TOPs up to 5% in the diet for 13 weeks in rats study (this later study being a detailed toxicological study in accordance with international toxicological testing requirements). There was also no evidence of oestrogenic activity from the available studies.

Efficacy studies were performed in mice, rabbits and hamsters to determine the cholesterol lowering effects of TOPs. The results suggested that TOPs were well tolerated in animals up to 2% (w/w) in the diet for a period of 20 weeks. The absence of any histopathological changes is also reassuring as if any clinical signs were present these may have been of minor nature.

[10] Tikkanen et al (2001) Effect of a diet based on low-fat foods enriched with non-esterified plant sterols and mineral nutrients on serum cholesterol. American Journal of Cardiology, 88, 1157-1162.
[11] Hallikainen MA and Uusitupa M (1999) Effects of low-fat stanol-ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolaemic subjects. American Society for Clinical Nutrition, 69, 403-10.

Efficacy studies including the data and results from clinical studies in humans involving mildly hypercholesterolaemic individuals in a variety of food matrixes, including milk demonstrated the effectiveness of TOPs incorporated into food products to reduce cholesterol absorption.

There is no evidence of adverse health effects in these human studies, apart from some minor reductions in vitamin A at doses of 0.9, 1.8 and 3.6 g/day and reductions in subjects dosed at 3.6 g/day in mean alpha-carotene levels observed between day 0 and week 4 (23% reduction) compared to placebo values in a 28 day study in which tall-oil non-esterified phytosterols were administered in a milk based beverage.

The overall conclusion from the human studies was that administration of TOPs in the diet at 3.6 g/day for a period up to 28 days was well tolerated. The study by Plant and Mensink (1998) using 4 g/day of a phytostanol mixture for 8 weeks further supports the safety of TOP which contain significant amounts of phytostanols.

Table 1 Summary table of efficacy/safety studies in humans submitted by Parmalat with Application A508

Tall-oil Phytosterol mixture	Dose/Duration	Food matrix	Efficacy	Adverse effects	Reference
Sitostanol ester 70% and 30% campestanol-ester	4g/day for 8 weeks in 34 subjects (mean age 33 years) with normal cholesterol levels	Margarine	Not examined	No adverse effects noted and blood chemistry and haematology was normal.	Plat and Mensink (1998)
Sitostanol 20% and a mixture of sitosterol and campesterol[12]	1.7g/day for 30 days in 32 males (aged 25-60 years) with hypercholesterolaemia	Edible oil	Mean total cholesterol reduced 20%; LDL 24%	1 subject with diarrhoea associated with influenza. No blood chemistry, urinalysis or clinical data available for independent review.	Jones (1999)
Sitosterol 51%, sitostanol 25%, campesterol 13% and campestanol 4%.	0, 0.9, 1.8 or 3.6g/day in 4 groups of 33 subjects with hypercholesterolaemia	Full milk	4.3 to 9.1% reduction in mean total cholesterol; 7.4 to 13.2% in LDL	Some minor changes in blood chemistry and haematology parameters. Clinical signs and symptoms were not confined to a specific sex and were generally considered unrelated to treatment as there was no dose response and there was no significant difference between treatment groups. Reductions in mean levels of alpha-carotene at doses of 3.6g/day.	Pritchard and Beer (2000)

[12] Exact percentages not stated in the methods

Sitosterol 60%, sitostanol 18%, campesterol 14% and campestanol 3%.	0 or 1.8g/day for 30 days in males and females (aged 21-75 years).	Chocolate	6.4% reduction in mean total cholesterol and 10.3% in mean total LDL	No reported adverse clinical effects. No blood chemistry, urinalysis or clinical data available for independent review.	deGraf et al (2002)

1. Jones PJH (1999) Cholesterol-lowering efficacy of a sitostanol-containing phytosterol mixture with a prudent diet in hyperlipidemic men. Am. J. Clin. Nutr., *69*, 1140-50.

Test material:	Group 1-controls-North American diet considered to be healthy in terms of macronutrient and fat content*. Group 2-diet plus TOPs** in a margarine matrix (edible oils).
Test groups:	32 males aged 25-60 years. 16 males/group with primary hypercholesterolaemia (6 to 10 mmol/L).
Dose:	1.7 g/day for 30 days double blind study
GLP:	Not stated.

*Protein 15%; carbohydrate 50% and fat 35%.

**TOPs-sitostanol 20% and a mixture of sitosterol and campesterol (exact % not stated in the methods).

Subjects underwent a routine physical examination and detailed blood chemistry before and on day 30 of the study. Blood samples were collected on days 0, 10, 20, 29 and 30 in order to measure total, LDL and HDL cholesterol and triglycerides. Samples were also collected at days 40 and 50 post treatment. The parameters measured from the blood chemistry analysis other than the lipid analysis, were not stated in the methods section.

Results

All 32 subjects completed the study and the authors reported that all subjects tolerated the experimental diet without any adverse effects (other than 1 subject who reported diarrhoea associated with a bout of influenza) and that the blood chemistry and urinalysis was normal throughout the treatment period. This data was not available for independent review and as such cannot be confirmed by FSANZ.

There was no significant difference between controls and treated groups in mean body weights.

Reductions in mean total (20%) and LDL cholesterol (24%) were achieved in the sitostanol enriched TOPs treated group; whereas, reductions in controls was 10% (total) and 9% (LDL) respectively at day 30. HDL and triglyceride concentrations did not change significantly during the study in control or treated groups.

In conclusion, this study demonstrated that in human subjects with hypercholesterolaemia that significant reductions in total and LDL-cholesterol could be achieved at doses of TOPs mixtures in a margarine based product up to a level of 1.7g/day over a period of 32 days.

An independent assessment of whether any adverse clinical effects, changes in clinical chemistry parameters and/or urinalysis was not possible, as the data was not presented in the paper. It could not be determined from the methods the relative percentages of sitosterol and campesterol in the TOP mixture.

2. Pritchard H and Beer M (2000) To determine the effect of increasing doses of tall oil derived phytosterols (Phytrol ^{TM}) on the plasma lipid levels of hypercholesterolaemic patients. Novartis Consumer Health and Forbes Meditech Inc. Final study. 14 November 2000.

Test material:	Group 1-Lactose-free milk* (controls), Groups 2-4 milk with TOPs**
Test groups:	132 subjects (33/group) with primary hypercholesterolaemia and no other health concerns aged 25 to 60 years.
Dose:	0.9, 1.8 or 3.6 g/day over 28-days-double blind placebo controlled study.
GLP:	Not stated.

* 3.6 g fat/100 g

** TOPs-sitosterol 51.3%, sitostanol 25.3%, campesterol 13.3% and campestanol 4.4%.

Study conduct

In a 2-week period before treatment subjects underwent a physical examination and a detailed medical history was taken and blood chemistry was performed. Various criteria for inclusion/exclusion in the study were ascertained. At the start of treatment subjects were instructed to take three drinks per day for the 4-week period. A physical examination and blood was collected at each visit (at 3.5 and 4 weeks). One hundred and thirty two human volunteers consumed four different TOPs mixtures (including a placebo group) in a milk-based drink, for a 4-week period ranging in doses from 0 to 3.6 g/day.

Nine subjects discontinued the treatment due to various factors (withdrew consent, adverse events, protocol deviation, did not receive treatment or unable to drink 3 drinks/day). The adverse effects reported were pain in the kneecap (unrelated to treatment), moderate constipation and elevations in ALT and AST, which could have been related to treatment.

In each study period, fasting blood samples were collected at -2, -1, 0, 3.5 and 4 weeks for analysis of lipids (total cholesterol, HDL and LDL and triglycerides), enzymes (alkaline phosphatase, LDH, SGOT, SGPT), glucose, creatinine, BUN, uric acid and total bilirubin. Standard haematology and urinalysis parameters were determined. The study assessed all relevant confounding factors during the administration period, including lifestyle factors, bodyweight, disease status and medicine use.

Results

At a dose of 1.8g/day reductions in total and LDL cholesterol were 5.5 and 8.6% respectively; and at 3.6g/day reductions of 9 and 13% respectively.

At all dose levels (including the placebo group) mild to moderate adverse clinical effects were reported (ranging from general symptoms, skin, respiratory, cardiovascular, gastrointestinal and musculoskeletal effects) in 52% of subjects. However, these clinical signs and symptoms were not confined to a specific sex and were generally considered unrelated to treatment as there was no dose response and there was no significant difference between treatment groups.

There were no differences between treatment groups in weight post treatment. However, overall there were significant increases in weight among all subjects at all doses. There were no significant increases in blood pressure or pulse rate post treatment at all doses and no differences between groups other than an increase in systolic blood pressure at a dose of 0.9 g/day compared to placebo.

Subjects who were treated at a dose of 0.9 g/day had significantly increased platelet counts and eosinophils at the end of treatment. At a dose of 1.8 g/day significant increases were noted in red blood cell counts, haemoglobin and haematocrit during treatment. Increases were noted in alanine transaminase (ALT) and decreases in uric acid in placebo subjects post-treatment. At a dose of 1.8 g/day a significant increase in alkaline phosphatase was observed during treatment, however, at the highest dose this was not significant. However, none of the changes in blood chemistry differed between the four treatment groups.

Subjects on whom urinalysis were performed was small and as such no statistical tests of significance other than specific gravity and pH were performed.

In the placebo group there was a significant increase in urinary pH at the end of treatment; however, no significant differences in specific gravity were noted. No treatment related effects were noted in the parameters measured form the available data.

Vitamin A and E and alpha and beta-carotene levels were compared at the start of treatment and at week 4 post-treatment.

At the start of treatment there were no differences between treatment groups except in subject's dosed at 1.8g/day who had significantly ($p<0.05$) lower mean levels of vitamin A when compared to placebo (11% reduction). At week 4 post-treatment significant reductions in vitamin A of 10% ($p<0.005$), 12% ($p<0.001$) and 9% ($p<0.01$) compared to placebo controls for that group were observed at doses of 0.9, 1.8 and 3.6g/day respectively. However, this lacked a dose-response and there were no other significant differences between treatment groups between day 0 and week 4 post-treatment with respect to either the change or the relative change in vitamin A levels between the start and 4-week treatment levels.

There were no significant differences between groups with respect to vitamin E levels.

There were no significant differences between treatment groups at day 0 or 4-weeks post-treatment in either alpha or beta-carotene levels. A significant ($p<0.01$) reduction in subjects dosed at 3.6g/day in mean alpha-carotene levels was observed between day 0 and week 4 (23% reduction) compared to placebo controls.

In conclusion, this study demonstrated that human subjects tolerated doses of TOPs mixture in a milk-based beverage up to a level of 3.6 g/day over a period of 28 days without significant adverse effects being experienced by subjects. However, reductions in alpha-carotene levels were observed at the highest dose used.

3. deGraf J, Pernette RW, de Sauvage Nolting et al (2002) Consumption of tall oil-derived phytosterols in a chocolate matrix significantly decreases plasma total and low-density lipoprotein-cholesterol levels. British Journal of Nutrition, *88*, 479-488.

Test material:	Group 1 controls received chocolate alone. Group 2-chocolate plus TOPs*.
Test groups:	31 males or females aged 21-75 years with primary hypercholesterolaemia (5.5 to 8 mmol/L).
Dose:	1.8g/day for 30 days double blind placebo-controlled study
GLP:	Not stated.

*TOPs-sitosterol 60%, sitostanol 18%, campesterol 14% and campestanol 3%.

Study conduct

In a 4-week period before treatment subjects underwent a physical examination and a detailed medical history was taken and blood chemistry was performed. Various criteria for inclusion/exclusion in the study were ascertained. At the start of treatment subjects were instructed to have three chocolate servings per day for the 4-week period. A physical examination and blood was collected at 3 and 4 weeks.

Seventy human volunteers consumed either a placebo chocolate (31 subjects) or a chocolate containing the TOP mixture (31 subjects) with meals at a total dose of 1.8g/day for 4 weeks.

Two subjects discontinued the treatment; the first in the placebo group (due to an adverse event which was not stated in the paper) and the other subject withdrew their consent after treatment had started. Eight subjects were excluded from the study based on the pre-protocol exclusion criteria.

At weeks 3 and 4 recordings of lipid levels (total cholesterol, HDL and LDL and triglycerides) and routine blood chemistry, haematology and urinalysis was performed. Any adverse clinical effect was recorded.

Results

At a dose of 1.8 g/day reductions in mean total and mean LDL cholesterol were 6.4% and 10.3% respectively at following 4 weeks of treatment. HDL and triglyceride concentrations did not change significantly between control and treated groups.

It was stated in the study that no significant changes were observed between controls and treated groups in blood chemistry, haematology or urinalysis parameters and no significant adverse clinical effects were observed. An independent assessment was not possible, as the data was not presented in the paper.

4. Plat J and Mensink RP (1998) Safety aspects of dietary plant sterols and stanols. In Post-graduate Medicine, Special Report: New Developments in the Dietary Management of High Cholesterol, 32-38.

Test material:	Group 1-oil-based margarine and shortening (controls), Group 2 Margarine and shortening with a tall oil phytostanol ester mixture or a vegetable oil ester mixture*
Test groups:	112 subjects (42 controls and either 34 or 36 treated subjects) with normal cholesterol levels.
Dose:	4g/day of free phytosterols for eight weeks.
GLP:	Not stated.

* Sitostanol ester 70% and 30% campestanol- ester

Study conduct

Fasting blood samples were taken at week 0 and then 112 subjects with normal cholesterol levels consumed a baseline diet for 4 weeks and then one of the following three test diets for the remaining eight weeks:

- 42 subjects consumed unsupplemented diets (controls);
- 36 subjects consumed spread and shortening with 6.4 g/day plant stanol esters derived from tall oil; or
- 34 subjects consumed spread and shortening with 6.4 g/day plant stanol esters derived from vegetable oil.

Treated subjects were instructed replace their usual spread at breakfast and lunch with phytostanol-ester enriched spreads and cooking fat at dinner was replaced with phytostanol-ester enriched shortening. Clinical chemistry and haematology were recorded at week 4 (baseline) and at week 12 (end of the treatment period). Subjects also completed questionnaires about any possible adverse effects during the treatment period.

Results

There were no significant differences in reported adverse effects or in haematology and blood chemistry parameters between control and treated groups. It is concluded that human subjects tolerated doses of either a phytostanol-ester mixture or a vegetable oil mixture up to a level of 4g/day (free phytostanols) without any significant adverse effects.

Attachment 4

Dietary Exposure Assessment Report

Summary

An application was received by FSANZ requesting the Food Standards Code (the Code) to be amended to allow the use of tall oil phytosterols (TOPs) as a novel food ingredient, under Standard 1.5.1 – Novel Foods, for use in low fat milks (fat content < 1.5%).

A dietary exposure assessment was undertaken to determine the impact of allowing TOPs to be added to the above foods. The assessment took into account the existing permission under Standard 1.5.1 to add TOPs to edible oil spreads (the 'baseline' scenario), the proposed addition of TOPs to low fat milks (the 'low fat milks' scenario) and a combination of these products (the 'low fat milks plus baseline' scenario). In each scenario, addition of phytosterols at a level equivalent to 0.8 g free phytosterols per serve was assumed for edible oil spreads and 0.9 g free phytosterols per serve for low fat milks. It was further assumed that all edible oil spreads and low fat milks contained added free phytosterols. Intrinsic levels of phytosterols in foods were not taken into consideration.

Modelling was conducted assuming that consumers do not change the amounts and general types of foods they eat, simply substituting phytosterol-containing edible oil spreads or low fat milks for their non-phytosterol counterparts. Food consumption data from the most recent Australian and New Zealand National Nutrition Surveys (NNSs) – the 1995 Australian NNS of those aged 2 years and above, and the 1997 New Zealand NNS of those aged 15 years and above were used. Exposure was estimated for the target populations (those aged 40-64 years and 65 years and above), for the general population, and for two non-target groups – children aged 2-12 years (Australia only) and women of childbearing age (16-44 years), as a proxy for pregnant and lactating women.

When it was assumed that consumers maintain their existing eating patterns, simply substituting phytosterol containing spreads or low fat milks for their non-phytosterol counterparts, estimated mean dietary exposure (expressed as free phytosterols) did not exceed 1.9 g per day in any population group assessed under any of the scenarios considered. At the 95th percentile of exposure, no population group assessed exceeded 4.8g free phytosterols per day for any of the scenarios modelled. The analysis shows that, for the target population group in particular, edible oil spreads contribute more to dietary exposure to added free phytosterols (78-84% of exposure) than low fat milks, according to the available data on food consumption patterns.

Introduction

Information supplied by the applicant

The applicant is seeking approval to use TOPs in foods at levels formulated to provide between approximately 2 and 3 grams per day of free phytosterols to target consumers (through 2-3 serves of products). The products containing added TOPs are targeted specifically to consumers over the age of 40 years who have concerns about their blood cholesterol level. However, casual consumption by other non-target population groups, including children, must also be considered.

Since no dietary exposure assessment was provided by the applicant, FSANZ conducted a dietary exposure assessment to estimate the potential exposure to phytosterols if they were added to the proposed foods.

Existing phytosterol-containing products

There are a small number of edible oil spreads currently on the market that contain phytosterols. These products carry label claims stating that phytosterols assist in lowering cholesterol absorption and recommend that 2-3 serves of phytosterol-containing foods be consumed each day in order to achieve the recommended level of intake. Permission for the use of added phytosterols in these products is contained in Standards 1.5.1 and 2.4.2 of the Code, which allows the addition of phytosterol esters at no more than 137 g/kg (equivalent to 1.37 g per 10 g serve of spread), or the addition of tall oil phytosterols at no more than 80 g/kg (equivalent to 0.8 g free phytosterols per 10 g serve).

Natural occurrence of phytosterols

Major sources of naturally occurring phytosterols are vegetable fats and oils, and nuts and seeds (Food Standards Agency, 2002). Reported average intakes of phytosterols from unfortified foods vary in the range of 160 to 500 mg per day (Thurnham, 1999). These levels are substantially lower than would result from addition of phytosterols to foods.

Post launch monitoring in Europe

The Unilever Company conducted post launch monitoring in Europe of the use of yellow fat spreads containing added phytosterol esters, following approval to add these esters by the European Commission. For regular users of spreads containing added phytosterol esters, median household consumption was between 15 g and 18 g per day, which represents slightly less than 2 x 10 g serves per day. Research suggested that these consumption amounts represent consumption by a single person in the households and are lower than had been predicted at the time of approval of phytosterol esters, when consumption of the spreads was predicted to be 20 – 30 g per person per day. The ninety-fifth percentile consumption did not exceed 45 g (4.5 serves) per day. The majority of households where these spreads were used did not include children and between 87% and 91% of regular purchasers of these spreads had no children living at home (Scientific Committee on Food, 2002).

Dietary Modelling

The dietary exposure assessment was conducted using dietary modelling techniques that combine food consumption data with food chemical concentration data to estimate the exposure to the food chemical from the diet. The dietary exposure assessment was conducted using FSANZ's dietary modelling computer program, DIAMOND.

Dietary exposure = food chemical concentration x food consumption

The exposure was estimated by combining usual patterns of food consumption, as derived from national nutrition survey (NNS) data, with proposed levels of use of TOPs (expressed as free phytosterols) in foods.

Dietary Survey Data

DIAMOND contains dietary survey data for both Australia and New Zealand; the 1995 NNS from Australia that surveyed 13 858 people aged 2 years and above, and the 1997 New Zealand NNS that surveyed 4 636 people aged 15 years and above. Both of the NNSs used a 24-hour food recall methodology.

The dietary exposure assessment was conducted for both Australian and New Zealand populations. For the Australian population, the following groups were included in the exposure assessment: the whole population aged 2 years and above; the target groups of people aged 40–64 years and those aged 65 years and above; and specific non target groups of special interest including children aged 2–12 years and females of child bearing age, aged 16–44 years. For the New Zealand population, the sub-groups included: the whole population aged 15 years and above; the target groups of people aged 40–64 years and 65 years and above; and non target group of females of child bearing age, aged 16–44 years. No New Zealand survey data are available for children aged 2-12 years.

The target group for phytosterol containing products is identified as people aged 40 years and above because it is this age group who are likely to have increasing concerns about their general health and who are likely to be interested in reducing an elevated blood cholesterol level through dietary means. People aged 65 years and above were assessed separately because of the potential for some people in this target group to experience inadequate diets or reduced nutrient bioavailability.

Children generally can experience higher dietary exposures due to their smaller body weight, and higher consumption of food per kilogram of body weight compared to adults. An exposure assessment was therefore also conducted on younger non-target age groups because of a possibility that children may consume these products if available in the household. In addition, to estimate the exposure of pregnant and lactating women to phytosterols from enriched products, exposure was estimated in a proxy group, women of childbearing age (16-44 years).

Additional Food Consumption Data or Other Relevant Data

No further information was required or identified for the purpose of refining the dietary exposure estimates for this application.

Concentration levels and serving sizes

The levels of free phytosterols in low fat milks used in the exposure assessment were derived from the Application. Levels of free phytosterols per serve were converted to concentrations in mg/kg to enable them to be entered into DIAMOND. Serve sizes are based on average product serve sizes from food packages - including 1 serve of edible oil spreads (10 g) and 1 glass of milk (250 mL). The foods and proposed levels of use are summarised below in Table 1.

Table 1: Proposed levels of use of non-esterified phytosterols in foods

Food Code	Food Name	Serve size (g)	Proposed level of free phytosterols per serve (g/serve)	Concentration Level used in modelling (mg/kg)
1.1.1.2	Low fat milks (<1.5% fat), unflavoured, including skim milks	250	0.9	3 600
2.2	Edible oil spreads, including reduced fat spreads	10	0.8	80 000

In estimating dietary exposure using DIAMOND, the whole category for each food was assumed to contain phytosterols since neither NNS has specific consumption data for phytosterols containing foods due to such foods being unavailable at the time of the surveys.

Estimating risk

Estimated dietary exposures are compared to a reference health standard in order to determine the potential risk to health of the population or its sub-groups. Free phytosterols do not have an established reference health standard such as an Acceptable Daily Intake (ADI). Therefore, estimated exposures were simply reported in gram amounts per day

Intakes of TOPs up to 3.6 g/day have been associated with reductions in LDL cholesterol and have been used in recent clinical trials to study safety and efficacy in different food matrices.

How were the estimated dietary exposures calculated?

The DIAMOND program allows free phytosterols concentrations to be assigned to food groups. All foods in this group are assigned the concentration of free phytosterols shown in Table 1. Estimated dietary exposures were calculated for the following three scenarios:

- phytosterols in edible oil spreads, including margarines only (baseline scenario);
- phytosterols in low fat unflavoured milks only (low fat milks scenario); and
- phytosterols in edible oil spreads and low fat milks combined (low fat milks + baseline scenario).

An individual's exposure to free phytosterols was calculated using their individual food records from the dietary survey. The DIAMOND program multiplies the specified concentration of free phytosterols by the amount, if any, of edible oil spreads or low fat milks that an individual consumed in order to estimate the exposure from each of these foods. Once this has been completed for the foods specified to contain phytosterols, the total amount of free phytosterols consumed from all foods is summed for each individual. Population statistics (mean and high percentile exposures) are then derived from the ranked exposures of individuals who consumed added phytosterols.

The consumer populations differ in each of the three scenarios assessed. Consumers who choose to eat edible oil spreads do not necessarily also choose to eat low fat milks. In the baseline + low fat milks scenario, the consumer population includes those who consume only edible oil spreads and those who consume only low fat milks as well as those who consume both these foods.

Therefore mean consumer exposure in the baseline + low fat milks scenario does not represent the result of simply summing mean consumer exposure from the baseline scenario and from the low fat milks scenario, since the consumer population is not exactly the same.

Percentage contributions of each food group to total estimated exposures are calculated by dividing the sum of consumers' exposures from a food group by the sum of all consumers' exposures from all foods, and multiplying this by 100.

Food consumption amounts for each individual take into account where each food in a classification code is consumed alone and as an ingredient in mixed foods.

Assumptions in the dietary modelling

Assumptions made in the dietary modelling include:

1. food consumption amounts are those reported in the NNSs, as it is assumed people will not change eating habits but simply substitute one product type for another;
2. where a permission is given to a food group classification, all foods in that group contain phytosterols at the concentration specified in Table 1;
3. for the purpose of this assessment it is assumed that 1 mL is equal to 1 g for all foods; and
4. there is no contribution to phytosterols exposure through the use of complementary medicines (Australia) or dietary supplements (New Zealand).

The second assumption will lead to a conservative estimate of dietary exposure to phytosterols, as it is highly unlikely that all foods within a group, such as all available brands of margarine, would actually contain added phytosterols.

Limitations of the dietary modelling

A limitation of estimating dietary exposure using 24-hour recall data is that it may not be an accurate reflection of typical exposure over a lifetime. Hence, estimated dietary exposure for high consumers is likely to be an overestimate.

While the results of national nutrition surveys can be used to describe the usual intake of groups of people, they cannot be used to describe the usual intake of an individual (Rutishauser, 2000). In particular, they cannot be used to predict how consumers will change their eating patterns as a result of an external influence such as the availability of a new type of food.

Results

Estimated dietary exposures to phytosterols

The estimated dietary exposures of consumers to free phytosterols, for the different food groups, mean and 95th percentile are shown below in Figures 1 and 2 (baseline scenario, 'low fat milks' scenario and 'low fat milks plus baseline' scenario) for Australia and Figures 3 and 4 (baseline scenario, 'low fat milks' scenario and 'low fat milks plus baseline' scenario) for New Zealand. Numerical data are also provided for New Zealand and Australia in Table 2 (edible oil spreads), Table 3 (low fat milks) and Table 4 (edible oil spreads and low fat milks).

Results for consumers only (eaters of foods containing free phytosterols) are presented rather than data from the whole survey population because the purpose of the risk assessment is to consider the potential impact of phytosterols addition to a variety of foods on people who report eating these foods. All values reported are expressed as free phytosterols and are reported in grams/day.

Figure 1: Estimated mean dietary exposure to free phytosterols for different population groups and scenarios for Australia

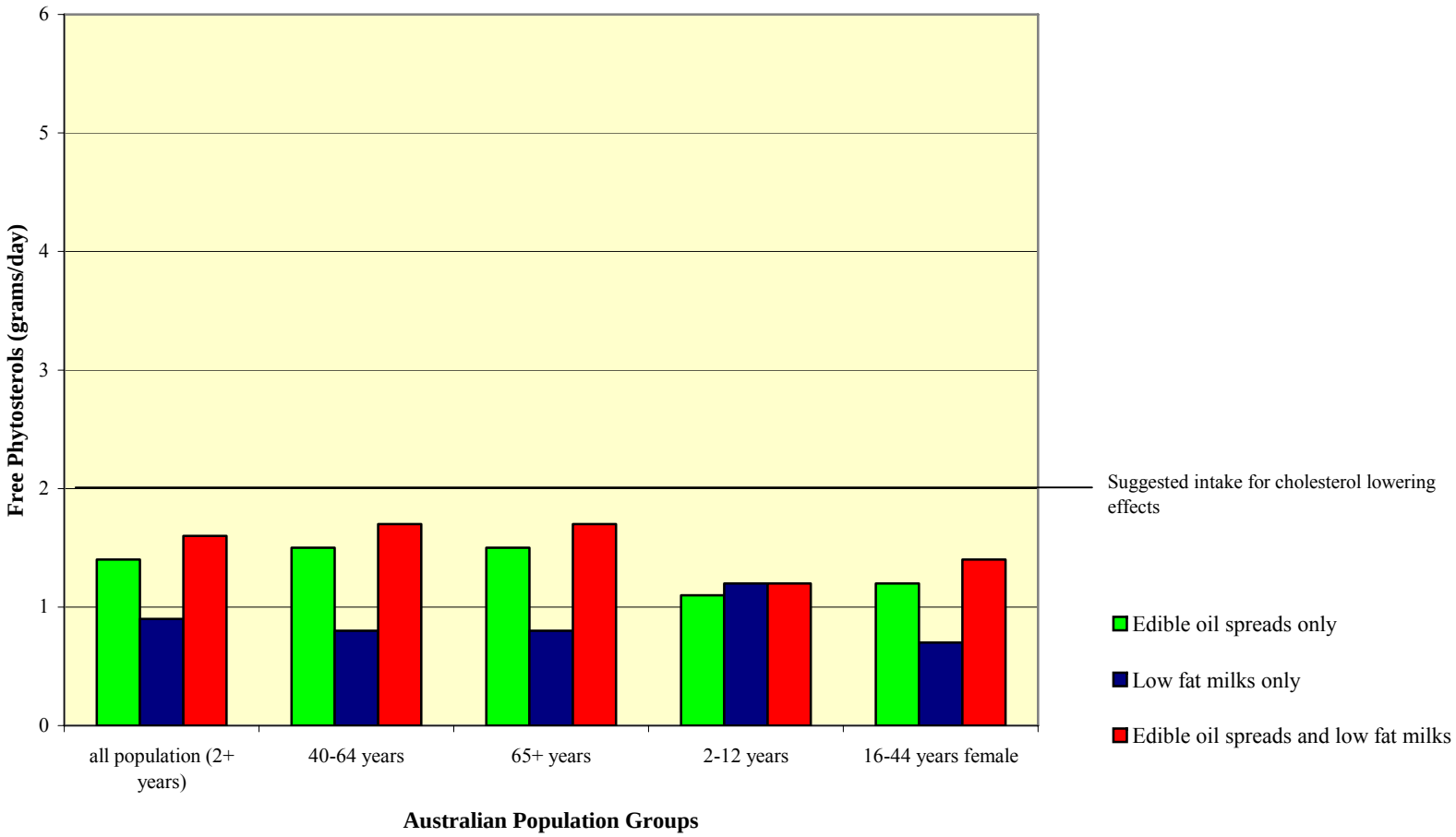


Figure 2: Estimated 95th percentile dietary exposure to free phytosterols for different population groups and scenarios for Australia

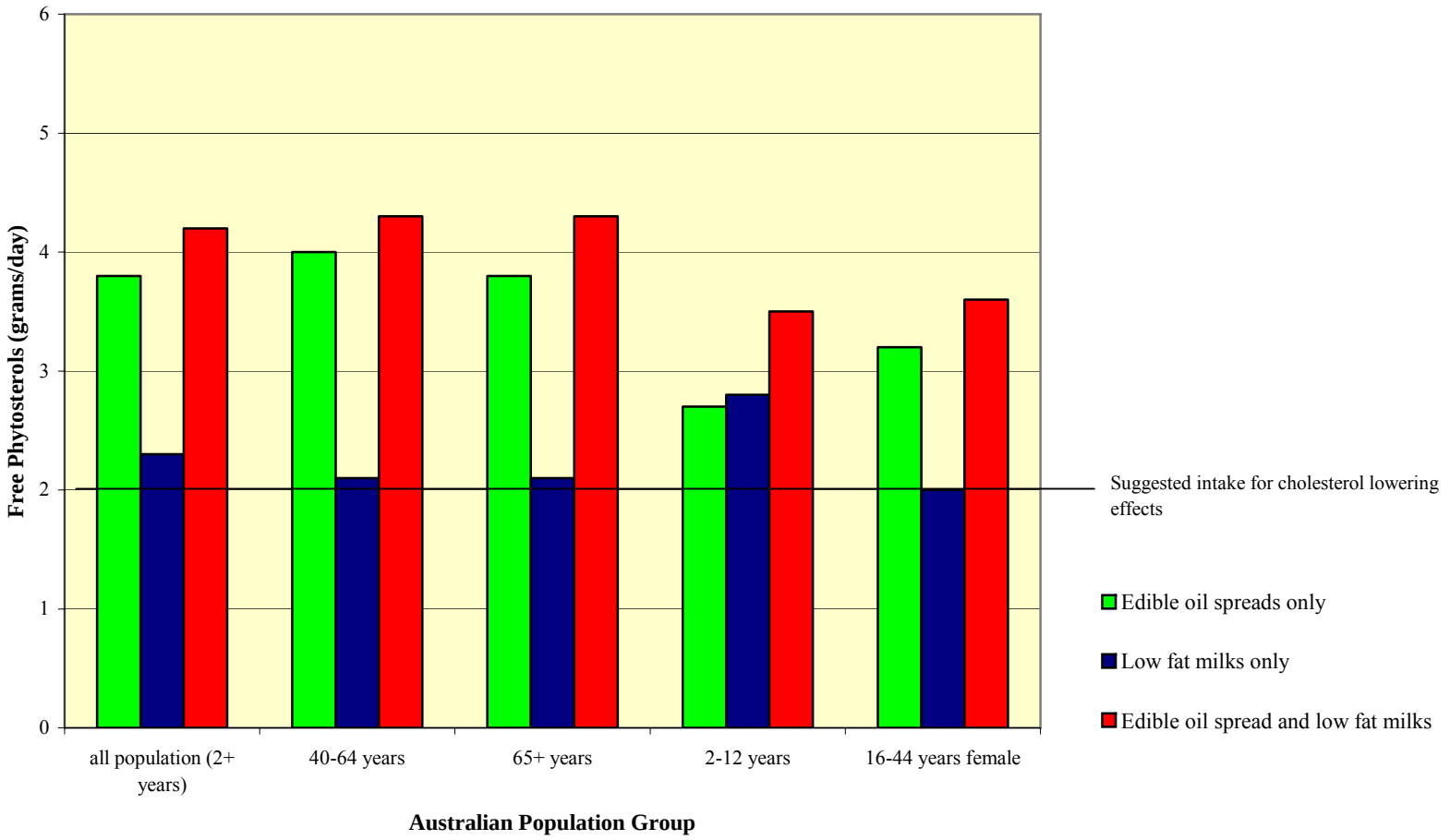


Figure 3: Estimated mean dietary exposure to free phytosterols for different population groups and scenarios for New Zealand

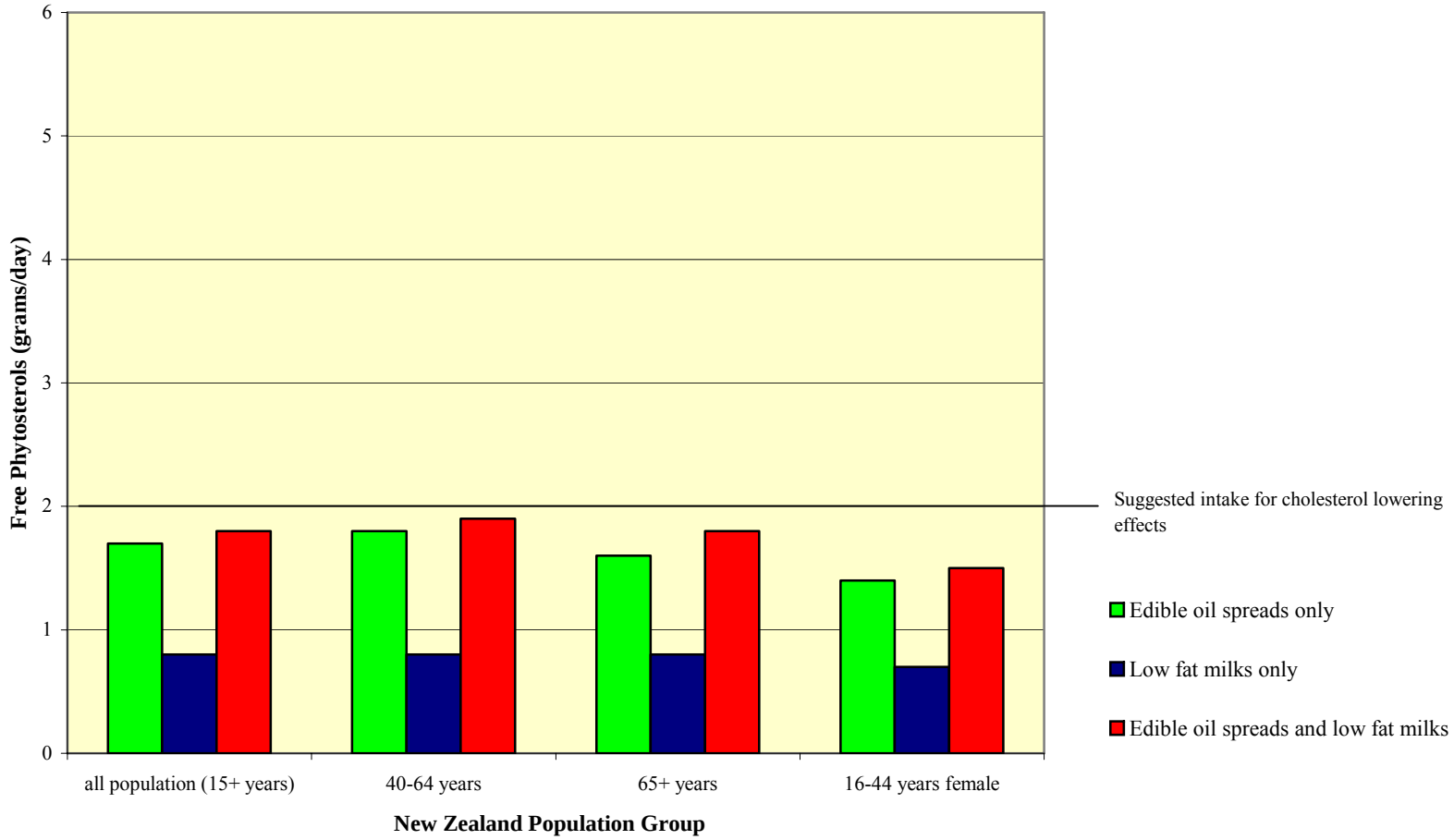
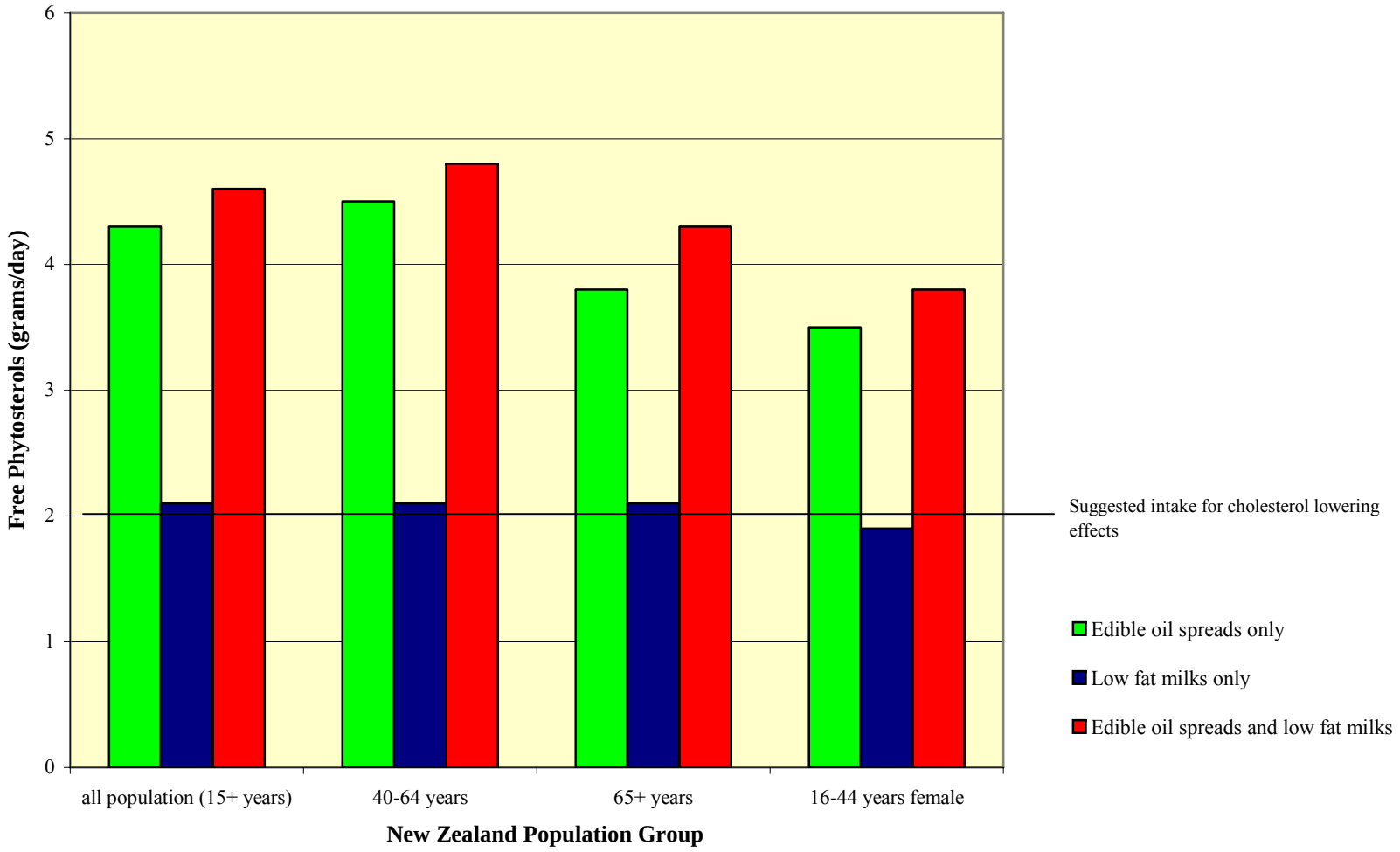


Figure 4: Estimated 95th percentile dietary exposure to free phytosterols for different population groups and scenarios for New Zealand



1) Estimated dietary exposure to free phytosterols from edible oil spreads ('baseline' scenario)

Table 2: Estimated dietary exposure to free phytosterols from edible oil spreads, for different population groups for Australia and New Zealand

Country	Population group	Number of consumers of phytosterols	Consumers as a % of total respondents[#]	Mean consumer exposure g/day	95th percentile consumer exposure g/day
Australia	Whole population (2 years+)	11 002	79	1.4	3.8
	40-64 years	3 372	78	1.5	4.0
	65+ years	1 557	79	1.5	3.8
	2-12 years	1 754	84	1.1	2.7
	16-44 years female	2 428	76	1.2	3.2
New Zealand	Whole population (15 years+)	3 093	67	1.7	4.3
	40-64 years	1 184	69	1.8	4.5
	65+ years	606	74	1.6	3.8
	16-44 years female	946	63	1.4	3.5

Total number of respondents for Australia: whole population (2+ years) = 13 858, 2-12 years = 2 079, 40-64 years = 4 318, 65+ years = 1 960, 16-44 years female = 3 178; New Zealand: whole population (15+ years) = 4 636, 40-64 years = 1 725, 65+ years = 817, 16-44 years female = 1 509.

