PHYTOSTEROL-ESTERS:

USE IN A RANGE OF FOOD PRODUCTS

VOLUME 1 OF 3

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Date: July 2002
Document reference: D02-018

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SUMMARY

Under Regulation (EC) No 258/97 on Novel Foods and Food Ingredients, Unilever received approval for the use of phytosterol-esters as a novel food ingredient in Yellow Fat Spreads in European Commission Decision 2000/500/EC of 24 July 2000 (EC, 2000). Under Article 3 of this decision, Unilever was required to establish a surveillance programme to accompany the marketing of the product. The results of this surveillance programme, referred to as Post Launch Monitoring, showed that the intakes of the spread was lower than that assumed in the Novel Foods submission with no evidence of adverse health effects.

This indicates that there is an opportunity to offer consumers alternative or additional healthy foods to deliver optimal cholesterol-lowering benefits without increasing the intake of phytosterols above the level already approved. This application seeks approval for the use of phytosterol-esters to be included as a cholesterol-lowering ingredient in 'milk' and 'yoghurt' type products. This is in addition to the approved use in Yellow Fat Spreads.

The phytosterol-esters to be used in the 'milk' and 'yoghurt ' type products are identical to those currently used in Yellow Fat Spreads. The 'milk' and 'yoghurt' type products containing phytosterol-esters have been tested for their microbiological and chemical stability over time, including the impact of pasteurisation, and these have been found to be similar to standard products.

The phytosterol-esters will be added to the product such that a 250ml serving of the 'milk' type product will provide 1g of free phytosterols. The 'yoghurt' type product will be produced in individual serving pots with phytosterol-esters added such that each individual pot provides 1g free phytosterols. The recommended intake will be 2-3g free phytosterols/day.

The cholesterol-lowering effect of phytosterol-esters has been demonstrated in various food types including 'milk' and 'yoghurt' type products. The effect is comparable to that seen with Yellow Fat Spreads.

The range of products will be labelled with clear instructions on how to eat an appropriate amount of the spreads, 'milk' or 'yoghurt' type products to obtain an average of 2-3g of free phytosterols per day to optimise cholesterol-lowering benefits. Consumers will also be informed that consuming higher amounts will not provide any significant additional cholesterol-lowering benefit. Labelling will continue

to include the information from the original approval indicating target consumers, lack of suitability for children, pregnant and lactating women and advice to those receiving cholesterol-lowering medication. This will be adapted, if necessary, in line with the Scientific Committee on Foods current deliberations on multiple intakes of phytosterol products.

If consumers use the product as recommended on the labelling then it is anticipated that the intake will be 2-3g of free phytosterols per day. This level of intake does not exceed that originally expected from the use of Yellow Fat Spreads containing 8% phytosterol-esters approved by the EC.

There is no evidence to suggest that consumers will not follow the labelling advice regarding recommended intakes, particularly as this states that there is no additional cholesterol-lowering benefit from eating more than the recommended 2-3g free phytosterols/day. However, should consumers not follow the labelling advice then the potential daily intake of phytosterols has been modelled based on the consumption patterns of unfortified products. This has been done using both intake data from dietary surveys and consumer purchase data. This shows that even if consumers do replace all spread, 'milk' and 'yoghurt' type product intake with phytosterol-ester products the potential daily intake of phytosterol-esters is still within the range of intakes considered in the original risk assessment and does not raise any toxicological concerns.

However, it is highly unlikely that consumers will replace all intakes of spread, 'milk' and 'yoghurt' type products by the equivalent phytosterol-ester products in this way. Post Launch Monitoring data and studies of consumer purchase data of phytostanol-ester products in Finland and the UK indicates that intakes of cholesterol-lowering foods are lower than those of the unfortified counterparts. This is confirmed by UK consumer purchase data that indicates that consumers who buy phytosterol/stanol-ester products also buy unfortified products.

In conclusion, this application demonstrates that extension of the range of phytosterol-ester products available in the EU to include 'milk' and 'yoghurt' type products in addition to Yellow Fat Spreads will not lead to over-consumption of phytosterols resulting in adverse public health effects.

1. INTRODUCTION

Under Regulation (EC) No 258/97 on Novel Foods and Food Ingredients, Unilever submitted an application seeking approval for the use of phytosterol-esters as a novel food ingredient in Yellow Fat Spreads. A list of the original submission documents is given in Appendix 1 and where appropriate referenced throughout this document. This application was approved in European Commission Decision 2000/500/EC of 24 July 2000. Under Article 3 of this decision, Unilever was required to establish a surveillance programme to accompany the marketing of the product. A document (D01/019) reporting the findings of this Post Launch Monitoring was submitted to the European Commission (EC) in January 2002.

This report concluded that Yellow Fat Spreads containing phytosterol-esters were being bought by the target population, intakes were <20g/day and there was no evidence of adverse health effects, expected or unexpected. At <20g spread/day intakes were lower than the assumptions made in the original Novel Foods application.

Based on the findings of this report, Unilever would like to extend the range of product types into which phytosterol-esters may be added. By offering consumers alternative or additional healthy foods, that are usually consumed on a daily basis, optimal cholesterol-lowering benefits can be achieved. With appropriate labelling, the intake of phytosterol-esters will not exceed that previously approved by the EC.

This application seeks approval for the use of phytosterol-esters to be included as a cholesterol-lowering ingredient in ‘milk’ and ‘yoghurt’ type products. This is in addition to the approved use in Yellow Fat Spreads, also referred to as spread(s) in this document.