Estimated mean exposure to free phytosterols among consumers of edible oil spreads does not exceed 1.8 g per day (see Table 2 above), equivalent to slightly more than 2 serves of phytosterol-containing spreads per day. The highest mean exposures to free phytosterols in Australia were for the target groups of those aged 40-64 years and those aged 65 years and above. For New Zealand, the highest mean dietary exposures were for the target group of those aged 40-64 years. High consumers (95th percentile) of free phytosterols from edible oil spreads have estimated dietary exposures up to 4.5 grams per day, equivalent to approximately 5 1/2 serves of phytosterol-containing spreads per day. The population group with the highest 95th percentile exposures are the 40-64 year age group for both countries and also the whole population group (aged 15+ years) for New Zealand.

2) Estimated dietary exposure to free phytosterols from low fat milks ('low fat milks' scenario)

Table 3: Estimated dietary exposure to free phytosterols from low fat milks, for different population groups for Australia and New Zealand

Country	Population group	Number of consumers of phytosterols	Consumers as a % of total respondents[#]	Mean consumer exposure g/day	95th percentile consumer exposure g/day
Australia	Whole population (2 years+)	4 262	31	0.9	2.3
	40-64 years	1 717	40	0.8	2.1
	65+ years	681	35	0.8	2.1
	2-12 years	303	15	1.2	2.8
	16-44 years female	1 108	35	0.7	2.0
New Zealand	Whole population (15 years+)	1 509	33	0.8	2.1
	40-64 years	649	38	0.8	2.1
	65+ years	310	38	0.8	2.1
	16-44 years female	434	29	0.7	1.9

Total number of respondents for Australia: whole population (2+ years) = 13 858, 2-12 years = 2 079, 40-64 years = 4 318, 65+ years = 1 960, 16-44 years female = 3 178; New Zealand: whole population (15+ years) = 4 636, 40-64 years = 1 725, 65+ years = 817, 16-44 years female = 1 509.

Estimated mean dietary exposure to free phytosterols among consumers of low fat milks does not exceed 1.2 g per day (see Table 3 above), reflecting the smaller number of serves consumed per day of this food than of edible oil spreads. The highest mean exposure in Australia is for those aged 2-12 years. High consumers (95th percentile) of free phytosterols from low fat milk have estimated dietary exposures up to 2.8 grams per day, equivalent to the phytosterol content of slightly more than 3 serves of low fat milk per day. Again the group with the highest 95th percentile exposure is the 2-12 year age group for Australia.

The proportion of Australians and New Zealanders who consume low fat milks (31% and 33%, respectively) is substantially lower than the proportion who consume edible oil spreads (79% and 67%, respectively).

3) Estimated dietary exposure to free phytosterols from edible oil spreads and low fat milks ('low fat milks plus baseline' scenario)

Table 4: Estimated dietary exposure to free phytosterols from edible oil spreads and low fat milks, for different population groups for Australia and New Zealand

Country	Population group	Number of consumers of phytosterols	Consumers as a % of total respondents[#]	Mean consumer exposure g/day	95th percentile consumer exposure g/day
Australia	Whole population (2 years+)	11 885	86	1.6	4.2
	40-64 years	3 737	87	1.7	4.3
	65+ years	1 682	86	1.7	4.3
	2-12 years	1 803	87	1.2	3.5
	16-44 years female	2 691	85	1.4	3.6
New Zealand	Whole population (15 years+)	3 532	76	1.8	4.6
	40-64 years	1 359	79	1.9	4.8
	65+ years	677	83	1.8	4.3
	16-44 years female	1 100	73	1.5	3.8

Total number of respondents for Australia: whole population (2+ years) = 13 858, 2-12 years = 2 079, 40-64 years = 4 318, 65+ years = 1 960, 16-44 years female = 3 178; New Zealand: whole population (15+ years) = 4 636, 40-64 years = 1 725, 65+ years = 817, 16-44 years female = 1 509;

When free phytosterols are added to low fat milks as well as edible oil spreads, estimated mean exposure to free phytosterols increases slightly from 1.4 g to 1.6 g per day for the Australian consumer population, and also increases slightly from 1.7 g to 1.8 g per day for the New Zealand consumer population (see Table 4 above). Estimated mean dietary exposure does not exceed 1.9 g per day for any population group and is highest for New Zealanders aged 40-64 years. High consumers of free phytosterols (95th percentile) from edible oils spreads and low fat milks have estimated dietary exposures of between 3.5 g to 4.8 g per day for all population groups assessed. The population group with the highest 95th percentile exposure is New Zealanders aged 40-64 years.

The addition of phytosterols to low fat milks as well as to edible oil spreads results in only a slight increase in predicted mean consumer phytosterols exposure compared to baseline exposure; an increase of 0.2 g/day for all Australians and 0.1 g/day for all New Zealanders. These findings reflect both the greater number of serves of edible oil spreads consumed on average and the much larger number of consumers of edible oil spreads than of low fat milks in the low fat milks + baseline scenario. As noted earlier, the DIAMOND program derives results from each individual's food consumption patterns.

Major contributing foods to total estimated dietary exposures

The relative contributions of edible oil spreads and low fat milks to estimated exposures to free phytosterols are displayed in Figures 5 and 6. More detailed results are presented in **Attachment 1**.

Foods may be high contributors to phytosterols exposure when they have a high concentration of free phytosterols, when they are consumed in large quantities and/or are consumed by a large proportion of the survey population.

Edible oil spreads are more important contributors to dietary exposure to TOPs than are low fat milks, on a population basis, assuming that eating patterns recorded in 1995 and 1997 (for Australia and New Zealand respectively) are maintained.

Figure 5: Percent contribution of each food group to free phytosterols dietary exposure for Australia

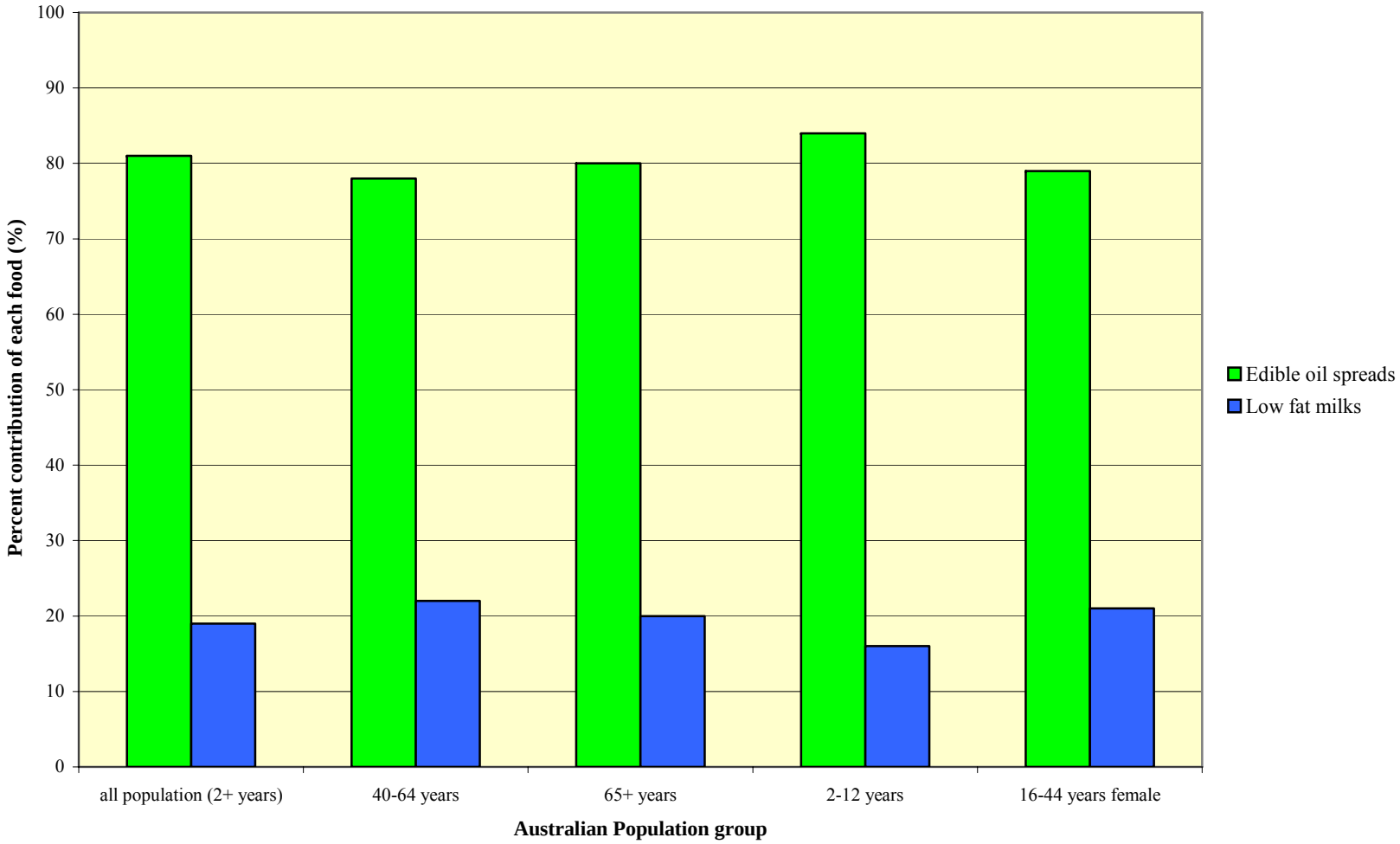
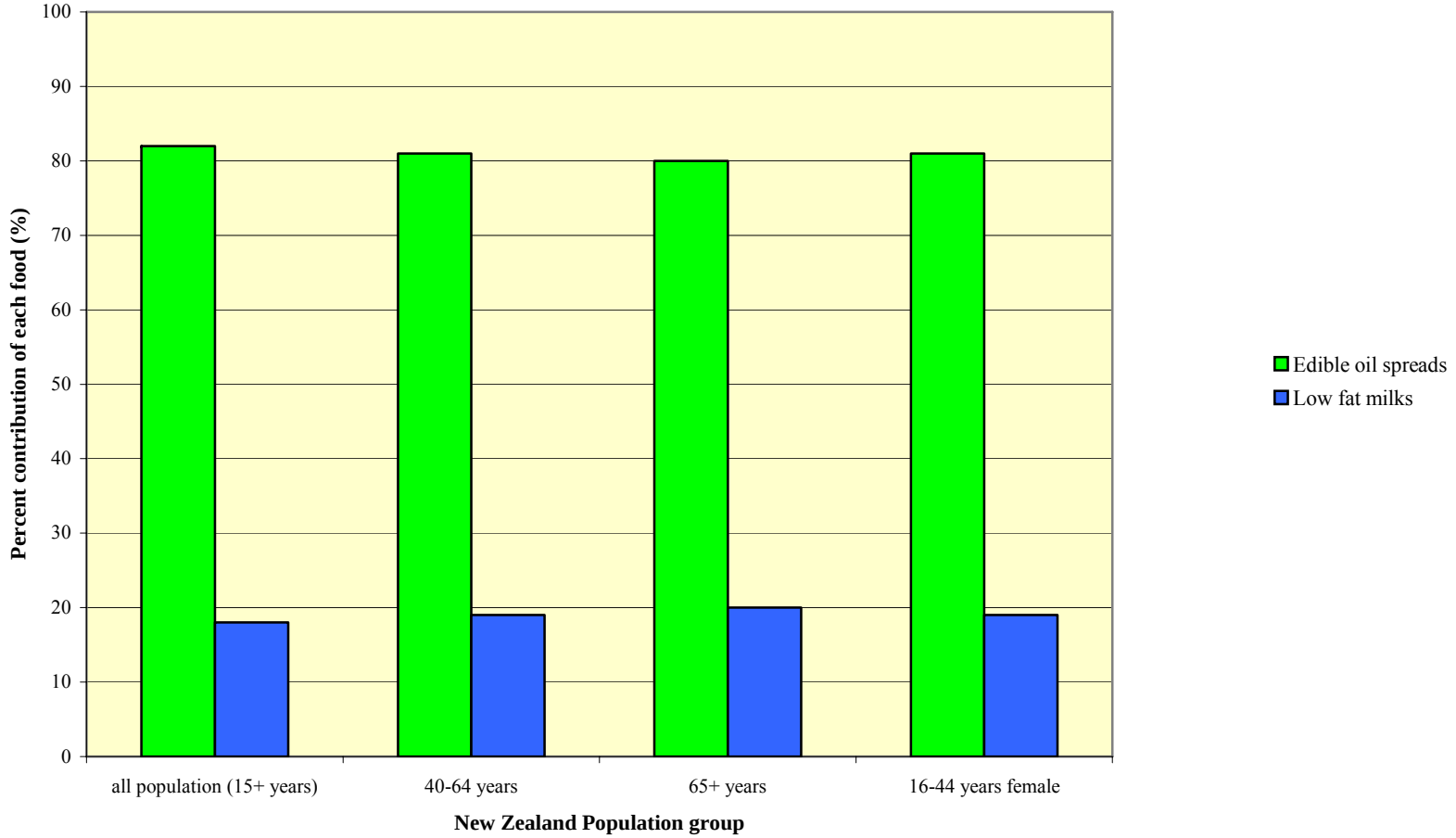


Figure 6: Percent contribution of each food group to free phytosterols dietary exposure for New Zealand



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Annex 1

Major contributors to free phytosterols from edible oil spreads and low fat milks for Australia and New Zealand

Table A1.1: Major contributing foods to estimated free phytosterols dietary exposure for Australia and New Zealand, for different age groups

Country	Age group	*Major contributing foods and percent of total free phytosterols exposures*
Australia	Whole population (2+ years)	Edible oils and margarines (81%) Low fat milks (19%)
	40- 64 years	Edible oils and margarines (78%) Low and milks (22%)
	65+ years	Edible oils and margarines (80%) Low fat milks (20%)
	2 - 12 years	Edible oils and margarines (84%) Low fat milks (16%)
	16 – 44 years female	Edible oils and margarines (79%) Low fat milks (21%)
New Zealand	Whole population (15+ years)	Edible oils and margarines (82%) Low fat milks (18%)
	40- 64 years	Edible oils and margarines (81%) Low fat milks (19%)
	65+ years	Edible oils and margarines (80%) Low fat milks (20%)
	16-44 years female	Edible oils and margarines (81%) Low fat milks (19%)

Attachment 5

NUTRITION ASSESSMENT REPORT

For Application A433 Phytosterol esters in breakfast cereal bars
Application A434 Phytosterol esters in low-fat milk and low-fat yoghurt

1. Introduction

The aim of this review is to evaluate information on the potential nutritional effects of phytosterols in the diet arising from the proposed fortification of breakfast cereals and low-fat dairy products. This review forms part of the assessment of two applications submitted to Food Standards Australia New Zealand (FSANZ) requesting permission to add 1.3 g of phytosterol esters per serve to breakfast cereal bars, low-fat milk and low-fat yoghurt products.

The conclusions from this report are directly applicable to Application A508 in which the Applicant applied for permissions to use phytosterols from a tall oil source in low-fat milks, since the individual components of phytosterol esters overlap to some extent with the components of tall oil phytosterols (TOPs). It is proposed that each milk product will contain 0.9g of TOPs/250 mL serving size. The proposed dose levels for TOPs fall within the range of doses that were used in the studies evaluated below.

Currently, only phytosterol-enriched edible oil spreads are available in both New Zealand and Australia, and are being promoted as foods that can lower cholesterol absorption.
This review considers data from recently conducted studies and other currently available information on the nutritional safety of plant sterols if consumed in a broader range of products such as the proposed low-fat milk, low-fat yoghurt and breakfast cereal. Unless otherwise stated, this report refers to phytosterol amounts in their esterified form.

2. Potential Effect of Phytosterols on Antioxidant Absorption

2.1 Sources and roles of antioxidants

Antioxidants are defined as substances that, when present at low concentrations compared with those of an oxidisable substrate, significantly prevent or delay oxidation of the substrate. This may mean that the presence of an antioxidant can inhibit or slow down a biological process involving an oxidation reaction. Dietary antioxidants may inhibit oxidative damage to proteins, lipids, carbohydrates and DNA *in vivo* which are of major interest in nutritional research,

Food-derived antioxidants, mostly from dietary plants can exert a range of possible beneficial effects. This has been established clearly for α-tocopherol and vitamin C (Handbook of Antioxidants, Eds. E. Cadenzas and L. Packer, 2002). Many hundreds of compounds present in food may act as potential antioxidants in a variety of different ways depending on their particular physico-chemical properties. It is possible for an antioxidant to protect (against oxidation) in one biological or food system, but to fail to protect or even sometimes promote oxidative damage in others.

As well as some of the vitamins, a class of plant compounds known as the carotenoids (including α- and β-carotene, lycopene, β-cryptoxanthin, zeaxanthin, lutein) may function as antioxidants, although in most instances their antioxidant roles are not well-defined. Some of the carotenoids (α- and β-carotene, and β-cryptoxanthin) are precursors of vitamin A.

As carotenoids are essentially hydrophobic molecules, the uptake of carotenoids in the intestinal mucosal cells is aided by the formation of bile acid micelles in the lumen of the small intestine. Plant sterols lower blood cholesterol by reducing the absorption of dietary and biliary cholesterol, and therefore are associated with reduced absorption of some fat-soluble vitamins (such as vitamin E), and the lipophilic carotenoids (such as β-carotene). The assessment of the potential nutritional effects of phytosterol-enriched foods therefore focuses on the effects of plant sterols on the circulating levels of carotenoids and fat-soluble vitamins.

2.2 Vitamin A - Retinol

Vitamin A is a fat-soluble vitamin important for vision, immunity, growth and as an antioxidant. Vitamin A activity can be obtained from two classes of compounds – retinol and some carotenoids. The adult recommended dietary intake (RDI) of vitamin A is 750μg of retinol equivalents per day. The estimated average requirements (EAR) for vitamin A is 500μg for men and 400μg for women. Although plasma retinol concentrations are used as an indicator for vitamin A status, due to a homeostatic mechanism, they are insensitive and fall only in the later stages of deficiency. Vitamin A deficiency is common in developing countries, affecting vision with xerophthalmia and night blindness.

2.3 β-Carotene and other carotenoids

Carotenoids are the basic source of yellow, orange and red plant pigments, and are most commonly consumed as components of fruit and vegetables (Basu 2001). β-Carotene and other carotenoids are classified as either provitamin A or nonprovitamin A carotenoids. The provitamin A carotenoids (α-carotene, β-carotene and β-cryptoxanthin) can be converted into retinol. The function of these carotenoids includes antioxidant activity.

Non-provitamin A carotenoids such as lycopene, lutein and zeaxanthin have been suggested through observational studies to be inversely associated with some chronic diseases such as heart disease and cancer (Basu 2001).

2.3.1 Sources

The predominate dietary sources of carotenoids are fruits and vegetables. Sources of β-carotene include dark green leafy vegetables and yellow or orange fruits and vegetables including carrots, kale, silverbeet, spinach, pumpkin/squash, sweet potato, apricots, mango and watermelon (Lister 2003).

2.3.2 Absorption

The carotenes are normally ingested in a food matrix, which is critical to their absorption. Their chemical structure, with a hydrocarbon backbone, renders them insoluble in water and they must be in the form of micelles in order to be absorbed in the intestinal tract.

The presence of fat in the small intestine stimulates the secretion of bile from the gall bladder and increases the size of micelles, in turn facilitating the uptake of carotenes into the intestinal mucosa. Once in the mucosal cells, the carotenes are incorporated into chylomicrons for transport in the lymphatic system. The uptake of carotenes through the mucosal cells is via passive diffusion.

2.3.3 Bioavailability

The bioavailability of dietary carotenes depends on

i) digestion of the food matrix;
ii) formation of lipid micelles in the gastrointestinal tract;
iii) uptake of carotenoids by mucosal cells; and
iv) transport of carotenoids and their products to the lymph or portal circulation.

The source of carotenoids is also a factor in their bioavailability. Synthetic carotenoids (as dietary supplements) are absorbed far more readily than those that occur naturally in foods. Studies have indicated that up to 70% of synthetic carotenoids are absorbed compared with only 5% of naturally-occurring ingested carotenoids.

Bioavailability is optimized when dietary fat is consumed during the same period as the carotenoid. The processing and cooking of fruits and vegetables also affect bioavailability. Carotenoids are less available from raw than cooked fruits and vegetables, and processing techniques such as mechanical homogenization have also been shown to enhance the bioavailability of β-carotene (Cadenas 2002).

2.3.4 Contribution of β-carotene to Vitamin A intake

There are no known adverse health effects from consuming a diet low in carotenes provided that there is adequate retinol in the diet. The contribution from consumption of β-carotene equivalents[13] to vitamin A is about 50% in both Australia and New Zealand according to National Nutrition Surveys in both countries.

2.3.5 Seasonal variation

Fruits and vegetables are the main source of carotenoids in the diet. As might be expected from the seasonal nature of many fruits and vegetables, it has been observed that there is a concomitant seasonal variation in serum carotenoids (and retinol) levels in humans. This was confirmed in a study investigating seasonal variation in serum nutrient levels in 111 healthy individuals. The study reported significant differences ($p<0.05$) in serum concentrations of α-carotene, β-carotene and β-cryptoxanthin across a seasonal time scale, with both α and β-carotene levels higher in summer and β-cryptoxanthin levels higher in winter. Plasma β-carotene levels could vary naturally up to 50% between seasons (Omedilla 1994).

In addition to seasonal variation in β-carotene levels, weekly variation has also been observed in individuals. In a 12-week Australian study where consecutive blood samples were collected from 12 subjects, the intra-individual and inter-individual variation was 39 and 36 % respectively (Lux 1994).

[13] β-carotene equivalents = μg β-carotene + (0.5 μg other provitamin A carotenoids)

Following the initial study period, blood samples were taken monthly for the following six months showing a peak of plasma β-carotene in the months of spring.

2.3.6 Carotenoids and chronic disease

Epidemiological studies have indicated that people with higher intakes of fruits and vegetables may have a reduced risk of heart disease, stroke or some cancers compared with those with lower intakes. With such apparent broad health benefits, research has focussed on the antioxidant components and properties of such diets. Recently, a study into the health benefits of citrus fruit[14] reported that many of the major diseases of concern in Australia and New Zealand have a dietary component. These include cardiovascular conditions such as atherosclerosis, heart disease and stroke, cancers, obesity, dental caries, asthma, periodontal disease, type-2 diabetes, osteoporosis, cataracts and many others. Reductions in the incidence of chronic disease associated with the consumption of citrus fruits for example are thought to be attributable to an array of biologically active substances in fruits including vitamin C, folic acid, carotenoids, dietary fibre, potassium, selenium and a range of other phytochemicals.

Despite this epidemiological evidence regarding the benefits of fruit and vegetables, randomised controlled trials indicate that β-carotene and vitamin E when taken as food supplements have no beneficial effects in the prevention of heart disease and may result in a small increase in the incidence of lung cancer in the group supplemented with β-carotene (Lee 1999, Eichholzer 2001, Asplund 2002).

In general, due to the complexity of nutrients and non-nutrients in fruits and vegetables, it has not been possible to attribute the protective effects to any single nutrient or class of nutrients. Rather, and notwithstanding genetic diversity in the population, any health benefits are associated with consuming a diet that is rich in fruits and vegetables, possibly in combination with a range of other 'healthy' lifestyle choices, such as avoiding smoking and engaging in regular exercise. Nevertheless, plant compounds with antioxidant activity, such as β-carotene, are currently the focus of further scientific attention to more broadly examine potential physiological effects.

2.4 Vitamin E

There are eight naturally occurring forms of vitamin E in plants: four tocopherol and four tocotrienols. The abundance and bioavailability of each form of natural vitamin E varies considerably. Vitamin E can also be synthesised chemically. Vitamin E is a powerful antioxidant; it plays an essential role in the protection of cell membranes and plasma lipoproteins from free radical damage.

2.4.1 Sources

The major food sources of vitamin E include broccoli, dark leafy vegetables, avocado, kiwi fruit along with cold pressed vegetable oils, nuts, seeds, soy beans, wheatgerm and wholegrains (Lister 2003).

[14] The Health Benefits of Citrus Fruits, Report to Horticulture Australia Ltd Project No: CT01037, Dr. Katrine Baghurst, Consumer Science Program, CSIRO Health Sciences & Nutrition, June 2003.

2.4.2 Bioavailability

Vitamin E is a fat-soluble vitamin. Its absorption in the small intestine is enhanced by the presence of fat, causing an increase in the formation of micelles required to absorb vitamin E into the mucosal cells lining the small intestine. Once in the mucosal cells, Vitamin E is incorporated into chylomicrons and enters the circulation via the lymphatic system.

2.4.3 Deficiency

Vitamin E deficiency is rare in humans, as is toxicity (Institute of Medicine 2000). Due to the protective effect on LDL oxidation, a serum tocopherol/cholesterol ratio of 2.25μmol/mmol is thought to be the lowest satisfactory serum value for oxidative protection. The RDIs for vitamin E of 10 mg/day and 7 mg/day tocopherol equivalents for men and women respectively are based on this ratio. Phytosterol ingestion has not been shown to have an impact on plasma vitamin E levels.

3. The nutritional effects of phytosterol ingestion in the target consumer group

3.1 Recommended serum cholesterol levels

The National Heart Foundations of both Australia and New Zealand recommend that people attempt to keep their individual total serum cholesterol level below 4 mmol/L to reduce the risk of heart disease. The Australian Institute of Health and Welfare (AIHW) state that individual total blood cholesterol levels above 5.5 mmol/L are an indication of a greatly increased risk of developing heart disease and that levels above 6.5 mmol/L are considered to indicate extremely high risk.

It is suggested by the New Zealand Guidelines Group that doctors classify individuals by risk according to age, blood pressure, smoking and diabetes status. Those classified as high-risk, with a total serum cholesterol level greater than 5.5 mmol/L, be recommended for 6-12 weeks of dietary intervention, before being considered for treatment with appropriate medication: dietary intervention should be continued indefinitely[15].

Phytosterol ester-enriched foods are primarily targeted to consumers over 40 years of age with concerns about a mildly elevated blood cholesterol measurement. Due to the direct link with diet, mild hypercholesterolaemia may be adequately addressed by strategic changes to the diet such as selectively choosing low-fat versions of staple foods, by using products containing plant sterols (currently edible oil spreads and margarines), and/or by increasing relative consumption of fruits and vegetables.

[15] www.nzgg.org.nz

3.2 Studies on the effects of phytosterol ester-enriched foods

The applicants have submitted two studies undertaken by CSIRO Health Sciences and Nutrition to investigate (a) the efficacy of phytosterol esters in a variety of food matrices (Study 1), and (b) the effects of high intakes (10.7 g/day phytosterol esters) on nutritional, blood lipid and biochemical parameters (Study 2). This nutritional assessment focuses primarily on the results and information provided by Study 2, together with some additional data from Study 1. A detailed assessment of the data provided by Study 1 is presented elsewhere in this report (Attachment 2).

Submitted studies

Study 1 LDL Cholesterol Lowering with Phytosterol Ester-Enriched Bread, Cereal, Milk and Yoghurt in a Multi-Centre Trial. P.M. Clifton, P.J. Nestel and D.R. Sullivan, CSIRO Health Sciences & Nutrition, 2002.

Study 2 The Effect of Consuming Higher Dietary Intakes of Phytosterol-esters Over an Extended Period in Mildly Hypercholesterolaemic People. P.M. Clifton, P.J. Nestel and D.R. Sullivan, CSIRO Health Sciences & Nutrition, 2002.

3.2.1 Objective and methodology

The objective of Study 2 was to measure effects on serum lipids, fat-soluble vitamins (vitamins A, D and E only), plasma carotenoids, plasma phytosterols, and other physiological/biochemical parameters in free living humans provided with specific phytosterol-fortified foods providing 10.7 g/day phytosterol esters (equates to 6.6g/day of free phytosterols). Three test foods were used in this study: phytosterol ester-enriched bread, breakfast cereal and table spread, as well as a matched diet with no added phytosterols (as a control). The study also aimed to investigate any nutritional effects, particularly on plasma carotenoid levels, of additional dietary fruits and vegetables when co-consumed with the test foods.

Thirty-five mildly hypercholesterolaemic (cholesterol levels 5.0 – 7.5 mmol/l) women and men were recruited into this study which was conducted over 16 weeks at two clinical research centres, one in Adelaide and one in Melbourne. All subjects undertook dietary regimens in a non-randomised manner and were instructed not to consume self-purchased phytosterol-enriched products during the course of the study. The study was single blind and foods were appropriately coded. The dietary periods of the study are presented in Table 1.

Table 1. Dietary regimen

Time period	Description
Weeks 1 & 2 - **Baseline** Control (2 weeks)	Usual diet plus **phytosterol-free** forms of test foods (bread, breakfast cereal and spread) at the same quantities as the next two periods.
Weeks 2-8 **Period 1** Sterol-enriched food (6 weeks)	Usual diet plus **phytosterol-enriched** bread, breakfast cereal and spread contributing 10.7 g/day phytosterol esters.
Weeks 9-14 **Period 2** Sterol-enriched food plus additional fruit and vegetables (6 weeks)	Usual diet plus **phytosterol-enriched** foods (as above) with **additional vegetable and/or fruit** intake.*

Weeks 15-16 **Period 3** Free living (sterol wash-out) (2 weeks)	Usual diet plus **phytosterol-free** forms of test foods in the same quantities as the previous two periods.

* Dietary advice was given to consume at least 5 serves of fruit/vegetables every day, with at least 1 serve of either pumpkin, sweet potato, carrot, tomato, apricot, broccoli, or spinach (1 serve = half a cup).

Serum lipids (total cholesterol, HDL cholesterol, triglycerides) were determined on two consecutive days at the end of each period (weeks 2, 8, 14, 16). LDL cholesterol levels were calculated. Plasma carotenoids, plasma fat-soluble vitamins (A, D and E) and plasma phytosterols were measured at the end of each period (as above).

Carotenoid levels 'adjusted' for LDL-cholesterol

In the analysis of results, changes in carotenoids and fat-soluble vitamins have been provided as adjusted and non-adjusted levels, on the assumption that:

1. the carotenoids are transported in the circulation within low density lipoprotein (LDL) carriers, and reduced LDL-cholesterol levels will naturally result in reduced levels of these substances; and
2. due to the antioxidant role of carotenoids in protecting LDL particles against oxidation, it is generally considered appropriate to consider the magnitude of change as a ratio to LDL-cholesterol.

3.2.2 Results

Dietary compliance was monitored using food frequency questionnaires and daily records of fruit and vegetable consumption. The authors report that compliance with the dietary regimen was above 95% for all periods, except for the washout period (Period 3) at one study centre, where it fell to around 70%. Compliance with the additional fruit and vegetable intake (total of 5 per day) in Period 2 at the two study centres was 83% and 86% respectively.

There were no significant changes in total dietary fat, saturated fat, or energy between the periods in the study. Intake of β-carotene increased by 41% in Melbourne ($p=0.001$) and fibre intake also increased by 2 g/day ($p=0.04$) from period 1 to period 2. In the Adelaide group, β-carotene intake increased by 23% ($p=0.023$) and fibre intake increased by 3.3 g/day ($p=0.002$) from period 1 to period 2.

The results of the analyses of fat soluble nutrients (adjusted for total cholesterol) from Study 2, are presented in Table 2.

Table 2 Mean levels (± SD) of plasma carotenoids and fat-soluble vitamins on a diet containing 6.6 g/day phytosterols, with and without additional dietary fruit and vegetables, combined data from both study centres (n=35). The levels are adjusted for total cholesterol (μmol/L/TC mmol/L). FV = 5 daily serves fruits and vegetables.

Period	Lutein	α-tocopherol	Lycopene	α-carotene	β-carotene
Baseline	0.077^{1} ±0.034	6.03^{1} ±0.99	0.13^{1} ±0.06	0.024^{1} ±0.025	$0.105^{1,3}$ ±0.091
Period 1 (Phytosterol)	0.067^{2} ±0.03	5.85^{1} ±0.97	$0.12^{1,2}$ ±0.06	0.020^{2} ±0.014	0.082^{2} ±0.057
% change	**-14%**	**-3%**	**-11%**	**-23%**	**-26%**
Period 2 (Phytosterol + FV)	$0.073^{1,2}$ ±0.031	5.68^{2} ±0.84	0.11^{2} ±0.05	0.023^{1} ±0.013	$0.083^{2,3}$ ±0.051
% change	**-6%**	**-6%**	**-22%**	**-5%**	**-21%**
Period 3 Washout	0.075^{1} ±0.034	6.07^{1} ±1.22	$0.12^{1,2}$ ±0.05	0.023^{1} ±0.013	0.092^{1} ±0.059
% change	**-3%**	**0%**	**-11%**	**-4%**	**-13%**

Values with different superscripts within each column are significantly different ($p<0.05$) from each other.

There was a significant fall in plasma carotenoid levels measured during the first study period ($p<0.05$), with α-carotene and β-carotene reduced by 23% and 26% respectively across the combined data for all participants. At the end of the second study period, following consumption of additional fruit and vegetables, plasma α-carotene levels had increased significantly back to baseline values. Beta-carotene levels increased again only during the washout period when all phytosterol fortified foods were removed from the diet. Plasma lutein levels decreased by 14% during period 1, and increased again during period 2 with the daily consumption of additional fruits and vegetables, to levels consistent with the baseline and washout period. Plasma α-tocopherol levels were not affected by consumption of phytosterols, with measurements lower than baseline and washout only during the high fruit and vegetable intake period. Plasma lycopene levels were decreased by 11% during the first period which extended to 22% following the period of added fruit and vegetable consumption, with some recovery during the two-week washout period. Levels of plasma vitamin D did not change significantly during any of the study periods (data not shown).

3.2.3 Additional analyses from Study 1

The results of similar nutritional and biochemical investigations were also provided from Study 1 in which the daily consumption of phytosterol esters was 1.6 g/day from 3 different phytosterol enriched foods (either bread, breakfast cereal, low-fat milk or yoghurt) tested sequentially over a period of twelve weeks. As in the previous experimental design, plasma carotenoids and two fat-soluble vitamins (A and E only) were measured.

When data from both the Melbourne and Adelaide centres were combined, only β-carotene levels were significantly decreased (by approximately 10%) by milk providing 1.6 g/day phytosterol esters (Table 3).

The reduction in α-carotene levels when adjusted for cholesterol was approximately 6%, which was not statistically significant. There was no change of nutritional significance in levels of lutein, retinol, vitamin E or lycopene.

Table 3 Effect of diets containing 1.6 g/d of phytosterols on absolute and adjusted plasma carotenoids (μmol/L) and fat-soluble vitamins (μmol/L) from Melbourne and Adelaide study centres combined (n=40), milk data versus the control only. (Mean ± SD, TC = total cholesterol).

Period	Lutein	Retinol	α-tocopherol	Lycopene	α-carotene	β-carotene
Control (TC 6.56)	0.44 ±0.23	2.34 ±0.43	37.4 ±9.6	0.65 ±0.37	0.13 ±0.08	0.56 ±0.44
Milk (TC 5.90)	0.41 ±0.21	2.35 ±0.39	34.5** ±5.9	0.62 ±0.37	0.11** ±0.06	0.45** ±0.30
% change	**-6.6%**	**+0.6%**	**-7.7%**	**-4.9%**	**-16.1%**	**-19.4%**
Adjusted control	0.067 ±0.035	0.36 ±0.08	5.71 ±1.37	0.10 ±0.05	0.02 ±0.012	0.084 ±0.066
Adjusted milk	0.070 ±0.037	0.40 ±0.08	5.88 ±0.99	0.10 ±0.06	0.019 ±0.010	0.076* ±0.053
% change	**+4%**	**+33.3%**	**+2.9%**	**+4.9%**	**-5.7%**	**-9.3%**

*p<0.05, **p<0.01

The additional results from Study 1 allows a comparison of data from one type of phytosterol-enriched test food separately and therefore provides some further insights into the physiological effects of phytosterol ingestion according to the food delivery matrix. The consumption of phytosterols in both milk and bread significantly lowered adjusted β-carotene levels by 14% and 8% respectively, despite the phytosterol-enriched bread failing to show a significant reduction in cholesterol (Melbourne data). This suggests that phytosterols in milk are more effective in the gut at interfering with both cholesterol and β-carotene absorption. However, the milk data obtained from the Adelaide centre does not show the same pattern. Adjusted β-carotene levels were not significantly lower than the controls, despite a decrease in LDL-c (14.4%) and total cholesterol. The authors conclude that it is therefore not inevitable that β-carotene levels will fall in combination with a cholesterol-lowering effect.

Effects of phytosterol intake

All measures of plasma carotenoids following phytosterol intakes of 1.6 g/day and 6.6 g/day regardless of food source are compared in Table 4. With the exception of lycopene, where the adjusted level was not significantly different (p=0.07) from the control, all measurements showed a statistically significant reduction in carotenoids at the higher level of phytosterol intake (6.6 g/day).

In addition, the data indicate that the reduction in plasma carotenoids is more pronounced at higher intakes of phytosterols. There was no effect of phytosterol intake level on the change in plasma α-tocopherol level (data not shown).

Table 4 Comparison of low (1.6 g/d) and high (6.6 g/d) phytosterol intakes on plasma carotenoids (μmol/L), combined from all test periods: milk and bread in Melbourne, bread in Sydney, milk in Adelaide (Mean ± SD).

Period	Lutein Low PS intake (n=76)	Lutein High PS intake (n=35)	Lyco-pene Low PS intake (n=76)	Lyco-pene High PS intake (n=35)	α-carotene Low PS intake (n=76)	α-carotene High PS intake (n=35)	β-carotene Low PS intake (n=76)	β-carotene High PS intake (n=35)
Baseline /Control	0.43^{1} ±0.22	0.50^{1} ±0.21	0.67 ±0.35	0.87 ±0.40	0.13^{1} ±0.09	0.15^{1} ±0.15	0.53^{1} ±0.41	0.69^{1} ±0.58
Phyto-sterol	0.41 ±0.21	0.40^{2} ±0.18	0.61 ±0.36	0.71 ±0.35	0.12^{2} ±0.08	0.12^{1} ±0.08	0.47^{2} ±0.36	0.49^{2} ±0.34
% change	**-4%**	**-22%**	**-7%**	**-19%**	**-7%**	**-23%**	**-13%**	**-30%**
Adjusted control	0.068 ±0.035	0.077^{1} ±0.034	0.10 ±0.05	0.13^{1} ±0.06	0.021 ±0.014	0.024^{1} ±0.025	0.083^{1} ±0.062	0.11^{1} ±0.09
Adjusted phyto-sterol	0.070 ±0.036	0.067^{2} ±0.030	0.10^{1} ±0.05	0.12^{1} ±0.06	0.020 ±0.015	0.020^{2} ±0.014	0.078^{2} ±0.062	0.082^{2} ±0.057
% change	**+3%**	**-14%**	**-1%**	**-11%**	**-1%**	**-17%**	**-7%**	**-26%**

Values with different superscripts are significantly different ($p<0.05$) from each other.

3.2.4 Results across both studies

Ten of the subjects participated in both Study 1 and Study 2 allowing a comparison of low intakes of phytosterols (1.6 g/day in milk and bread) with higher intakes (6.6 g/day in bread, cereal and spread) on plasma carotenoid levels in the same individuals (data not shown). The authors note that although the number of subjects was small, the results indicate that the reduction in β-carotene was approximately the same at both levels of phytosterol consumption, being in the order of 20% (adjusted for cholesterol). These results also provide some indication of the effect of the food matrix on plasma cholesterol and carotenoid measurements, observing that 6.6 g/day of phytosterol in bread, cereal and margarine did not reduce adjusted plasma β-carotene any more than 1.6 g/day of phytosterol in milk, which was highly effective in lowering serum cholesterol.

3.2.5 Discussion of results

The decreases in plasma carotenoid levels recorded in Study 2 were consistent with the decreases observed from additional biochemical analyses in Study 1, in general showing some relationship with levels of intake of phytosterols and the nature of the food matrix. Thus, while phytosterol-enriched milk showed the greatest reduction in cholesterol absorption, it also resulted in lower plasma carotenoid levels. The reduction in plasma carotenoid levels with 6.6 g/day phytosterols (in bread, cereal and spread) was not different to that reported in the literature for lower levels (1.6 – 3.2 g/day) phytosterol consumption. Even 1 g/day of phytostanols has been reported to lower lipid-standardised (adjusted) β-carotene levels by 14.4% (Mensink, 2002). In general, a comparison of the data from the different study centres highlights the great variability in plasma β-carotene levels. The authors comment that carotenoid absorption is not a well-regulated process in humans and levels can fluctuate widely according to a variety of physiological and environmental factors.

Fruit and vegetable intake

The results from Study 2, where subjects were asked in the second period to consume 5 servings per day of fruits and vegetables, suggest that increased consumption of carotenoid-rich fruit and vegetables does not completely restore plasma levels to baseline for all of the carotenoids examined. Lutein and α-carotene levels appeared to respond positively to additional fruits and vegetables in the diet in the presence of phytosterol-enriched foods. Lutein and lycopene were reduced with higher levels of phytosterol intake (6.6 g/day) but were not affected at lower intake (1.6 g/day) levels (Tables 3 & 4).

The results also indicate that the reduction in β-carotene levels with consumption of phytosterol-enriched foods in general was not compensated by additional fruits and vegetables in the diet. The authors noted a maximum fall in β-carotene of approximately 30% (unadjusted for cholesterol) in all groups regardless of the level of phytosterol intake. However, despite this effect, after 12 weeks of consumption of phytosterol-enriched foods, plasma β-carotene levels were still at levels associated with the lowest risk of all-cause mortality in US adults, according to epidemiological studies cited in the Institute of Medicine Dietary Reference Intakes (2). Furthermore, retinol levels remained constant at all study centres irrespective of the amount of phytosterol consumption.

Study 2 did not attempt to examine the reduction in carotenoids at different time points and therefore does not provide any information on a pattern of reduction with ongoing phytosterol intakes. Nevertheless, as the effects were detectable early in the study and carotenoid levels returned almost completely to baseline in the two-week washout period when phytosterol-enriched foods were removed from the diet, it is likely that the reduction in carotenoid absorption had stabilised, along with the reduction in cholesterol absorption, due to the physiological linkage. Data with respect to carotenoid levels after long-term use (years rather than months) of phytosterol-enriched foods has not been presented.

3.2.5 Nutritional issues

The results from both CSIRO studies provide evidence that the effects of free phytosterol consumption up to 6.6 g/day has no significant impact on the general nutritional status of adults over the medium-term. The data also suggest that this level of consumption may be safe over longer periods of time.

Comparisons between Study 1 and Study 2 suggest that a higher intake of phytosterols has a greater potential to compromise levels of certain carotenoids, without any concomitant benefit in terms of a reduction in LDL-cholesterol. The nature of the food matrix in which the phytosterols are presented is a factor in the cholesterol-lowering effects and therefore also in the secondary nutritional effects.

However, there is no evidence in the literature that the observed reduction in some fat-soluble nutrients, most significantly β-carotene, with consumption of phytosterol-enriched foods will result in adverse health outcomes. Epidemiological studies show that fruit and vegetable consumption is inversely associated with cardiovascular disease and some cancers (e.g. gastric cancer), but to date it has not been possible to elucidate the role of individual plant components with any certainty. Clinical intervention trials using β-carotene supplements in the diet either had no benefit or caused harm, leading to speculation that a host of other compounds (or a synergistic mix) in fruits and vegetables contribute to the beneficial effects, or that an increased intake of β-carotene may merely be a marker of a 'healthy' lifestyle which in itself has been associated with a lower risk of some chronic diseases.

Increasing the intake of fruit and vegetables when consuming phytosterol-enriched foods resulted in a modest improvement in the levels of some carotenoids and therefore validates the use of advisory statements on the packaging of these products. In addition, additional consumption of fruits and vegetables is consistent with other public health messages in relation to the prevention of a range of common diseases with a dietary component.

The authors claim that the cholesterol lowering effect of phytosterol-enriched spreads can conservatively be translated to an estimated reduction of 15-20% in the risk of developing cardiovascular disease. Studies suggest that a similar reduction in the risk of heart disease can apply to high consumers of fruits and vegetables (at the 90^{th} percentile) compared to low consumers (at the 10^{th} percentile). For the same reduction in cardiovascular disease risk, the authors claim that use of phytosterol-enriched products represents a smaller dietary change for consumers when compared to the magnitude of the dietary changes required to convert from a low to a high consumer of fruits and vegetables.

In assessing the overall potential risk that can be attributed to a reduction in plasma β-carotene levels resulting from consumption of phytosterol-enriched foods, the authors cite European studies (Westrate and Meijer, 1998 & Hendriks *et al*, 1999) that claim α- and β-carotene levels measured in the Dutch population are 20% lower that the baseline levels in the submitted CSIRO studies. In addition, the plasma lycopene levels are reported to vary between 26-60% of Australian mean levels. A broad natural variation therefore already exists in different geographical populations, and significant fluctuations in carotenoid levels may also arise from adherence to a low-fat diet, seasonal variation and a variety of other environmental variables.

One environmental variable is in the nature of the diet itself. A short-term study measuring the effects of fibre and fibre sources on plasma carotenoids (Nutrition Epidemiology Group, Nuffield Institute for Health, UK – 2001) reported that both plasma α- and β-carotene are negatively affected by the consumption of cereal and cereal products. In a free-living population consuming their usual diet, fibre from cereals had a negative effect particularly on α- and β-carotene (8.4% and 6.6% reduction in plasma levels respectively for a doubling of fibre intake). These results are consistent with other reports indicating that high intakes of dietary fibre impair the bioavailability of carotenoids.

3.3 Published studies

Table 5 and 6 summarises results from the CSIRO studies and other studies published in the scientific literature investigating the nutritional effects of phytosterol-enriched foods. Taken together, these studies provide evidence that consumption of phytosterols up to 3 g/day by mildly hypercholesterolaemic adults would have no significant nutritional effects on fat-soluble vitamin or carotenoid status. Although most studies do show a reduction in plasma β-carotene and α-carotene levels, only some have shown the reduction to be statistically significant (CSIRO 2002, Gylling 1999, Davidson 2001, Mensink 2002, Hendriks 2003, Raeini-Sarjaz 2002).

Two studies have investigated the effects of phytosterol intakes higher than 3 g/day, however the majority of studies are not long-term. In addition, because of differences in experimental design and in some cases the absence of specific dietary information, the majority of results show effects of dietary phytosterols only in terms of the cholesterol:β-carotene ratio, and do not record changes in any other fat-soluble nutrients.

3.3.1 Studies with higher intakes of phytosterols

Davidson *et al* (2001) studied three test groups of 23 subjects each, who consumed 0, 3, 6, or 9 g/day of phytosterol esters in reduced fat spreads for eight weeks. Blood concentrations of measured fat-soluble vitamins (vitamins A, D and E) remained within normal reference ranges. There was no statistical difference in serum vitamin response for these nutrients in those subjects who consumed 9 g/day phytosterols compared with the two groups consuming 3 g/day and 6 g/day respectively.

Pair wise comparisons of β-carotene levels after the intervention period indicated significant differences between the 9 g/day group compared to the control and the 3 g/day group ($p<0.05$). Only the control group and 9 g/day group also differed significantly with respect to serum α-carotene levels. The authors concluded that consumption of phytosterols at a level of 9 g/day was safe and well tolerated.

It should be noted that the reduced-fat spread and salad dressing used as phytosterol-ester delivery vehicles in this study did not produce the expected magnitude of reduction in LDL-cholesterol levels. Despite this, reductions in levels of fat-soluble vitamins and serum carotenoids were recorded. In addition, all groups receiving phytosterols showed a relatively small increase in corresponding serum phytosterol levels indicating that the significance of the results from a nutritional perspective may be limited.

3.3.2 Research with controlled diets

Although there are two published studies investigating the nutritional effects of phytosterol consumption in the context of a controlled diet, only one provides information that is relevant to this assessment.

Raeini-Sarjaz *et al*. (2002) reported no effect of consumption of esterified plant sterols (or stanols) on serum fat-soluble vitamins or carotenoid concentrations when consumed in conjunction with a diet adequate in fruit and vegetables, compared to baseline diets.

The study involved 15 hypercholesterolaemic males administered a daily amount of 1.92 g/70 kg body weight of plant sterol esters in a metabolic kitchen setting in the context of a diet formulated to meet the Canadian Recommended Nutrient Intakes. Measurements for serum retinol, α- and γ-tocopherol, vitamins D and K, lycopene, lutein, α- and β-cryptoxanthin, and α- and γ-carotene were conducted. The authors concluded from their results that moderate consumption of plant sterol and stanol esters would not be expected to affect fat-soluble vitamin and carotenoid concentrations in conjunction with a healthy diet.

3.3.3 Fruit and vegetable consumption

A study by Noakes *et al.* (2002) specifically examined whether consuming daily amounts of foods high in carotenoids prevents a reduction in plasma carotenoid concentrations in subjects who consume plant sterol (or stanol) esters. Forty-six hypercholesterolaemic subjects completed a three way, double blind, crossover comparison in which 25 g/day of one of the following 3 spreads were consumed for 3 weeks: control (placebo/sterol free), sterol–ester (2.3 g/day plant sterol esters) or stanol-ester (2.5 g/day plant stanol esters). During the study period, subjects were advised to eat five or more servings per day of fruits and/or vegetables, of which at least one serving was to be carrots, sweet potatoes, pumpkin, tomatoes, apricots, spinach or broccoli.

As expected, there was a reduction in total cholesterol with consumption of sterol esters (-6.1%) and stanol esters (-7.3%), compared with the control spread. The decrease in the LDL-cholesterol concentration was 7.7% with consumption of sterol ester-enriched spread and 9.5% with consumption of stanol ester-enriched spread. There were no significant changes in HDL-cholesterol or triacylglycerol concentrations.

Consumption of the different spreads did not significantly change the concentrations of retinol and lutein, which the authors note is consistent with their transport by retinol binding protein, and HDL (40%) respectively. Similarly, α-tocopherol concentrations were not significantly different among the spread periods or between the spread periods and baseline period. After standardising for lipids, there were no significant differences in plasma carotenoid concentrations between the experimental groups and the control. However, before lipid adjustment, both the sterol and stanol periods significantly lowered the β-carotene concentration by 9% compared to the control period, but not compared with the baseline period. When the 1-week baseline and control periods were analysed separately, the levels of lutein, α-carotene and β-carotene increased by 11%, 29% and 13% respectively, demonstrating the effects of increasing dietary intake of the specified fruits and vegetables, in the absence of plant sterols. Interestingly, the concentration of plasma lycopene did not change significantly during the study.

The authors concluded that daily consumption of an average of one extra daily serving of high-carotenoid fruit or vegetables, compensates plasma concentrations of α- and β-carotene and maintained concentrations of lipid-standardised plasma carotenoids in subjects consuming sterol or stanol-enriched spreads. The conclusions of this study suggest that compliance with dietary advice to consume specified fruits and vegetables, in conjunction with phytosterol-enriched foods, is likely to compensate for a decrease in carotenoid levels.

3.3.4 Long-term studies

There are few long-term studies investigating the nutritional effects of phytosterol consumption. Gylling (1999) investigated the effects on carotenoids and fat-soluble vitamins of ingestion of 2-3 g/day phytosterols over 12 months. Serum cholesterol and vitamin concentrations were measured at 0 and 12 months. The levels for serum α-tocopherol, α-carotene, β-carotene and cholesterol were all significantly lower in experimental subjects compared with controls after 12 months. However, when levels were adjusted for LDL concentration, β-carotene was the only nutrient significantly lower than the controls.

A one-year study by Hendriks *et al*. (2003) involved 185 volunteers randomised into either a control or experimental group who consumed 1.6 g/day of phytosterol esters in a margarine-type spread. Carotenoids were measured at both 26 and 52 weeks and compared to baseline and to the control group. In absolute terms, serum β-carotene levels were reduced by 22% at 26 weeks and by 25% at 52 weeks in the experimental group compared to baseline. Serum α-carotene levels were reduced by 11% at 26 weeks and by 15% at 52 weeks in the experimental group compared to baseline. When the results were corrected for LDL concentration, only α-carotene was reduced in the experimental group who consumed the phytosterol-fortified spread.

The study reported no change in LDL and cholesterol concentration (a plateau effect) in the second half of the study period between 26-52 weeks, and the researchers concluded that the nutritional effects had reached a plateau by the mid-time point.

3.3.5 Studies in hypercholesterolaemic children

Five studies investigated the effects of phytosterol esters in children (Gylling 1995, Tammi 2000, 2001 & 2002, Amundsen 2002), however only two of these investigated nutritional parameters. All children in these studies were either hypercholesterolaemic, or were genetically susceptible to high cholesterol levels.

One study of 38 children (each of whom had a parent with hypercholesterolemia) who were supplemented with 1.6 g/day phytosterol esters, showed significant decreases in serum concentrations of β-carotene and lycopene, with the difference in β-carotene disappearing after statistical adjustment for cholesterol. Twenty-one of the 38 children took either fish oil, or vitamin A, D or E supplements (Amundsen 2002).

Another study that measured the serum antioxidant levels of 72 six-year old children consuming 1.5 g/day plant stanols over a three-month intervention period showed that serum β–carotene and β-carotene/LDL concentration was significantly lowered as a result of treatment. α-Carotene and lycopene were not measured (Tammi 2000).

The results of these studies confirm that consumption of phytosterols can result in a reduction in carotenoid levels in all consumers irrespective of age, where there is a concomitant reduction in cholesterol absorption.

3.3.6 Normocholesterolemic children

Studies examining the effects of phytosterol-enriched foods in children with normal cholesterol levels are not available. This is because the primary research interest in the cholesterol-lowering effects apply to adult consumers with slightly raised cholesterol levels that are not high enough to require therapeutic intervention, but are above recommended levels for reducing risk factors associated with the development of cardiovascular disease. Given the target consumer group, it is unlikely that data in children other than with genetic/familial hypercholesterolaemia will become available.

3.3.7 Older adults

The NHMRC Dietary Guidelines for Older Australians (1999) and other papers (for example, Heseker 1994) suggest that older adults (over 65 years) generally have changing nutrient requirements because of age-related changes in body composition and physiological function. The changing nutrient requirements could include a higher dietary requirement for carotenoids (e.g. β-carotene), and vitamins C and E due to increased oxidative stress. At the same time, due to a general decline in physical activity and subsequent energy intake, and reductions in the bioavailability of certain nutrients with increasing age, it is recognised that meeting any increased nutritional requirements depends on varying factors affecting diet, eating habits and lifestyle.

Despite these variables, according to data from the Australian National Nutrition Survey (1995-96), the mean nutrient intakes for both males and females in the over 65 age-group of vitamin A-retinol equivalents is almost double the RDI for males and approximately 1.5 times the RDI for females. The New Zealand National Nutrition Survey (1996-97) also indicated the average intake of vitamin A-retinol equivalents was approximately 1.5 times the RDI for men and women over 65 years of age. These data indicate that in terms of retinol equivalents, the current levels of intake by elderly consumers in Australia and New Zealand are generally well above daily requirements.

While there are no studies currently available that specifically examine the nutritional effects of phytosterol-enriched foods in older-age consumers, the NHMRC guidelines stress the importance of variety in the diet in order to provide a more complete profile of nutrients and non-nutrients. This recognises the importance of whole foods, particularly fruits and vegetables, as beneficial in reducing the risk of developing chronic diet-associated diseases. Health benefits to be derived from a diet rich in fruits and vegetables are likely to be attributable to the synergistic effects of a complex mix of phytochemicals including carotenoids, flavonoids and isoflavonoids, polyphenols, isothiocyanates, indoles, sulphoraphane, monoterpenes, xanthin, and non-digestible polysaccharides.

Given this information, the significance of a reduced level of one carotenoid, β-carotene (a pro-vitamin), with consumption of phytosterol-enriched foods should be considered in the context of the significant increase in the incidence of peripheral vascular disease, cerebrovascular disease and arteriosclerosis in the older adult population, and the measurable health benefits provided by a lower blood cholesterol level in this age group.

In the context of a changing physiology, older consumers may need to adapt dietary habits and eating patterns to compensate for a variety of changing nutrient requirements, in order to maintain optimal health.

The dietary advice to consume greater amounts of fruits and vegetables when consuming phytosterol-enriched foods is therefore consistent with broad public health messages to this population group.

3.3.8 Pregnant and lactating women

Currently there is no research specifically investigating the nutritional effects of consumption of phytosterol-enriched foods by pregnant and lactating women. On the contrary, pregnant and lactating women have been excluded as subjects on nutritional grounds. The Scientific Committee on Food (SCF, 2003) considers that use of phytosterol-enriched foods by pregnant and lactating women is inappropriate because of the resultant lowered absorption of both dietary cholesterol and β-carotene, and the lack of information on whether this would have an adverse nutritional impact on women with increased physiological load.

Currently in Australia and New Zealand, phytosterol-enriched edible oil spreads and margarines are required to carry a mandatory advisory statement to ensure that pregnant and lactating women do not consume these products. This cautionary approach is therefore consistent with the views expressed by other independent scientific committees.

3.3.9 Phytosterolaemia

Sitosterolaemia is a rare genetic (autosomal recessive) disorder in which affected individuals hyper-absorb and retain both cholesterol and other (plant, fish) sterols. The effects of this genetic condition are tendon and tuber xanthomas, arthralgias and arthritis, accelerated atherosclerosis and premature coronary artery disease (SCF 2003). The potential impact of phytosterol-enriched foods on patients with this disorder is discussed in more detail in the safety assessment at Attachment 2.

3.3.10 Phytosterols as antioxidants

The oxidation of biological molecules is known to be associated with the development of numerous disorders and pathological events such as atherosclerosis, cancer and various age-dependent processes. Chemical compounds and substances such as vitamin E that suppress oxidation have therefore become a focus of study over recent times to explore more fully their potential *in-vivo* antioxidant properties. As well as vitamins and other nutrients, plant substances such as polyphenols (rich in red wine and tea) act to protect biological molecules and tissues from oxidative damage, thereby contributing to the antioxidant pool in the body.

A recent paper (Yoshida and Niki, 2003) explored the antioxidant properties of plant sterols (campesterol, β-sitosterol, stigmasterol) and reported that phytosterols themselves can act as an antioxidant *in-vitro*, a modest radical scavenger in solution, and physically as a stabiliser in liposomal membranes. The possible antioxidant role of phytosterols *in-vivo* remains as a future subject for study.

Summary – Nutritional effects of phytosterols

Plant sterols (phytosterol-esters in this assessment) have been shown in a large number of studies to lower the absorption of dietary and biliary cholesterol thereby decreasing the levels of LDL-cholesterol in the circulation. As cholesterol absorption is reduced, there is a concomitant effect on the absorption of some lipophilic nutrients.

When these secondary nutritional effects were examined in further studies, reductions in α- and β- carotene, lycopene, lutein and cryptoxanthin were observed, while vitamin E and vitamin A levels remained unaffected. Additional carotenoid-rich fruits and vegetables in the diet, when co-consumed with the phytosterol-enriched foods, partially compensated for the lower bioavailability of carotenoids in the presence of phytosterols.

With some variability, consumption of phytosterol-enriched foods generally results in a reduction in β-carotene levels of approximately 20-25%. This reduction does not translate into an overt nutritional deficiency as absolute levels remain within a broad natural range and there is no measurable effect on retinol or vitamin A levels. The nutritional significance of a reduction in β-carotene levels therefore cannot be directly measured or assessed. In terms of antioxidant status, other nutrients such as vitamin C and vitamin E are not affected by consumption of phytosterols and other phytochemicals present in fruits and vegetables contribute to the complexity of the diet and overall health.

In light of the secondary nutritional effects, consumption of phytosterol-enriched foods is not appropriate for children, or pregnant or lactating women on the general assumption that there is no direct necessity to lower absorption of dietary cholesterol in these groups. Given their requirements for optimal nutrition, these population groups would therefore derive no particular immediate health benefit from increasing their intake of phytosterols. In contrast, consumers over the age of 40 years, and particularly those with slightly elevated cholesterol levels, can make simple dietary changes that may effectively reduce one of the known risk factors in the development of atherosclerosis and cardiovascular disease.

The data submitted with these applications indicate that consumption of phytosterol-enriched foods providing up to approximately 10.7 g/day phytosterol-esters is safe from a nutritional perspective. Furthermore, other information from published studies suggests that intake of phytosterol esters at higher levels (up to approximately 9 g/day) is not associated with adverse effects arising from a reduction in some carotenoids. However, the effects of free phytosterol consumption above 4.3 g/day on nutritional parameters, or over the long-term, have not been extensively researched, and there is therefore a lack of detailed information in this area. Furthermore, as there is no additional cholesterol lowering effect with increased phytosterol intake above approximately 3 g/day, there is no additional benefit in consuming unlimited amounts of phytosterol-enriched foods.

The results of several studies suggest daily consumption of 5 serves of fruits and vegetables, particularly those high in β-carotene, when choosing phytosterol-enriched foods, may assist in maintaining the levels of some carotenoids. The European SCF recommends that consumers be made aware of the potential β-carotene lowering effect of phytosterol-enriched products by the provision of appropriate dietary advice relating to the regular consumption of fruits and vegetables.

INTERNATIONAL REVIEWS ON THE NUTRITIONAL ASPECTS OF PHYTOSTEROLS IN FOODS

European assessment

Foods containing added phytosterols have been available in Europe since the mid 1990's. As part of the process of assessment, the Scientific Committee on Food (SCF) of the European Commission has considered various safety aspects of phytosterol esters and has produced several opinion reports (2000a, 2002a, 2002b, 2003) reviewing in particular the nutritional effects of phytosterols, and the long-term effects of elevated levels of phytosterols from multiple dietary sources.

Previously, the Committee concluded that yellow fat spreads containing up to 8% of free phytosterols are safe for human consumption. It was noted that ingestion of approximately 20g of phytosterol-enriched spread per day for one year reduced β-carotene concentration by 20%. The Committee considered that although this reduction was within the normal range and within normal seasonal variation, it may become of greater nutritional relevance for individuals with a sub-optimal vitamin A status.

On the basis of results from several different trials using plant sterols or stanols, decreases in blood carotenoids plateau at consumption levels of 2.2 g/day (Plat et al. 2000). Apart from the carotenoid lowering effect, the Committee found that no other nutritionally relevant changes were evident when considering the results of several randomised trials of plant sterol or stanol margarines in humans, some of which lasted for one year.

The SCF considers that the greatest nutritional effect of phytosterol esters appears to be upon β-carotene, with only minimal effects on fat-soluble vitamins and other carotenoids. Based on the general acceptance that consumption of up to 10 mg/day of β-carotene from carotenoid-rich fruits and vegetables confers non-specific health benefits, the Committee has recommended the consumption of carotenoid rich fruit and vegetables to counterbalance the expected reduction of blood β-carotene arising from long-term consumption of phytosterol enriched foods.

The Committee concluded that, due to the lack of evidence of benefits from phytosterols at higher levels of intake, consumption of free phytosterols exceeding a range of 1-3 g/day (equivalent to 1.6 – 4.8 g/day phytosterol esters) was inadvisable. They also considered that with an ever-increasing number of potential foods as candidates for phytosterol enrichment, additional measures may be required to manage potentially excessive intakes (SCF 2003).

Review by the Mayo Clinic

In 2003 the Mayo clinic published a paper summarizing the deliberations of 32 experts on the safety of sterols and stanols (Katan 2003). The paper was a meta-analysis of 41 trials aimed at determining the safety of phytosterol intake at a level of 2 g of free stanols or sterols per day in relation to heart disease. The authors suggest that reduction of LDL cholesterol levels by 10% could be expected to reduce the incidence of ischaemic heart disease by between 12 and 20 % over 5 years.

The meta-analysis of 18 trials investigating the effects of sterol and stanols intake on plasma concentrations of fat-soluble vitamins showed statistically significant reductions in α-carotene (9%), β-carotene (28%) and lycopene (7%). On statistical correction for total cholesterol, only the decrease in β-carotene remained significant. The authors considered that the decrease in β-carotene could be prevented by the addition of 'adequate' fruit and vegetables to the diet.

This review noted that plasma β-carotene levels are affected by a variety of dietary factors. Olestra and wheat bran have been shown to significantly decrease β-carotene levels, as have some lipid lowering drugs (probucol and cholestryamine). Therefore, based on currently available information, there is no evidence that decreased levels of β-carotene are associated with increased health risks.

TABLE 5 Details of the studies of the Effect of Phytosterol Consumption on Plasma Fat-soluble Vitamins and Carotenoids

Authors	Number of Subjects	Cholesterol status at baseline	Dietary intake	Smokers/non smokers	Mean Age	Weight at baseline	Fruit and vegetable intake
CSIRO, 2002	Adelaide 13 women 10 men	Combined centres: TC 6.59 ±1.01 mmol/l HDL 1.35±0.38 mmol/l LDL 4.46±0.91 mmol/l	8281 kJ/day Fat 24% TE SAFA 10.3% TE	Not discussed	53.3 yrs	BMI 27.9	phase 1 not discussed, phase 2- 83% compliance with 5 serves / day
	Melbourne 10 men 2 women	Combined centres: TC 6.59 ±1.01 mmol/l HDL 1.35±0.38 mmol/l LDL 4.46±0.91 mmol/l	6853 kJ/day Fat 33% TE SAFA 12.5% TE	Not discussed	59.7 yrs	BMI 27.6	phase 1 not discussed, phase 2- 86% compliance with 5 serves /day
Gylling, 1999	102 active subjects 49 controls	TC >5.58 mmol/l	Fat 85g/day SAFA 34g MUFF 32 g PUFA 15g	Not discussed – not in exclusion criteria	50±1 yrs	BMI 26	not discussed
Davidson 2001	0 g/day n=21 3.0 g/day n=21 6.0 g/day n = 19 9.0 g/day n=23	mildly hypercholesterolaemic	TE 2019 Kcal/day Fat 33% TE SAFA 11%TE MUFA 12.6% TE PUFA 6.4%TE	74 smokers 10 non-smokers	46 yrs	79 kg	not discussed
Nestel P 2001	22 subjects 4 men 18 women	mildly hypercholesterolaemic TC >5.5 mmol/l	Fat 34%TE SAFA 11.5%TE	non smokers	60±9 yrs (34-70 yrs)	BMI 24±1 (18.3-26.9)	not discussed
Raeini-Sarjaz 2002	15 men	hypercholesterolaemic TC 6-10 mmol/l	All food prepared in metabolic unit. Fat 35% TE SAFA 15% MUFA 10% PUFA 10%	not discussed	37-64 yrs	not discussed	not discussed

TABLE 6 Results of the studies of the Effect of Phytosterol Consumption on Plasma Fat-soluble Vitamins and Carotenoids

Mensink 2002	30 subjects 30 controls 16 men 44 women	TC 5.14±0.78 mmol/l men TC 5.12±0.80 mmol/l women	Energy/day S 9.5 MJ, C 11.3 MJ Fat % TE S 29.1%, C 31.7% SAFA S 10.8%, C 11.4% MUFA S 10.9%, C 12.2% PUFA S 5.3%, C 5.9%	7 smokers	36±14 yrs	BMI 23.3±2.7	not discussed
Westrate 1998	95 subjects	TC 5.35±1.06 mmol/l	FAT 41% TE SAFA 15.5% MUFA 14% PUFA 10%	not discussed	45±12.8 yrs	24.2±2.16	not discussed
Hendricks 1999	100 subjects 42 men 58 women	TC 5.10±0.97 mmol/l (2.71-7.42 mmol/l)	Fat 33% TE SAFA 13.5% MUFA 11.6% PUFA 6.0%	not discussed	37±10 yrs	22.8 ± 2.5 (17.7-28.6)	not discussed
Hallikainen 2000	22 subjects 14 women 8 men	TC 6.87±1.28 mmol/l	Standardised background diet designed for 8 different levels of energy requirement Fat 34% TE SAFA <12% MUFA 14% PUFA 8%	not discussed	50±11 yrs	26 ± 3.4	no information on fruit and vegetable intake
Hendricks 2003	190 subjects Experimental 44 men, 45 women Controls 46 men, 50 women	TC 5.9 ± 0.98 mmol/l		6 smokers control 11 smokers exp.	48±8 yrs	24.9 ± 3.2	no information

ns No significant difference
TC Total Cholesterol

Study	Level of intake	Food source	Length of study	Cholesterol	α-Tocopherol	α -Carotene	β -Carotene	Retinol	Lutein	Lycopene
CSIRO	6.6 g/day	bread, breakfast cereal, table spread	total 12 weeks 2 phases-6 weeks each 2nd phase with extra F&V		P1 –10% p<0.05 P2 - 13% p<0.05	ns	cf baseline P1 -28% p<0.05 P2 –28% p<0.05	ns	P1 –23% p<0.05 P2 –15% p<0.05	P1 –18% p<0.05 P2 –30% p<0.05
					P1 –15% p<0.05 P2 –7% p<0.05	ns	ns	ns	P1 -15% p<0.05 P2 –7% p<0.05	P1 -18% p<0.05 P2 –23% p<0.05
			Adelaide and Melbourne combined	TC –8.5% LDL –13% (p<0.05)	ns	P1 –31% p<0.05 P2 ns p<0.05	P1 –30% p<0.05 P2 –26% p<0.05	ns	ns	ns
Gylling 1999	3 g/day for 6 months, then either 2 or 3 g/day for 6 mths	Margarine	52 weeks	TC -9% (P<0.001)	-10±1% (P<0.05) Proportion to cholesterol unchanged	ns	sig ↓ (p<0.05)	ns	-	-

Davidson 2001	0 g/day 3 g/day 6 g/day 9 g/day	Reduced fat spread and salad dressing	8 week treatment period	ns between groups	ns	ns	ns	ns	ns	ns
				ns between groups	ns	ns	ns	ns	ns	ns
				Total:HDL -9.6±14.9% p<0.008	ns	Significantly lower than 0 and 3g/day p<0.004	Significantly lower than 0 and 3g/day p<0.001	ns	ns	ns
Nestel P 2001	2.4 g/day	breads and breakfast cereal	12 weeks	LDL –13.6% P<0.001	ns	ns	ns	ns	-	ns
Raeini-Sarjaz 2002	sterols 1.92 g/70 kg bw/day	margarine (controlled diet)	3 weeks		ns	increased P<0.01	ns	ns	ns	ns
Mensink 2002	3 g/day	low fat yoghurt 450 ml/day	4 week double blind, placebo controlled	control vs. ex groups: TC –8.7% (P<0.001) LDL –13.7% (P<0.001)	ns	not measured	β-C:LDL -12.9 ±21.2% cf. control P=0.038	ns	ns	-
Westrate 1998	1.5-3.3 g/day	Margarine sterols - soybean sheanut rice-bran sitostanol ester 5.0 mg/kg carotene	3.5x 4 weeks	control vs. ex groups: TC – 8-13%	-	α and β-carotene combined decreased from av 220 µg/l in first period to 168 µg/l in fourth.		-	-	↓ from period 1 – 4 85µg/l to 63µg/l
Hendricks 1999	0.83, 1.61, 3.24 g/day	Margarine	3.5x 4 weeks	Sig ↓ TC in all phases HDL ↓ after 1.61 &3.2g cf baseline	-6% 1.61g -8% 3.2g α-toc/TC ns	Combined α and β-carotene concentrations -11% w/ 0.83g/day -19% w/ 3.24g/day		-	-	lyco/TC ns

Hallikainen 2000	5x4 weeks in the order: 2.4, 2, 1.6, 0, 0.8 g/day	Rapeseed oil Margarine 25g/day	20 weeks	1.6,2.4&3.2g TC sig lowered LDL sig lowered	ns	ns	ns	-	-	-
Hendricks 2003	1.6 g/day	Margarine 5.7 mg/kg carotenoids	1 year	TC ↓4% LDL ↓ 6%	ns	sig ↓ cf with controls after 26 and 52 weeks but no sig diff for /TC	sig ↓ cf with controls after 52 weeks	ns	sig ↓ cf with controls after 26 and 52 weeks	ns

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Attachment 6

Summary of Submissions received

(First Round)

Submitter	Comment
Australian Food and Grocery Council	The AFGC considers that FSANZ has erred in not making a decision at the time of initial assessment to determine whether the application warrants a variation to a regulatory measure. AFGC disputes that efficacy in relation to labelling statements has anything to do with a safety assessment under Standard 1.5.1-Novel Foods as there is no requirement for provision of efficacy data. AFGC supports that an assessment should be undertaken on the potential nutritional effects of phytosterols. However, they consider that there are options that could be exercised that could adequately protect consumers if adverse effects were found following the assessment. AFGC considers that conditions of use are an essential part of fulfilling the requirements of being a novel food. AFGC supports the option to approve the general use of TOPs as its first preference, followed by approval in all milks and then approval in low-fat and no-fat milk products.
New Zealand Food safety Authority (NZFSA)	NZFSA advocates a cautious approach when assessing applications to extend the use of phytosterols in foods and agree that the issues identified at Initial Assessment should be fully evaluated. Concerned that widening of permissions may lead to over consumption of phytosterols without any additional cholesterol-lowering benefits, yet may affect absorption of some fat-soluble vitamins and carotenoids. NZFSA considers that the product categories should be decided at the outset, rather than approving an increasing number of product categories on a case-by-case basis. Product labels should state the recommended number of serves/day that would provide a benefit and that consumption above recommended servings would not provide additional cholesterol lowering effects.
Dietitians Association of Australia (DAA)	Believes there are some benefits in broadening the range of foods that contain phytosterols. However, the potential for non-target groups (such as children, pregnant and lactating women and people with normal cholesterol levels) to increase their intake of phytosterols is a concern that needs addressing. Supports mandatory advisory statements that are clearly legible and visible to consumers. DAA is unable to support any of the current proposed options without reviewing the safety, efficacy data and dietary exposure data.

Valerie James	A 508 should be rejected because the Applicant has not provided evidence of any benefits for making available a wider choice of phytosterol-containing products.
Richard James	A508 should be rejected and not reconsidered until the applicant proves from controlled, monitored and peer-reviewed studies that its product is safe for adding to foods and beverages.
Food Technology Association of Victoria Inc	Support the application to amend the Code to permit the use of TOPs in low-fat and no-fat milk. Several issues are required to be addressed: • The overall phytosterol issue should be addressed at one time rather than by several different applications which would allow an assessment of the impact on the total diet • The editorial note in Standard 1.5.1 and Clause 2 (1) of Standard 2.4.2 require review and revision as it is unclear what the situation is with the use of phytosterols and phytosterol esters in the same products • The proposed labelling statements from the Applicant require careful consideration as they currently imply a pharmaceutical dose statement. • Option 3 to approve phytosterols in any food to a maximum permitted level is too general at this stage.
Sanitarium Health Food Company	Sanitarium is unable to support any of the options outlined in A508 as inadequate information is available at this stage regarding the safety of higher intakes of phytosterols from a wider variety of sterol fortified foods.
Nestlé Australia Ltd	Supports option 3 and approve the general use of tall oil phytosterols in a range of foods. FSANZ needs to use previous information on the costing study following the introduction of mandatory nutrition labelling to determine the impact on target groups consumers.
Unilever Australasia	Supports option 2 and also the comments from the AFGC. Additional comments: • Request that a level of 1g of TOPs per serving/food group be considered as a more adequate level to allow consumers to meet the recommended levels of 2-3g/day. • Suggest that consideration be given to a common labelling format for multiple foods containing phytosterols. • Request consideration of specifications accepted by other regulatory agencies to be included as part of this application and also reviewing the specifications to include both the free sterol and ester forms. Question the need for minimum limits of sterols.
Dairy Australia	Support the use of TOPs as ingredients in low-fat and no-fat milk provided that careful consideration is given to labelling and usage of foods containing TOPs. Did not support option 3 as this may lead to over consumption by inappropriate groups and may encourage consumption of diets incompatible with Australian Dietary Guidelines.