The ‘milk’ type products would include skimmed, semi-skimmed and vegetable oil based milk variants. The ‘yoghurt’ type products would include a range of natural and fruit flavoured yoghurts. It is understood that, under EU Milk legislation (EC Directive 95/2) and the varying national legislation across member states on Yoghurt, the addition of phytosterol-esters, and other ingredients required to stabilise the products, will prevent the use of the term ‘milk’ and ‘yoghurt’, to describe these Novel Foods. Therefore, to ensure clarity in this document, phytosterol-esters are considered to be the Novel Food Ingredient and the ‘milk’ and ‘yoghurt’ type products with added phytosterols-esters the Novel Foods.

This document provides evidence to confirm the safety of phytosterol-esters in these products.

2. SPECIFICATION OF THE NOVEL INGREDIENT

The novel ingredient is phytosterol-esters and is identical to the ingredient used in Unilever's Yellow Fat Spreads that were previously approved under Regulation (EC) No 258/97 on Novel Foods and Food Ingredients. A full description of the ingredient and the specification was provided in the original EU Novel Foods submission in Unilever Documents D97/042 and D98/002.

3. PRODUCTION METHODS

3.1 *Production methods for the phytosterol-esters*

The production methods used to produce the phytosterol-esters are identical to those used to produce the phytosterol-esters used in Unilever's Yellow Fat Spreads. A full description of these methods was provided in the original submission in Unilever Documents D97/042 and D98/002.

3.2 *Description of the Novel Foods*

The Novel Foods are standard 'milk' and 'yoghurt' type products with added phytosterol-esters. The application covers the addition of phytosterol-esters, and agents used to stabilise them in:

- skimmed, semi-skimmed and vegetable oil based milk;
- low fat yoghurts made with live bacteria, available in a range of natural and fruit flavours (containing fruit pieces).

The 'milk' type product will be sold in standard 1 Litre milk cartons containing 6.4g phytosterol-esters per carton (1g free phytosterols per 250mL serving).

The 'yoghurt' type product will be sold in individual 150g pots or multipack of 4x125g pots. Each yoghurt pot, regardless of size, will contain 1.6g phytosterol-ester (1g free phytosterols).

The recommended intake will be 2-3 servings per day from the range of foods containing phytosterol-esters. This will be equivalent to a daily intake of 2-3 g free phytosterols.

Table 1*. *Example Ingredient Lists For A 'Milk' And 'Yoghurt' Type Product

Example Product	***Ingredient List***
Semi-Skimmed Milk with Phytosterol-esters	semi-skimmed milk (99%), plant sterol esters (0.7%), stabiliser : carageenan, emulsifier : E471
Low Fat Cherry Yoghurt with Phytosterol-esters	low fat yoghurt (76%), sugar, cherries (8%), plant sterol esters (1.1%), stabilisers (modified starch, pectin, xanthan gum), natural flavourings, acidity regulator (trisodium citrate), emulsifier (E471), bifidobacterium

The projected future pro.activ product range is illustrated in the diagram below.

3.3 *Process for producing milk products containing phytosterol-esters*

Milk products containing phytosterol-esters are made using the same process and procedures as conventional fortified milks/milk drinks and no additional controls are considered necessary. Storage and distribution temperatures used are the same as conventional milks, fortified milk and milk drinks and the same Hazard Analysis and Critical Control Point (HACCP) schemes are used to control product safety and quality. The only additional process required is to control the amount and quality of phytosterol-esters added.

3.4 *Processing for producing yoghurt products containing phytosterol-esters*

Yoghurt products containing phytosterol-esters are made using the same process and procedures as conventional yoghurts and no additional controls are considered necessary. Storage and distribution temperatures used are the same as conventional yoghurts and the same Hazard Analysis and Critical Control Point (HACCP) schemes are used to control product safety and quality. The only additional process required is to control the amount and quality of phytosterol-esters added.

4. ANTICIPATED INTAKE/EXTENT OF USE OF THE NOVEL FOOD INGREDIENT

4.1 *Current intake of phytosterol-esters from cholesterol-lowering spreads*

In Unilever's original application for the use of phytosterol-esters in Yellow Fat Spreads a number of assumptions were made about use. These were:

- Typical daily intake of the product would be 20-30g
- Upper 95th percentile intake levels would be around 57g in the UK and 70g in the Netherlands
- Consumers would be mainly over 45 years old and concerned about their cholesterol level

The typical daily intake and upper intake levels were based on published information on the consumption of Yellow Fat Spreads in the UK and the Netherlands and were consistent with product marketing information from Unilever commissioned trials. The assumption about the consumer profile was based on our own market research and the sales performance of Raisio's Benecol (Yellow Fat Spread containing phytostanol-esters) in Finland.

As part of Unilever's Post Launch Monitoring scheme the estimated daily intake of phytosterol-esters (as free phytosterols) from its cholesterol-lowering spreads (Flora/Becel/Fruit d'or pro.activ) was obtained using independent market research (consumer purchase) data. This showed that the amount of spread purchased per household across the five main markets in Europe varied between 15 and 18g/day for regular users of the product (intakes were higher for regular users than for occasional/once only users). Upper (95th percentile) intakes varied between 27 and 45g/day. In general, intakes per household were similar irrespective of the number of people in the household indicating that usage was predominately by one person in each household. Phytosterols are added to the spread at a level of 8% (as free phytosterols) as approved by the EC. Therefore, at these levels of spread use individual intake of phytosterols is estimated to be 1.2-1.4g/day with 95th percentile intakes of 2.2-3.6g/day. As can be seen from *Table 2* (below) all intakes are lower, in particular the 95th percentiles than the pre-market assumptions.