Environmental Health Unit, Queensland Health	Does not support the option to permit TOPs in low-fat and no-fat milk. Raised the following concerns: • The long-term effects are unknown; • Raises concerns over the use of food as medicines; • The cost of phytosterol-containing foods is high and raises issues of inequity for some consumers (e.g. from lower socio-economic groups); • Phytosterols have oestrogenic activities; • Sufferers of homozygous sitosterolaemia need to restrict their intakes of plant sterols; • The safety of use of these products by non-target consumers needs further consideration.
New Zealand Dietetic Association	Does not support the Application due to insufficient knowledge on the safety of higher doses and long-term exposure to phytosterols in foods. This is particularly important in vulnerable groups such as children and pregnant women.
Rosemary Stanton	Does not support the option to permit TOPs in low-fat and no-fat milk. Summary of concern: • loss of fat soluble vitamins, carotenoids and other fat soluble phytochemicals which may be protective against cancers; • lack of research on hundreds of other carotenoids; • lack of need for more phytosterol products and the presumption that they should be given precedence over other health considerations; • ease of over-consumption if more permission are granted; • unlikely restriction by consumers to 2 serves/day; • lack of evidence that consumers will consume extra fruit and/or vegetables to make up for the loss of carotenoids.

(Second Round)

Submitter	**Comment**
Fonterra Co-operative Group Limited (New Zealand)	**Supports** Application A508 and the drafting.
George Weston Foods	**Supports** Application A508

AFGC	**Supports** approval of A508. AFGC maintains that in relation to the efficacy of phytosterol-containing products that it is not an objective of FSANZ to presume what statements or claims manufactures might make and then demand proof of them as there are adequate powers under State, Territory and New Zealand Food Acts, the Trade Practices Act and fair trading legislation to control false or misleading claims on food packages or in advertising. As FSANZ has assessed the clinical data on the efficacy of foods containing plant sterols, further assessment should not be necessary in the event that a Standard for health claims is established. AFGC recommends the drafting to be changed to allow for capacity in I L containers of a little over 1 Litre (to allow for headspace in packages) to the following: *'Supplied in a package, the nominal capacity of which is no more than 1 Litre'.* The new subclause 5 (1) in Standard 2.5.1 requires TOPs to be added to milk where the total phytosterol (from a tall oil source) added is 3.6g/L of milk. However, this does not allow for product fluctuations. The AFGC recommend a change in the drafting to the similar wording as is used in subclause 2(1)(h) of Standard 2.4.2 which limits the amount of TOPs to 'no more than 80g/kg' in edible oil spreads and margarine.
Dairy Australia	The dairy industry supports Option 2: to '*Permit the addition of tall oil phytosterols (TOP) in low fat milks' (<1.5 g total fat/100 g liquid milk with 0.9 g TOP/250 ml serving size of milk).* The target audience is consumers over the age of 40 years with concerns about plasma cholesterol levels. However, there should be consistency between this Application and Application 434 in relation to the number of serves of phytosterol containing foods that are recommended daily – 'two serves', 'two to three serves', to 'up to three serves' per day, are quoted. The dairy industry recommends '*up to three serves/day'* be adopted. Recommend the wording of the Standard be amended to include 'no more than' and a maximum level of 4g of phytosterols per litre of milk to allow for normal production variances (i.e. 3.6g/litre plus a 10% variance).
Nestle Australia and Nestle New Zealand	**Supports** the approval of tall oil phytosterols in low-fat milks. Also supports the recommendation from Dairy Farmers to change the number of serves to up to 3 serves/day for a consistent message for all phytosterol Applications. Recommend that the limit of addition of tall oil phytosterols be worded to be consistent with other foods, i.e., is should state 'no more than 3.6g/L NOT the current words in the drafting of where the total phytosterol (from a tall oil source) added is 3.6g/L of milk.

Unilever Australasia	**Support** the Draft Assessment document out for public comment with respect to Applications A508 and the recommendation for this application to proceed with the recommended option 2. Supports the approval of all applications seeking to use plant sterols in foods. Post-launch monitoring information for the yellow fat spreads in Europe, demonstrates that even in regular users, there is a reluctance to consume table spreads in appropriate amounts to supply sufficient plant sterols to see a beneficial effect. The current applications provide consumers with a wider choice of foods and a better opportunity to include plant sterol enriched foods in their diet. The proposed regulations in terms of container sizes are too restrictive to allow flexible product development to meet consumer expectations of product range. Given the proposed restrictions as to food matrix, successive applications to FSANZ would be required each time for each new product, which would be significantly onerous on food manufacturers. Supports the provision of information to consumers to prevent confusion about consumption of phytosterol enriched products and advocates the use of labelling requirements that would be common to all products, as is being considered in the European Union.
Food Technology Association of Victoria Inc	**Supports** Application A508 and made the following comments: The term 'low-fat milk' is not otherwise defined in the Code. This should be rectified prior to this Proposal being finalised; Attachment 2 refers to 'No Fat Liquid Milk' in the primary heading, which is not defined in the attachment and was not requested as part of the original Application; In the Draft Variations, clause 5 requires that Tall Oil Phytosterols when used in milk should be supplied in a package which is no more than 1 litre capacity. This means that TOPs will be supplied in smaller packs, i.e. 200, 250, 500 mL capacities which in turn are pack sizes consumed by children. Yet the product is not recommended for children, who usually do not read labels in any depth. Also as these types of products will be marketed at the public with overweight problems, it is conceivable in the current climate of obesity (including children) that children will feel encouraged to purchase and consume these products.
Dietitians Association of Australia	Supports the Application, and the cautious expansion of the range of foods permitted to contain added phytosterols. Considers that the dietary modelling should have treated adolescents as a distinct population group because of their propensity to consume large quantities of the foods in question. The advisory statements should appear in a prominent place and in a prominent font on the label of foods containing added plant sterols.

New Zealand Food safety Authority (NZFSA)	**Support** the proposed labelling statements. However, it is important that the Final Assessment report provides clarification on why the recommended level of consumption is three serves/day. In order that consumers can avoid the potential for over-consumption (for example by mixing of tall oils and phytosterol ester containing products) it is suggested that clause 2 of Standard 1.5.1 is amended as follows: • Tall oil phytosterols are labelled as 'plant sterols' (tall oil phytosterols)' and; • Phytosterol esters are labelled as 'plant sterols' (phytosterol esters)' The Applicant's proposed labelling and packaging of their product includes clear advice on the label that a minimum level of consumption is required for a cholesterol lowering effect. However, we note that this information is not part of the proposed mandatory labelling information described in the Draft Variations to the table to clause 2 of standard 1.2.3 in Attachment 1. We question if this is the intention, or if this information will be communicated voluntarily.
Queensland Health	Queensland Health **strongly opposes** the use of tall oil phytosterols (TOPs) as a novel food ingredient in low fat milk products under Standard 1.5.1 – Novel Foods, in the *Australia New Zealand Food Standards Code*. Accordingly, we support Option 1 – prohibit the use of TOPs in low-fat milks. Considers that plant sterols are unnecessary for the prevention and management of chronic disease and reaffirms that a diet high in fruits and vegetables and wholegrains, moderate in lean meat and dairy foods, and low in saturated fat and sugar as providing the most effective health outcomes. Expresses disappointment that the addition of plant sterols to a broader range of foods is being addressed on a case-by-case basis rather than as a larger issue involving government, industry and consumers. Does not consider there is any valid comparison to be made in the availability of fat-modified foods, and the potential availability of foods containing plant sterols, as dietary interventions to address diet-related health issues. Limiting consumption to 2-3 serves per day implies a therapeutic dose, which is inappropriate in foods. Questions the 'broad natural range' referred to by FSANZ in the Draft Assessment Report in relation to β-carotene levels. Provided a list of references that suggest reduced β-carotene levels of the order of 20-25% may be associated with a range of chronic diseases. The dietary exposure assessments are based on out of date dietary data. Queensland Health also considers that the new clinical trials that are presented in this Draft Assessment Report still indicate a paucity of trials that consider the long term safety of these products. Only one study is presented that considers usage for a year. As such, it seems reasonable and prudent that more data be made available to confirm safety over the long term. Questioned whether consumers have demonstrated that their use of them is

	likely to be informed and appropriate.
Tasmanian Department of Health and Human Services	**Does not support** the broader use of phytosterols or phytosterol esters in food. Raised similar issues to the Queensland Health submission.
Department of Health Western Australia (Late submission)	**Does not support** the extension of use of phytosterols derived from tall oils. The committee considered that elevated cholesterol levels should be managed under medical supervision that extending the use into other products would lead to over-consumption, there are no studies to demonstrate that prolonged use is safe, and that the appropriate regulation of these products is by the Therapeutic Goods Administration.
Public Health Association of Australia Inc	Opposes the Application because phytosterols ought to be regarded as therapeutic agents, not as food. There is no comparison between allowing reduced fat products in the food supply and potentially allowing the deliberate addition of plant sterols to foods, for the purposes of lowering blood cholesterol. There is a paucity of data on the long-term health effects of plant sterols, particularly the potential effects on levels of α-tocopherol and β-carotene, and the safety assessment did not adequately address this issue. The data used in the dietary exposure assessment is out of date and does not reflect major changes in the food supply over the past 10 years. Expresses support for the recommended risk management strategies regarding labelling, etc, should the Application be approved. Recommends that consumers be made as aware as possible of the maximum number of serves per day through labelling. However, the words '*recommended daily intake*' could easily be confused with Recommended Dietary Intake (RDI), which applies to nutrients, and therefore should not be allowed. Post-market monitoring would be useful for phytosterol enriched products.
Valerie James	**Does not support**. There is not history of safe use for these products and it is necessary for the Applicant to prove both safety and benefits.

Australian Consumers Association (ACA)	**Does not support** this application because it considers that some of the issues raised by submitters at Initial Assessment have not been adequately addressed, including; o insufficient knowledge of long term effects, o insufficient knowledge of safety of higher doses especially for vulnerable groups, o the potential impact on non-target consumers, o the potential impact on fat soluble vitamins, carotenoids and other phytochemicals, o the potential for over consumption if more permissions are granted, o the lack of up-to-date national consumption data on which to base an assessment. The ACA: • supports the mandatory requirement for advisory statements, however warns FSANZ against relying on such statements as they place the onus of responsibility on the consumer; • expresses concern that increasing permissions for foods containing phytosterols may lead to over consumption among both target and non-target consumer groups and may have a potential impact on beta carotene levels; • believes there should be a more considered and systematic approach to the addition of phytosterols to foods; • consider that post-market monitoring would be useful for phytosterol enriched products; and • are concerned that the impact analyses in the Draft Assessment Reports of these Applications do not consider the full range of impacts for consumers.

Attachment 7

5-05
3 August 2005

FIRST REVIEW REPORT

APPLICATION A433

PHYTOSTEROL ESTERS DERIVED FROM VEGETABLE OILS IN BREAKFAST CEREALS

APPLICATION A434

PHYTOSTEROL ESTERS DERIVED FROM VEGETABLE OILS IN LOW-FAT MILK & YOGHURT

APPLICATION A508

PHYTOSTEROLS DERIVED FROM TALL OILS AS INGREDIENTS IN LOW-FAT MILK

CONTENTS

Decision

FSANZ re-affirms its approval of Applications A433, A434 and A508, subject to the specified amendments in this First Review, and supported by the risk management strategies proposed at Final Assessment because:

1. The assessment of Applications A433, A434 and A508 was consistent with existing policy guidance on novel foods, endorsed by the Ministerial Council in December 2003;

2. Policy guidance for substances other than vitamins and minerals is under development and is not a basis for delaying these Applications;

3. A health claim for phytosterols was not assessed as part of these Applications as, at this time, such claims are not permitted;

4. Two independent expert reviewers agree that FSANZ comprehensively evaluated the nutritional effects of phytosterols at Final Assessment, and lower serum beta-carotene levels are not a public health concern;

5. Expert medical opinion on the impact of phytosterols on individuals with the metabolic syndrome or diabetes raises no particular nutritional concerns;

6. FSANZ agrees that mandatory advisory statements should be more conspicuous on packaging and therefore an Editorial Note has been inserted in Standard 1.2.9 Legibility Requirements, to clarify the requirements of the Code, pending a full review of this Standard; and

7. FSANZ will prepare a fact sheet on plant sterols for wide distribution to medical and health care professionals and the general public. In conjunction with information from public health organisations and a wide range of industry-initiated activities including advertising, brochures, pamphlets and consumer advice lines, this will ensure that there is sufficient educational material available to allow informed consumer choice.

Summary Table

Matters addressed in the First Review of Applications A433, A434 and A508 seeking to broaden the use of phytosterol esters and tall-oil phytosterols

Ministerial Council issue	Measures taken at Final Assessment	Additional measures at First Review
1. Consistency with existing policy guidance on **(i) novel foods;** **(ii) health claims; and** **(iii) the addition to food of substances other than vitamins and minerals.**	• **FSANZ must comply with statutory obligations in relation to the assessment of applications.** • **Applications cannot be delayed to await new policy guidelines.** **Novel foods** • Phytosterol-esters and tall-oil phytosterols already approved in the Code as novel foods. • Current applications seek to broaden use to other foods. • Existing guidelines require a pre-market safety assessment. • Assessments consistent with existing policy guidelines for novel foods. **Health claims** • Currently not permitted. • No previous or current assessment of a health claim for phytosterols.	• **FSANZ has addressed the standards issues only. Policy issues are discussed briefly:** **Novel Foods** • Existing policy guidelines endorsed in December 2003. • Proposal P291 to review Standard 1.5.1 Novel Foods (at Draft Assesm'nt) will not change the existing policy. • No impact on the assessment of the current Applications. **Substances other than vitamins and minerals** • FRSC sub-committee developing policy guidance on a broad range of substances. • No delay of the current Applications is justified. **Health claims** • Proposal P293 is at Draft Assessment. A claim relating to phytosterols would need to be an application under the new standard.
2. Protection of public health and safety. **(i) Consumption of phytosterol-enriched foods can result in a decrease in serum β-carotene; and** **(ii) There is evidence that individuals with metabolic syndrome or diabetes already have lower β-carotene levels than the normal population.**	• **FSANZ linked permissions to**: High-fibre breakfast cereal • Restrictions on sugar content • No breakfast cereal bars Low-fat milk • Maximum 1 litre container • No flavourings Low-fat yoghurt • Maximum 200 g punnet size **Current mandatory statements**: • Diet should be low in saturated fats and high in fruit and vegetables; • Not recommended for infants, children, pregnant or lactating women; • Seek medical advice with cholesterol-lowering medications. **Additional mandatory statement:** • No additional benefits when consumed in excess of 3 serves/day. **Additional condition of use:** Foods to which phytosterols have been added may not be used as ingredients in other foods.	• **FSANZ sought external opinion on the nutritional issues, which confirmed that there are no outstanding health concerns.** • Professor John W. Erdman (USA) agrees with FSANZ that lower β-carotene levels are not a nutritional concern. • Professor Martijn Katan (The Netherlands) does not consider lower serum β-carotene levels as a safety concern. • Professor John McNeil (FSANZ Fellow) does not consider that phytosterols are of particular nutritional concern for individuals with metabolic syndrome or diabetes. • Dr Bob Boyd (FSANZ Chief Medical Advisor) does not consider that there is evidence for harmful effects from a reduction in β-carotene.
3. Provision of adequate information to enable informed choice.	• **Ingredient labelling** – either tall oil phytosterols or phytosterol esters. • Industry advertising, brochures, leaflets and consumer advice lines. • Consumer familiarity with existing products.	• **Insertion of an Editorial Note** to reinforce the legibility and presentation requirements of the Code for mandatory statements. • **Pledge to review Standard 1.2.9 – Legibility Requirements.**

1. Introduction

On 10 December 2004, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Applications A433, A434 and A508, which seek to broaden the range of foods to which phytosterols (plant sterols) may be added. Applications A433 and A434 seek permission to add phytosterol esters derived from vegetable oils to breakfast cereals, low-fat milk and yoghurt; A508 seeks permission to add tall oil phytosterols (TOPs) to low-fat milk. Approval of all three applications involves variations to Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations, Standard 1.5.1 – Novel Foods, Standard 2.5.1 – Milk, and Standard 2.5.3 Fermented Milk Products of the *Australia New Zealand Food Standards Code* (the Code).

Following a request for a formal review, FSANZ normally has three months to prepare a response, however, due to the complexity of issues in this case, FSANZ sought an extension of time and is required to complete the review by 12 August 2005.

2. Objectives of review

The objective of this Review is to reconsider the draft variations recommended to the Ministerial Council by FSANZ in October 2004 in light of the Council's concerns as outlined in Section 3.

3. Grounds for the review

A First Review was requested on the grounds that approval of the Applications:

- is not consistent with existing policy guidelines set by the Ministerial Council;
- does not protect public health and safety; and
- does not provide adequate information to enable informed choice.

The Ministerial Council provided additional information (see **Attachment 2**) concerning the grounds on which the First Review is based, which have been summarised by FSANZ as follows:

- the draft variations to the standards are not consistent with existing policy guidelines on novel foods, health claims and fortification of food set by the Ministerial Council;

- the Applications do not adequately address Public Health Nutritionists' concerns about the observed reductions in serum beta-carotene of approximately 20% as a consequence of consuming foods with added phytosterol esters;

- mandatory advisory statements on currently approved phytosterol-enriched table spreads are inadequately presented on packages, raising questions about whether information is accessible to consumers;

- these foods represent a trend towards medicalisation of the food supply;

- based on overseas approvals for foods with added phytosterols, it is likely that there will be an increase in the number of applications seeking approval in Australia, which will lead to an increased level of health claims, either implied or stated;

- approvals will inevitably lead to potential problems with health claims, especially in regard to products that have low efficacy such as breads and cereals; and

- there is an apparent lack of supporting education and awareness programs for health professionals to advise patients on how such products should be used, especially in combination with cholesterol-lowering medicines.

In addition at Final Assessment, FSANZ reviewed six research papers (submitted by two jurisdictions) reporting on low serum beta-carotene levels associated with metabolic syndrome or diabetes (see below). After evaluating the papers, FSANZ concluded that the information was not directly relevant to the assessment of these applications because the studies did not fully assess confounding risk factors, which may reduce beta-carotene levels in the subjects. The Ministerial Council requested that FSANZ re-examine the information contained in these publications and identify which of the studies did not control for confounding factors.

The following studies were reviewed by FSANZ at Final Assessment:

- Ford, ES, Will, JC, Bowman, B. (1999). Diabetes mellitus and serum carotenoids: Findings from the 3rd NHANES. *Am J Epi* 149 (2): 168-176.
- Suzuki, K, Yoshinori, I, Nakamura, S. (2002). Relationship between serum carotenoids and hyperglycemia: a Population based cross sectional study. *J Epi* 12(5):357-366.
- Abahusain, MA, Wright, J, Dickerson J.W.T. (1999). Retinol, alpha-tocopherol and carotenoids in diabetes. *Eur J Clin Nutr* 53:630-635.
- Ylonen, K, Alfthan G, Groop, L (2003). Dietary intakes and plasma concentrations of carotenoids and tocopherols in relation to glucose metabolism in subjects at high risk of type 2 diabetes: the Botnia dietary study. *Am J Clin Nutr* 77:1434-41.
- Ford, ES, Mokdad, AH, Giles, W.H. (2003). The metabolic syndrome and antioxidant concentrations; Findings from the 3rd NHANES. *Diabetes* 52:2346-2352.
- Osganian, SK, Stampfer, MJ, Rimm, E. (2003). Dietary carotenoids and risk of coronary artery disease in women. *Am J Clin Nutr* 77:1390-9.

4. Background

Currently, phytosterol esters (derived from vegetable oils) and un-esterified phytosterols (derived from tall oils) are permitted for use in edible oil spreads under Standard 1.5.1 - Novel Foods. This standard requires a pre-market safety assessment. Novel foods or novel food ingredients that have been assessed under the Standard, when approved, are listed in the Table to clause 2 and may have specified conditions of use. In this case, phytosterols must be declared in the ingredient list, and three advisory statements must be presented on packaging to advise consumers on how to use the products appropriately[16].

[16] It should be noted that although the permission for tall oil phytosterols exists in the Code, there are no tall oil products on the market. The two currently available brands of phytosterol-enriched table spreads (Logicol® and ProActive®) both contain vegetable oil-derived phytosterol esters.

The Applicants for A433, A434 and A508 consider there is demand in Australia and New Zealand to expand the range of phytosterol-enriched products, in addition to the table spreads, to broaden consumer choice and support innovation in the food industry. The Applications seek permission to add 0.8 – 1.0 g plant sterols per serve to food categories such as high-fibre breakfast cereal, low-fat milk and low-fat yoghurt.

Consumption of phytosterols has been shown to reduce absorption of dietary cholesterol leading to lower serum LDL-cholesterol levels, and thus foods with added phytosterols are targeted primarily to consumers over the age of 40 with concerns about their cholesterol levels. Many studies have found that the optimal cholesterol-lowering effect is achieved when consumption is between 2-3 g plant sterols per day, irrespective of the type of sterols consumed. The FSANZ assessment focused on (i) the safety of phytosterol esters and tall oil phytosterols at proposed levels of use when used in breakfast cereal, low-fat milk and yoghurt, (ii) their efficacy in the relevant food matrices to ensure truth in labelling, and (iii) the suitability of the products to target consumers.

Considering the range of phytosterol-enriched foods already available in overseas markets, Applications A433, A434 and A508 represent a conservative request for expanding the choice of products available to consumers in Australia and New Zealand. Further constraints on products were imposed by FSANZ during the course of the assessments by (i) restricting the sugar content of the cereal product, (ii) restricting the maximum permitted unit size of milk and yoghurt products, and (iii) permitting only a very narrow range of additives in milk necessary for technical reasons to suspend vegetable fats in an aqueous environment. Flavourings, for example, are not permitted in phytosterol-enriched milk.

4.1 Efficacy of plant sterols

Most studies showing the cholesterol-lowering effect have used edible oil spreads or margarine-type products enriched with plant sterols. Before other categories of phytosterol-enriched foods could be approved, FSANZ required evidence of the cholesterol lowering effect in the relevant food matrices. The efficacy data were considered necessary to ensure that any statements used by manufacturers relating to the cholesterol-lowering effects were valid for foods such as cereals and dairy products. A health claim was not part of the assessment of these applications.

4.2 Overseas regulation

In Europe, plant *sterols* in their various forms are permitted in yellow fat spreads, milk based products, yoghurt products, salad dressings, spicy sauces, fermented milk type products, soya drinks and low-fat cheese type products. Plant *stanols* are permitted on the market in the EU, without being subject to review, because they were marketed in a member State before the Novel Foods Regulation came into force. Initially, the products were edible oil spreads (margarines), but this has broadened to other foods such as fresh cheese, snack bars, salad dressing and yoghurt. Given the similarities in composition of the plant sterols (sterols, stanols and their conjugated esters), and similar conclusions regarding safe levels of consumption, the EC has moved to common labelling requirements and specifications for all phytosterol products, irrespective of their plant source. In addition, the UK Advisory Committee on Novel Foods and Processes (ACNFP) has recently issued a positive opinion for an application proposing to add 0.4% of phytosterols to fruit juices including tomato juice and nectars (May, 2005).

In the USA, the Food and Drug Administration (FDA) have raised no objection to a number of food products that may contain plant sterol and stanol esters in amounts up to 20%, on the basis of the GRAS notification. Notifications include vegetable oil spreads, salad dressings, health drinks, cereal health bars, yoghurt type products, fruit juice (orange) and vegetable oils for baking and frying. The FDA has also allowed manufacturers of products containing added phytosterol and stanol esters to make a health claim (for reducing the risk of coronary heart disease). There are a number of specific restrictions with which the products must comply before such a health claim may be made. Foods that are allowed to use this interim health claim include sterol esters in spreads and salad dressings, and stanol esters in spreads, salad dressings and snack bars.

5. Conclusions from the Final Assessment Reports

Applications A433, A434 and A508 were progressed in parallel because of similarities in terms of safety, labelling issues and food categories under assessment. The Executive Summary and Statement of Reasons for each of these applications, which were approved at FSANZ13 in October 2004, are in this report at **Attachment 2**.

The Board agreed to the recommendations at Final Assessment in view of the stringent risk management measures developed by FSANZ for all phytosterol-enriched products, including the existing table spreads. In terms of labelling, an additional mandatory advisory statement to the effect that *foods containing added plant sterols do not provide additional benefits when consumed in excess of three serves per day* was proposed to ensure that target consumers would be fully informed on the appropriate use of the products, irrespective of whether the added sterols were from a vegetable-oil or tall-oil source. Conditions of use were also extended to the effect that *foods containing added plant sterols must not be used as ingredients in other foods.*

6. Issues addressed in First Review

6.1 Policy issues

The Ministerial Council considered that the proposed draft variations to the Code were not consistent with existing policy guidelines set by the Council in relation to (i) novel foods, (ii) health claims, and (iii) fortification.

6.1.1 Response

In addressing the review of these applications, FSANZ considers it necessary to separate the standards issues from the policy issues raised by the Ministerial Council.

In dealing with applications to amend the Code, FSANZ must comply with its statutory obligations under the FSANZ Act. There are no provisions in the Act for an assessment to be deferred or delayed on the grounds that the application intersects with issues currently under consideration by FRSC, which will lead to the development of policy guidelines.

In the case of the three current phytosterol applications, the information detailed below indicates that FSANZ has been consistent with existing policy guidelines.

6.1.1.1 Policy guidance on novel foods

FSANZ received policy guidance on novel foods from the Ministerial Council recommending that FSANZ review Standard 1.5.1 – Novel Foods, while giving consideration to the higher order and specific principles of that policy guidance and to a number of issues raised during consultation on policy development. The main issues identified were the ambiguity of the definitions for 'non-traditional food' and 'novel food', how determinations are made with respect to novelty (i.e. whether a food is deemed to be novel and subject to the pre-market requirements of the standard) and difficulties with enforcement of the standard.

In response to this policy guidance, FSANZ has raised a Proposal (Proposal P291) to review the regulations for novel foods and the mechanism for making determinations as to novelty. A Standard Development Advisory Committee (SDAC) has been established to assist during the review. It is not intended that existing novel food permissions be revisited during the review. Similarly, it was not anticipated that any novel food application being assessed during the review of the Novel Foods Standard would be delayed as a result of the review.

It has been acknowledged at the first SDAC meeting and through submissions to the Initial Assessment Report that the current standard effectively ensures public health and safety by requiring a pre-market safety assessment of novel foods. In this regard, progressing Applications A433, A434 and A508 while Standard 1.5.1 is being reviewed is appropriate and not inconsistent with current policy guidance.

6.1.1.2 Policy guidance on health claims

There was no consideration of a health claim in the assessment of the previous applications for use of phytosterols (in edible oil spreads) and health claims have not been considered in relation to the current applications. Any such consideration would need to be the subject of a future application contingent upon the establishment of a standard for health claims.

In December 2003, the Ministerial Council agreed to a Policy Guideline on Nutrition, Health and Related Claims, with the exception of biomarker maintenance claims. This latter issue was subsequently resolved in May 2004.

In response to the Ministerial Council Policy Guideline, FSANZ raised Proposal P293, in order to develop a new Standard for the regulation of nutrition, health and related claims. Proposal P293, is developing a regulatory framework for both high level and general level claims. High level claims, which reference a serious disease or condition, will be prohibited unless pre-approved by FSANZ. For example, serum cholesterol is proposed as a biomarker for cardiovascular disease. However, general level claims which do not reference a serious disease or condition will be generally permitted provided they can be substantiated and provided they comply with any criteria or conditions specified in the Standard.

The issues surrounding the development of the Standard are highly complex and FSANZ is currently undertaking a range of activities, including consumer research, to support the development of the Standard. Proposal P293 is currently at Draft Assessment.

Until the new Standard is finalised and agreed to by Ministers, manufacturers must comply with the current requirements in the Transitional Standard for Health Claims, Standard 1.1A.2 in the Code.

In addition to other matters, this Standard prohibits claims in food labels and advertising that contain the name of, or make reference to, any disease or physiological condition. Failing to comply with this requirement when making any voluntary statement about a food constitutes a breach of the Code. Any labelling statement about a food that is required under the Code is not a 'claim' and so is not subject to Standard 1.1A.2.

6.1.1.3 Policy guidance on the addition to food of substances other than vitamins and minerals

The Food Regulation Standing Committee (FRSC) sub-committee that developed policy on fortification for vitamins and minerals has commenced work on the addition to food of substances other than vitamins and minerals with a view to developing a policy guideline. The scope of what is being considered by the sub-committee is broad and includes substances such as non-culinary herbs, plant and animal extracts, amino acids and amino acid derivatives, probiotics and others, some of which may have some pharmacological or physiological properties. Excluded from the scope of the considerations are substances added to foods for a technological purpose, vitamins and minerals and whole foods. Phytosterols would be included in the initial scope of this work by the FRSC sub-committee, as would other substances that have already been considered by FSANZ as novel foods.

There are inter-relationships with this policy development process and health claims, novel foods and the foods-therapeutic goods interface. An issues paper was released for public comment on 22 February 2005 and the submissions received have been summarised. In addition, a stakeholder workshop was held on 1 March to clarify the intent and scope of the policy guideline. Both of these processes informed the development of a policy options consultation paper which has now been endorsed by FRSC and will be released for public comment. It is not yet clear what the resulting policy guideline will address. However, progression of Applications A433, A434 and A508 does not depend on the outcome of this process since there is currently a clear mechanism for dealing with novel food applications under Standard 1.5.1 – Novel Foods.

6.2 Nutritional issues – Reduction in β-carotene

The Ministerial Council considered that the proposed draft variations to the Code do not protect public health and safety. This concern primarily relates to the observed reduction in serum beta-carotene levels with consumption of phytosterol esters.

The Ministerial Council also requested a second appraisal of six published research papers submitted as references to FSANZ by two jurisdictions at Final Assessment. The papers report on observational studies showing low serum beta-carotene levels in association with the metabolic syndrome or chronic disease such as diabetes.

6.2.1 Response

It is well established that consumption of plant sterols reduces the absorption of cholesterol in the intestine, leading to lower LDL-cholesterol levels in the blood. At the same time, consumption of phytosterol-enriched foods (particularly those with added phytosterol esters) can result in a decrease in serum β-carotene levels of approximately 20-25%.

However, the levels of β-carotene in serum are known to fluctuate widely as a consequence of many dietary and environmental factors and a decrease of this magnitude falls within a broad natural variation. As β-carotene has the most potent pro-vitamin A activity of the carotenoids, it is important to note the evidence consistently showing no change in vitamin A levels in consumers of phytosterol-enriched products.

Assigning a level of significance to a reduction in β-carotene levels has therefore proved elusive due to evidence that:

1. Pro-vitamin A activity is the only universally accepted biological function of β-carotene[17];
2. serum retinol levels (vitamin A) are *not* reduced with consumption of phytosterol esters; and
3. as carrier LDL-cholesterol decreases by whatever means, a decrease in serum β-carotene is expected.

Moreover, published epidemiological studies and properly conducted trials on dietary antioxidants such as β-carotene have generated equivocal results with respect to potential health benefits of these compounds, and have even reported that high levels could be harmful. At Final Assessment, FSANZ therefore considered it reasonable to conclude that as reduced serum β-carotene levels arising from the consumption of phytosterol-enriched foods were clearly not associated with decreases in vitamin A, a public health and safety concern could not be demonstrated.

It should also be noted that there were no statistically significant reductions in β-carotene levels following consumption of TOPs, however reductions in α-carotene (23%) were observed at the highest levels of exposure (3.6g/day). FSANZ concluded at Final Assessment that this reduction in α-carotene does not suggest a public health and safety concern particularly as reductions in vitamin A following consumption of TOPs were not observed.

6.2.2 External review of nutrition assessment

To address this issue as part of the review, FSANZ sought the opinion of two independent experts who were specifically asked to comment on the significance of the decrease in β-carotene in terms of nutritional health, and the overall validity of the conclusions of the nutrition assessment report prepared by FSANZ at Draft Assessment. The reviewers were:

(i) Dr John W. Erdman, Professor, and Nutrition Research Chair, Department of Food Science and Human Nutrition of the University of Illinois at Urbana - Champaign in the United States; and
(ii) Professor Martijn Katan, Wageningen Centre for Food Science, in the Netherlands.

These reviewers were chosen for their knowledge and expertise in carotenoid nutrition or their familiarity with safety issues associated with the use of plant sterols in foods. Professor Erdman's report is at **Attachment 3** to this Report.

[17] Carotenoids: Linking Chemistry, Absorption, and Metabolism to Potential Roles in Human Health and Disease, Deming, D.M. *et al*., Ch. 10, Handbook of Antioxidants, 2nd Edition, 2002, ISBN: 0-8247-0547-5

The European reviewer, Professor Katan, was the principal author of a comprehensive Review entitled *Efficacy and Safety of Plant Stanols and Sterols in the Management of Blood Cholesterol Levels,* published in 2003 in the Mayo Clinic Proceedings. This paper reviewed the results of 18 trials testing the effects of plant sterols on plasma concentrations of fat-soluble vitamins, showing that reductions in the plasma concentrations of the carotenes were observed. Concerning these reductions, the Review states: *part of this reduction probably is due to reduced absorption of carotenes and the rest to reduced concentrations of the lipoprotein carrier, LDL*. Once the results were corrected for lower cholesterol levels, only a statistically significant reduction in β-carotene remained. The authors later refer to further research showing that *the decrease in beta carotene could be prevented by adding sufficient fruits and vegetables to the diet*. When approached by FSANZ, Professor Katan did not provide a formal report on the nutrition assessment but provided the following comments:

Personally I would not be concerned about beta-carotene, as there is no evidence for a beneficial effect of beta-carotene apart from a weak vitamin A activity, and there is even definite evidence for harm of high intakes.

In general, both external reviewers expressed no concerns about the reduction in β-carotene levels arising from the consumption of phytosterol-enriched foods. Apart from minor corrections, Professor Erdman considered the FSANZ analysis of nutritional issues to be thorough and balanced, and endorsed the conclusions reached in the FSANZ nutrition report.

While fortification with β-carotene is not a consideration for phytosterol-enriched products, a mandatory advisory statement encouraging the consumption of additional fruits and vegetables in conjunction with phytosterol-enriched foods is required on product labels. This approach is now supported by additional recently published evidence showing that there are compensatory increases in the serum levels of carotenoids (α- and β-carotene, lycopene) with consumption of fruits and vegetables, especially varieties rich in these nutrients. The mandatory advisory statement thus aims to ensure that consumers will be provided with sufficient information to enable them to use phytosterol-enriched products safely.

6.2.3 Review of the dossier of references by FSANZ

FSANZ considers the information provided in the six references (listed in Section 3) was not directly relevant to the assessment of phytosterol-enriched foods because the studies focused on examining the relationship between nutritional parameters (carotenoids, dietary antioxidants) in population groups with metabolic syndrome and therefore at high risk of developing diabetes, or who were already in a diabetic state. Given the range of significant metabolic changes that are known to occur with this condition, and the concomitance of other known associated risk factors (high blood pressure, obesity, low HDL-cholesterol, elevated triglycerides and blood sugar), a lower β-carotene level could well be an indicator for a number of adverse physiological changes that have occurred in association with the condition or the onset of disease.

Therefore, it could reasonably be argued that the results of these studies report on subjects who already have impaired health status and have progressed towards a diabetic state, and are therefore not typical consumers in the target age group. Furthermore, it is likely that individuals displaying the signs and symptoms of metabolic syndrome would be seeking medical or other health professional advice, particularly in relation to their dietary requirements and food choices.

With sufficient educational material available to health and medical professionals, FSANZ considers that individuals in this distinct population group with metabolic syndrome would be under supervision and would therefore have access to informed dietary advice concerning foods appropriate for their health needs.

In an otherwise healthy population of consumers, no such conclusions can be drawn concerning the significance of a lower β-carotene level as a consequence of consuming phytosterol-enriched foods. Whereas the link between elevated LDL-cholesterol levels and a risk of developing chronic diseases such as atherosclerosis and coronary heart disease is well established, the effects of a reduced level of β-carotene on general nutrition are not known, particularly where vitamin A levels are maintained.

The Mayo Clinic Review concluded: ***Adverse health outcomes due to observed decreases in beta-carotene levels in plasma are speculative and are of no major concern***.

6.2.4 Expert medical review of the dossier of references

To address this issue as part of the First Review, the dossier of references on metabolic syndrome and diabetes was provided to the Chief Medical Advisor for FSANZ, Dr Bob Boyd, and to an external reviewer - Professor John McNeil, Department of Epidemiology & Preventive Medicine, Monash University, for independent evaluation. A full report of these evaluations is provided at **Attachment 4**.

The Chief Medical Advisor provided the following comments:

Taken together, there is no evidence in these papers that reduced carotenoid intake increases the risk of diabetes or cardiovascular disease. There is evidence of an inverse relationship between serum carotenoid levels and glucose intolerance, but not even possible evidence of what is the cause / effect. Nothing in these papers studies the difference in diabetes rates or glucose intolerance between populations who have different diets or seasonal changes in their diet, which might equate to the changes in dietary intake of fat-soluble anti-oxidants caused by intake of phytosterols.

In summarising the study reports, Professor McNeil provided the following comments:

Persons in the early stages of glucose intolerance were shown to have lower circulating levels of carotenoids in several studies reviewed above. These results appear to be relatively consistent across different populations and study types.

There are several possible explanations for this finding, ranging from impaired absorption to suppression of levels as a result of increased oxidant activity. The possibility also exists that high levels of carotenoids are protective against the development of diabetes, but at present it is not possible to be sure which of these possibilities is most likely. It is possible/likely also that increased beta-carotene levels reflect a generally healthier diet (possibly accompanied by other aspects of a healthy lifestyle).

Present data does not warrant use of beta-carotene supplementation for prevention of diabetes since present evidence falls well short of proving a causal relationship. This is also supported by other data including:

1. *Large scale trials of beta-carotene have failed to identify a health benefit (these provide more reliable data than do observational studies), and may cause harm. These studies are briefly reviewed in Osganian et al (2003);*

2. *Positive data presented largely concerns surrogate health measures (eg fasting, glucose levels, HbA1c) rather than clinically significant endpoints; and*

3. *An analogy may exist with other anti-oxidants, eg. vitamin E, which have shown positive associations in observational studies, but negative results in trials.*

Concerns about small decreases in beta-carotene levels of the order likely to occur with phytosterols consumption (20%) are not supported by presently available evidence.

In summary, the data presented raise matters worthy of additional study, but fall well short of proving any causal relationship between beta-carotene intake and the development or worsening of diabetes.

Despite the lack of evidence for adverse nutritional outcomes, FSANZ has adopted a cautious approach to the regulation of phytosterol-enriched foods, and the current standard requires manufacturers to advise consumers that these products should be consumed as part of a diet low in saturated fats and high in fruits and vegetables. This advice is also consistent with current public health messages on the nature of a healthy diet.

6.3 Labelling issues

In requesting a First Review of Applications A433, A434 and A508, the Ministerial Council expressed the concern that should phytosterol-enriched breakfast cereal, low-fat milk and low-fat yoghurt be available on the market, there are no requirements to compel manufacturers to present the mandatory advisory statements (MAS) more conspicuously on packaging. Therefore, the Ministerial Council argues that the availability of a broader range of phytosterol-enriched products could be more likely to lead to inappropriate use of the products by consumers.

6.3.1 Response

The issue of specific legibility criteria for mandatory advisory statements[18] was examined and discussed with the jurisdictions during the review of the *Australian Food Standards Code* and the New Zealand Food Regulations, culminating in the development of Standard 1.2.9 Legibility Requirements of the Code. At that time it was agreed that as advisory statements were of lesser importance in relation to protection of public health and safety (compared to mandatory warning statements), it was not necessary to prescribe additional specific legibility criteria or a minimum print size.

General provisions regarding legibility and prominence are supported by a 'User Guide to Standard 1.2.9' to assist manufacturers with adherence to the principles on which the standard operates. Whether the presentation of MAS on the current packaging of phytosterol-enriched table spreads can be considered adequate and in compliance with these general principles is an enforcement matter.

[18] Under Proposal P 142-Print Size and Quality of Prescribed Information Appearing on a Food Label

However, changes to the labelling standards and general legibility requirements in the Code would have a major impact on industry. In addition, changes made on the basis of specific permissions for novel foods must be considered as setting a precedent and could potentially lead to broader trade implications by creating inconsistencies with Codex and/or European Union requirements.

In the context of the current applications, FSANZ therefore considered a number of options for strengthening the presentation of MAS on packaging of phytosterol-enriched foods without causing conflict with the existing framework of the Code. The background to this issue, and four possible regulatory options are discussed more fully in **Attachment 5**.

Following comprehensive evaluation of the options, the preferred course of action is to clarify the legibility requirements in Standard 1.2.9 by the addition of an editorial note. An editorial note is preferred at this stage because:

- it is the least prescriptive option and therefore is most consistent with the principles upon which Standard 1.2.9 and the Code are based;

- it would apply more generally to all labelling requirements rather than just to advisory statements on phytosterol products;

- it goes some way to addressing jurisdictional concerns; and

- it is more consistent with Codex and the EU requirements.

In addition, within a defined time period after completion of this First Review of Applications A433, A434 and A508, FSANZ proposes to undertake a broader review of Standard 1.2.9 in relation to the legibility of all mandatory warning statements, advisory statements and declarations. The benefits of this approach are:

- FSANZ would be able to assess Standard 1.2.9 within the context of the whole Code and the principles on which it was developed, rather than within the confined context of the three current phytosterol Applications;

- the effectiveness of Standard 1.2.9 could be re-evaluated in terms of public health and safety considerations;

- the concerns of the jurisdictions would be addressed in a more systematic way; and

- any amendment resulting from such a review would be based on evidence and would be less likely to have a negative impact on the operation of the other labelling standards.

The insertion of an editorial note to Standard 1.2.9 is a minor amendment that is considered to address the labelling concerns expressed by the Ministerial Council without compromising the integrity of the existing labelling provisions and without imposing undue regulatory burden on the food industry. The Editorial Note proposed for Standard 1.2.9 is included in the draft variations to the Code at **Attachment 1**.

It should be emphasised that manufacturers of phytosterol-enriched foods will undoubtedly ensure that consumers recognise these products through the use of product-specific promotional material, advertising and conspicuous labelling. The higher pricing regimens will further discriminate phytosterol-enriched foods from their conventional forms. With additional information on phytosterols available through consumer information lines, brochures, advertising, FSANZ fact sheets, public health organisations (such as the National Heart Foundation), health departments and health professionals, the MASs should be regarded as merely one means of communicating information to target consumers to ensure that they receive adequate guidance on the appropriate use of the products.

6.4 Education for health professionals

The Ministerial Council considers that health professionals have insufficient knowledge to enable them to provide advice or instruct consumers on the appropriate use of phytosterol-enriched products, especially for individuals who may be under medical supervision and also using cholesterol-lowering medication on prescription.

6.4.1 Response

As submissions were received from organisations such as the Australian Heart Foundation, the Dietitians Association of Australia and the New Zealand Dietetic Association, as well as from a number of individual dietitians and nutritionists, FSANZ concluded that there was a high level of awareness amongst health professionals and the community in general concerning the availability of phytosterol-enriched foods in the market place. Edible oil spreads containing phytosterol esters have been permitted in Australia and New Zealand since 1999 and consumers have therefore been exposed to these products for at least 5 years. Based on this period of use, it would be reasonable to conclude that there is already a background level of knowledge in the community concerning plant sterols, especially with those consumers who currently use the phytosterol ester-enriched table spreads.

Nevertheless, in view of the concerns expressed by the Council, if the current Applications are approved, FSANZ will prepare a fact sheet on phytosterols that could be used by health professionals in their capacity as advisors on dietary interventions for individuals with concerns about a high LDL-cholesterol level. The fact sheet would include information on:

(i) the safe and appropriate use of phytosterol-enriched products;
(ii) the optimal amounts of phytosterols (2-3 g per day) that have been shown to result in a cholesterol lowering effect;
(iii) the benefits of eating at least 5 serves per day of fruits and vegetables when using phytosterol-enriched products;
(iv) the need to continue to use any medication prescribed by a doctor for control of cholesterol levels; and
(v) the unsuitability of these products for infants, children and pregnant or lactating women who do not, in general, need to lower cholesterol levels.

These messages reinforce the mandatory advisory statements that manufacturers are required to portray on the packaging of their products, and are consistent with other publicly available information on plant sterols from organisations such as the National Heart Foundation.

6.4.1.1 Adequate information to enable informed choice

Consumers of approved phytosterol-enriched products currently have access to a range of information sources. These include a consumer information line to assist with advice on purchasing and consumption of phytosterol-containing table spreads, and leaflets attached to the packaging. Additional strategies proposed by the Applicants include (i) advertising specific for the target audience, and (ii) educational material distributed to medical and other health professionals.

7. Additional issues

7.1 Food technology requirements

Since completion of the Final Assessment Report, the applicants seeking permission to use phytosterol-esters and tall-oil phytosterols in low-fat milk (Dairy Farmers and Parmalat respectively) have advised FSANZ that the draft variations to the Code do not allow the product formulations necessary to suspend vegetable-oil components (plant sterols) in the aqueous environment of milk. Emulsifiers are required for technical reasons in order to solubilise the sterol components and distribute them evenly through the product.

FSANZ purposefully linked the proposed permissions for phytosterol-enriched low-fat milk in the Code to Standard 2.5.1 Milk in order to ensure that the products would not be open to the full suite of additives listed in Standard 1.3.1 Food Additives, particularly the flavourings, and would be consistent with the current permissions for phytosterols, which are linked to Standard 2.4.2 Edible Oil Spreads.

Minor drafting changes have therefore been necessary to ensure that manufacturers are able to produce a phytosterol-enriched milk using the necessary additives required by their specific product formulations. The drafting changes include permissions to use emulsifiers and thickeners such as sodium alginate, carrageenan and guar gum with phytosterol-esters, and microcrystalline cellulose with tall-oil phytosterols. These additive inclusions are considered minor and have been inserted into the revised draft variations to the Code, at **Attachment 1** to this report.

7.2 Use of generic term ‘plant sterols’

The New Zealand Food Safety Authority (NZFSA) raised the issue that the proposed mandatory advisory statement referred to ‘phytosterol-esters’ for Applications A433 and A434, but to ‘plant sterols’ for Application A508. The NZFSA suggested that the use of the same generic term ‘plant sterols’ would be preferable for all Applications, to reinforce the message to consumers that 2-3 serves per day of phytosterols from any source, either vegetable-oil or tall-oil, would be equivalent in terms of their daily consumption.

FSANZ acknowledges that this small change standardises the mandatory advisory statement for all products enriched with phytosterols and ensures that consumers will regard both TOPS and phytosterol-esters as one group of compounds with similar properties, and therefore will assist in their use of the products. Accordingly, the Ministerial Council is asked to note the minor change in the draft variation to Standard 1.2.3 (statement 4) for Applications A433 (and A434) to bring the wording in line with the draft variations proposed for Application A508, at **Attachment 1**. The statement thus reads for all three Applications:

Foods containing added plant sterols do not provide additional benefits when consumed in excess of three serves per day.

8. Review Options

Three options were considered in this Review:

1. re-affirm approval of the previous draft variations to Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations, Standard 1.5.1 – Novel Foods, Standard 2.5.1-Milk, or Standard 2.5.3 – Fermented Milk Products of the Code; or

2. re-affirm approval of the previous draft variations to the Code as listed above, subject to specified amendments as a result of the Review; or

3. withdraw approval of the previous draft variations to the Code as listed above.

In view of the insertion of an Editorial Note to address the labelling concerns of the Ministerial Council and the insertion of specific additive permissions to address the food technology requirements of the Applicants, Option 2 is the preferred option. The revised draft variations to the Code are at **Attachment 1**.

9. Decision summary

FSANZ has considered the policy issues, public health and safety concerns and labelling issues raised by the Ministerial Council in relation to the applications to approve the use of phytosterol esters in breakfast cereal, low-fat milk and low-fat yoghurt and tall-oil phytosterols in low-fat milk. These applications were assessed in the context of the existing regulatory framework for novel foods, and represent an extension of use of currently permitted novel foods. The safety and nutritional aspects of phytosterol-enriched foods have been adequately assessed and no outstanding issues remain. The insertion of an Editorial Note should clarify and reinforce the requirements of the Code with respect to the legibility and presentation of mandatory advisory statements.

The issues raised by the Ministerial Council in this First Review, have been addressed by the measures adopted at Final Assessment and by the additional measures carried out during this First Review period. These are presented in the **Summary Table** at the front of this report.

10. Conclusion

On completion of this First Review, FSANZ reaffirms its approval of the draft variation to Standards 1.2.3, 1.5.1, 2.5.1 and 2.5.3 of the Code permitting the extended use of phytosterol esters and tall oil phytosterols, subject to the amendments specified in this report, and supported by the extensive risk management measures proposed at Final Assessment.

ATTACHMENTS

1. Draft variations to the *Australia New Zealand Food Standards Code.*
2. Applications A433, A434 and A508 – Executive Summary and Statement of Reasons from Final Assessment Reports
3. External reviewer's report on FSANZ Nutrition Report
4. Evaluation of published references
5. Options for labelling of phytosterol-enriched foods

ATTACHMENT 1

Draft Variations to the *Australia New Zealand Food Standards Code*

APPLICATION A433

To commence: On gazettal

[1] ***Standard 1.2.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Food regulated in Standard 2.4.2 containing phytosterol esters	Statements to the effect that - 1. the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; and 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

substituting –

Foods containing added phytosterol esters	Statements to the effect that - 1. the product should be consumed as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication; and 4. foods containing added plant sterols do not provide additional benefits when consumed in excess of three serves per day.

[2] ***Standard 1.2.9*** *of the Australia New Zealand Food Standards Code is varied by inserting after subclause 2(1) –*

Editorial note:
The requirements of this Standard will not be met where prescribed information is placed other than on the outside of a package where it is readily accessible by a consumer prior to purchase and not obscured by an outer covering. The requirements of this Standard will also not be met where prescribed information is printed in a small font so the statement cannot be read easily.

Within 24 months of the gazettal of this editorial note, Standard 1.2.9 Legibility Requirements will be reviewed.

[3] Standard 1.5.1 *of the Australia New Zealand Food Standards Code is varied by –*

[3.1] *omitting from the* Table to clause 2 –

Phytosterol esters	The requirements in clause 2 of Standard 1.2.3. The name 'phytosterol esters' or 'plant sterol esters' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to food – (1) according to Standards 1.3.4 and 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food.

substituting –

Phytosterol esters	The requirements in clause 2 of Standard 1.2.3. The name 'phytosterol esters' or 'plant sterol esters' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to edible oil spreads – (1) according to Standard 2.4.2; and (2) where the total saturated and trans fatty acids present in the food are no more than 28% of the total fatty acid content of the food. May only be added to breakfast cereals, not including breakfast cereal bars, if – (1) the total fibre content of the breakfast cereal is no less than 3 g/50 g serve; (2) the breakfast cereal contains no more than 30g/100g of total sugars; and (3) the total phytosterol ester added is no more than 26g/kg. Foods to which phytosterol esters have been added may not be used as ingredients in other foods.

[3.2] *inserting after the* Table to clause 2 –

Editorial note:

Novel Foods must meet the requirements of Standard 1.3.4 - Identity and Purity.

APPLICATION A434

To commence: On gazettal

[1] ***Standard 1.3.1*** *of the Australia New Zealand Food Standards Code is varied by inserting in* Schedule 1*, after* item 1.1.2 –

1.1.3 Liquid milk to which phytosterol esters have been added

401	Sodium alginate	2	g/kg
407	Carrageenan	2	g/kg
412	Guar gum	2	g/kg
471	Mono- and diglycerides of fatty acids	2	g/kg

[2] ***Standard 1.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting in* column 2 *of the* Table to clause 2 *corresponding to the entry for* Phytosterol esters –

May only be added to milk in accordance with Standard 2.5.1. May only be added to yoghurt in accordance with Standard 2.5.3.

[3] ***Standard 2.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting after the* Editorial note *to clause 4* –

5 Phytosterol Esters

Phytosterol esters may only be added to milk –

(a) such that the milk contains no more than 1.5 g total fat per 100 g; and
(b) that is supplied in a package, the labelled volume of which is no more than 1 litre; and
(c) where the total phytosterol ester added is no more than 5.2 g/litre of milk.

[4] ***Standard 2.5.3*** *of the Australia New Zealand Food Standards Code is varied by inserting after the* Editorial note *to clause 3* –

4 Phytosterol Esters

Phytosterol esters may only be added to yoghurt –

(a) that contains no more than 1.5 g total fat per 100 g; and

(b) that is supplied in a package, the capacity of which is no more than 200 g; and

(c) where the total phytosterol ester added is no more than 1.3 g.

APPLICATION A508

To commence: On gazettal

[1] ***Standard 1.2.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Food regulated in Standard 2.4.2 containing tall oil phytosterols	Statements to the effect that – 1. the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; and 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

substituting –

Foods containing added tall oil phytosterols	Statements to the effect that - 1. the product should be consumed as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication; and 4. foods containing added plant sterols do not provide additional benefits when consumed in excess of three serves per day.

[2] **Standard 1.3.1** *of the Australia New Zealand Food Standards Code is varied by inserting in Schedule 1 after* item 1.1.2

1.1.3 Liquid milk to which tall oil phytosterols have been added

460	Microcrystalline cellulose	5	g/kg

[3] ***Standard 1.5.1*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Tall oil phytosterols	The requirements in clause 2 of Standard 1.2.3. The name 'tall oil phytosterols' or 'plant sterols' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to food - (1) according to Standards 1.3.4 and 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food.

substituting –

Tall oil phytosterols	The requirements in clause 2 of Standard 1.2.3. The name 'tall oil phytosterols' or 'plant sterols' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to edible oil spreads – (1) according to Standard 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food. May only be added to milk in accordance with Standard 2.5.1. Foods to which tall oil phytosterols have been added may not be used as ingredients in other foods.

[4] ***Standard 2.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting after the Editorial note to clause 4 –*

5 Tall oil phytosterols

Tall oil phytosterols may only be added to milk –

(a) such that the milk contains no more than 1.5 g total fat per 100 g; and
(b) that is supplied in a package, the labelled volume of which is no more than 1 litre; and
(c) where the total phytosterol (from a tall oil source) added is no more than 3.6 g/litre of milk.

ATTACHMENT 2

Executive Summary and Statement of Reasons from Final Assessment Reports

Application A433 – Final Assessment Report

Statement of Reasons

FSANZ agrees to approve the use of phytosterol esters derived from vegetable oils in breakfast cereals, subject to specified conditions of use, for the following reasons:

- there are no anticipated public health and safety concerns associated with the use of phytosterol esters derived from vegetable oils in high fibre, low sugar breakfast cereal when used in conjunction with the risk management measures proposed;

- there is evidence that phytosterol esters derived from vegetable oils can, following consumption, reduce levels of LDL cholesterol in humans when incorporated into breakfast cereals;

- the nutrition assessment indicates that phytosterol esters derived from vegetable oils have no significant adverse nutritional effects at the proposed levels of use. The reduction in the absorption of β-carotene is within the normal variation which results from physiological and environmental factors;

- conditions of use, including an additional labelling statement, are proposed as part of a comprehensive risk management strategy to ensure appropriate use of phytosterol-containing foods by target consumers, and to discourage use by non-target consumers;

- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and

- the Regulatory Impact Statement indicates that, for the preferred option, namely, to approve the use of phytosterol esters derived from vegetable oils as novel food ingredients in breakfast cereals, the benefits of the proposed amendment outweigh the costs.

Executive Summary

Goodman Fielder has submitted an application to FSANZ seeking approval for the use of phytosterol esters derived from vegetable oils as a novel food ingredient in breakfast cereals under Standard 1.5.1 – Novel Foods, in the *Australia New Zealand Food Standards Code* (the Code). Originally, the applicant sought approval for breakfast cereal bars, fibre-increased bread and low-fat salad dressing. The latter two foods were withdrawn by the applicant. Since breakfast cereal bars are compositionally similar to breakfast cereals, the scope of the assessment was broadened to breakfast cereals.

Standard 1.5.1 prohibits the sale of novel foods or novel food ingredients unless they are listed in the Table to clause 2 of the Standard, and comply with any special conditions of use stipulated in the Table. Approval for use requires a safety assessment to be undertaken. Current permissions to use phytosterol-esters as novel food ingredients are limited to edible oil spreads and margarines. There is currently no permission to add phytosterol esters to a broader range of foods.

Purpose and scope of the Application

Free phytosterols are chemically and structurally related to animal-derived cholesterol. These properties confer the ability to interfere with the mechanism of cholesterol absorption in the human intestine. When ingested in various food matrices, phytosterol esters can potentially decrease low density lipoprotein (LDL) cholesterol levels in the blood. Products with added phytosterol esters are primarily targeted to adult consumers, particularly those over 40 years of age. The purpose of the Application is to increase the range of phytosterol enriched foods available to these consumers.

Approval of a health claim is not a consideration in this assessment. Clinical data establishing that phytosterol esters can lower LDL cholesterol levels when added to breakfast cereal have been evaluated to ensure the validity of labelling statements associating plant sterols with a reduction in the absorption of cholesterol.

Risk assessment

Two new clinical studies were submitted in support of the Application. As well as testing efficacy in different food matrices (breakfast cereal, fibre-increased bread, low-fat milk and low-fat yoghurt), a range of physiological/biochemical parameters were also measured to detect potential adverse health effects. When incorporated into breakfast cereal, phytosterol esters have a modest cholesterol lowering effect. Daily consumption rates between 2.6 g and 10.7 g phytosterol esters are well tolerated, and no adverse physical or physiological effects were detected. The results from the clinical studies are consistent with other published studies, some investigating consumption of phytosterols for periods up to 12 months.

The investigations into the nutritional effects of phytosterols on absorption of carotenoids and some fat-soluble vitamins found that serum β-carotene levels were most affected, showing a reduction of approximately 25%, which to some extent was dependent on the nature of the food matrix and on cholesterol-lowering effects. However, the reduction in β-carotene levels is not associated with a reduction in retinol or vitamin A levels and is within a broad natural variation for this provitamin.

The results from the dietary exposure assessment which considered phytosterol-containing spreads and/or breakfast cereal indicate that mean exposure to free phytosterols did not exceed 1.7 g/day for any population group assessed in this scenario. At the highest level of consumption, estimated exposure to free phytosterols is between 4.0 g/day and 4.4 g/day for all population groups assessed. Estimated mean and maximum dietary exposures are expected to be highest for consumers aged 40-64 years (a major fraction of the target group) in both New Zealand and Australia.

When all proposed foods in Applications A433 and A434[19] (high-fibre, moderate-sugar breakfast cereal plus low fat milk and yoghurt) are considered, the results of the dietary exposure assessment indicate that estimated mean dietary exposure from all foods did not exceed 1.9 g/day in any population group, and highest mean consumption levels were in the target population groups (over 40 years of age) in both Australia and New Zealand. At the 95th percentile of exposure, no population group exceeded 4.7 g free phytosterols per day, equivalent to 7.6 g phytosterol esters. The highest consumers of phytosterol esters are therefore likely to be well under the upper level of consumption of 10.7 g/day used in the clinical studies which produced no evidence of adverse health effects. The results also suggest that the major source of dietary exposure to added phytosterols is from edible oil spreads for all population groups assessed.

The overall conclusion of the risk assessment is that phytosterol ester enriched breakfast cereal is not associated with adverse health effects at the levels proposed by the Applicant, and can result in a cholesterol lowering effect. Adult consumers in the target population group are major consumers of the foods in question, and by maintaining their established dietary habits are likely to use the foods in amounts considered safe and appropriate.

Risk management

Phytosterol ester enriched foods can be consumed safely by the target population group and may assist in reducing LDL cholesterol levels. However, in general, children and pregnant or lactating women do not need to reduce cholesterol absorption, and products containing added phytosterols are therefore less appropriate for these groups.

Comprehensive risk management options have been considered, to encourage appropriate use by the target population group and discourage consumption by non-target groups. The recommended measures include (i) allowing high-fibre, moderate-sugar breakfast cereal to contain phytosterol esters (this excludes breakfast cereal bars); (ii) prescribing the maximum amount of phytosterol esters that may be added to breakfast cereal; (iii) retaining the three mandatory advisory statements currently required under Standard 1.2.3 (for edible oil spreads and margarines), and adding one additional mandatory advisory statement to the effect that phytosterol-enriched foods do not provide additional benefits when consumed in excess of three serves per day; and (iv) imposing an additional condition of use prohibiting phytosterol enriched foods from being used as ingredients in other foods.

It is proposed that the new labelling requirements apply to all foods with added plant sterols, including the edible oil spreads and margarines.

Public consultation

Fifteen submissions were received in the first round of public consultation and twenty-five submissions were received during the second public consultation period. Approximately half of the submissions were in favour of the application. These submissions supported a more varied range of products than the current permission allows to expand consumer choice and improve opportunities for product innovation.

[19] Application A434 seeks permission to add phytosterol esters derived from vegetable oils in low-fat milk and low-fat yoghurt.

The major issues of concern raised by those opposed were the potential nutritional effects, the potential for adverse effects in non-target consumers, and the choice of food products, namely breakfast cereal, milk and yoghurt which are widely consumed in Australia and New Zealand. The issues raised in public submissions have been addressed in the report and, where appropriate, through the risk management strategies outlined.

Application A434 – Final Assessment Report

Statement of Reasons

FSANZ agrees to approve the use of phytosterol esters derived from vegetable oils in low-fat milk and low-fat yoghurt, subject to specified conditions of use, for the following reasons:

- there are no anticipated public health and safety concerns associated with the use of phytosterol esters derived from vegetable oils in low-fat milk and low-fat yoghurt when used in conjunction with the risk management measures proposed;

- there is evidence that phytosterol esters derived from vegetable oils can, following consumption, reduce levels of cholesterol in humans when incorporated into low-fat milk and low-fat yoghurt products;

- the nutrition assessment indicates that phytosterol esters derived from vegetable oils have no significant adverse nutritional effects at the proposed levels of use. The reductions in the absorption of β-carotene are within the normal variation which results from physiological and environmental factors;

- conditions of use, including an additional labelling statement, are proposed as part of a comprehensive risk management strategy to ensure appropriate use of phytosterol-containing foods by the target consumers, and to discourage use by non-target consumers;

- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and

- the Regulatory Impact Statement indicates that, for the preferred option, namely, to approve the use of phytosterol esters derived from vegetable oils as novel food ingredients in low-fat milk and low-fat yoghurt, the benefits of the proposed amendment outweigh the costs.

Executive Summary

Dairy Farmers submitted an application to FSANZ seeking approval for the use of phytosterol esters derived from vegetable oils as a novel food ingredient in low-fat milk and low-fat yoghurt under Standard 1.5.1 – Novel Foods, in the *Australia New Zealand Food Standards Code* (the Code).

Standard 1.5.1 prohibits the sale of novel foods or novel food ingredients unless they are listed in the Table to clause 2 of the Standard, and comply with any special conditions of use stipulated in the Table.

Approval for use requires a safety assessment to be undertaken. Current permissions to use phytosterol esters as novel food ingredients are limited to edible oil spreads and margarines. There is currently no permission to add phytosterol esters to a broader range of foods.

Purpose and scope of the Application

Free phytosterols are chemically and structurally related to animal-derived cholesterol. These properties confer the ability to interfere with the mechanism of cholesterol absorption in the human intestine. When ingested in various food matrices, phytosterol esters can potentially decrease low density lipoprotein (LDL) cholesterol levels in the blood. Products with added phytosterol esters are primarily targeted to adult consumers, particularly those over 40 years of age, interested in achieving a lower cholesterol level without major changes to their diet. The purpose of the application is to increase the range of phytosterol-enriched foods available to these consumers.

Approval of a health claim is not a consideration in this assessment. Clinical data establishing that phytosterol esters can lower LDL cholesterol levels when added to low-fat milk and low-fat yoghurt have been evaluated to ensure the validity of labelling statements associating plant sterols with a reduction in the absorption of cholesterol.

Risk assessment

Two new clinical studies were submitted in support of the Application. As well as testing efficacy in different food matrices (breakfast cereal, fibre-increased bread, low-fat milk and low-fat yoghurt), a range of physiological/biochemical parameters were also measured to detect potential adverse health effects. When incorporated into low-fat milk and low-fat yoghurt, phytosterol esters had a modest cholesterol lowering effect. Daily consumption rates between 2.6 g and 10.7 g phytosterol esters were well tolerated, and no adverse physical or physiological effects were detected. The results from the clinical studies are consistent with other published studies, some investigating consumption of phytosterols for periods up to 12 months.

The investigations into the nutritional effects of phytosterols on absorption of carotenoids and some fat-soluble vitamins found that serum β-carotene levels were most affected, showing a reduction of approximately 25%, which to some extent was dependent on the nature of the food matrix and on cholesterol-lowering effects.

However, the reduction in β-carotene levels was not associated with a reduction in retinol (Vitamin A) levels and was within a broad natural variation for this provitamin.

The results from the dietary exposure assessment which considered phytosterol-containing spreads, low-fat milk and low-fat yoghurt indicate that mean exposure to free phytosterols would be 1.6 g/day for the Australian population and 1.9 g/day for the New Zealand population. For both countries, estimated mean dietary exposure is expected to be highest for consumers aged 40-64 years, which is a major fraction of the target group. At the highest level of consumption (95^{th} percentile), estimated exposure to phytosterols is expected to be between 4.2 g/day and 4.7 g/day for all population groups assessed.

When all proposed foods in Applications A433[20] and A434 (high fibre/moderate sugar breakfast cereal, plus low fat milk and yoghurt) are considered, the results of the dietary exposure assessment indicate that estimated mean dietary exposure from all foods did not exceed 1.9 g/day in any population group, and highest mean consumption levels were in the target population groups (over 40 years of age) in both Australia and New Zealand. At the 95th percentile of exposure, no population group exceeded 4.7 g free phytosterols per day, equivalent to 7.6 g phytosterol esters. The highest consumers of phytosterol esters are therefore likely to be well under the upper level of consumption of 10.7 g/day used in the clinical studies which produced no evidence of adverse health effects. The results also suggest that the major source of dietary exposure to added phytosterols is from edible oil spreads for all population groups assessed.

The overall conclusion of the risk assessment is that phytosterol ester-enriched low-fat milk and low-fat yoghurt are not associated with adverse health effects at the levels proposed by the Applicant, and can result in a cholesterol lowering effect. Adult consumers in the target population group are major consumers of the foods in question, and by maintaining their established dietary habits are likely to use the foods in amounts considered safe and appropriate.

Risk management

Phytosterol ester enriched foods can be consumed safely by the target population group and may assist in reducing LDL cholesterol levels. However, in general, children and pregnant or lactating women do not need to reduce cholesterol absorption, and products containing added phytosterols are therefore less appropriate for these groups.

Comprehensive risk management options have been considered, to encourage appropriate use by the target population group and discourage consumption by non-target groups. The recommended measures include (i) prescribing the maximum amount of phytosterol esters that may be added to low-fat milk and low-fat yoghurt; (ii) retaining the three mandatory advisory statements currently required under Standard 1.2.3 (for edible oil spreads and margarines), and adding one additional mandatory advisory statement to the effect that phytosterol-enriched foods do not provide additional benefits when consumed in excess of three serves per day; (iii) imposing a restriction on the maximum container size to 1 litre for milk, and 200g for yoghurt; and (iv) imposing an additional condition of use prohibiting phytosterol enriched foods to be used as ingredients in other foods.

It is proposed that the new labelling requirements apply to all foods with added plant sterols, including the edible oil spreads and margarines.

Public consultation

Sixteen submissions were received in the first public consultation period and twenty-two submissions were received during the second consultation period. A small majority of submissions were in favour of the Application. Of those in favour, all supported increased consumer choice and improved opportunities for product innovation.

[20] Application A433 from Goodman Fielder seeks permission to add phytosterol esters to breakfast cereal.

The major issues of concern raised by those opposed were the potential nutritional effects, the potential for adverse effects in non-target consumers, and the choice of food products, namely milk and yoghurt which are widely consumed in Australia and New Zealand. The issues raised in public submissions have been addressed in the report and, where appropriate, through the risk management strategies outlined.

Application A508 – Final Assessment Report

Statement of Reasons

FSANZ agrees to approve the use of TOPs in low-fat milk subject to specified conditions of use, for the following reasons:

- there are no anticipated public health and safety concerns associated with the use of TOPs in low-fat milk when used in conjunction with the risk management measures proposed;

- there is evidence that TOPs when incorporated into low-fat milk can, following consumption, reduce cholesterol absorption in humans;

- the nutrition assessment indicates that TOPs have no significant adverse nutritional effects at the proposed levels of use;

- conditions of use, including an additional labelling statement, are proposed as part of a comprehensive risk management strategy to ensure appropriate use of TOP-enriched low-fat milk by the target consumers, and to discourage use by non-target consumers;

- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and

- the Regulatory Impact Statement indicates that, for the preferred option, namely, to approve the use of TOPs as a novel food ingredient in low-fat milks; the benefits of the proposed amendment outweigh the costs.

Executive Summary

Purpose and scope of the Application

Parmalat Australia Ltd has submitted an Application to FSANZ seeking approval for the use of tall oil phytosterols[21] (TOPs) as a novel food ingredient in low-fat milk under Standard 1.5.1 – Novel Foods, in the *Australia New Zealand Food Standards Code* (the Code). Parmalat is specifically seeking to extend the current permissions to allow use of TOPs in low-fat milk.

Standard 1.5.1 requires that novel foods undergo a safety assessment before being permitted in the food supply. If approved, the novel food is listed in the Table to the Standard and must comply with any special conditions of use also listed in the Table.

[21] i.e. phytosterols derived from tall oils

Efficacy of TOPs

TOPs are added to foods with the intended purpose of lowering cholesterol absorption. The Applicant has submitted efficacy studies including the data and results from clinical studies involving mildly hypercholesterolaemic individuals in a variety of food matrixes, including milk. The available human studies do provide information in relation to the effectiveness of TOPs incorporated into food products to reduce cholesterol absorption. However, there is no specific evaluation of any health claim being considered as part of this Application. Irrespective of whether any statement is considered a health claim, all statements on the label should be true and not mislead consumers.

Technical properties of TOPs

Tall oil phytosterols as well as phytosterols derived from edible vegetable products are comprised of varying ratios of the same four primary phytosterol substances sitosterol, sitostanol, campesterol and campestanol, with varying amounts of minor components such as stigmasterol and brassicasterol. The physiological activity of phytosterol products is due to the presence of these compounds. However, TOPs do not necessarily need to be esterified to improve their solubility as the Applicant has indicated that they can be incorporated into low-fat milks.

Risk assessment

The data support the safety of TOPs in both the target and non-target population at the level of dietary exposure that would be achieved by addition of TOPs to low-fat milk at the levels proposed to be used by the Applicant (0.9g/250 mL serve). The estimated mean dietary exposure to TOPs did not exceed 1.9 g/day in any population group assessed. The 95th percentile dietary exposure for the target population was 4.8 g/day, the majority of which is derived from edible oil spreads. While this level of exposure is higher than that used in the human studies, FSANZ is proposing additional risk management measures to reduce over-consumption of TOP containing low-fat milks. The overall conclusion of the risk assessment is that low-fat milk enriched with TOPs is not associated with any adverse effects.

Risk management

In order to ensure appropriate use of TOP-enriched low-fat milk by the target group and to discourage use by the non-target groups, the following risk management measures are proposed:

4. retain the current mandatory advisory statements in Standard 1.5.1;

5. prescribe an additional labelling statement that indicates that there is no additional benefit from consuming greater than 2-3 serves/day; and

6. prescribe additional conditions of use, namely: (i) that low-fat milk must not contain more than 3.6g/litre of free phytosterols (from a tall oil source); (ii) the fat content must not contain more than 1.5g total fat/100g liquid, and (iii) maximum container size is to be specified at 1 litre (i.e. the labelled volume must be no more than 1 litre); and (iv) that foods containing added plant sterols must not be used as ingredients in other foods,

Additional risk management strategies have been proposed by the Applicant. Ongoing monitoring (possibly via a survey) of the use of phytosterols in foods would provide additional reassurance of the effectiveness of the proposed risk management measures.

Other issues raised in public submissions

Other issues raised in the public submissions consisted of comments on the specific requirements and intent of the novel foods standard, specifications and labelling for phytosterols in general, the possibility of inequity for consumers of lower socio-economic groups and the issue of medicalisation of the food supply if TOP-containing products are approved.

Impact analysis of regulatory options

The options identified were to permit or not permit the use of TOPs in low-fat milk, or to permit the use of TOPs generally. The impact analysis shows that the second option (to permit TOPs in low fat milk) satisfies the objectives based on the outcome of the scientific risk assessment and the Regulatory Impact Statement (RIS), taking into account matters raised following the public consultation period.

These matters included the following:

- an assurance of the safety of TOPs;
- the provision of adequate labelling so as to give consumers informed choices for purchases of products containing TOPs;
- advisory statements and conditions of use to manage inappropriate use and over-consumption of products; and
- the provision of benefits to industry and governments, in terms of enhanced market opportunities and trade.

ATTACHMENT 3

Evaluation of the Nutrition Assessment Report

Fortification of phytosterol esters in breakfast cereals and yoghurt

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University of Illinois at Urbana-Champaign

Overall, this is an excellent report that provides an accurate and complete assessment of the published scientific evidence of the impact of consumption of phytosterol/stanols and their esters upon carotenoid bioavailability. In the "Summary of nutritional effects of phytosterol esters" (Section 3.4), the conclusion that consumption of phytosterol-enriched foods generally results in a reduction in B-carotene levels of approximately 20-25% is supported both by literature cited and by the European and Mayo Clinic assessments (Sections 4.1 and 4.2, respectively). There appears to be no safety issues with consumption of foods containing these phytosterols other than the small effect on carotenoids and the concern that children and pregnant and lactating women should not consume these products.

Clearly, the question is whether the small reduction of serum B-carotene is an acceptable risk considering the positive cholesterol reduction resulting from these products. To date, the answer has been yes, that the small reduction of B-carotene does not present a public health concern. There has not been any evidence that vitamin A status is altered. While it has been suggested that carotenoids may play other roles in health, none has been demonstrated in vivo for B-carotene. Carotenoids are excellent in vitro singlet oxygen quenchers but the significance of this antioxidant function in vivo is unclear. Lutein and zeaxanthin appear to be important for proper macular pigment function and consumption of lycopene from tomato products may reduce the risk of prostate cancer. However, B-carotene appears only to function as a source of Vitamin A. Until there is in vivo evidence to contrary, this is only this function that should be considered in regards to this report.

This reviewer concurs with the conclusions of the report. While a decrease of 20% in serum B-carotene is not ideal, it could be attenuated with dietary adjustment. There is a mandatory advisory statement on the label of foods in Australia that reads, "the product should be consumed in moderation as part of a diet low in saturated fats and high in fruits and vegetables". This label should inform the consumer to enhance intake of foods high in carotenoids. Further, urging consumers to meet the 5-A-Day recommendations for fruits and vegetables would also be advisable. Food Standards Australia New Zealand could also consider suggesting an enrichment of products with a small amount of B-carotene, although this reviewer would not deem this necessary.

There are a few minor comments on the document:

1. Section 2.2, first sentence. Vitamin A is not an antioxidant. Only the carotenoids are antioxidants.

2. Section 2.3.4 and paragraph 2 under section 3.3.7. Is it known what percentage of adults in Australia or New Zealand have very low total vitamin A intake? For example, if a small percentage is below the EAR for Vitamin A, then there is less concern about the impact of phytosterols. Evaluation of mean intakes of RAE is important but more important is the percentage of person with very low intake. Often there is a biphasic, not a bell shaped intake curve for this vitamin.

3. Section 2.4. In the USA, the DRI report concluded that only 2R forms of alpha tocopherol are considered as having Vitamin E activity.

ATTACHMENT 4

Evaluation of Published References

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The question is whether carotenoids such as beta-carotene:

1. Protect against the development of diabetes
2. Protect against the adverse vascular and other effects associated with diabetes

Carotenoids:

- Diverse group of compounds found in plants
- Include the compounds that give flowers their colour
- Possess antioxidant activity
- Protect cells from oxidative stress by quenching free radicals
- Together with tocopherols, carotenoids are thought to be an important defence against oxidative stress

Glucose intolerant states:

- Characterised by chronic hyperglycaemia due to relative deficiency of insulin
  - Chronic hyperglycaemia leads to auto-oxidation of glucose and causes nonenzymatic glycation of proteins, associated with increased oxidative stress
  - increased lipid peroxidation
  - increased free radical activity
- Free radicals shown to impair insulin action
  - Some dietary studies of diabetes incidence have suggested that increased consumption of vegetables may reduce risk of developing diabetes

The papers provided are summarised viz:

1. Ford, E.S. *et al* Diabetes mellitus and serum carotenoids: findings from the third National Health and Nutrition Examination Survey
1.1.1.1.1 Am J Epidemiology 1999;149: 168-76

Methods:

- cross- sectional study conducted in US between 1988 and 1991
- multistage probability design making results generalisable to US population
- 1665 participants had glucose tolerance test, analysed according to old WHO criteria
- concurrent collection of socio-demographic variables, health status, lifestyle variables, 24 hr diet recall & physiological variables

Results:

277 impaired glucose tolerance, 148 newly diagnosed diabetics, 230 known diabetics;

- diabetics & IGT group differed from non-diabetics in age, race, education, health status, smoking status, physical activity, prevalence of overweight, alcohol consumption, blood pressure, serum cotinine and diet
- after adjusting for these potential confounders, variation in serum carotenoid concentrations remained with higher levels in non-diabetics
- beta-carotene showed the strongest relationship with levels 13% lower in ITTs and 20% lower in newly diagnosed diabetics cf normals
- lycopene levels also inversely related with levels 6% and 17% lower than in normal

Author's conclusions:

- cross-sectional nature of data limits inferences on temporality and causation
- data emanate from a cross-sectional study and therefore directionality of any relationship is always an issue
- several possibilities to explain results including residual confounding, unadjusted confounding, diabetes causing poor absorption, or carotenoids protecting against development of diabetes.