Table 2. A summary of the daily phytosterol intakes for regular users from the Post Launch Monitoring report

	Pre-market assumptions		***Post Launch Monitoring***	
	Daily spread intake	*Daily free phytosterol intake (g/day)*	*Daily spread intake (g/day)*	*Daily free phytosterol intake (g/day)*
Average intake	20-30g	1.6-2.4g	15-18g	1.2-1.4g
95th percentile intake	57g (UK) 70g (NL)	4.6g (UK) 5.6g (NL)	27-45g	2.2-3.6g

Furthermore the Post Launch Monitoring also confirmed that pro.activ is being bought predominately by the target consumers, i.e. those over 45 years old.

Extension of the product range will provide an opportunity for consumers to optimise the cholesterol-lowering benefit of phytosterol-esters by providing additional or alternative products. It will also provide consumers who do not eat spreads the cholesterol-lowering benefit of phytosterol-esters in food products. Evidence from consumer carelines confirms that consumers would like additional or alternative products to spreads. To maximise the benefit of any additional products these should also be foods that are used on a regular basis as part of a healthy diet. 'Milk' and 'yoghurt' type products are considered suitable alternative products and are consistent with consumer's requests.

4.2 *Phytosterol and Phytostanol Foods on the EU market*

Since Novel Foods Approval in 2000, Unilever has launched Yellow Fat Spreads containing phytosterol-esters in 12 EU countries (Netherlands, Austria, Belgium, Finland, France, Germany, Greece, Ireland, Portugal, Spain, Sweden and the UK).

In addition to this, foods containing phytostanol esters, the hydrogenated forms of phytosterols, which are not covered by EC258/97, are available in many EU countries. Examples of these currently on the market in the EU include:

- Yellow Fats Spreads (fat contents from 32 and 63%)
- Yoghurts (Natural, Vanilla, Toffee and fruit flavours including strawberry, raspberry, apricot and black cherry)
- Semi-Skimmed Milk
- Chicken Balls
- Chicken Gratin (Chicken dish with potatoes and cream)

- Sausages
- Salads (Potato and Beetroot, mayonnaise based)
- Cereal Bars (Chocolate Chip, Raisin Nut and Apricot)
- Soft Cream Cheeses (Natural and Garlic & Herbs)

Examples of the range of phytosterol/phytostanol products available in the EU are presented in *Appendix 2*.

4.3 *Potential market for the Novel Food(s)*

The Post Launch Monitoring on Yellow Fat Spreads has confirmed the pre-market assumptions about the type of consumer that will purchase cholesterol-lowering products. The pro.activ Yellow Fat Spread has a low market share (0.1-2.5%) across most EU Yellow Fat Spread markets. The planned range extensions of 'milk' and 'yoghurt' type products, like the spread, will be targeted at the 'cholesterol concerned' and, due to the cost of phytosterols, will carry premium prices significantly above standard '(unfortified)' variants. The pro.activ 'milk' and 'yoghurt' type products are expected to be purchased by a similar target population to the spread with market shares estimated at less than 1.0% in each category. This assumption is supported by marketing information, showing a low market share for comparable phytostanol-ester products in EU countries where these are available.

4.4 *Product Labelling*

At present, pro.activ spreads are labelled in accordance with the Scientific Committee on Foods decision (SCF, 2000) and European Commission Decision 2000/500/EC of 24 July 2000. Although the translations vary slightly, in general the pack label states:

- Pro.activ may not be nutritionally appropriate for people with special dietary needs (pregnant and breast feeding women, and children under five);
- If taking cholesterol-lowering medication seek your doctor's advice.

The labelling of the pro.activ range of spreads, 'milk' and 'yoghurt' type products will continue to include the information from the original approval indicating target group, lack of suitability for children, pregnant and lactating women and advice to those receiving cholesterol-lowering medication. In addition, all products will be labelled to reflect consumer use of a range of cholesterol-lowering foods containing phytosterol-esters.

The labelling will provide clear instructions on how to eat an appropriate amount of the spreads, 'milk' or 'yoghurt' type products to obtain on average 2-3g of free phytosterols per day to optimise cholesterol-lowering benefits. Consumers will also

be informed that consuming higher amounts will not provide any significant additional cholesterol-lowering benefit.

For example:
The yoghurt pot will be labelled:

> *Recommended: 2-3 servings of pro.activ foods daily for optimum cholesterol reduction. This 125/150g pot is one serving*
> *Extra servings will not provide additional cholesterol-lowering benefit.*

The milk carton will be labelled:

> *Recommended: 2-3 servings of pro.activ foods daily for optimum cholesterol reduction. One serving of this product is 250ml, equal to one medium sized glass.*
> *Extra servings will not provide additional cholesterol-lowering benefit.*

As with pro.activ spread, where it is not possible to include large amounts of text on labels, further details will be available through carelines, websites and accompanying leaflets. This will include descriptions on how to use the entire pro.activ range, for example:

Recommended: 2-3 servings of pro.activ foods daily for optimum cholesterol reduction. Extra servings will not provide additional cholesterol-lowering benefit

pro.activ Range	***1 Serving =***	
pro.activ milk	250ml = ¼ of 1Lt carton	1 bowl of cereal **or** 1 medium glass **or** 1 mug
pro.activ spread	2 ½ tsp of spread = 12g	2 slices of toast for breakfast **or** 2 slices of bread in a sandwich **or** 1 serving on top of a baked potato or hot vegetables
pro.activ yoghurt	125g/150g = 1 pot of yoghurt	As a dessert or snack anytime of day

- To continue the cholesterol-lowering effects of pro.activ foods, keep eating two or three servings everyday as part of your healthy diet;
- A healthy diet should contain plenty of fruit and vegetables.

The labelling will be adapted, if necessary, in line with the Scientific Committee on Foods current deliberations on multiple intake of phytosterol products.

4.5 *Anticipated intake of phytosterol-esters from the Novel Food(s)*

It is anticipated that the intake of phytosterol-esters from the range of food products will be consistent with the product labelling/consumer information that will accompany the marketing of the products and be in the range of 3.2-4.8g of phytosterol-esters per day (2-3g of free phytosterols).

Current experience indicates that consumers will follow the advice on product usage. However, should consumers not follow this advice and replace **all** current spread, 'milk' and 'yoghurt' type product usage with phytosterol-ester containing products then the potential intake of phytosterols has been modelled based on available information on intakes of these product types. This would represent a worst case scenario phytosterol intake.

In order to calculate the potential intake of phytosterols from the consumption of spreads, 'milk' and 'yoghurt' type products it is necessary not only to know how much of these products are consumed daily but also how much of each of these products is consumed in combination with the others.

Two possible sources of data are available:

- Dietary survey data
- Consumer purchase data

(i) Dietary survey data

It is difficult to make such calculations with any accuracy using data that are published in summary reports of diet and nutrition surveys as often only mean values are reported. Food intake data will not be normally distributed so estimates made from a mean value will not provide an accurate estimate of the midpoint of the distribution or provide any information on the distribution of intakes. Some surveys do provide percentile data for individual foods or food groups, but they do not provide any information on the proportion of consumers consuming all three products or how much of these products are eaten in combination. Not all consumers will eat all the products everyday so it is important to understand the combination of intakes from the different products in order to make realistic estimates of intake. Therefore, calculating intakes from multiple sources in the diet can only be done by accessing the individual dietary records from dietary surveys. Publicly available dietary survey data suitable for performing these detailed intake assessments were only available for the UK and the Netherlands. For other EU countries the data was either out of date, not detailed enough or not available to third parties for this type of exercise.

Estimates of the potential intakes of phytosterols from the consumption of spread, 'milk' and 'yoghurt' type products have been calculated using data from the UK National Diet and Nutrition Surveys (Gregory *et a*l., 1990; 1995; 2000; Finch *et al*., 1998) and the Dutch National Food Consumption Survey 1997-1998 (Zo eet Nederland, 1998) as individual dietary intakes are available from these surveys. The calculations for the UK were performed by Unilever but the calculations for the Netherlands were performed by TNO Nutrition and Food Research, Zeist, Netherlands. Full access to the data from the Dutch survey is available only by this route.

The calculations were performed for all sectors of the population starting from the age of 1.5 years in the UK and one year in The Netherlands. However, it should be noted that the phytosterol-ester containing products are not marketed for children. The calculations were performed for the UK population to look at the potential distributions of intake of phytosterols from the consumption of at least one spread, 'milk', or 'yoghurt' type product and from the consumption of all three products. For the Dutch population only the potential intakes for the consumption of all three products was calculated but the data is available separately for males and females.

It is assumed that the level of addition of phytosterol-esters in each product provides:

- 1g free phytosterols in12.5g Yellow Fat Spread (current fortification level)
- 1g free phytosterols in each pot of yoghurt (125g/150g)
- 1g free phytosterols in 250ml milk

By calculating the potential intakes of phytosterols using intake data from dietary surveys the implicit assumption being made is that all the spread, 'milk' and 'yoghurt' that is consumed is being replaced by products containing phytosterol-esters.

Median (50^{th} percentile) and 95^{th} percentile potential phytosterol intakes from consumption of spread, 'milk' and 'yoghurt' type products are given in Table 3. (overleaf). Box and whisker plots indicating the distribution of intakes are attached in *Appendix 3*. The boxes represent the 10^{th} and 90^{th} percentile, the whiskers the 5^{th} and 95^{th} percentiles and the bar within the box the median (50^{th} percentile).

In the UK those with the highest potential intakes of phytosterols are aged 65+ but the 50^{th} percentile intake was below 3g per day even for consumers of all three products. The highest 95^{th} percentile intakes were in the same age group with a maximum potential intake of 5g free phytosterols/day. In the Netherlands potential intakes for males were higher than for females with those in the 46-65 age group having the highest median intake. The highest 95^{th} percentile intake was for males aged 6-16 but as phytosterol-ester products are not targeted at this age group it is unlikely that this intake would apply for cholesterol-lowering products.

Table 3. Potential phytosterol intakes (g/person/day) from the consumption of spread, 'milk' and 'yoghurt' type products estimated from dietary survey data.