2. Abahusain, M.A. *et al* Retinol, alpha-tocopherol and carotenoids in diabetes Eur J Clin Nutr 1999; 53: 630-35

Methods:

- clinic-based case-control study undertaken in Saudi Arabia
- 107 type 2 diabetic patients recruited from diabetic clinic of a hospital (aged 28-74 years)
- 43 healthy controls selected from university faculty staff & employees
- fasting blood sample and 10h urine collection from all subjects
- retinol binding protein (RBP), alpha & beta-carotene and alpha tocopherol measured by HPLC
- dietary questionnaires

Results:

- serum beta-carotene and serum & urine RBP were significantly lower in diabetics than in controls ($p=0.002$ for beta-carotene)
- negative correlation between beta-carotene levels and fasting blood glucose levels ($r = -0.18$, $p<0.008$)

Author's conclusions:

- multiple factors may be responsible for lower beta-carotene levels including malabsorption, infections, low dietary intake or low fat in diet
- increased oxidation in diabetics may result in reduced antioxidant levels

- "whether beta-carotene should be considered as a therapeutic agent in diabetes requires further studies".

3. Suzuki *et al* Relation between serum carotenoids and hyperglycaemia: a population based cross-sectional study
Journal of Epidemiology 2002;12:357-366

Methods:

- case-control comparison conducted amongst rural Japanese
- cases selected from population based survey undertaken annually
- of 1691 subjects studied , 151 had HbA1c values of 5.6% or greater and another 133 were known diabetics
- two controls randomly selected for each subject in the 'elevated HbA1c group and for each known diabetic
- fasting serum levels analysed for alpha and beta carotene, beta-cryptoxanthin, zeaxanthin & lutein, canthaxanthin, retinol & alpha-tocopherol. TBARS levels also measured as an indictor of oxidative stress
- health questionnaire including dietary intakes of major foods also sought

Results:

- serum levels of carotenoids excluding canthaxanthin were about 30% lower in the high HbA1c group than in healthy controls or than in the diabetics (this was a statistically significant difference)
- high HbA1c group also reported higher intake frequency of carrot and pumpkin but not with other fruits and vegetables

Authors' conclusions:

- we suggest that individuals with high HbA1c values display lower serum carotenoids due to both low intake frequencies of fruit and vegetables and increased production of reactive oxygen species by chronic hyperglycaemia
- results from this study suggest that intake of fruit and vegetables rich in carotenoids might be a protective factor against hyperglycaemia

4. Ylonen *et al* Dietary intake and plasma concentrations of carotenoids and tocopherols in relation to glucose metabolism in subjects at high risk of type 2 diabetes: the Botnia Dietary Study
Am J Clin Nutr 2003; 77: 1434-41

Methods:

- cross sectional study involving 81 male and 101 female first and second degree non-diabetic relatives of patients with type 2 diabetes
- fasting and 2-hr blood glucose levels, plus insulin & non-esterified fatty acid levels, measured during glucose tolerance test
- plasma antioxidant concentrations measured by HPLC
- antioxidant intake data based on three day dietary records

- linear regression used to relate study relationship between glucose & fatty acid levels and plasma levels of alpha and beta carotenoid, lycopene, alpha and gamma-tocopherol.

Results:

- in males dietary carotenoids were lower in those with higher fasting plasma glucose concentrations ($p<0.05$)
- in males plasma beta-carotene levels were inversely associated with markers of insulin resistance ($p=0.003$)
- in females plasma beta-carotene concentrations were directly associated with fasting plasma glucose
- no association seen with levels of lutein/zeaxanthin, lycopene or beta-cryptoxanthin

Authors' conclusions:

- our finding of an inverse association between plasma beta-carotene concentrations in men is consistent with previous studies but our finding in women contrasts with these findings
- taken together the available data do not show a consistent effect of carotenoids and tocopherols on glucose metabolism
- the observed inverse relationship between dietary carotenoids and fasting plasma glucose concentrations warrants further studies to define whether a diet high in carotenoid rich fruit and vegetables has a role in the prevention of diabetes in a high risk population.

5. Osganian SK *et al* Dietary carotenoids and risk of coronary artery disease in women
Am J Clin Nutr 2003; 77: 1390-9

Methods:

- cohort study of 73,286 female nurses who completed a semi-quantitative food-frequency questionnaire in 1984
- questionnaire assessed consumption of carotenoids and other nutrients
- cohort followed for 12 years for development of incident coronary artery disease

Results:

- 998 incident cases of CAD identified during follow-up of cohort
- modest but statistically significant relationship between intake of alpha and beta carotene and CAD risk
- for women in highest versus lowest quintiles of alpha & beta-carotene intake the relative risk of developing CAD was 0.74 and 0.80 respectively ($p<0.05$)

Authors' conclusions:

- higher intakes of foods rich in alpha or beta-carotene are associated with a reduced risk of CAD

- at this time greater consumption of fruit and vegetables remains the most appropriate public health recommendation

6. Ford, E.S. *et al* The metabolic syndrome and antioxidant concentrations: findings from the third National Health & Nutrition Examination Survey Diabetes 2003; 52: 2346-52

Methods:

- cross-sectional analysis of data from third NHANES study in US (1988-94)
- examined data on circulating concentrations of vitamins A, C & E, retinyl esters, five carotenoids and selenium in 8808 US adults with and without metabolic syndrome
- adjusted for age, sex, race, ethnicity, education, smoking status, cotinine concentrations, physical activity, fruit and vegetable intake, and vitamin and mineral use

Results:

- individuals with metabolic syndrome had significantly lower concentrations of retinyl esters, vitamin C, and carotenoids (except lycopene)
- amongst 2254 persons with metabolic syndrome mean beta-carotene was 0.30 umol/l +/- 0.01 compared with 0.41 +/- 0.01 in remainder
- consumption of fruit and vegetables also lower amongst those with metabolic syndrome

Authors conclusions:

- because persons with metabolic syndrome have low concentrations of several antioxidants they may be an interesting group in whom to study effects of antioxidant supplementation or dietary modification to enhance antioxidant intake

ANALYSIS

Persons in the early stages of glucose intolerance shown to have lower circulating levels of carotenoids in several studies reviewed above. These results appear to be relatively consistent across different populations and study types.

There are several possible explanations for this finding, ranging from impaired absorption to suppression of levels as a result of increased oxidant activity. The possibility also exists that high levels of carotenoids are protective against the development of diabetes, but at present it is not possible to be sure which of these possibilities is most likely. It is possible/likely also that increased beta-carotene levels reflect a generally healthier diet (possibly accompanied by other aspects of a healthy lifestyle).

Present data does not warrant use of beta-carotene supplementation for prevention of diabetes since present evidence falls well short of proving a causal relationship. This is also supported by other data including:

1. Large scale trials of beta-carotene have failed to identify a health benefit (these provide more reliable data than do observational studies), and may cause harm. These studies are briefly reviewed in Osganian *et al* (2003);

2. Positive data presented largely concerns surrogate health measures (eg fasting, glucose levels, HbA1c) rather than clinically significant endpoints; and

3. An analogy may exist with other anti-oxidants, eg. vitamin E, which have shown positive associations in observational studies but negative results in trials.

Concerns about small decreases in beta-carotene levels of the order likely to occur with phytosterols consumption (20%) are not supported by presently available evidence.

In summary, the data presented raise matters worthy of additional study, but fall well short of proving any causal relationship between beta-carotene intake and the development or worsening of diabetes.

PHYTOSTEROLS AND CHRONIC DISEASES

Comments from Chief Medical Advisor for use in preparing the First Review of Applications A433, A434 and A508

12 June 2005

I have been provided with copies of six published papers submitted to Food Standards Australia New Zealand (FSANZ), all of which relate to relationships between dietary intake of carotenoids and chronic diseases. Five papers relate to the metabolic syndrome, hyperglycaemia and type II diabetes mellitus. One relates to risk of coronary heart disease in women.

Coronary heart disease

Summary

The 2003 paper by Osganian et al in the American Journal of Clinical Nutrition set out to study the relationship between the dietary intake of specific carotenoids and risk of coronary artery disease amongst women enrolled in the Nurses Health Study in the United States between 1984 and 1996. Phytosterol fortification of foods was not a factor in the American diet at the time the study was undertaken.
Numerous studies prior to this one had shown that a higher intake of fruits and vegetables was associated with a lower risk of coronary artery disease. One of the health claims being reviewed to see whether it can be accepted as a pre-approved high-level health claim upon the coming into force of Application 293-Nutrition, Health and Related Claims concerns just this relationship.

The result was a modest, but significant inverse relationship between higher intakes of β-carotene and α-carotene and the incidence of fatal and non-fatal myocardial infarction. (26% and 20% respectively between the highest and lowest quintiles of intake). There was no significant risk reduction shown with any of the other carotenoids. Several intervention studies have shown no effect from β-carotene supplementation of the diet and the authors admit that they have probably not ruled out confounding from issues such as heavier fruit and vegetable eaters having a generally more healthy lifestyle, or some other components of fruit and vegetables affecting cardiovascular health.

Conclusion

The general issues traversed in this paper were available to the experts involved in the Mayo Clinic Review of Phytosterols in 2003, and the European Union expert group. While supporting fruit and vegetable consumption, the paper does not draw any conclusion about the adverse effects of reducing the absorption of fat soluble vitamins and antioxidants.

This paper provides no convincing evidence that :

(a) anti-oxidants reduce the risk of cardiovascular disease
(b) reducing the absorption of carotenoids related to reduced abdominal absorption of dietary lipids is a risk factor for cardiovascular disease.

Metabolic Syndrome, Hyperglycaemia and Type II Diabetes

In a 2003 paper by Ford et al in *Diabetes* the Metabolic Syndrome is characterised by a person having at least 3 of the following criteria; abdominal obesity, hypertriglyceridaemia, low levels of LDL cholesterol, high blood pressure, and high fasting glucose. It is known that this group is more likely to develop Type II diabetes.

Between 1988 and 1996 some 23% of US adults from a random sample of 8,800 met the criteria for metabolic syndrome. They were older, more likely to be white, had fewer years of education, were less likely to be involved in regular physical exercise, had higher lipid concentrations, higher serum insulin levels and consumed fewer fruits and vegetables than the others in the sample. On serum analysis the metabolic syndrome group were reported as having sub-optimal levels of several antioxidants, including, inter alia, the carotenoids. The authors suggest that the relationship between antioxidant blood levels and the development of diabetes is a field for further study. There is no comment on the possible effect of altering abdominal absorption of lipids on diabetes.

The same principal author had used participants in the same Third National Health and Nutrition Examination Survey to compare the serum concentration of some five carotenoids in people with normal glucose tolerance, impaired glucose tolerance, newly diagnosed diabetes and long-standing diabetes. After adjustment for possible confounding, serum levels of β-carotene, α-carotene and lycopene were inversely related to the degree of abnormality of the glucose tolerance test. The evidence of an association and is backed up by other studies. However, the authors admit that little is known about the absorption of carotenoids and raise the question whether their findings could have been caused by the impaired glucose tolerance interfering with the absorption of lycopene and α and β-carotenes, rather than a "sub-optimal" carotene level failing to prevent developing diabetes.

There is no convincing evidence that reduced intake of dietary carotenes are related to diabetes in this paper.

A study from Finland, published in the American Journal of Clinical Nutrition in 2003 concluded that, in a population of men at high risk of diabetes, there was an inverse relationship between their intake and plasma concentration of carotenoids and plasma glucose levels, raising the question whether diets rich in fruit and vegetables may assist in the prevention of diabetes. This study cannot be considered as evidence of harm from lowering abdominal lipid absorption.

A Japanese study in 2002 by Suzuki et al, published in the Journal of Epidemiology found an inverse relationship between blood glucose levels and the consumption of pumpkin and carrots (but no other fruits and vegetables), and the same inverse relationship between the serum levels of six carotenoids and plasma glucose.
The evidence of a relationship is "probable" because of some confounders that may not have been fully corrected for. However, there is no convincing evidence about cause and effect and nothing to link these findings to dietary lipid consumption.

A Saudi Arabian paper in 1999 set out to study the effect of diabetes on serum levels of vitamin A and some carotenoids. It found serum β-carotene levels lower in diabetics than control subjects, but no other significant relationships. The discussion in the paper is solely around how diabetes (or the prescribed dietary regimens for people with diabetes) may affect the β-carotene levels.
Therefore there is no evidence provided to relate reduced carotenoid intake with the risk of developing diabetes.

Summary

Taken together, there is no evidence in these papers that reduced carotenoid intake increases the risk of diabetes or cardiovascular disease. There is evidence of an inverse relationship between serum carotenoid levels and glucose intolerance, but not even possible evidence of what is the cause / effect. Nothing in these papers studies the difference in diabetes rates or glucose intolerance between populations who have different diets or seasonal changes in their diet, which might equate to the changes in dietary intake of fat-soluble antioxidants caused by intake of phytosterols.

G R Boyd
Chief Medical Advisor
Food Standards Australia New Zealand

ATTACHMENT 5

OPTIONS FOR LABELLING OF PHYTOSTEROL-ENRICHED FOODS

1. Background

Under current permissions, there is a requirement for three mandatory advisory statements (MAS) to appear on labels of phytosterol-enriched edible oil spreads and margarines. As there are no legal requirements on the presentation of the statements, manufacturers are at liberty to present them according to their own requirements. The Ministerial Council expressed the view that depiction of these MAS on current packaging of phytosterol-enriched products is inadequate to ensure that consumers are informed about the appropriate use of the products.

In requesting a First Review of Applications A433, A434 and A508, the Ministerial Council expressed the concern that should phytosterol-enriched breakfast cereal, low-fat milk and low-fat yoghurt be available on the market, there are no requirements to compel manufacturers to present the MAS more prominently on packaging. Therefore, the Ministerial Council argues that the availability of a broader range of phytosterol-enriched products could be more likely to lead to inappropriate use of the products by consumers.

The issue of specific legibility criteria for mandatory advisory statements[22] was examined and discussed with the jurisdictions during the review of the *Australian Food Standards Code* and the New Zealand Food Regulations, culminating in the development of Standard 1.2.9 Legibility Requirements of the Code. A background to those discussions is in **Addendum 1**. At that time it was agreed that as advisory statements were of lesser importance in relation to protection of public health and safety (compared to mandatory warning statements), it was not necessary to prescribe additional specific legibility criteria or a minimum print size.

2. Review objectives

Specific objectives of the labelling review are to:

- consider the issues raised by the jurisdictions in relation to the adequacy of the presentation of mandatory advisory statements (MAS) on packaging of current phytosterol-enriched foods; and

- consider the impacts of a range of revised labelling options that aim to address these concerns.

2.1 Current labelling requirements

Three MAS are currently required on food regulated in Standard 2.4.2 (Edible Oil Spreads) containing phytosterol-esters and tall oil phytosterols. These requirements are listed in the Table to clause 2, Standard 1.2.3 and are statements to the effect that -

1. the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables;

[22] Under Proposal P 142-Print Size and Quality of Prescribed Information Appearing on a Food Label

2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; and

3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

Other than the general legibility requirements in Standard 1.2.9, there are no specific legibility requirements in the Code for MAS.

As part of the risk management strategy for Applications A433, A434 and A508 an additional MAS was proposed as follows:

Consuming greater than 3 serves per day of products containing plant sterols provides no additional benefit.

At Final Assessment, FSANZ considered that this statement would encourage appropriate use of all phytosterol-enriched foods by consumers, and be consistent with the data that demonstrated the safety of plant sterols (both phytosterol-esters and tall oil phytosterols) for high level consumers within the target group.

3. Specific labelling issues raised in the Review

Jurisdictions have raised concerns that even on current phytosterol-enriched products, the presentation of the MAS is inadequate, sometimes found on the bottom of containers or inside the outer packaging, raising questions about whether consumer access to information and legibility is being adequately protected. For example, one product brand presents the MAS on a removable cardboard sleeve that is likely to be removed after purchase. Therefore the MAS may not be accessible by other members of a household.

In the context of Application A434, small punnets of yoghurt are normally sold in packs of two or four surrounded by a removable outer cardboard sleeve. The jurisdictions contend that for these products it is likely the MAS will again only be accessible to a purchaser of the product but not necessarily to all consumers in a household.

An additional issue raised by the Ministerial Council is that the statements are almost illegible because of the small font size used. These labelling concerns are therefore likely to apply to the broader range of phytosterol-enriched foods if the current applications are approved.

4. Revised labelling options

Four options were considered to address the issues raised by the jurisdictions:

4.1 Option 1 - Status quo

Under the status quo, the existing MAS for foods containing phytosterol esters and tall oil phytosterols would remain in Standard 1.2.3. Legibility and prominence issues would be covered by the general provisions in Standard 1.2.9, supported by the User Guide to Standard 1.2.9.

4.2 Option 2 - Use of an editorial note to clarify the legibility requirements in Standard 1.2.9

Under Option 2, the general legibility requirements in Standard 1.2.9 would be clarified. This could be done by including an editorial note after the general requirements in clause 2 to clarify the intent of the words 'written or set out legibly and prominently such as to afford a distinct contrast to the background…' . For example, the editorial note could state that words or statements provided on the inside or underside of a label would not be considered as 'legible' or 'prominent'.

4.3 Option 3 - Additional clause in Standard 1.2.9 to strengthen the legibility requirements for advisory statements

Under Option 3, an additional clause could be included in Standard 1.2.9 setting out specific legibility requirements for advisory statements. For example, the clause could specify that advisory statements should not be placed on a removable sleeve, must not be placed on the underside or inside of a label and must be in a minimum font size of X mm.

A similar provision would also be required in the Standard for warning statements, given that warning statements apply where there is a higher public health and safety risk.

4.4 Option 4 - Additional provisions in Standard 1.5.1

Under Option 4, the existing MAS for foods containing phytosterol-esters and tall oil phytosterols would be transferred from Standard 1.2.3 and transferred to Standard 1.5.1 - Novel Foods. These statements would be listed in Column 2 of the Table to clause 2 as Conditions of Use. Other specific requirements – for example, that advisory statements should not be placed on a removable sleeve, must not be placed on the underside or inside of a label and must be in a minimum font size of X mm, would also be included in Column 2.

5. Impact of regulatory options

OPTION 1	
Advantages	**Disadvantages**
• Less cost to manufacturers of phytosterol products that are currently complying with the Code, as relabelling or repackaging would not be required.	• Does not specifically address jurisdictional concerns in relation to labelling of phytosterol products although it could be argued that these issues could be dealt with by enforcement action.
• Consistent with the principles underpinning Standard 1.2.9 and the principle of minimum effective regulation on which the Code is based.	
• Consistent with EU requirements for phytosterol-containing foods and general labelling requirements by Codex, which are not prescriptive in terms of legibility/prominence of advisory statements.	
OPTION 2	

• By clarifying the general legibility requirements, it may better address jurisdictional concerns than Option 1.	• Editorial note is not legally enforceable therefore jurisdictional concerns may not be fully addressed.
• Clarification of legibility requirements would apply generally, rather than just to the advisory statements on phytosterol products.	• Could still be considered unnecessarily prescriptive and not consistent with principles underpinning Standard 1.2.9.
• Consistent with the principles underpinning Standard 1.2.9 and the principle of minimum effective regulation on which the Code is based.	
OPTION 3	
• More effective in addressing jurisdictional concerns than Options 1 and 2.	• Unnecessarily prescriptive and not consistent with principles underpinning Standard 1.2.9 or the Code generally.
• Would apply to all advisory statements not just advisory statements on phytosterol products.	• Potentially more prescriptive than warning statements which have a higher public health and safety risk, unless a similar provision is included for warning statements.
	• Inconsistent with EU requirements for phytosterol-containing foods and general labelling requirements by Codex, which are not prescriptive in terms of legibility/prominence of advisory statements. Possible implications for international trade.
	• Additional costs to manufacturers of phytosterol products associated with repackaging/relabelling.
OPTION 4	
• Addresses jurisdictional concerns in relation to labelling of phytosterol products.	• Inconsistent with FSANZ objectives of reduced prescriptiveness and minimum effective regulation and general labelling provisions in the Code.
• 'Disguises' mandatory advisory statements as 'conditions of use', thereby drawing attention away from what could be considered as a conflict with other advisory statements and labelling requirements in the Code.	• No evidence provided to indicate why advisory statements on phytosterol containing products should be more prescriptive than other labelling requirements (e.g. allergen labelling or warning statements).
	• Possible flow on effects to other advisory statements and other labelling provisions.
	• Effectively creating another class of statements without any clear rationale for this.
	• Additional costs for manufacturers of phytosterol products associated with repackaging/relabelling.
	• Inconsistent with EU requirements for phytosterol-containing foods and general labelling requirements by Codex which are not prescriptive in terms of legibility/prominence of advisory statements. Possible implications for international trade.

1.1.1.1.2 Evaluation of options

Option 1, may not be a viable option considering that jurisdictions have already indicated that they require strengthening of the current mandatory labelling statements. If this option is followed the Applications may not be approved by ANZFRMC.

Options 3 and 4 are not preferred for the following reasons:

- the labelling standards would be amended in the absence of any evidence that the specific issues outlined by the jurisdictions are a problem, either for consumers or enforcement agencies;
- the amendments jeopardise the principles, previously agreed to by the Ministerial Council, upon which the Code has been developed;
- the amendments compromise the integrity of the Code; and
- the amendments are matters of policy, which should more appropriately be referred to FRSC for policy guidance.

6. Preferred option

The preferred option is Option 2 – clarifying the legibility requirements in Standard 1.2.9 by use of an editorial note for the following reasons:

- other than Option 1, it is the least prescriptive option and therefore is most consistent with the principles upon which Standard 1.2.9 and the Code are based;
- it would apply more generally to all labelling requirements rather than just to advisory statements on phytosterol products;
- it goes some way to addressing jurisdictional concerns relating to phytosterol-enriched foods; and
- it is more consistent with the current general labelling requirements for MAS by Codex and the specific EU requirements for phytosterol-enriched foods.

Additional Recommendation

FSANZ also proposes a broader review of Standard 1.2.9 in relation to all mandatory warning statements, advisory statements and declarations via a specific Proposal that aims to address the issue of effectiveness of current labelling provisions in the longer term. However, approval of the current Applications (A433, A434 and A508) would not be conditional on completion of the review of Standard 1.2.9.

The benefit of this approach is that:

- FSANZ could assess the application of Standard 1.2.9 within the context of the whole Code and the principles on which it was developed rather than within the context of the three current phytosterol applications;
- the current effectiveness of Standard 1.2.9 would be evaluated;
- it allows consideration of any public health and safety considerations that have emerged since the first review of Standard 1.2.9;
- the concerns of the jurisdictions would be considered in a more systematic way; and
- any amendment resulting from such a review would be based on evidence and would be less likely to have a negative impact on the operation of the other labelling standards.

Addendum

1. Background to Standard 1.2.9: Proposal P142 – Print Size and Quality of Prescribed Information Appearing on a Food Label

Addendum 1

Background to Standard 1.2.9: Proposal P142 – Print Size and Quality of Prescribed Information Appearing on a Food Label

During the review of the Code considered issues relating to print size and quality of information appearing on labels in Proposal P142.

FSANZ considered that prescribed information should be regulated using basic legibility criteria only, and the requirement that all prescribed information be prominent, legible and in English ensures information is easily legible to the prospective purchaser while allowing manufacturers greater flexibility in label design. Including more words than this was considered to unnecessarily duplicate the intention of the requirement.

FSANZ considered that warning statements should be treated in a more prescriptive manner in relation to print size and quality than other prescribed information due to their direct role in the protection of public health and safety. Warning statements are subject to basic legibility criteria and a minimum print size of 3 mm (or 1.5 mm in the case of small packages) even though this is more stringent than Codex requirements. As advisory statements are of lesser importance in relation to protection of public health and safety FSANZ considered it was not necessary to prescribe additional specific legibility criteria or a minimum print size.

Requiring that warning statements be more noticeable, or regulating the positioning of the statement was also considered as part of P142. The majority of warning and other statements are placed at the manufacturers discretion and as there appeared to be no disadvantages to the consumer it was not considered necessary to prescribe the position of these statements.

Attachment 8

7-06
4 October 2006

SECOND REVIEW REPORT

APPLICATION A433
PHYTOSTEROL ESTERS DERIVED FROM VEGETABLE OILS IN BREAKFAST CEREALS

APPLICATION A434
PHYTOSTEROL ESTERS DERIVED FROM VEGETABLE OILS IN LOW-FAT MILK & YOGHURT

APPLICATION A508
PHYTOSTEROLS DERIVED FROM TALL OILS AS INGREDIENTS IN LOW-FAT MILK

For Information on matters relating to this Report or the assessment process generally, please refer to http://www.foodstandards.gov.au/standardsdevelopment/

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Decision

FSANZ re-affirms its approval of Applications A433, A434 and A508, subject to drafting amendments specified in this Second Review, and supported by appropriate risk management measures because:

8. The recently established Phytosterols Expert Advisory Group evaluated safety concerns raised by jurisdictions in relation to nutritional effects, possible interactions with cholesterol-lowering medications and long-term usage of phytosterol-enriched foods and concluded that there was no basis for health concerns;

9. A change to permit a minimum and maximum amount of plant sterols in a product will assist consumers to:

(i) more easily monitor a daily intake of plant sterols;
(ii) consume an efficacious amount; and
(iii) use the products cost effectively;

10. Revised mandatory advisory statements will provide information to consumers at the time of purchase that is consistent with the safety evidence for different population groups;

11. A survey of New Zealand and Australian consumers found that users of phytosterol-enriched margarines are in the target group, use the products in moderation and for the appropriate health reasons. Recent post-market monitoring in Europe, where a broader range of phytosterol-enriched foods has been available for some time, shows that consumers welcome choice of products, and over-consumption does not occur;

12. A review of Standard 1.2.9 Legibility Requirements will go ahead, but the insertion of an Editorial note is a practical, interim measure to clarify the legibility requirements of the Code for mandatory advisory statements;

13. FSANZ and the National Heart Foundation of Australia will collaborate in broadly based education activities that will significantly increase the visibility of information on plant sterols in the context of heart-healthy nutrition and dietary advice;

14. FSANZ will also prepare its own educational material on phytosterol-enriched foods suitable for wide distribution to professional organisations and the general public, linking to other sources of information on plant sterols;

15. Approval of the current applications is a conservative extension of use of plant sterols into foods types that are compatible with a healthy diet message; and

16. The development of policy guidance on the addition to food of non-vitamins and minerals and a new Standard for Health, Nutrition and Related Claims should not halt the progression of Applications A433, A434 and A508.

Summary Table

Issues addressed in the Second Review of Applications A433, A434 and A508 seeking to broaden the use of phytosterol esters and tall-oil phytosterols.

MINISTERIAL COUNCIL ISSUE	FSANZ RESPONSE
1. Protection of public health and safety.	• Officials of jurisdictions contacted to seek clarification on concerns. • Formation of the Phytosterols Expert Advisory Group to consider safety issues holistically. • Further assessment of nutritional issues in the context of Australian data on beta-carotene levels. • Further assessment of effects of plant sterols used in conjunction with cholesterol-lowering medication. • Assessment of recently published literature on plant sterol-enriched foods and effects in children. • Further explanation of the potential benefits to consumers from a wider choice of phytosterol-enriched foods and clarification on the restrictions to breakfast cereals. • Consideration of several, recent post-market monitoring reports on phytosterol-enriched foods in Europe. • Revision of specifications for the tall oil phytosterols.
2. Provision of adequate information to enable informed choice.	• TNS social research commissioned to conduct a survey of consumers in New Zealand and Australia of phytosterol-enriched spreads to ascertain behaviour patterns and motivation. • Revision of the mandatory labelling statements for packaging of all phytosterol-enriched foods. • Established professional links with the National Heart Foundation of Australia to assist with the development and implementation of community education initiatives providing information relevant to the appropriate use of plant sterols, and dietary/nutritional advice in relation to heart disease.
3. Policy issues.	• Provided further explanation regarding the impact of the proposed health claims standard and the development of policy guidance for the addition to food of non-vitamins and minerals.

Key changes as a result of the Second Review

PREVIOUS ASSESSMENT	ASSESSMENT AT SECOND REVIEW
t sterols (as free sterols) or no more than 0.9 g tall oil plant sterols in one serve of food.	**follows:** ***a maximum of 1.0 g plant sterols (either vegetable oil or tall oil) per serve of food*** • The minimum amount is based on efficacy and the maximum amount is based on avoidance of consumer deception. • All plant sterols, whether derived from a vegetable oil or tall oil source, will be permitted within the same range, to avoid consumer confusion between the two types of phytosterols permitted in the FSC. • Dietary exposure estimates, including the use of phytosterol-ester enriched table spreads, show that mean daily consumption would be within 1-3 g.
sory statements: *consumed in moderation as part of a diet low in saturated fats and high in fruits and vegetables.*	**e effect that:** ***oduct, it should be consumed as part of a healthy diet*** • Plant sterols permitted only in foods that are compatible with a healthy diet i.e. low-fat milk, low-fat yoghurt and breakfast cereal with a compositional profile that is not attractive to children. • Advice to consume carotenoid-rich fruit and vegetables is not justified on the grounds that the reduction in serum beta-carotene is not indicative of any nutritional deficiency and is within natural variation. • Healthy diet message compatible with other public health messages in relation to diet and chronic disease.
sory statements: *mmended for infants, children and pregnant or lactating women unless under medical supervision.*	**e effect that:** ***suitable for children under the age of five years and pregnant or lactating women.*** • Many studies in hypercholesterolaemic children show the efficacy and safety of plant sterol-enriched foods. However, young children do not need to consume specific foods to achieve a cholesterol reduction. • Similarly, pregnant and lactating women do not need to lower serum cholesterol levels.
sory statements: *rol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.*	**atement.** • Clinical studies show that consumption of plant sterol-enriched foods can lead to a modest reduction in cholesterol levels, even in individuals on cholesterol-lowering medication, and is not a health concern. • There is no scientific evidence of adverse interactions of plant sterols in conjunction with cholesterol-lowering medication, particularly the statins, as they work by different physiological mechanisms. • Plant sterol-enriched foods may provide a more cost-effective means of reducing cholesterol in those who cannot achieve a reduction using prescribed medication alone.

PREVIOUS ASSESSMENT	ASSESSMENT AT SECOND REVIEW
isory statement: *plant sterols do not provide additional benefits when consumed in excess of three serves per day.*	**e effect that:** ***ide additional benefits when consumed in excess of three grams per day.*** • Consumers can more easily monitor their daily intake in grams of plant sterols across a range of foods. • Advises consumers that more than 3 g per day plant sterols do not provide any additional cholesterol-lowering benefit, thereby encouraging cost-effective use of the products. • There are no standardised serve sizes for these products, although manufacturers often indicate a recommended serving size on packaging.
e: 'plant sterols' must be used when declaring the ingredient in the ingredient list , as prescribed in Standard 1.2.4	**rement.** • Manufacturers of phytosterol-enriched table spreads currently use the more generic term 'plant sterols'. • Consumers can readily monitor daily intake in grams of plant sterols by reference to the ingredient list.
e: hytosterols or phytosterol esters have been added may not be used as ingredients in other foods.	**rement.** • Manufacturers will not be permitted to use phytosterol-enriched foods in the preparation of other mixed foods.
r the tall oil phytosterols are listed in the Schedule to Standard 1.3.4 Identity and Purity.	**or the tall oil phytosterols** • New specifications for the tall oil phytosterols incorporate a minimum 97% level of purity, with a maximum of 3% minor sterols. The revised specifications also incorporate a reduction in the 'total heavy metals' component from a maximum of 10 ppm down to 2 ppm.
n Standard 1.2.9 Legibility Requirements)	**torial note to read as follows:** ***s Standard will not be met where prescribed information is placed other than on the outside of a package where it is readily accessible by a consumer prior to purchase, or during the life of the product, and not obscured by an outer covering. The requirements of this Standard will also not be met where prescribed information is printed in a small font so the statement cannot be read easily.*** • Intended only as an interim measure to reinforce the principles

PREVIOUS ASSESSMENT	ASSESSMENT AT SECOND REVIEW
	underpinning Standard 1.2.9, pending a systematic review of the effectiveness of the Standard.

All drafting changes for Applications A433, A434 and A508 are at **Attachment 1**.

1. Introduction

In September 2005, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a Second Review of Applications A433, A434 and A508. These applications seek to broaden the range of foods to which phytosterols (plant sterols) may be added as follows:

Application A433	Addition of phytosterol esters* derived from vegetable oils to breakfast cereals
Application A434	Addition of phytosterol esters* derived from vegetable oils to low-fat milk and yoghurt
Application A508	Addition of phytosterols derived from tall oils** to low-fat milk

***Phytosterol esters** are plant sterols derived from edible vegetable oils which have been esterified with long-chain fatty acids from vegetable oil sources.
****Tall oil phytosterols** (non-esterified) are a by-product of the pulping process from coniferous trees.

Approval of all three applications involves variations to Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations, Standard 1.5.1 – Novel Foods, Standard 2.5.1 – Milk, and Standard 2.5.3 Fermented Milk Products of the *Australia New Zealand Food Standards Code* (the Code).

The purpose of the Second Review is to respond to the issues raised by the Ministerial Council, as outlined in Section 3. FSANZ has addressed these issues by seeking additional information from key stakeholders, undertaking further research and engaging external expertise. An extension of time was granted until 27 July 2006 to complete the review.

2. Objectives of review

The objective of the Second Review is to reconsider the draft variations notified to the Ministerial Council by FSANZ in July 2005 following completion of the First Review.

3. Grounds for the review

A Second Review was requested on the grounds that approval of the draft variations:

- does not protect public health and safety; and
- does not provide adequate information to enable informed choice.

The Ministerial Council provided additional comments concerning the grounds on which the Second Review is based. These comments have been broadly categorised in the following groups:

- Long term safety of phytosterols;
- Possible interactions with cholesterol-lowering medication;
- Nutritional effects;
- The effectiveness of labelling and advisory statements; and
- Consumer education and the role of health professionals.

Specific advice was also requested on the sterol composition of the tall oil phytosterols (TOPS) on the basis of changes to the specifications in the European Union.

4. Background

Currently, under Standard 1.5.1 - Novel Foods, phytosterol esters and tall oil phytosterols (plant sterols) are permitted for use only in edible oil spreads. As separate novel food ingredients, they are listed individually in the Table to clause 2 and are subject to specified conditions of use. Plant sterols must be declared in the ingredient list, and three advisory statements must be presented on packaging to advise consumers on how to use the products appropriately[23].

Consumption of plant sterols reduces absorption of dietary cholesterol leading to lower serum LDL-cholesterol levels. Foods containing added plant sterols are therefore targeted primarily to adult consumers with concerns about their cholesterol levels. Manufacturers seek to expand the range of phytosterol-enriched products primarily to broaden consumer choice.

In October 2004, the FSANZ Board approved the Final Assessment of Applications A433, A434 and A508. The FSANZ assessment focused on (i) the safety of phytosterol esters and tall oil phytosterols at proposed levels of use when used in breakfast cereal, low-fat milk and yoghurt, (ii) their efficacy in the relevant food matrices to ensure truth in labelling, and (iii) the suitability of the products to target consumers.

The optimal cholesterol-lowering effect is achieved when consumption is between 2-3 g plant sterols per day, irrespective of the type of sterols consumed. To ensure that target consumers were informed about this, an additional advisory statement was proposed to the effect that:

foods containing added plant sterols do not provide additional benefits when consumed in excess of three serves per day.

As an additional risk management measure, the conditions of use were also extended to the effect that:

foods containing added plant sterols must not be used as ingredients in other foods.

In December 2004, the Ministerial Council requested a First Review of the Applications on the grounds that there were remaining standards and policy issues. After consideration of these issues, in July 2005, the Board reaffirmed its approval of the draft variations recommended to the Ministerial Council.

4.1 Phytosterol-enriched foods in other countries

A variety of phytosterol-enriched foods are approved in Europe and the USA in the following categories:

[23] It should be noted that although the permission for tall oil phytosterols exists in the Code, there are no tall oil products on the market. The two currently available brands of phytosterol-enriched table spreads (Logicol® and ProActive®) both contain phytosterol esters from vegetable oils.

(1) Fats and oils
(2) Dairy products
(3) Beverages
(4) Bakery products

Because of the complexity of the approval process for individual products in the European Union, FSANZ sought information from the food industry on the regulatory status and availability of phytosterol-enriched products in Europe. The information received is at **Attachment 2**. Milk and fermented milk products have been approved under the Novel Foods Regulation (EC No. 258/97) since 2004. Recently in 2006, the range of approved products was extended to rye bread.

4.2 Other applications

Some phytosterol-enriched products available in Europe contain the target amounts required for a cholesterol-lowering benefit in a single serve of food. For example, a single-shot of drinking yoghurt can contain two grams of plant sterols. Such products diversify the phytosterol-enriched foods market in general and, for some consumers, undoubtedly offer a simpler choice for obtaining the target amount of plant sterols in one meal event. FSANZ would consider any future applications for products that offer a suitable quantity of plant sterols in a single serve of food.

5. Issues in the Second Review

Formation of Expert Advisory Group

FSANZ formed a Phytosterols Expert Advisory Group, chaired by the Chief Medical Advisor Dr Bob Boyd, to broaden the technical input into the Second Review. The Group is comprised of invited members with identified expertise and knowledge on phytosterols from a variety of professional backgrounds. As well as researchers, academics and a clinician, representatives from organisations such as the Dietitians Association of Australia, the New Zealand Dietetics Association and the National Heart Foundation of Australia (NHF) were invited into the Group[24].

The Group's purpose and function is to provide advice to FSANZ on the interpretation and evaluation of available scientific evidence relevant to consideration of the efficacy, safety and nutritional effects of phytosterol-enriched foods. Through representatives from health professional organisations, the Group also provided advice in relation to a number of consumer-related issues.

At a meeting in May 2006, the Phytosterol Expert Advisory Group discussed specific technical issues identified in the comments received from the Ministerial Council at Second Review. Through a consensus approach, the meeting was able to address a number of key concerns using the most recent scientific information and progressive thinking on the role of phytosterol-enriched foods in the context of a healthy diet.

[24] **Phytosterol Expert Advisory Group**: Dr Alex Chisholm, University of Otago (Dunedin, NZ); Dr Peter Clifton, CSIRO Human Nutrition; Ms Barbara Eden, National Heart Foundation of Australia; Ms Linda Hodge, Dietitians Association of Australia; Professor Paul Nestel, Baker Medical Research Institute; Dr Manny Noakes, CSIRO Human Nutrition; Professor Brian Priestly, Director, Australian Centre for Human Health Risk Assessment (Department of Epidemiology and Preventive Medicine, Monash University, Melbourne).

Wherever relevant, the deliberations and conclusions of the meeting have been used in addressing the following issues.

5.1 Protection of public health and safety

5.1.1 Long term safety of phytosterols at high levels of consumption

The Expert Advisory Group was not aware of more recent long term studies (greater than twelve months) on phytosterols, however considered that extrapolation from the results of the large number of published studies showing no safety concerns was appropriate.