Country/data set	*Age group*	*Number of households*	*50th percentile (g/person/day)*	*95th percentile (g/person/day)*
UK – dietary survey Consumers of at least one of spread, 'milk' and 'yoghurt' type products	1.5-4.5	1258	0.56	2.16
	4-15	1229	0.81	2.40
	16-45	906	0.72	2.92
	45-64	493	0.82	2.95
	65+	882	1.27	3.67
UK – dietary survey Consumers of all 3 products	1.5-4.5	140	1.36	3.22
	4-15	240	1.53	3.11
	16-45	100	1.88	4.25
	45-64	49	1.85	4.35
	65+	76	2.72	5.01
Netherlands – dietary survey Consumers of all 3 products (males)	1-5	15	2.83	3.19
	6-16	23	4.26	8.19
	17-45	72	3.84	6.78
	46-65	73	4.58	6.63
	65+	40	4.52	6.23
Netherlands – dietary survey Consumers of all 3 products (females)	1-5	21	2.31	2.87
	6-16	37	3.3	4.0
	17-45	103	3.45	4.97
	46-65	97	3.74	5.66
	65+	10	3.81	6.14

Consumption patterns in the UK dietary survey were similar for all age groups. For example in the 46-54 age group the consumption patterns were as follows:

- 100% of consumers drank milk
- 35% of consumers ate spread
- 21% of consumers ate yoghurt
- 35% of consumers drank milk and ate spread
- 11% of consumers ate spread and yoghurt
- 21% of consumers drank milk and ate yoghurt
- 11% of consumers used all three products.

(ii) Consumer purchase data

As detailed dietary survey data was only available for the UK and the Netherlands consumer purchase data has been obtained for a number of other EU markets. France, Germany and Finland, are key EU markets for pro.activ spread so were considered appropriate for this exercise. It was also intended to include a Southern European country but consumer purchase data suitable for estimating individual intakes was not available for any of these countries. However, when intakes are considered on a per capita basis the countries selected do give a representative distribution of intakes of spread, 'milk' and 'yoghurt' type products throughout the EU.

Consumer purchase data similar to that obtained for the Post Launch Monitoring were obtained for purchases of spread, 'milk' and 'yoghurt' type products. In order to gain some idea of how representative the consumer purchase data are, data were also obtained for the UK and compared with the dietary survey data described above.

Description of data

Consumer purchase data were obtained from AC Neilsen (Consumer Panel 2002) for the UK, France, Germany and Finland. When members of the registered households go shopping they do so in the normal way but on returning home they scan the barcodes of all their purchases into a special barcode reader unit that then transfers the information to a centralised database at the market research company.

The data provides information on what the households buy, when they buy it and what demographic group (age, size of household etc) the purchaser belongs to. The technique is non-invasive and as panel members are not aware of which purchases are being monitored, it is able to provide real purchase patterns and supplies a link between purchase data and consumer type. It also allows a detailed estimate of intake.

In each country data on spread, 'milk' and 'yoghurt' type product purchases were collected from a common panel of households over a 12 week period in late 2001 – early 2002. In order to estimate the potential intake of phytosterols from the consumer purchase data on spread, 'milk' and 'yoghurt' type products the following assumptions have been made:

- All the spread, 'milk' and 'yoghurt' products that are purchased contain phytosterols
- All the spread, 'milk' and 'yoghurt' products that are purchased is consumed during the 12 or 26 week period of data collection
- There is no spoilage or wastage of the food that is purchased
- Use is only by individuals that live in the house

- Spread, 'milk' and 'yoghurt' products are not purchased and consumed outside the home.

The first three assumptions are conservative and are likely to lead to an overestimate in the intake of phytosterols. In the case of the final assumption, whilst it is possible that people may purchase and eat spread, 'milk' and 'yoghurt' type products outside the home, they are extremely unlikely to purchase and eat phytosterol-containing products in the same manner, simply because of the limited availability of these products. These products are more likely to be purchased at supermarkets, taken home (and hence scanned) before being taking outside the home again to be eaten. Further details of how the calculations were performed can be found in *Appendix 4*.

As indicated previously, the data are collected at the household level. Where there is more than one individual in a household, it cannot be determined with any certainty who in the household is consuming the products. However, reasonable estimates of intake can be calculated for one-member households.

Good dietary survey data are available for the UK population. However, consumer purchase data from the UK was obtained and used to calculate potential phytosterol intakes from the consumption of spread 'milk' and 'yoghurt' type products. This information was then compared with the intake distributions obtained using dietary survey data in order to get a view of how representative intakes calculated from the consumer purchase data are and to identify any differences there may be between the datasets. Intake distributions calculated from spread, 'milk' and 'yoghurt' type product consumption from both datasets can be found in *Appendix 5.*

Comparison of the potential intakes of phytosterols calculated from UK consumer purchase data with those calculated from the dietary survey data, indicates that the consumer purchase data can provide a good estimate of intakes.

Estimated intakes from the consumer purchase data for one member households in the UK, Germany, France and Finland are shown in Table 4 (overleaf). Box and whisker plots indicating the distribution of intakes are attached in *Appendix 6*.

The UK consumer purchase data are consistent with the dietary survey data with the highest potential intakes estimated to be in the 45-64 and 65+ age groups. Consumers of all three products had 50th percentile intakes of around 2.4g free phytosterols/day with 95th percentile intakes of 5.7g/day. Similar potential intakes were estimated for the German population again with the target age group having the highest potential intakes of phytosterols. In France the target age group also had the highest potential intakes but the 50th percentile intakes were slightly lower than for the UK and Germany at around 2g free phytosterols/day although the highest 95th percentiles were similar to UK and Germany at 5.5g/day. The highest potential intakes were in Finland where 50th percentile intakes were estimated to be around 3.5g free phytosterols/day and 95th percentile intakes of 7.7g/day. As for the other countries, the target age groups had the highest potential intakes.

Table 4. Potential phytosterol intakes (g/person/day) from the consumption of spread, 'milk' and 'yoghurt' type products estimated from consumer purchase data for one member households.

Country/Data set	*Number*	*Age group*	*50th percentile (g/person/day)*	*95th percentile (g/person/day)*
UK Consumers of at least one of spread, 'milk' and 'yoghurt' type products	126	25-34	0.82	3.48
	177	35-44	1.03	3.83
	441	45-64	1.51	4.65
	565	65+	1.62	4.95
UK Consumers of all 3 products.	33	25-34	1.77	4.35
	39	35-44	1.91	4.63
	126	45-64	2.44	5.75
	187	65+	2.37	5.67
Germany Consumers of at least one of spread, 'milk' and 'yoghurt' type products	94	<30	1.30	3.81
	230	30-39	1.26	3.90
	191	40-49	1.47	4.50
	211	50-59	1.43	4.83
	515	≥60	1.70	4.92
Germany Consumers of all 3 products.	55	<30	1.51	3.86
	96	30-39	1.78	4.69
	84	40-49	1.76	5.27
	83	50-59	2.13	7.23
	233	≥60	2.31	5.69
France Consumers of at least one of spread, 'milk' and 'yoghurt' type products	46	15-24	0.69	2.05
	144	25-34	0.95	2.95
	341	35-49	1.17	3.52
	215	50-59	1.18	4.10
	162	60-64	1.51	4.48
	317	65+	1.43	4.29
France Consumers of all 3 products.	8	15-24	1.26	2.64
	53	25-34	1.53	4.12
	116	35-49	1.71	4.28
	91	50-59	2.00	4.88
	71	60-64	2.05	5.57
	131	65+	2.08	5.15
Finland Consumers of at least one of spread, 'milk' and 'yoghurt' type products	58	<35	2.17	5.30
	69	35-49	1.95	5.00
	100	50-64	3.05	6.82
	167	65+	3.02	6.67
Finland Consumers of all 3 products.	40	<35	2.26	5.73
	37	35-49	2.47	4.29
	66	50-64	3.48	6.85
	84	65+	3.30	7.72

Consumption patterns derived from the UK consumer purchase data for one member households in the target population were as follows:

- 96% of consumers drank milk
- 55% of consumers ate spread
- 54% of consumers ate yoghurt
- 54% of consumers drank milk and ate spread
- 32% of consumers ate spread and yoghurt
- 54% of consumers drank milk and ate yoghurt
- 32% of consumers used all three products

The percentage consumers in each group do differ from the figures for the dietary survey data. This is probably due to the difference in the time period being studied, for the dietary survey it was relatively short period (<1 week) whereas the consumer purchase data was from a 12 week period. However, the dietary survey data are consistent with the consumer purchase data in showing that not all consumers buy all three product types being considered. Consumer purchase data for France, Finland and Germany showed similar consumption patterns of the three products to the UK data.

In summary, the dietary survey data and consumer purchase data have allowed estimates of the potential intakes of phytosterols based on intakes of unfortified foods. The data also takes into consideration the consumption patterns of these three product types which is important as not all consumers will use all the products. Based on the data from the UK, the dietary survey data is comparable with the consumer purchase data for estimating daily food intakes. Looking at the whole data set, potential intakes of phytosterols were comparable across all the countries studied. As these countries are considered to be representative of spread, 'milk' and 'yoghurt' type product intake across Europe on a per capita basis it is anticipated that there would not be any significant differences in potential phytosterol intakes in other EU countries.

4.6 *Current intakes of all cholesterol-lowering products containing phytosterols and phytostanols*

The estimates of phytosterol intakes obtained from the dietary surveys and the consumer purchase data assume that all spread, 'milk' and 'yoghurt' type products will be replaced by the corresponding products containing phytosterol-esters. In reality this situation is considered unlikely and so the intakes represent a worst case scenario. This is confirmed by consumer purchase data that shows that most households buying phytosterol/stanol-ester cholesterol-lowering products also buy the equivalent unfortified products. For example, in the UK over 90% of single member households in the target consumer group bought unfortified spread in addition to a phytosterol/stanol-ester spread in the same time period. Similarly, over

90% of single member households in the target group buying Benecol yoghurt in the UK also bought unfortified yoghurt.

In order to gain further insight into how realistic the predicted intakes are, consumer purchase data for cholesterol-lowering products from the UK and Finland have also been assessed. In both countries a range of phytostanol products is available as well as phytosterol-ester containing spreads. The data was collected as described earlier, with the exception that it was collected over 26 weeks, and used to estimate total daily phytosterol/phytostanol intakes.

Table 5. Potential phytosterol and phytostanol intakes (g/person/day) from the consumption of cholesterol-lowering products estimated from consumer purchase data.

Country/data set	*Age group*	*Number of households*	*50th percentile (g/person/day)*	*95th percentile (g/person/day)*
UK – per household	25-34	31	0.22	1.10
	35-44	49	0.22	2.42
	45-64	196	0.55	2.51
	65+	148	0.77	2.42
UK – per one member household	45-64	21	0.66	1.98
	65+	42	0.50	1.87
Finland – per household	35-49	33	0.22	1.53
	50-64	83	0.44	2.28
	65+	80	0.36	3.03
Finland – per one member household	50-64	14	0.45	2.30
	65+	38	0.33	2.75

As with the other consumer purchase data, the same assumptions have been made. However, it should be noted that the purchase data indicate that other spread and yoghurt products (non phytosterol/phytostanol products) were purchased during the 26-week period. Frequency of purchase data were not available so the phytosterol/ phytostanol products may have only been used for a short period of time during the 26-week period the data were collected and non-phytosterol/phytostanol products may have been consumed at other times during this period. In order to obtain some idea of intake levels it has been necessary to assume that the phytosterol/phytostanol products were consumed daily during the 26-week period. This may lead to an underestimate of intake levels since the same volume of product could have been consumed in a shorter period of time. However, in terms of the risk assessment, it is prolonged daily use that is relevant.