Additional toxicological studies in animals were published between 2001-2004, and these had confirmed the absence of any adverse effects. Phytosterols are only poorly absorbed, and a number of potential toxicological effects had been examined and ruled out as a concern.

There are many studies examining safety in humans, and the effects on uptake of fat-soluble nutrients was the most significant finding, although these were variable in different studies. Low amounts of dietary phytosterols are currently being explored as anti-cancer agents, particularly for hormone-dependent cancers.

Studies on the effects of dietary phytosterols are available for both normocholesterolaemic and hypercholesterolaemic people. Previously, FSANZ has focused on studies using subjects with normal or mildly elevated cholesterol levels. Consideration of the studies using hypercholesterolaemic subjects, usually those in whom high cholesterol levels occur in families, broadens the available evidence as these tend to be longer term studies.

A 2004 Norwegian study examined the long-term compliance and changes in plasma lipids, plant sterols and carotenoids in children and parents with familial hypercholesterolaemia (FH) consuming phytosterol ester-enriched spread. The duration of the study was 6 months. A total of 37 children (7-13 y) and 20 parents (32-51 y) diagnosed with heterozygous FH were required to consume 20 g per day of phytosterol-enriched spread as part of their lipid lowering diet. The mean daily intake of phytosterols corresponded to 1.2 g in the children and 1.5 g in the parents. Most parents, but no children, used statins in addition to the dietary intervention. There was a reduction of approximately 11% in LDL cholesterol levels in both groups. The authors reported that lipid-adjusted serum alpha- and beta- carotene decreased by 17% and 11% respectively in the children at the end of the controlled phytosterol period. However, levels of both nutrients increased again during the follow-up period. Of note, serum alpha- and beta-carotene concentrations were unchanged in the parents. There were no adverse effects reported and the study concluded that long-term compliance of phytosterol consumption was associated with sustained efficacy in cholesterol reduction (Amundsen et al., 2004).

With respect to tall oil phytosterols (Application A508 only), FSANZ acknowledges that there have been no long term studies at higher levels of consumption, with studies limited to 28 days (3.6 g/day) or 8 weeks (1.8 g/day). However, given the higher proportion of stanols in the tall oil preparations, large studies examining the safety of plant stanol-enriched foods are relevant.

The Stresa Workshop25 whose findings were published in the Mayo Clinic Proceedings (Katan et al. 2003), is one of the most comprehensive reviews on the efficacy and safety of plant stanols and sterols. This review concluded that consuming 2 g per day of stanols and sterols lowers LDL cholesterol levels by 10%, and based on epidemiological data and trials with cholesterol-lowering drugs, long-term use likely will lower coronary heart disease risk by between 12% to 20% in the first 5 years, and by 20% over a lifetime. The Workshop further concluded:

> *Safety testing of [plant] sterols and stanols has exceeded that of ordinary foodstuffs that are eaten widely and generally recognised as safe; and*
> *Adverse health outcomes due to observed decreases in beta carotene levels in plasma are speculative and are of no major concern.*

With respect to the potential oestrogen-disrupting effects of phytosterols in foods, studies on tall oil phytosterols previously evaluated by FSANZ under Application A417[26], found no evidence of *in vitro* or *in vivo* oestrogenic activity in rats or humans. In addition, the former EU Scientific Committee on Food (SCF) Final Report (3 October 2002) stated that newly submitted studies provided sufficient reassurance of the absence of endocrine effects via the oral route (SCF, 2002). In addition, the Stresa Workshop report references several studies, including long-term and in vitro and in vivo studies, in reaching a conclusion that plant sterols do not bind to the oestrogen receptor and that there is no evidence of oestrogenic activity of stanols.

Based on the large number of safety/efficacy studies in humans and toxicological studies in animals, FSANZ concluded that there is no evidence to suggest that adverse effects would result from longer term consumption of phytosterols, from either tall oil or vegetable oil sources. On the contrary, phytosterols were well tolerated, efficacious in the food matrices under consideration (over and above a background low-fat diet) and raised no safety concerns in adults or children. High levels of consumption (up to 10 g per day) have been shown in clinical studies to be safe, providing a safe margin of exposure when compared to the expected level of consumption of 2-3 g per day.

5.1.1.1 Conclusion

Phytosterol-enriched foods are well studied in both adults and children and in situations of varying cholesterol status and there are no indications of adverse long-term effects. They have been available in the food supply for more than 10 years without raising safety concerns. Limitations on the level of consumption are recommended primarily because increasing intake beyond 3 g per day produces little additional reduction in LDL-cholesterol.

5.1.2 Beta carotene and diabetes

The Expert Group agreed that no causative link between lower serum beta-carotene levels and type 2 diabetes has been established. On the basis of current information, the biological meaning of the observations reported by Ford *et al* (2003) was not resolved.

[25] The Stresa Workshop facilitated the combined deliberations of 32 scientific experts on the safety of sterols and stanols.
[26] Application A417 – An application assessed in 2000/2001 seeking permission to use non-esterified phytosterols from a tall oil source as a Novel Food ingredient in edible oil spreads.

The papers by Ford *et al* are analyses of the US Third National Health and Nutrition Examination Survey (NHANES). The NHANES are cross-sectional surveys conducted at regular intervals in the US and are similar to the 1995 Australian and 1997 New Zealand National Nutrition Surveys and the 1999-2000 Australian Diabetes, Obesity and Lifestyle (AusDiab) Study (Dunstan, Cameron). Serum carotenoids were measured in the Queensland participants of the AusDiab study and, like the results reported by Ford *et al*, analysis shows that those with diabetes have lower mean serum beta-carotene levels than those without diabetes (Coyne 2005).

In a cross-sectional survey, all factors are measured at the same time – i.e. diabetes presence and level of serum beta-carotene were measured in the same sample of blood – therefore it is not possible to know whether the diabetes led to the low serum beta-carotene levels or the low serum beta-carotene levels led to the diabetes. Either is theoretically possible: diabetes may increase the level of oxidants which might "use up" anti-oxidants leading to lower serum levels or alternatively, low serum beta-carotene levels may create an oxidative environment that may predispose to diabetes development. In a 10 year follow-up study, Wang *et al* found no prospective association between baseline plasma carotenoids and the risk of type 2 diabetes in middle-aged and older women (Wang *et al*, 2006).

The strongest way to examine these questions is to conduct a randomised controlled trial in which participants without diabetes are given beta-carotene or placebo and followed over time to determine whether the incidence of diabetes differs between the groups. Liu *et al* (1999) randomised 22,071 healthy US male doctors aged 40-84 years to 50 mg beta-carotene or placebo on alternate days. Over the next 12 years, the incidence of type 2 diabetes was the same in both groups (RR=0.98, 95%CI: 0.85-1.12).
Therefore it must be concluded that, in the studies of Ford and Coyne, serum beta-carotene levels act as a marker for some other factor that could be related to diabetes, but is not itself shown to be the causal agent.

Furthermore, a reduction in serum beta-carotene in the order of 20% should be put into perspective. In the Queensland AusDiab participants, mean serum beta-carotene levels ranged from 0.46 umol/L in men aged 25-43 years to 0.79 umol/L in men aged 75 years and older (i.e. young men have levels 42% lower than older men), and from 0.59 umol/L in women aged 25-34 years to 1.25 umol/L in women aged 75 years and older (i.e. young women have levels 53% lower than older women) (Coyne 2002). In other words, the age and sex-related range of mean serum beta-carotene levels across the Queensland population is much larger than the reduction seen in studies on plant sterols.

The Stresa Workshop (Katan *et al* 2003) also reports a similar conclusion with respect to other chronic diseases such as coronary heart disease and cancers. The Workshop concluded that a decrease in serum beta-carotene levels caused by plant sterols should be viewed in the context of other dietary factors that influence circulating levels. As well as dietary and seasonal factors, some lipid-lowering drugs cause decreases in serum beta-carotene levels beyond the expected decrease from the lower LDL-cholesterol levels. Several long-term trials (such as the Lipid Research Clinics Coronary Primary Prevention Trial) in which the health of subjects on certain cholesterol-lowering medication was followed for up to 10 years, found that significantly reduced beta-carotene levels were not associated with an increased incidence of coronary events or cancers.

5.1.2.1 Conclusion

A 25% reduction in serum beta-carotene levels is not considered significant in the context of fluctuations that occur naturally due to environmental factors. Furthermore, current reports of diabetes and low carotenoids do not constitute evidence that a reduction in serum beta-carotene in the order of 25% is causal with respect to disease outcomes. Rather, the available evidence indicates that a reduction of this magnitude in serum beta-carotene levels has no effect on vitamin A levels and cannot be directly associated with an adverse impact on nutritional status.

5.1.3 Possible interactions with cholesterol-lowering medications

There are several groups of drugs used to lower serum cholesterol levels, acting on different aspects of cholesterol metabolism. Sites of action, modes of action and side-effect profiles differ, however there are no reports in the literature of adverse interactions between phytosterol-enriched foods and cholesterol-lowering medications.

Two groups of drugs, the anion-exchange resins and the more recently introduced ezetimibe act, like the phytosterols, within the gut to inhibit the absorption of cholesterol. There is no evidence of hazard from combining these non-absorbed agents. Gastro-intestinal side-effects limit the use of the resins and these may possibly be increased if drugs are used in combination. The fibrate group act mainly by reducing serum triglycerides. Although there are precautionary statements about combining fibrates and statins, there are no recognised hazards from combining fibrates with drugs acting within the gut. The same would apply to phytosterols.

Statins (HMG Co-A reductase inhibitors) are overwhelmingly the most prescribed cholesterol lowering drugs. They act predominantly in the liver by blocking cholesterol synthesis. There is increasing evidence that "aggressive" cholesterol lowering treatment, such as combining optimum doses of statins with a drug working at another site, such as ezetimide, produces additional clinical benefits. There is no evidence that this combination treatment with statins increases side-effects or risks. Phytosterols and ezetimibe have similar actions, both blocking cholesterol absorption in the gut. Therefore it can be concluded that a phytosterol/statin combination is likely to be safe and effective.

Prolonged statin therapy is reported to cause increases in the levels of all plant sterols in the blood (cholesterol-adjusted), and small but significant increases in serum campesterol levels (unadjusted) (Tikkanen, 2005). However, the levels of plant sterols remain much lower than those observed in patients with sitosterolaemia (a rare metabolic disorder in which all naturally occurring plant sterols in the diet are hyperabsorbed). To put this into perspective, mean serum levels of plant sterols from consumption of phytosterol-enriched margarine represent only 5%-15% of the concentrations of plant sterols in the serum of patients with sitosterolaemia. A mechanism has been proposed to explain the increased absorption of plant sterols with concomitant statin use: a medication-induced reduction in biliary cholesterol leads to a diminished cholesterol pool in the intestine, which allows more plant sterols to become incorporated in mixed micelles, which in turn facilitates their uptake in enterocytes.

Overall, the evidence indicates an additive cholesterol-lowering effect of plant sterols combined with statin therapy.

A trial conducted on patients using statins found an additional reduction of 10% in LDL levels with incorporation of stanol ester-enriched spread into the diet (Blair *et al*, 2000). The additional efficacy is reported to be greater than the effects usually achieved by doubling the statin dose (which normally provides an extra reduction in LDL-cholesterol levels in the order of 5%-7%).

5.1.3.1 Conclusion

Plant sterols can have an additional small cholesterol-lowering effect in people who are using cholesterol-lowering medications such as the statins. There are no reports in the literature of adverse effects from the consumption of phytosterol-enriched foods. Cholesterol-lowering medications are available on prescription only, and there are no reports of adverse interactions between plant sterols and cholesterol-lowering drugs. On the contrary, for those patients who have failed to respond adequately to medication, consumption of plant sterols may be a suitable (and more cost-effective) dietary intervention for further improving their cholesterol levels.

5.1.4 Specifications for tall oil phytosterols

The initial EU application for permission of tall oils was rejected because the purity of the nominated tall oil was 95%, with the remaining 5% of the sterols unknown. A later application reduced the levels of unknown sterol compounds to less than 1%.

The Applicant has provided FSANZ with revised specifications for tall oil phytosterols, incorporating a minimum purity level of 97%, with a maximum of 3% minor sterols. The revised specifications also incorporate a reduction in the 'total heavy metals' component from a maximum of 10 ppm to 2 ppm. These amendments have been included in revised drafting in the Schedule to Standard 1.3.4 Identity and Purity, at **Attachment 1**.

5.1.4.1 Conclusion

As there are no products containing tall oil phytosterols currently on the market in Australia and New Zealand, the revised specifications will not impact on any Australian or New Zealand manufacturers. Any tall oil products that enter the food supply in the future must comply with the new specifications.

5.1.5 Elevated serum cholesterol levels should be managed medically

Many studies have shown that the optimal cholesterol lowering effect from plant sterols is achieved when consumption is between 2-3 g per day. In approving a broader range of phytosterol-enriched foods, FSANZ has confined the permission to foods with a healthy compositional profile. Foods such as low-fat milk, low-fat yoghurt and high-fibre breakfast cereal are compatible with healthy eating patterns.

People with hypercholesterolaemia would be expected to be under medical supervision, however the preferred means of lowering a mildly elevated cholesterol level is through changes to the diet. Phytosterol-enriched foods are part of a package of dietary and lifestyle advice to help people self-manage their cholesterol levels. In addition, the food vehicle choices in these Applications are broadly compatible with current public health guidelines.

Some consumers with a slightly elevated cholesterol level may already be eating a 'healthy' diet. For these people, consumption of phytosterol-enriched foods involves a conservative dietary change that can assist them with achieving individual health-related goals or dietary preferences. The results of the consumer survey (see Section 5.3) indicate that consumers who are current users of phytosterol-enriched spreads are motivated by concern about their health, particularly cholesterol levels.

In terms of prescribed medications, patient compliance has always been an issue for clinicians. The availability of a broader range of phytosterol-enriched foods could not reasonably be considered to impact directly on this issue, given that people disregard medical advice for a variety of reasons. In addition, there would be a negligible cost benefit in choosing phytosterol-enriched foods over prescribed cholesterol-lowering medication.

5.1.5.1 Conclusion

Consumption of phytosterol-enriched low-fat milk, yoghurt and breakfast cereal has been shown to give small reductions in serum cholesterol levels irrespective of the background diet. Approval of these Applications therefore provides consumers with an additional range of appropriate dietary choices, over and above low saturated fat products, for addressing concerns about cholesterol levels.

5.1.6 Consumption of phytosterol-enriched products by non-target groups

FSANZ acknowledges that regular consumption of phytosterol-enriched foods is not generally appropriate for children, and pregnant or lactating women since there may be no necessity to lower blood cholesterol levels in these groups. Notwithstanding the absence of a health benefit, the modest reduction in cholesterol that may result from an increased intake of phytosterols by non-target groups is not likely to be physiologically or nutritionally significant.

Based on the findings of the consumer research undertaken by FSANZ (Section 5.3), and similar findings in the United Kingdom from a post-market consumer survey (ACNFP, 2006), FSANZ considers that the approval of a limited range of phytosterol-enriched foods would not be expected to significantly increase the likelihood of consumption by non-target groups for a number of reasons:

(i) Phytosterol-enriched foods are specialised, niche products, marketed to a limited consumer sector (adults with cholesterol concerns);
(ii) The evidence indicates that current users of phytosterol-enriched margarines choose the product for a health (cholesterol-lowering) benefit;
(iii) Post-market surveys in Europe, where additional phytosterol-enriched products are available, found they are used in moderation by the target group of consumers;
(iv) Lifestyle and dietary advice, including the use of phytosterol-enriched foods, is already available from dietitians, General Practitioners, and public health organisations such as the NHF;
(v) The food industry also provide advice on the suitability of products to consumer groups (via product information lines, promotional material and advertising);
(vi) Mandatory labelling on packaging advises against consumption by children and pregnant or lactating women; and

(vii) FSANZ is committed to preparing additional educational material that will be available for consumers on the website and distributed to health professionals.

5.1.6.1 Conclusion

Occasional consumption of phytosterol-enriched foods by non-target groups would not be a cause for concern. Consumer education strategies combined with appropriate risk management measures and consumer-specific marketing should ensure that the public has sufficient knowledge about phytosterol-enriched products to be able to make well-informed decisions on foods that are appropriate to their health needs.

5.1.7 Reduced beta carotene levels in individuals with a low fruit and vegetable intake.

A lower beta-carotene level would be of greater nutritional concern if consumption of phytosterols affected retinol (vitamin A) levels. However, a reduction in retinol has never been reported in studies on phytosterols, even with consumption up to 10 g per day.

People who have a high fruit and vegetable intake could have low serum beta-carotene if the fruit and vegetables they choose are apples, bananas, pears, nashi pears, cucumber, potatoes, inside leaves of iceberg lettuce, eggplant, corn, blueberries, dark grapes, strawberries or parsnip. Some of these foods have quite high levels of anthocyanins and other plant nutrients that are also antioxidants. Conversely, a low fruit and vegetable diet consisting of one carrot per day could result in a moderately high beta-carotene level.

5.1.7.1 Conclusion

Fruits and vegetables in the diet contribute a complexity of vitamins and other nutrients. Public health educators continue to promote the daily consumption of minimum quantities of fruits and vegetables as part of a healthy diet. Consumption of plant sterols is generally expected to lead to a reduction in LDL-cholesterol levels in the range of 5%-15%, a reduction which the National Health and Medical Research Council (NHMRC) equates to a significant reduction in cardiovascular disease risk. In this context, a moderate reduction in serum beta-carotene is not a health concern.

5.2 Labelling and consumer information

5.2.1 Advisory versus warning statements

FSANZ's labelling risk management framework for decision-making was developed during the review of the former Australian *Food Standards Code* and is outlined below:

High risk
Where the risk to public safety is potentially life threatening and it can reasonably be assumed that the general population or the specific target group is unaware of the potential safety risk, a prescribed labelling statement is needed to alert consumers of the risk. Warning Statements are required where the risk to public health and safety is high and awareness of the potential risk is low.

Medium risk
Advisory statements are provided where the general population or a sub group of the population are largely unaware of a potential, but non life threatening risk to public health and safety and need advice about that risk.

Low risk
Where a risk to public health and safety is determined to be low because the likelihood of an adverse event occurring is rare and the consequences minor, it should be sufficient to rely on general labelling provisions and existing food law to manage the risk. An education initiative could be used to raise awareness of and promote the use of general labelling information (FSANZ, 2002).

FSANZ has assessed the potential risk to public health and safety as low with respect to the consumption of phytosterol enriched products by non-target groups, and therefore a warning statement would be inappropriate.

Labelling is only one means of providing advice to consumers, recognising that its effectiveness as a source of information varies with the consumer and the nature of the food product. Despite these variables, advisory statements on phytosterol-enriched products provide the appropriate *level* of risk management advice in relation to the low risk to public health and safety posed by these foods.

5.2.1.1 Conclusion

A warning statement on phytosterol-enriched foods would be inconsistent with the existing framework and is not justified on public health and safety grounds.

5.2.2 Revision of advisory statements

Currently, the labelling of phytosterol-enriched table spreads must include three advisory statements. A fourth statement was proposed with the approval of these Applications. However, the Second Review triggered a re-evaluation of the purpose and effectiveness of the advisory statements as risk management tools. As a result of the review, FSANZ now proposes three new mandatory advisory statements for all phytosterol-enriched foods including the table spreads.

(i) Fruit and vegetable consumption

One of the current advisory statements required on phytosterol-enriched spreads requires words to the effect that *the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables*.

The Expert Advisory Group considered the effectiveness of this statement in correcting for the small reduction in beta-carotene observed with consumption of phytosterol-enriched foods. Given that there is no specific reference to *carotenoid* rich varieties, the wording of the statement could mislead consumers on the potential benefits of any additional fruits and vegetables when consuming plant sterols. Moreover, as *carotenoid* is not in common use as a term to describe particular nutrients, additional words to this effect would be likely to lead to some degree of consumer confusion.

FSANZ also considered that adding a list of carotenoid-rich fruits and vegetables to the labelling requirements would not meaningfully assist consumers to raise blood levels of beta-carotene because of a number of variables including seasonal variations, cooking and bioavailability. In addition, while a diet low in saturated fat is regarded as a healthy alternative, phytosterols have been studied in both a normal and low-fat background diet and are similarly effective in lowering cholesterol absorption.

Given the complexity of the additional message concerning consumption of carotenoid-rich fruit and vegetables necessary with phytosterol-enriched foods, FSANZ considers that consumer education on this issue could be undertaken more effectively through other types of educational approaches. FSANZ notes that a healthy diet message encouraging the consumption of fruits and vegetables is currently part of wider public health initiatives to lower the incidence of obesity and certain diseases in the population. In addition, organisations such as the NHF produce material for use by health professionals such as General Practitioners, cardiologists, clinical dietitians and nutritionists. FSANZ can also contribute to the education process by producing a fact sheet for the website and for public distribution, and provide links to information available on other websites.

To strengthen the capability of a consumer education initiative, FSANZ and the NHF have recently agreed to collaborate on the preparation of material providing information on (i) plant sterols in general, and (ii) the potential role of phytosterol-enriched foods in the diet for the purpose of lowering LDL-cholesterol levels, for both health professionals and the general public. As well as publications, the NHF supplements its educational role with other activities that directly link the distribution of information to its target audiences.

Providing information on phytosterol-enriched foods in addition to that provided on food labels should ensure that more consumers are able to access sufficient factual information to enable informed choice in the management of their diet.

5.2.2.1 Conclusion

While it is broadly consistent with public health messages, on the basis of more recent scientific evidence, the current statement on fruits and vegetables is superfluous and potentially misleading for consumers of phytosterol-enriched foods. A revised mandatory statement to the effect that ***when consuming plant sterol enriched foods, these should be consumed as part of a varied and healthy diet*** is considered to be more appropriate in the context of general dietary advice.

(ii) Non-target consumer groups

One of the current advisory statements required on phytosterol-enriched spreads requires words to the effect that *the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision.*

The Expert Advisory Group noted that while studies in pregnant women were not available, the effects of phytosterols in children with familial hypercholesterolaemia were well studied. While consumption by children with hypercholesterolaemia was without adverse physiological effects, it was generally agreed that children do not derive a benefit to the same extent as adults from a reduction in their cholesterol levels.

For this reason, it was therefore considered appropriate to compare the use of advisory statements currently required on packaging of foods such as low-fat milk and beverages made from soy or rice for the purpose of informing consumers that these foods are unsuitable for children under the age of two years.

5.2.2.2 Conclusion

On the basis of available safety data, a revised mandatory statement to the effect that ***the product may not be suitable for children under the age of five years, and pregnant or lactating women*** is proposed for all phytosterol-enriched foods.

(iii) Efficacy of plant sterols

The Ministerial Council noted that the nature of the food vehicle appears to be a factor in the overall cholesterol-lowering effect of plant sterols. Milks are particularly effective (up to 15% reduction), while some studies show that yoghurts and breakfast cereal generally lead to reductions of 5%-8%. The Expert Group agreed that many other factors could also affect efficacy and there would be no advantage for consumers by making this information a mandatory labelling requirement for phytosterol-enriched foods.

There are insufficient data to show that different food matrices consistently produce a similar degree of efficacy. For example, the data for yoghurt vary considerably, with the literature reporting differing results (some papers show 5% reduction, while others report a 10% reduction), even when the same amounts of plant sterols are used. Other studies show phytosterols are effective in orange juice while some show no significant cholesterol-lowering effect. Phytosterols are generally more effective in a meal that contains fat. In addition, small variations in efficacy can arise due to the way in which the plant sterols are incorporated into the product (there are 5 patented processes), and even with batch-to-batch variation. This situation is not unique to phytosterol-enriched products and applies to any other nutrient or food component, where the benefits that are transferred to an individual may vary due to a combination of factors.

In general, the data do not support providing consumers with information to this level of detail for the following reasons:

- some variability between studies means that an unqualified statement could be misleading;
- this type of information is not provided for other foods (or drugs);
- there are variations between individuals due to metabolic profiles and lifestyle factors; and
- the NHF dietary advice is simply to eat a variety of (recommended) foods.

Rather than focus consumer attention on the food matrix, the Expert Advisory Group concluded that information on the minimum amount of plant sterols required to achieve a cholesterol-lowering effect would be more useful to consumers for allowing them to make informed choices. Based on a large number of published studies, the optimal cholesterol lowering benefits are achieved when consumption of plant sterols is around 2-3 g per day. Furthermore, there is no significant improvement in cholesterol reduction above approximately 3 g per day, and therefore higher levels of consumption are unnecessary.

In previous assessments, FSANZ used number of serves as a means to communicate to consumers on appropriate consumption levels. However, FSANZ acknowledges that determining the food serving sizes could be an issue for some consumers. There are no international standards for typical food portion sizes that are useful, on an allocation basis, for a strategy for phytosterol enrichment. To some extent, the Applicants are using self-appointed portion sizes which may not correlate closely with consumer behaviour.

Revised drafting is therefore proposed which provides for **a minimum of 0.8 g and a maximum of 1.0 g per quantity (average serving size) of food**. The minimum level ensures that intake of phytosterol-enriched foods (of any type) is more likely to reach the optimal amounts for a cholesterol-lowering effect. On the other hand, the maximum level should assist consumers to avoid higher intakes that provide no additional cholesterol-lowering benefits. This range is also in good compliance with the safety recommendations on the entire intake of phytosterols from multiple sources (see additional dietary exposure estimates at **Attachment 4**).

A mandatory labelling statement to the effect that ***plant sterols do not provide additional benefits when consumed in excess of 3 grams per day*** is also proposed. Expressing amounts in grams of plant sterols rather than serves of food should make individual monitoring of consumption easier on a daily basis.

5.2.2.3 Conclusion

Changes to the drafted permissions for plant sterols in low-fat milk, yoghurt and breakfast cereal should ensure that consumers have sufficient labelling information to allow them to use the products cost-effectively.

5.2.3 Labelling statements on efficacy of plant sterols

A health claim was not part of the assessment of these Applications. Nevertheless, it is pertinent to note that, as part of Proposal P293 – Nutrition, Health and Related Claims, FSANZ is proposing that specific conditions must be met before a general level health claim can be made in relation to biologically active substances (including phytosterols). Currently, these conditions are:

- only 'contains'/'source' type descriptors are permitted;
- manufacturers will be required to substantiate the daily amount of the substance that will achieve the specific health effect;
- a serve of the food must contain at least 10% of the amount that must be consumed per day to achieve the specific health effect; and
- the claim must state the amount of the substance that is required to be consumed per day to achieve the health effect, in the context of a healthy diet including a variety of foods.

This Proposal is at Draft Assessment and subject to change.

5.2.3.1 Conclusion

Current labelling statements on table spreads are not regarded as health claims.

Any future application under a standard for nutrition, health and related claims would be required to meet the defined criteria and conditions for making a claim. Any high level claim will require pre-approval from FSANZ (see section 5.4.1 below).

5.2.4 Presentation and legibility of mandatory advisory statements

The size and legibility requirements of advisory statements on packaging are not explicitly defined in the Code. FSANZ acknowledges that the legibility of labelling statements can vary with products and is therefore open to interpretation. An Editorial Note to Standard 1.2.9 Legibility Requirements which clarifies for manufacturers what is expected in terms of placement and legibility of prescribed information is not legally binding.

FSANZ has previously agreed to review Standard 1.2.9 and a new Proposal is currently at the scoping stage. The purpose of the review will be to evaluate the effectiveness of the Standard for general labelling information requirements. However, the insertion of an Editorial Note is seen as an appropriate interim measure until the review of Standard 1.2.9 is completed.

FSANZ has noted that industry is conscious of this issue and has made efforts to improve the presentation and legibility of labelling information on existing phytosterol-enriched products. For example, mandatory advisory statements are no longer being presented on a removable outer cardboard sleeve, thereby improving consumer access to the information.

5.2.4.1 Conclusion

An Editorial Note is regarded as a practical, short term measure to reinforce the principles underpinning the Standard, pending a more comprehensive review.

5.3 Consumer knowledge and behaviour

FSANZ has previously claimed that consumers have some knowledge of phytosterol-enriched foods through the market availability of two brands of table spreads since 2001. From advertising and other marketing strategies as well as information on various websites, health professionals are also aware of the products, although it is unclear to what extent their awareness is translated to consumers.

A number of key consumer issues were raised in the Second Review request. These include:

- ***Target audience:*** including the possibility that those outside the target group of consumers will be primary consumers, such as children or pregnant or lactating women;

- ***Consumption levels:*** including frequency and quantity of enriched product and the potential for consumption in excess of recommended amounts;

- ***Understanding and comprehension:*** including the interpretation of serving sizes and label information; and

- ***Dietary and lifestyle behaviours:*** including possible changes to diet and exercise, such as an increased consumption of cholesterol/saturated fats or a reduction in the level of exercise.

There is a lack of data concerning the responses of consumers to plant sterol-enriched products in Australia and New Zealand. However there are a number of international studies that show consistent results with respect to key issues of concern. FSANZ is confident that conclusions can be drawn about how Australian and New Zealand consumers are likely to react to these products. In addition to the existing literature FSANZ commissioned a survey of Australian and New Zealand consumers of plant sterol-enriched spreads.

This section provides a summary of the findings relevant to the four key issues identified above. A detailed discussion of the findings is at **Attachment 3**.

5.3.1 Target audience

5.3.1.1 Plant sterol enriched products appear to occupy a small niche market.

Plant sterol enriched products are likely to be a niche product in Australia and New Zealand appealing to a small, but highly differentiable market segment. Existing Australian market data confirm that plant sterol enriched spreads are a small proportion of the overall spread market accounting for 3.7% by volume of the total Australian spread market (data supplied by industry).

5.3.1.2 Most users of plant sterol enriched products are older adults.

There are no Australian data that provide a measure of the number of individuals who use plant sterol enriched spreads. International studies carried out in the European Union and United States confirm that plant sterol enriched spreads are used by a minority of adults, less than 5% (Anttolainen *et al.* 2001; Simojoki *et al.* 2005; 2004 Gallop Study of Cholesterol Lowering Options provided by Goodman Fielder). Those who used the products were older, with 75 to 95% of purchasers being over 45 years old (SCF 2002).

5.3.1.3 Most purchasers of plant sterol enriched products do not have children in the household.

Plant sterol enriched products are generally recommended for use by adults and the potential that children may incidentally consume these products was raised in the second review. European research found that 79%-91% of households that had purchased plant sterol enriched spreads had no children (SCF 2002).

5.3.1.4 Purchasers are motivated by concern about their health, particularly cholesterol.

The FSANZ survey found health related concerns were the primary motivation for the largest group of enriched spread users followed by convenience. Of these the majority highlighted cholesterol as the major issue. Seven percent of enriched spread users reported their primary motivation for using enriched spread as ‘someone else in my household prefers it so I use it too’.

From a large nation-wide study in Finland on the use of plant stanol enriched spread the researchers concluded:

Users of plant stanol ester margarines are a self-selected group of persons who have taken an active interest in their health. They use plant stanol ester margarines as part of a generally healthy life-style and diet. Nevertheless, they commonly have a history of cardiovascular disease or are at risk to have it. Thus plant stanol ester margarine seems to be used by persons for whom it was designed and in a way it was meant: as part of efforts for cardiovascular disease risk reduction (Simojoki et al. 2005).

5.3.2 Consumption levels

5.3.2.1 There is no evidence that consumers of plant sterol enriched products consume too much – the reverse appears to be true.

The FSANZ survey found that adults who used plant sterol enriched spreads used them differently to those who did not use sterol enriched spreads. They tended to use less spread on bread and toast. This is consistent with a health based motivation that may be linked to reduction in fat intake more generally. Based on reported levels and frequency of plant sterol enriched spread use, it is likely that a proportion of consumers will not receive enough plant sterols through their current consumption of enriched spreads on bread and toast.

These results indicate current intakes of plant sterols from enriched spreads are below the optimal intake recommended for cholesterol reduction. As this could be due to the nature of the food vehicle itself, the availability of additional plant sterol-enriched products will increase the range of choice for consumers. Several post-market monitoring reports from European countries indicate however that increased product availability is not linked to excess consumption of plant sterols. Recent data collected in the UK across the major phytosterol-enriched products provide additional evidence that products are more likely to be under-consumed (ACNFP 2006; Bradford 2006, unpublished data).

5.3.3 Understanding and comprehension

5.3.1.1 Consumers have mixed understandings of the role of these products and labelling information.

Concerns about consumers' understanding of target audience, purpose and recommended serving size have been raised. The FSANZ survey suggested that consumers were mixed in their levels of understanding and comprehension with respect to these issues. They indicate some areas of limited understanding, particularly with regards to the suitability of plant sterol enriched products for children and consumers considered they had insufficient serve size information.

5.3.4 Dietary and lifestyle behaviours

A key concern raised in the second review request is the extent to which the consumption of plant sterol enriched products will lead to changes in dietary or lifestyle behaviours that are contrary to the National Dietary Guidelines or recommended exercise regimens. The contention is that consumers of plant sterol enriched products may gain a benefit from consumption of these products and consequently be less concerned about their health and accordingly be less inclined to adopt appropriate diet and lifestyle behaviours. For example consumers may eat more saturated fats as they believe their consumption of plant sterol enriched products will counteract their indulgence.

As there was no evidence to support or refute this contention the FSANZ survey specifically sought to collect data in order to better understand the motivations and likely behaviours of people in response to plant sterol enriched foods.

5.3.4.1 Consumers do not see plant sterol enriched spreads as a 'silver bullet' that will absolve them of further responsibility for health conscious behaviour.

The FSANZ survey found no significant differences between users and non-users of plant sterol enriched spreads in the level of exercise they carried out. In terms of diet there was a demographic distinction with younger users of enriched spreads having a 'better diet' than those who didn't use enriched spreads. There was no significant differences in diet between enriched-spread users and non-users in consumers of age 35 years and older. There was a minority of enriched spread users who reported that their diet and exercise had improved since using plant sterol enriched spreads. Overall, consumption of plant sterol enriched spread was not linked to either better or worse diet and exercise measures, although a minority of consumers considered they had improved diet and exercise levels.

The diet and the exercise findings highlight that those who consume plant sterol enriched spreads do not have significantly worse diets and exercise levels than those who do not use plant sterol spreads. This evidence does not support the contention that use of plant sterol enriched spreads are associated with less healthy diet and lifestyle choices. While the evidence does not suggest that those who consume plant sterol enriched spreads make healthier diet and lifestyle choices than those who do not consume these spreads, self-assessments of enriched spread users suggest there have been some improvements in diet and exercise for some individuals.

5.4 Policy considerations

FSANZ has previously stated that there are no provisions in the FSANZ Act for deferral of the assessment of an application on the grounds that it intersects with policy issues under consideration by FRSC, or pending finalisation of a new standard. Assessment of the current Applications has therefore progressed under the existing policy for Novel Foods, which calls for a pre-market safety assessment.

5.4.1 Health claims

Approval of these Applications to add phytosterols to breakfast cereal, low-fat milk and yoghurt **does not** constitute approval for a health claim in relation to these products. Assessment of a health claim would require examining data and information on phytosterols from a different perspective. Any future requests by manufacturers for assessment of a health claim would need to be submitted under the health claims standard, which is yet to be completed.

Proposal P293 Nutrition, Health and Related Claims is currently at the Preliminary Final Assessment stage but is not expected to be finalised until 2007. Claims which reference a biomarker or serious disease will be regulated as a high level claim and will be required to undergo pre-approval by FSANZ. However, general level claims which do not reference a serious disease or condition will be generally permitted provided they can be substantiated and provided they comply with any criteria or conditions specified in the Standard.

As serum cholesterol is proposed as a biomarker for serious disease, under the proposed regime, any claim that references serum cholesterol would be regulated as a high level claim. However, a claim that references dietary cholesterol, which is not a biomarker for a serious disease, would be regulated as a general level claim.

Until the new Standard is finalised, manufacturers must comply with the current requirements in the Transitional Standard for Health Claims, Standard 1.1A.2 in the Code. This Standard sets out the following restrictions on the use of health claims in food labels or in advertising:

- The label on or attached to a package containing, or an advertisement for, food shall not contain a claim or statement that the food is a slimming food nor has intrinsic weight reducing properties.

- Any label on or attached to a package containing, or any advertisement for, food shall not include a claim for therapeutic or prophylactic action or a claim described by words of similar import.

- Any label on or attached to a package containing or an advertisement for a food shall not include the word 'health' or any word or words of similar import as a part of or in conjunction with the name of the food.

- Any label on or attached to a package containing or any advertisement for food shall not contain any word, statement, claim, express or implied, or design that directly or by implication could be interpreted as advice of a medical nature from any person.

- The label on or attached to a package containing or any advertisement for food shall not contain the name of or a reference to any disease or physiological condition.

A failure to comply with these requirements when making any voluntary statement about a food constitutes a breach of the Code.

5.4.2 Other policy issues

The Policy Guideline on the Addition to Food of Substances other than Vitamins and Minerals is currently being developed by the FRSC. The scope of the policy is yet to be agreed but the initial scope included all substances that can potentially be added to food for a technological purpose, with the exception of vitamins and minerals. Therefore, foods or food ingredients such as phytosterols that have already been considered by FSANZ as novel foods may be included. There is a clear interface of this process with a review of the Novel Foods Standard.

Nevertheless, there is currently a clear mechanism for dealing with novel food applications under Standard 1.5.1 – Novel Foods. FSANZ considers that progression of Applications A433, A434 and A508 is consistent with the existing policy for novel foods and the transitional health claims standard and should not depend on the outcome of any review process that is not yet completed.

5.5 Nutrient criteria

Given that plant sterols lower LDL-cholesterol levels, it is appropriate that they be permitted in foods that are consistent with a healthy diet. Similarly, the products should not promote consumption patterns that are inconsistent with dietary advice to reduce cholesterol.
The nutrient criteria proposed for breakfast cereal was based on an existing range of products targeted specifically to adult consumers.

The primary purpose of imposing specific nutrient criteria on the phytosterol-enriched breakfast cereals[27] was to focus on those properties of the food that are considered to have a greater impact on the target consumer group, and at the same time be less attractive to children. The fibre and maximum sugar requirements proposed were modelled on a muesli-style product containing added fruit that was considered to be more compatible with adult preferences. On the basis of evidence gathered at that time, these requirements could not be met by breakfast cereal products that are typically marketed to children.

A small survey of the available range of breakfast cereals conducted by FSANZ showed a clear demarcation between 'high sugar' breakfast cereals and those of a more moderate type when assessed on the basis of the content of *added sugar*. Those breakfast cereals that have a total sugars content above 30g/100g use added sugar only (i.e. primarily sucrose) to achieve this level. For cereals with a range between 10-30g/100g of total sugars, the main contributor to total sugars is through the addition of fruit (as found in muesli style cereals), not refined sugar. As such, breakfast cereals typically contain either 0-10g/100g or 30+ g/100g of added sugars.

Sugar content across the range of breakfast cereals

Breakfast cereal category	Total sugars content (g/100 g)	Estimated added sugar content (% total sugar content)
Low/moderate in added sugar	1.5-11	0-11
Muesli style or those with added fruit	15-30	0-10
High in added sugar	31-53	31-53

Thus, the selected criteria were not specifically intended to classify a breakfast cereal into a 'healthy' category in terms of general nutrition advice. Moreover, regulating the use of phytosterols according to dietary ideals for sugar, fat and salt intake would introduce an inappropriate level of control that could not be justified on the basis of the safety evidence and the proposed levels of use.