Appendix 7 contains data on the distribution of phytosterol/phytostanol intakes calculated on a household basis and for one-member households purchasing at

least one of the products. In both datasets there was an insufficient number of households buying all three categories of products to enable this calculation to be done. In the UK dataset the percentage of households in the survey buying all three cholesterol-lowering products ranged from 0-0.5%. In Finland the figure ranged from 0-1.4% of households.

The calculations performed with the UK purchasing data indicate a similar 95th percentile intake for age groups 35-44years, 45-64years and 65+ years of 2.2-2.3g/day on a household basis. Data from one-member households is available for age groups 45-64 years and 65+ years only. In both cases intakes at the top of the distribution were below 2g/day. Calculations performed using the data from Finland indicate a maximum intake of 3g/day for households where the purchaser was aged 65+ years. The calculations were repeated for one-member households aged 50-64 years and 65+ years. Intakes at the 95th percentile level were approximately 2.2g/day and 3g/day respectively.

4.7 *Conclusions*

The following conclusions can be made regarding the anticipated intake/extent of use of the Novel Food Ingredient:

- Post Launch Monitoring of Yellow Fat Spreads has shown that intakes are lower than expected.

- Providing additional or alternative products will offer consumers the opportunity to optimise the cholesterol-lowering benefits of phytosterol-esters.

- Labelling will ensure intake levels of phytosterol-esters remain within that required to provide optimal cholesterol reduction (2-3g free phytosterols/day).

- Based on the labelling recommendations intakes are expected to be 2-3g free phytosterols/day

- Modelling with dietary survey and consumer purchase data from unfortified products allows potential intakes of phytosterols to be estimated. This provides an indication of worst case scenario intakes should the labelling advice be ignored.

- Consumer purchase data from the UK and Finland where a range of comparable phytostanol-ester products are available shows that intakes are much lower than predicted by modelling of unfortified products.

5. PREVIOUS HUMAN EXPOSURE TO THE NOVEL FOODS

In the EU there has been no previous exposure to phytosterol-esters in 'milk' and 'yoghurt' products. However, there has been significant human exposure to phytosterols in the diet and as cholesterol-lowering preparations and phytosterol-esters in Yellow Fat Spreads. In addition, there has been significant human exposure to the hydrogenated forms of phytosterols, phytostanols in a range of food products including Yellow Fat Spreads, 'milk' and 'yoghurt' type products in a number of EU countries. Phytostanols, have the same safety profile (Slesinski *et al*., 1999; Turnbull *et al*., 1999a; 1999b; 1999c; Whittaker *et al*., 1999) and cholesterol-lowering efficacy as phytosterols (Hallikainen *et al*., 2000; Weststrate and Meijer 1998).

A summary of the previous exposure to phytosterols, phytosterol-esters and phytostanol-esters in the EU is given in Table 6 below.

Table 6. Previous exposure to phytosterols, phytosterol-esters and phytostanol-esters in the EU

Ingredient	***Source***	***Average Daily Intake***	***How long***
Phytosterols	Diet: vegetable oils, fats, fruits, vegetables and seeds	Typical Western diet 200-400mg/day Vegetarians up to 680mg/day	Lifetime exposure
Phytosterols, mainly β-sitosterol	Cholesterol-lowering preparations, eg Sito-Lande	3-6g/day	Long term use (years)
Phytosterol-esters	Yellow Fat Spreads	1.2-1.5g/day	2 years in EU
Phytostanol-esters	Yellow Fat Spreads, soft cream cheese, yoghurt, milk, salads, cereal bars, salads, meat products	Estimated to be up to 3g/day based on the labelling recommendation of 2-3 servings /day	6+ years in Finland 3+ years in other EU countries

6. NUTRITIONAL ASPECTS

Phytosterols lower serum cholesterol by decreasing cholesterol absorption in the small intestine, with a consequential increase in faecal excretion of cholesterol. The principal mechanism of serum cholesterol-lowering is considered to be competition between cholesterol and the phytosterols for micellar solubilisation in the small intestine. The first studies demonstrating the cholesterol-lowering effect of phytosterols in humans were reported by Pollak in the early 1950's. Since then a large number of clinical studies with phytosterols have been conducted (Pollak, 1985). In these studies the phytosterols were given as the free sterols and not as fatty acid esters and both short term and long term (>1 year studies) are reported with many of the studies using large amounts of phytosterol preparations (up to 53g day).

Unilever has conducted a comprehensive investigation of the efficacy of phytosterol-esters. To date, over 30 clinical trials have been conducted involving over 2000 individuals at study sites in Europe, North America, Latin America, Africa, Asia and Australia.

Different study designs and conditions have been utilised including:

- parallel and cross-over designs,
- variation in the fat level of the spread,
- individuals on both habitual and Step 1 diet (low-fat diet),
- adults and children, males and females,
- normal to hypercholesterolaemics,
- individuals on statin or fibrate cholesterol-lowering drugs,
- diabetics.