8. Review Options

Three options were considered in this Review:

1. re-affirm the draft variations to Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations, Standard 1.2.9 – Legibility Requirements, Standard 1.3.1 – Food Additives, Standard 1.3.4 – Identity and Purity, Standard 1.5.1 – Novel Foods, Standard 2.5.1 – Milk, and Standard 2.5.3 – Fermented Milk Products of the Code approved at Final Assessment and First Review; or

[27] Application A433 only

2. re-affirm approval of the draft variations to the Code as listed above, subject to specified amendments as a result of the Second Review; or

3. withdraw approval of the previous draft variations to the Code as listed above.

Summary of specified amendments under Option 2:

1. A minimum of 0.8 g and a maximum of 1.0 g phytosterols per serve (one serve taken to be 250 ml low-fat milk, one punnet of yoghurt up to 200 g, 45 g cereal);

2. Three mandatory advisory statements:

(i) when consuming this product, it should be consumed as part of a healthy diet;
(ii) this product may not be suitable for children under the age of five years, and pregnant or lactating women; and
(iii) plant sterols do not provide additional benefits when consumed in excess of 3 grams per day.

3. Deleted the following advisory statement: consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

4. Existing specifications for the tall oil phytosterols replaced with new specifications relating to the purity of the sterol components and reduced levels of heavy metals.

5. Additional wording in the Editorial note inserted at First Review to Standard 1.2.9 – Legibility Requirements, to read (in part):

   The requirements of this standard will not be met where prescribed information is placed other than on the outside of a package where it is readily accessible by a consumer prior to purchase, and during the life of the product, and not obscured by an outer covering.

9. Conclusion and recommendation

The Second Review concludes that the preferred review option is Option 2. This re-affirms the approval for the addition of phytosterol esters in breakfast cereal, low-fat milk and low-fat yoghurt and tall oil phytosterols in low-fat milk according to the draft variation to Standards 1.2.3, 1.2.9, 1.3.1, 1.3.4, 1.5.1, 2.5.1 and 2.5.3 of the Code, as detailed in **Attachment 1**.

ATTACHMENTS

6. Draft variations to the *Australia New Zealand Food Standards Code*.
7. Approvals of phytosterol-enriched food products in Europe.
8. Social research on use of phytosterol-enriched spreads in New Zealand and Australia.
9. Report on additional dietary exposure estimates.
10. References

ATTACHMENT 1

Draft Variations to the *Australia New Zealand Food Standards Code*

APPLICATION A433

To commence: On gazettal

[1] ***Standard 1.2.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Food regulated in Standard 2.4.2 containing phytosterol esters	Statements to the effect that – 1. the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; and 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

substituting –

Foods containing added phytosterol esters	Statements to the effect that - 1. when consuming this product, it should be consumed as part of a healthy diet; 2. this product may not be suitable for children under the age of five years and pregnant or lactating women; and 3. plant sterols do not provide additional benefits when consumed in excess of three grams per day.

[2] ***Standard 1.2.9*** *of the Australia New Zealand Food Standards Code is varied by inserting after subclause 2(1) –*

Editorial note:
The requirements of this Standard will not be met where prescribed information is placed other than on the outside of a package where it is readily accessible by a consumer prior to purchase, and during the life of the product, and not obscured by an outer covering. The requirements of this Standard will also not be met where prescribed information is printed in a small font so the statement cannot be read easily.

Within 24 months of the gazettal of this editorial note, Standard 1.2.9 Legibility Requirements will be reviewed.

[3] ***Standard 1.5.1*** *of the Australia New Zealand Food Standards Code is varied by –*

[3.1] *omitting from the* Table to clause 2 –

Phytosterol esters	The requirements in clause 2 of Standard 1.2.3. The name 'phytosterol esters' or 'plant sterol esters' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to food – (1) according to Standards 1.3.4 and 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food.

substituting –

Phytosterol esters	The requirements in clause 2 of Standard 1.2.3. The name 'phytosterol esters' or 'plant sterol esters' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to edible oil spreads – (1) according to Standard 2.4.2; and (2) where the total saturated and trans fatty acids present in the food are no more than 28% of the total fatty acid content of the food. May only be added to breakfast cereals, not including breakfast cereal bars, if – (1) the total fibre content of the breakfast cereal is no less than 3 g/50 g serve; (2) the breakfast cereal contains no more than 30g/100g of total sugars; and (3) the total phytosterol ester added is no less than 26g/kg and no more than 32g/kg. Foods to which phytosterol esters have been added may not be used as ingredients in other foods.

[3.2] *omittin*g from the Editorial note *after the* Table to clause 2 –

The Table to Clause 2 contains conditions relating to novel foods. Nothing contained in this Code permits the mixing of phytosterol esters and tall oil phytosterols. .

APPLICATION A434

To commence: On gazettal

[1] ***Standard 1.3.1*** *of the Australia New Zealand Food Standards Code is varied by inserting in* Schedule 1, *after* item 1.1.2 –

1.1.3 Liquid milk to which phytosterol esters have been added

401	Sodium alginate	2	g/kg
407	Carrageenan	2	g/kg
412	Guar gum	2	g/kg
471	Mono- and diglycerides of fatty acids	2	g/kg

[2] ***Standard 1.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting in* Column 2 *of the* Table to clause 2 *corresponding to the entry for Phytosterol esters* –

May only be added to milk in accordance with Standard 2.5.1. May only be added to yoghurt in accordance with Standard 2.5.3.

[3] ***Standard 2.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting after the* Editorial note *to clause 4* –

5 Phytosterol Esters

Phytosterol esters may only be added to milk –

(a) such that the milk contains no more than 1.5 g total fat per 100 g; and
(b) that is supplied in a package, the labelled volume of which is no more than 1 litre; and
(c) where the total phytosterol ester added is no less than 5.2 g/litre of milk and no more than 6.4g/litre of milk.

[4] ***Standard 2.5.3*** *of the Australia New Zealand Food Standards Code is varied by inserting after the* Editorial note *to clause 3* –

4 Phytosterol Esters

Phytosterol esters may only be added to yoghurt –

(a) such that the yoghurt contains no more than 1.5 g total fat per 100 g; and
(b) that is supplied in a package, the capacity of which is no more than 200 g; and
(c) where the total phytosterol ester added is no less than 1.3 g and no more than 1.6g.

APPLICATION A508

To commence: On gazettal

[1] ***Standard 1.2.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Food regulated in Standard 2.4.2 containing tall oil phytosterols	Statements to the effect that – 1. the product should be consumed in moderation as part of a diet low in saturated fats and high in fruit and vegetables; 2. the product is not recommended for infants, children and pregnant or lactating women unless under medical supervision; and 3. consumers on cholesterol-lowering medication should seek medical advice on the use of this product in conjunction with their medication.

substituting –

Foods containing added tall oil phytosterols	Statements to the effect that - 1. when consuming this product, it should be consumed as part of a healthy diet; 2. this product may not be suitable for children under 5 years and pregnant or lactating women; and 3. plant sterols do not provide additional benefits when consumed in excess of three grams per day.

[2] ***Standard 1.3.1*** *of the Australia New Zealand Food Standards Code is varied by inserting in* Schedule 1 *after* item 1.1.2 –

1.1.4 Liquid milk to which tall oil phytosterols have been added

460	Microcrystalline cellulose	5	g/kg

[3] ***Standard 1.5.1*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 2 –

Tall oil phytosterols	The requirements in clause 2 of Standard 1.2.3. The name 'tall oil phytosterols' or 'plant sterols' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to food - (1) according to Standards 1.3.4 and 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food.

substituting –

Tall oil phytosterols	The requirements in clause 2 of Standard 1.2.3. The name 'tall oil phytosterols' or 'plant sterols' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4. May only be added to edible oil spreads – (1) according to Standard 2.4.2; and (2) where the total saturated and trans fatty acids present in the food is no more than 28% of the total fatty acid content of the food. May only be added to milk in accordance with Standard 2.5.1. Foods to which tall oil phytosterols have been added may not be used as ingredients in other foods.

[4] ***Standard 2.5.1*** *of the Australia New Zealand Food Standards Code is varied by inserting after the* Editorial note *to clause 4 –*

6 Tall oil phytosterols

Tall oil phytosterols may only be added to milk –

(a) such that the milk contains no more than 1.5 g total fat per 100 g; and
(b) that is supplied in a package, the labelled volume of which is no more than 1 litre; and
(c) where the total tall oil phytosterol added is no less than 3.2 g/litre of milk and no more than 4.0 g/litre of milk.

[5] ***Standard 1.3.4*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Schedule –

Specification for tall oil phytosterols derived from tall oils

Tall oil phytosterols (non-esterified) are derived from tall oil soap, a by-product of the pulping process and then purified.

Total Phytosterol/phytostanol content (%)	min. 95
Loss on drying (water (%))	max. 5.0
Solvents (%)	max. 0.5
Residue on ignition (%)	max. 0.1
Total Heavy metals (ppm)	max. 10
Cadmium (ppm)	max. 1.0
Mercury (ppm)	max. 1.0
Arsenic (ppm)	max. 2.0
Lead (ppm)	max. 0.25
Total aerobic count (CFU/g)	max. 10,000

Combined moulds and yeasts (CFU/g)	max. 100
Coliforms	Negative to test
E. coli	Negative to test
Salmonella	Negative to test

Major Sterol profile (%) as below –

Campesterol	min. 4.0	max. 25.0
Campestanol	min. 0.0	max. 14.0
β-Sitosterol	min. 36.0	max. 79.0
β-Sitostanol	min. 6.0	max. 34

substituting –

Specification for tall oil phytosterols derived from tall oils

Tall oil phytosterols (non-esterified) are derived from tall oil soap, a by-product of the pulping process and then purified.

Total Phytosterol/phytostanol content (%)	min. 97
Loss on drying (water (%))	max. 4.0
Solvents (%)	max. 0.5
Residue on ignition (%)	max. 0.1
Total Heavy metals (ppm)	max. 2
Cadmium (ppm)	max. 0.1
Mercury (ppm)	max. 0.1
Arsenic (ppm)	max. 0.1
Lead (ppm)	max. 0.1
Total aerobic count (CFU/g)	max. 10,000
Combined moulds and yeasts (CFU/g)	max. 100
Coliforms	Negative to test
E. coli	Negative to test
Salmonella	Negative to test

Major Sterol profile (%) as below –

Campesterol	min. 4.0	max. 25.0
Campestanol	min. 0.0	max. 14.0
β-Sitosterol	min. 36.0	max. 79.0
β-Sitostanol	min. 6.0	max. 34

Minor sterols (%)	max. 3.0

ATTACHMENT 2

European Union (EU) Regulation and the marketing of phytosterol/phytostanol containing food products in the EU[28]

In the European Union (comprised of 25 countries[29]) the use of phytosterols in foods is regulated under Regulation (EC) No. 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients.

Novel foods are foods and food ingredients that have not been used for human consumption to a significant degree within the Community before 15 May 1997. Regulation EC No. 258/97 lays out detailed rules for the authorisation of novel foods and novel food ingredients[30].

Before a novel food or food ingredient can be placed on the market, it must go through an applicant specific authorisation procedure. This involves a safety assessment. Decisions about authorisation prior to marketing are made by the European Commission (EC) and experts in the 25 Member States. Additional scientific input is provided, if requested, by the European Food Safety Authority[31].

To date the EC has granted eight applicant specific approvals (see Table 1):

Table 1: EC Approvals

Commission Decision	Applicant	Approved Food Formats
2000/500/EC	Unilever	yellow fat spreads
2004/333/EC	Archer Daniels Midland Company (ADM)	yellow fat spreads, salad dressing, milk type products, fermented milk type products, soya drinks, cheese type products
2004/334/EC	Pharmaconsult Oy Ltd.	yellow fat spreads, milk type products, yoghurt type products, spicy sauces
2004/335/EC	Unilever	milk type products, yoghurt type products
2004/336/EC:	Teriaka Ltd.	yellow fat spreads, milk based fruit drinks, yoghurt type products and cheese type products
2004/845/EC	Novartis (now Forbes Medi-Tech Inc.)	milk based beverages
2006/58/EC	Pharmaconsult Oy Ltd.	rye bread
2006/59/EC	Karl Fazer Ltd.	rye bread

NOTE: Approvals have been granted for phytosterols and phytostanols that are extracted from plants (vegetable and tall oil) and may be presented as free sterols and stanols or esterified with food grade fatty acids.

[28] Author: Tiina Mutru, Regulatory Affairs Manager, Unilever, United Kingdom. Date: June 2006

[29] Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, the Netherlands, UK.

[30] Note that plant stanols are not covered by this Regulation as yellow fat spreads containing stanol esters were launched in Finland prior to 15 May 1997. The European Commission (EC) decided that neither the spread nor the ingredient was covered by Regulation EC No. 258/97.

[31] European Union scientific body charged with providing independent and objective advice on food safety issues associated with the food chain.

The approved food formats, with added phytosterols, can be marketed in any of the 25 European Union countries.

Novel foods or novel food ingredients may follow a simplified procedure, only requiring a notification from the company, when they are considered by a national food assessment body as "substantially equivalent" to existing foods or food ingredients (as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained therein). Table 2 provides a summary of all the notifications that applicant companies (includes ingredient suppliers and food manufacturers) have submitted to the EC for the marketing of phytosterol ingredients that are considered to meet the criteria set out above.

Table 2: Notifications under Article 5 of the Novel Foods Regulation (EC) No. 258/97 specific to phytosterol ingredients[32]

Notifier	Food Format	Date of Notification
Corporacion Alimentaria Peffasanta SA (Spain)	milk type and fermented milk type products	7 June 2004
Teriaka Ltd. (Finland)	milk type products, soya drinks	1 July 2004
Novandie (France)	yoghurt type products	22 July 2004
Cognis (Germany)	milk type products, yoghurt type products, yellow fats spreads	23 July 2004
Danone (France)	yoghurt	29 July 2004
Dairygold (Ireland)	yellow fat spreads	30 August 2004
Lactogal Produtos Alimentares S.A. (Portugal)	milk and yoghurt type products	30 September 2004
Teriaka Lts. (Finland)	fermented milk type products	4 October 2004
Cargill (USA)	yellow fat spreads	24 October
Danone Vitapole (France)	fermented milk type products	23 November 2004
Cognis (Germany)	yellow fat spreads, salad dressings (including mayonnaise), milk type products, spicy sauces, milk based fruit drinks	20 April 2005
Forbes Medi-Tech Inc. (Canada)	yellow fat spreads, salad dressings, fermented milk type products, soya drinks, cheese type products, yoghurt type products spicy sauces, milk based fruit drinks (for plant sterol esters)	22 April 2005
Forbes Medi-Tech Inc (Canada)	yellow fat spreads, salad dressings, fermented milk type products, soya drinks, cheese type products, yoghurt type products spicy sauces, milk based fruit drinks (for Reducol™ sterols)	22 April 2005
Juustoporti Oy (Finland)	yoghurt type products	10 May 2005
Estavayer Lait (Switzerland)	milk type and yoghurt type products	11 May 2005
Forbes Medi-Tech Inc. (Canada)	yellow fat spreads, salad dressings, fermented milk type products, soya drinks, cheese type products, yoghurt type products spicy sauces, milk based fruit drinks (for Phyto-S-Sterols™)	20 May 2005
Novandie (France)	yoghurt type products and other diary products	27 May 2005

[32] Compiled using the following sources: The European Commission (DG Sanco), the UK Food Standards Agency Advisory Committee on Novel Foods and Processes (ACNFP), and the Finnish Food Safety Authority (Evira). Date of last information 8 May, 2006.

Notifier	Food Format	Date of Notification
MIFA AG (Switzerland)	yellow fat spreads	30 May 2005
Distribuigao Alimentar SA (Portugal)	milk based beverages	17 June 2005
Robert Wiseman & Sons Ltd.	milk based beverages	27 June 2005
Kerry Foods (Ireland)	yellow fat spreads	5 July 2005
Homann Feinkost GmbH & Co (Germany)	salad dressings and mayonnaises	5 July 2005
Walter Rau Lebensmittel-werke GmbH & Co	yellow fat spreads	13 July 2005
Fayrefield Foods Ltd.	yellow fat spreads	13 July 2005
Lacteas Garcia Baquero, SA (Spain)	cheese type products	22 July 2005
Granarolo S.p.a. (Italy)	fermented mil (yoghurt) type products	5 August 2005
SkUnemejerier (Sweden)	yoghurt type products	26 August 2005
Nom AG (Austria)	milk type products	2 September 2005
Degussa Food Ingredients GmbH (Germany)	yellow fat spreads, salad dressings; fermented milk type products, soya drinks; cheese type products; yoghurt type products, spicy sauces, milk based fruit drinks,	27 September 2005
Triple Crown AB (Sweden)	yoghurt type products and milk type products	11 November 2005
Westland Kaasspecialiteiten (The Netherlands)	cheese type products	12 January 2006
Prima Pharm (The Netherlands)	yellow fat spreads	16 January 2006
Poligono Industrial Torrehierro (Spain)	yellow fat spreads, yoghurt type products, milk type products	30 January 2006
Glanbia (Ireland)	yoghurt type products	7 February 2006
Dragsbark (Denmark)	yellow fat spreads	23 March 2006
Tucano Vertriebs GmbH & Co. (Germany)	soya drinks	13 March 2006

The following plant sterol/stanol containing food products are currently being marketed in the United Kingdom:

Food Company/Retailer	Product format
Unilever (Flora pro.activ)	· spreads (different variants i.e. low fat, light, olive) · yoghurts · milk · yoghurt drinks (1-a-day)
McNeil Nutritional Ltd. (Benecol)	· spreads (different variants light, olive) · cream cheese · yoghurt (1-a-day & range concept) · yoghurt drinks (1-a-day) · orange juice
Fayrefield Foods	· cheese
Danone (Danacol)	· mini-drinks (1-a-day)

Food Company/Retailer	Product format
Tesco (own range)	· spreads · yoghurts · milk · yoghurt drinks (1-a-day)
Asda (own range)	· yoghurt drinks (1-a-day)

NOTE: Products containing phytosterols/phytostanols should be presented in either single portions containing a maximum 3g of phytosterols/phytostanols (i.e. 1-a-day concept) or three portions containing maximum 1 g (10).

References:

1. Regulation (Ec) No 258/97 Of The European Parliament And Of The Council of 27 January 1997 concerning novel foods and novel food ingredients.

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ATTACHMENT 3

Consumer aspects of plant sterol enriched foods

FSANZ used a number of international studies to understand how consumers view and use these products, including research we commissioned. The 4 key findings were

- Plant sterol enriched products occupy a niche market of highly differentiated consumers.
- Consumers are an older section of the population and use is motivated by health concerns.
- Under consumption of plant sterol enriched products in the target audience is a greater issue than over consumption.
- Consumers of these products do not view them as 'magic bullets' that will resolve them of further responsibility for healthy behaviour.

A number of key consumer issues were raised in the Second Review request. These include:

- ***Target audience:*** including the possibility that those outside the target group of consumers will be primary consumers, such as children or pregnant or lactating women;
- ***Consumption levels:*** including frequency and quantity of enriched product and the potential for consumption in excess of recommended amounts;
- ***Understanding and comprehension:*** including the interpretation of serving sizes and label information; and
- ***Dietary and lifestyle behaviours:*** including possible changes to diet and exercise, such as an increased consumption of cholesterol/saturated fats or a reduction in the level of exercise.

There is a lack of data concerning the responses of consumers to plant sterol enriched products in Australian and New Zealand. However there are a number of international studies that show consistent results with respect to key issues of concern. FSANZ is confident that some conclusions can be drawn about how Australian and New Zealand consumers are likely to react to these products.

In addition to drawing on relevant consumer research and published scientific literature FSANZ requested the applicants to provide any additional data. Some of these data were provided on a commercial in confidence basis. An important source of data on plant sterol consumption levels and demographics of consumers was a post launch monitoring study of plant sterol enriched spreads in the European Union (SCF 2002).

FSANZ commissioned a survey of adult Australian and New Zealand consumers to provide additional data. Noting that the only allowable plant sterol products currently available for purchase in Australia and New Zealand are spreads, a random sample of users of this group of products were used as a proxy for the potential users of a broadened range of plant sterol enriched products. A random sample of users of non-plant sterol enriched spreads was used as a control group to test for differences between the two groups of spread users. The survey collected data using an on-line panel of adult consumers administered by TNS Social Research. The on-line approach used to collect data is likely to deliver a sample younger than the general population.

Target Audience

Plant sterol enriched products appear to occupy a small niche market.

Plant sterol enriched products are likely to be a niche product in Australia and New Zealand appealing to a small, but highly differentiable market segment. Existing Australian market data confirms that plant sterol enriched spreads are a small proportion of the overall spread market. In the 12 months to late September 2005, enriched spreads accounted for 3.7% by volume of the total Australian spread market (data supplied by Goodman Fielder). This is higher than equivalent market shares in the European Union at 1-1.5% and the United States at approximately 0.5% (data supplied by Goodman Fielder).

Most users of plant sterol enriched products are older adults.

There are no Australian data that provide a measure of the number of individuals who use plant sterol enriched spreads. Such data would require a very large random survey of the population to achieve a satisfactory sample of users given their low prevalence[33]. However international studies carried out in the European Union confirm that plant sterol enriched spreads are used by a minority of adults. Finnish studies found 4.5% to 4.7% of adults older than 35 used enriched spreads (Anttolainen *et al.* 2001; Simojoki *et al.* 2005). The Finnish studies excluded individuals under 35 as they were very uncommon users of enriched spreads (less than 0.07% of 24-35 year olds used plant sterol enriched spreads (Anttolainen *et al.* 2001)). In the United States approximately 2% of the general population consume plant sterol enriched foods or beverages (2004 Gallop Study of Cholesterol Lowering Options provided by Goodman Fielder).

Consumer research has consistently found a range of psycho-social and demographic variables influence health-related attitudes and behaviours to food (e.g. Childs and Poryzees 1998; Worsley and Scott 2000; Cox and Anderson 2004; Ikeda 2005). Accordingly the use of plant sterol enriched products is not uniform across socio-demographic groups. International research has generally found that the proportion of enriched product users increases with increasing age. In Finnish research using 1997-1998 data sets the mean age of enriched spread users was 59 years (Anttolainen *et al.* 2001). More recent research puts the highest incidence of Finnish enriched spread use at 9% for those aged 65-74. At the next decadal cohort older (75-84), and younger (55-64), 6% of each used enriched spreads (Simojoki *et al.* 2005). In Europe between 75 and 95% of purchasers were over 45 years of age (SCF 2002).

[33] At 3.7% market share a sample of at least 8,000 consumers would be required to deliver a sample of at least 300 enriched spread users.

The FSANZ survey found 50% of users were over 35 years. There was no significant difference in the age of users of enriched spreads and those who do not use enriched spreads. The age of users in this survey however may be an underestimate as the on-line methodology would be likely to generate a positive bias for younger respondents. The Finnish studies were carried out using mail-out methods and the data from the EU were collected using in-household techniques which are likely to reduce any age bias due to methodology.

Most purchasers of plant sterol enriched products do not have children in the household.

Plant sterol enriched products are primarily targeted to adults. The potential that children may incidentally consume these products was raised in the second review request. European research found that 79%-91% of households that had purchased plant sterol enriched spreads had no children (SCF 2002).

Purchasers are motivated by concern about their health, particularly cholesterol.

Health concerns are one category of motive that may influence food choice decisions, others include cost, convenience, familiarity and sensory appeal (Steptoe et al. 1995). In the FSANZ survey, plant sterol enriched spread users were asked what their primary motivations are for purchasing an enriched spread. Health related concerns were the primary motivation for the largest group of enriched spread users followed by convenience (Table 1). This is an expected finding with the majority of individuals motivated by health related issues with cholesterol being the major issue. Seven percent of enriched spread users reported their primary motivation for using enriched spread as 'someone else in my household prefers it so I use it too'.

Table 1: Motivations for using an enriched spread

Motivation	Proportion of enriched spread users
Health-related (total)	***68***
To lower cholesterol levels	30
To prevent me getting high cholesterol problems	20
To improve my health	13
Doctor/Health professional advised me to use it	5
Convenience (total)	***12***
Someone else in my household prefers it so I use it too	7
Pack size	4
It's the brand that's available at my local shop	1
Sensory appeal (total)	***9***
Flavour/taste	5
I like the texture/it spreads easily	4
Familiarity and Naturalness (total)	***9***
It contains natural ingredients	5
It's my usual brand	3
It contains the ingredients I prefer	1
Others (total)	***2***

Consumption levels

There is no evidence that consumers of plant sterol enriched products consume too much – the reverse appears to be true.

The FSANZ survey found that adults who used plant sterol enriched spreads used them differently to those who did not use sterol enriched spreads. While nearly all consumers of both plant sterol enriched and non-enriched spreads used them for spreading on bread and toast (98% and 97% respectively), the consumers of enriched spreads were less likely to use the spread in cooking and baking than the consumers of non-enriched spread (53% and 78% respectively). Similar proportions of each group used their spread at least daily (Table 2). Those who used enriched spreads were more likely to use less on their bread and toast than those who did not use enriched spreads. The majority of enriched spread users (73%) used less than 2 teaspoons on average for spreading on bread and toast, while the majority (87%) of other spread users used more than 2 teaspoons (Table 3). Such a finding is consistent with a health based motivation that may be linked to reduction in fat intake more generally.

Table 2: Frequency of spread use on bread and toast

Frequency of use	Enriched spread users (%)	Other spread users (%)
More than once a day	44	53
Around once a day	35	19
Around 2-3 times a week	17	26
Less than 2 times a week	4	2

Table 3: Quantity of spread used on bread and toast

Quantity of spread used	Enriched spread users (%)	Other spread users (%)
Less than 1 teaspoon	32	5
1 to less than 2 teaspoons	41	7
2-6 teaspoons	25	45
More than 6 teaspoons	3	42

Based on reported levels and frequency of plant sterol enriched spread use, it is likely that a proportion of consumers will not receive enough plant sterol through their current consumption of enriched spreads on bread and toast.

Data collected from the European Union covering the breadth of plant sterol enriched products available (including spreads, milks, yoghurts and drinking yoghurts) found the median intake of plant sterols/stanols ranged from 0.11 gram/day in Spain to a high of 0.45 gram/day in the Netherlands. At the 95th percentile the intake ranged from 0.67 gram/day in Spain to a high of 2.9 gram/day in the Netherlands (Bradford 2006, unpublished data). The United Kingdom, arguably the EU country most similar to Australia and New Zealand, had a median intake of 0.31 gram/day and 95th percentile intake of 2.36 gram/day.

The evidence indicates that current intakes of plant sterols only from enriched spreads are below the optimal intake recommended for cholesterol reduction. As this could be due to the nature of the food vehicle, the availability of additional plant sterol-enriched products will increase the range of choice for consumers. Post-market monitoring in other countries, where additional enriched products have been available for some time, suggests however that increased product availability is not linked to excess consumption of plant sterols.

Recent data collected in the UK across the major phytosterol-enriched products provide additional evidence that products are more likely to be under-consumed (ACNFP 2006; Bradford 2006, unpublished report).

Understanding and comprehension

Consumers have mixed understandings of the role of these products and labelling information.

Concerns about consumers' understanding of target audience, purpose and recommended serving size were raised in the second review request from the Ministerial Council. The FSANZ survey suggested that consumers were mixed in their levels of understanding and comprehension with respect to these issues. Forty-eight percent of enriched spread consumers were aware of the terms 'plant sterol' or 'phytosterol'. Fifty-eight percent perceived the main benefit of plant sterols to reduce cholesterol level and 25% were not sure of the main benefit. There were some age differences in the perceived benefits of plant sterols, with fewer younger people (less than 35 years old) identifying cholesterol reduction as the main benefit and more of them responding that they were unsure.

Table 4 indicates the main sources of information about plant sterols for users of enriched spreads. Articles and advertising were the most common sources of information, though doctors and other health professionals, supermarket and peer networks are also important sources of information. Data from the US indicate that health professionals were a more important source of information than advertising and print media for adults (2004 Gallop Study of Cholesterol Lowering Options provided by Goodman Fielder).

Table 4: Sources of information about plant sterols

Main sources of information	Proportion of enriched spread users (%)
Articles in newspapers, mags., TV	62
Advertising	58
Doctor/health professional	42
Supermarket	36
Family/friend recommended product	30
Manufacturers website	12

In addition to these sources of information, consumers also gain information from the packaging and labels. The survey tested enriched spread users' knowledge of the products with respect to plant sterols in a broader dietary context, serve sizes and target audience (Table 5). The findings indicate some areas of limited understanding, particularly with regards to the suitability of plant sterol enriched products for children. There was some awareness of appropriate serve size with the majority of consumers aware that extra serves would not deliver extra benefits, though recognising that eating extra serves was not harmful. Nonetheless, only 36% considered they had sufficient serve size information.

Plant sterol enriched margarines were not perceived as a 'magic bullet' with 89% of consumers recognising they still need to be concerned about other fats in their diet despite the use of plant sterol enriched spreads.

Table 5: Knowledge about plant sterol enriched products

Statement	Desirable response	Proportion
Diet-related statements		
If I use plant sterol margarines, I don't have to worry about the other fats in my diet	False	89%
If I currently have health problems, I should check with my doctor before using this product	True	56%
I should eat extra fruit and vegetables if I eat plant sterol margarine	True	38%
Serve size statements		
The more of this product I eat, the better it is for me	False	66%
Extra serves might be bad for my health	False	53%
I have enough information to decide how much plant sterol margarine I should consume each day	True	36%
Target audience statements		
Everybody can eat plant sterol margarine	False	38%
Plant sterol margarines are not suitable for children	True	26%

Dietary and lifestyle behaviours

A key concern raised in the second review request is the extent to which the consumption of plant sterol enriched products will lead to changes in dietary or lifestyle behaviours that are contrary to the National Dietary Guidelines or recommended exercise regimens. The contention is that consumers of plant sterol enriched products may gain a benefit from consumption of these products and consequently be less concerned about their health and accordingly be less inclined to adopt appropriate diet and lifestyle behaviours. For example consumers may eat more saturated fats as they believe their consumption of plant sterol enriched products will counteract their indulgence. As there was no evidence to support or refute this contention the FSANZ survey specifically sought to collect data in order to better understand the motivations and likely behaviours of people in response to plant sterol enriched foods.

Consumers do not see plant sterol enriched spreads as a 'silver bullet' that will absolve them of further responsibility for healthy behaviour.

An experimental study designed to identify the existence or not of causal links was outside the scope of the FSANZ survey, rather a quasi-experimental design was used in order to identify associations between enriched spread use or not on the one hand and diet and exercise behaviours on the other (Table 6). The test group was those who used plant sterol enriched spreads and the control group was those who did not use plant sterol enriched spreads. Two types of measures were used: 1) objective self-reported measures of diet and exercise derived from the Australian National Health Survey (ABS 2006); and 2) subjective self-reported measures of perceived impacts of plant sterol margarine consumption on diet and exercise.

If there was an association between plant sterol enriched spread use and diet or exercise then there would be a significant difference in the responses of the test and control groups for each of these measures. Additionally, if users are aware of any diet or exercise changes that *they* attribute to use of enriched spread this will be picked up in the subjective measures.

Table 6: Survey design to test for impact on diet and exercise behaviour

Measures	Test group	Control group
Objective measure of diet	✓	✓
Subjective measure of impact on diet	✓	×
Objective measure of exercise	✓	✓
Subjective measure of impact on exercise	✓	×

Consumers of plant sterol enriched spreads do not exercise less or eat worse than non-consumers.

In summary the survey found no significant differences between the test and control groups in the level of exercise they carried out. In terms of diet there was a demographic distinction with younger users of enriched spreads having a better diet than those who didn't use enriched spreads. There was no significant differences in diet between test and control groups of those 35 years and older. There were a minority of enriched spread users who reported that their diet and exercise had improved since using plant sterol enriched spreads. Consumption of plant sterol enriched spread was not linked to either better or worse diet and exercise measures, though a minority of consumers considered they had improved diet and exercise levels.

Diet was measured through the usual daily intake of fruit and vegetables. Individuals who had consumed 2 or more serves of fruit and 4 or more serves of vegetable a day were considered to have met their dietary intake of fruit and vegetables. A minority of both consumers and non-consumers of plant sterol enriched spreads surveyed satisfied this requirement. There were no significant differences in the proportion who satisfied this requirement between enriched and other spread users who were over 35 years of age. There was a slight age difference with younger (less than 35) enriched spread users being more likely to meet the fruit and vegetable requirements than younger people who did not use enriched spreads.

In terms of subjective impact on diet 55% reported their diet had stayed about the same since using enriched spreads and 43% reported it had improved (Table 6). Additionally 89% of respondents who used plant sterol enriched margarines noted considered the statement *If I use plant sterol margarines, I don't have to worry about the other fats in my diet* to be false. The consumption of plant sterol enriched spread may, at worst, be associated with no poorer diet than non-consumption of enriched spreads, and at best, be associated with a better diet for those under 35 years.

Exercise was measured adopting the approach of the National Health Survey (ABS 2006) which categorises individual's level of exercise into one of four 1 of 4 exercise level categories (sedentary, low, moderate, high) based on exercise time and intensity. Approximately 50% of respondents had low levels of exercise. There were no significant differences between plant sterol enriched spread users and other spread users in the level of exercise performed.

In terms of subjective impact on exercise levels, 71% reported their level of exercise had stayed about the same since using enriched spreads and 26% reported it had increased (Table 7). The consumption of plant sterol enriched spread may, at worst, be associated with no lesser levels of exercise than non-consumption of enriched spreads.

Table 7: Changes in diet and exercise levels since using plant sterol enriched spreads

Exercise/diet changes since using enriched spread	Exercise (%)	Diet (%)
Exercise increased a lot / Diet much healthier	8	11
Exercise increased a little / Diet somewhat healthier	18	32
Stayed about the same	71	55
Exercise decreased a little / Diet somewhat less healthy	1	1
Exercise decreased a lot / Diet much less healthy	2	0

The diet and the exercise findings highlight that those who consume plant sterol enriched spreads do not have significantly worse diets and exercise levels than those who do not use plant sterol spreads. This evidence does not support the contention that use of plant sterol enriched spreads are associated with less healthy diet and lifestyle choices. While the evidence does not suggest that those who consume plant sterol enriched spreads make healthier diet and lifestyle choices than those who do not consume these spreads, self-assessments of enriched spread users suggest there have been some improvements in diet and exercise for some individuals.

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ATTACHMENT 4

Phytosterols Dietary Exposure Assessment Report for the Second Review

Previous phytosterol exposure estimates

For applications A433, A434 and A508, estimates of dietary exposure were conducted assuming the concentration of free phytosterols was 0.8 g/serve (except for reduced and low fat milk in A508 which was assumed to contain 0.9 g/serve). Estimated exposures to free phytosterols from these three applications (and a combination of A433 and A434 which were assessed concurrently) were up to between 1.7 g/d and 1.9 g/d for mean consumers of free phytosterols and up to between 4.4 g/d and 4.8 g/day for 95th percentile consumers of free phytosterols across all of the population groups assessed.

Table 1 shows a summary of the dietary exposure assessments and results for A433, A434, A433 + A434 and A508.

Table 1: Summary of dietary exposure assessments previously reported at Final Assessment

	Application			
	A433 **Phytosterol esters in breakfast cereals**	**A434** **Phytosterol esters in low fat milk and yoghurt**	**A433 + A434**	**A508** **Tall oil Phytosterols in low fat milk**
Concentrations used*	0.8g/serve table spreads 0.8g/serve breakfast cereals	0.8g/serve table spreads 0.8g/serve reduced fat milk 0.8g/serve reduced fat yoghurt	0.8g/serve table spreads 0.8g/serve breakfast cereals 0.8g/serve reduced fat milk 0.8g/serve reduced fat yoghurt	0.8g/serve table spreads 0.9g/serve reduced fat milk
Population groups assessed	Australia: 2 years+, 40-64 years, 65 years+, 2-12 years, females 16-44 years New Zealand: 15 years+, 40-64 years, 65 years+, females 16-44 years			
Mean exposure*#	≤ 1.7 g/d	≤1.9 g/d	≤ 1.9 g/d	≤ 1.9g/day
95th percentile exposure*#	≤ 4.4 g/d	≤ 4.7 g/d	≤ 4.7 g/d	≤ 4.8g/day

* As free phytosterols.
# Less than or equal to the value presented across all of the population groups assessed.

Additional assessment

An additional assessment has been conducted by FSANZ to determine the estimated exposure to phytosterols should the concentration in the foods assessed previously in other applications be equal to 1.0 g/serve as free phytosterols. All food groups, population groups, food consumption data, serve sizes and methodologies remained the same as in previous assessments. This additional assessment was not conducted for A433 and A434 combined, however, it can be seen from Table 1 that estimated exposures for this scenario were similar to when the applications were assessed separately.

As expected, assuming foods contain 1.0 g free phytosterols per serve, the estimated exposures were slightly higher compared to previous estimates using a lower concentration. Estimated exposures were up to between 2.1 g/day and 2.4 g/day for mean consumers of free phytosterols and up to between 5.5 g/day and 5.9 g/day for 95th percentile consumers for free phytosterols across all of the population groups assessed. A summary of these results are shown in Table 2.

The target group of 40-64 years had the highest levels of exposure. Children aged 2-12 years (Australia only) and females of child bearing age (16-44 years) had lower exposures than the target group. (See Table 3 for further details on exposure for each population sub-group assessed).

Table 2: Summary of estimated dietary exposure to free phytosterols assuming a concentration of 1.0 gram of free phytosterols per serve

	Estimated dietary exposure for consumers of phytosterols*# (grams/day)	
Application	**Mean**	**95th percentile**
A433	≤ 2.1	≤ 5.5
A434	≤ 2.4	≤ 5.9
A508	≤ 2.3	≤ 5.8

* As free phytosterols.
# Less than or equal to the value presented across all of the population groups assessed.

Table 3: Estimated dietary exposure to free phytosterols assuming a concentration of 1.0 gram of free phytosterols per serve for various population groups assessed

			Estimated exposure (g/day)*	
Application	**Country**	**Population group**	**Mean**	**95th percentile**
A433	Australia	2 years+	1.8	5.0
		40-64 years	1.9	5.1
		65 years+	1.9	5.0
		2-12 years	1.4	3.5
		Females 16-44 years	1.6	4.1
	New Zealand	15 years+	2.0	5.4
		40-64 years	2.1	5.5
		65 years+	2.0	4.8
		Females 16-44 years	1.7	4.3

Application	Country	Population group	Estimated exposure (g/day)*	
			Mean	95th percentile
A434	Australia	2 years+	2.0	5.3
		40-64 years	2.1	5.4
		65 years+	2.2	5.4
		2-12 years	1.6	4.3
		Females 16-44 years	1.8	4.4
	New Zealand	15 years+	2.2	5.7
		40-64 years	2.4	5.9
		65 years+	2.3	5.3
		Females 16-44 years	1.9	4.6
A508	Australia	2 years+	2.0	5.2
		40-64 years	2.1	5.3
		65 years+	2.1	5.3
		2-12 years	1.5	4.2
		Females 16-44 years	1.7	4.3
	New Zealand	15 years+	2.2	5.6
		40-64 years	2.3	5.8
		65 years+	2.2	5.2
		Females 16-44 years	1.8	4.6

* As free phytosterols.

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