In addition, these studies have addressed other issues raised by the European Commission Scientific Committee on Foods and for which information was not available at the time of the original submission. In particular, two studies have been completed that investigate the effects of spreads containing phytosterol-ester when used in conjunction with cholesterol-lowering drugs i.e. statins and fibrates (Neil *et al*., 2001 and Nigon *et al*., 2001, respectively). These studies showed that phytosterol-esters can be used safely to provide an additional cholesterol-lowering effect to that of the medication alone.

Another study was carried out in a group of children with familial hypercholesterolaemia (Amundsen *et al*., 2001 & 2002). A significant cholesterol-lowering effect was seen in these children during the study period which was further maintained during a six month open label follow up period. The spreads were well tolerated by the children with no adverse events reported. Whilst there is no intention to market products containing phytosterol-esters to children, this study

confirmed the potential benefit of their use by children with familial hypercholesterolaemia.

In summary, since the original Novel Foods application was made a significant amount of new clinical data on phytosterol-esters are available considerably increasing our experience and understanding in this area. An update on the clinical studies carried out with spreads containing phytosterol-esters since the original submission has also been provided separately in Unilever document D01-033.

6.1 *Effect of the food matrix on the cholesterol-lowering effect of phytosterols*

The focus of recent scientific literature has been on the cholesterol-lowering effect of phytosterol-esters in Yellow Fat Spreads. However, their effectiveness in other food matrices has also been demonstrated. In a study reported by Volpe *et al*., (2001) the effects of a yoghurt based drink enriched with 1g/day of plant sterols (soybean extract) for four weeks and 2g/day of plant sterols for eight weeks were investigated. At 1g/day of the plant sterol extract total and LDL cholesterol were reduced by 6.7% and 11.1% respectively when compared to baseline after four weeks of use. After consuming 2g/day for eight weeks total and LDL cholesterol were reduced by 11.2% and 15.6% respectively. No significant changes were found in serum levels of fat soluble vitamins (A, D and E) and a number of male and female hormones. In another study the effects of plant stanol-esters in a low fat yoghurt were investigated (Mensink *et al.,* 2002). The plant stanol-esters were emulsified into a low fat (0.7%) yoghurt so as to provide 1g per 150ml cup of yoghurt. Daily consumption was three cups of yoghurt (total of 3g/phytostanol/day) over a three week period. LDL cholesterol was reduced by 13.7% compared to the placebo yoghurt and effects were found to be maximal after one week. There was a decrease of 14.4% in lipid corrected β-carotene levels but other carotenoids were not affected.

There have been no published studies on the cholesterol-lowering efficacy of phytosterol-esters in milk therefore Unilever commissioned a trial at CSIRO Health Sciences and Nutrition, Adelaide, Australia to address this deficiency. Thirty nine volunteers consumed both spread and milk in a four way comparison with each intervention lasting three weeks. The interventions were:

- control providing 25g spread and 300ml of milk
- 2g (free) phytosterol/day from 25g phytosterol spread with 300ml of control milk
- 2g (free)phytosterols from 300ml of phytosterol-ester milk and 25g/day of control spread;
- 4g (free) phytosterols/day from 25g phytosterol-esters spread plus 300ml of phytosterol-ester milk;

Phytosterol-esters in milk (2g/day), spread (2g/day) and the combination were equally efficacious in lowering both total and LDL cholesterol by 8-11%. Lipid adjusted serum β-carotene levels were reduced by 10% in the group receiving 2g

phytosterol/day in milk and the group receiving 4g phytosterols/day in both spread and milk but not in the group receiving 2g phytosterols/day in spread. Routine clinical chemistry and haematology parameters were unaffected by any treatment (Clifton, 2002).

The cholesterol-lowering effect of phytosterol-esters in salad dressings (Davidson *et al*., 2001; Judd *et al*., 2002) and lean ground beef has also been reported (Carr *et al.,* 2002; Matvienko *et al.,* 2002) with similar results to those obtained with other food matrices.

In summary, the cholesterol-lowering effect of phytosterol-esters is not influenced by the food matrix.

6.2 *Effect on carotenoids*

Clinical studies using 1-4g day of phytosterols (given as phytosterol-esters) have indicated a modest reduction (10-25%) in the absorption of the most lipophilic carotenoids (e.g. β-carotene). Comaparable reductions in carotenoids have been reported during both short term (three weeks) and long term (52 weeks) trials (Hendricks *et al*., 1999 & 2001). At the recommended intakes of 2-3g free phytosterols/day of the spreads, 'milk' and 'yoghurt' type products it is expected that any effects on carotenoid lowering will be within this range.

Carotenoids levels are influenced by various factors such as diet, person to person variation and seasonal variations (which are also linked to diet). The plasma level of carotenoids can vary from season to season by up to 30% depending on the main fruit and vegetables available at the time (van het Hof, 1999; Lux and Naidoo, 1994; Olmedilla *et al*., 1994; Saintot *et al*., 1995; Scott *et al*., 1996). Thus a reduction in carotenoids of 10-25% should be considered in the context of these other factors.

Furthermore, phytosterol-ester enriched spreads are recommended as part of a healthy diet rich in fruit and vegetables and the 'milk' and 'yoghurt' type products will be similarly labelled. As demonstrated by Judd *et al*.,(2002) and Noakes *et al*., (2002), this can have a significant influence on plasma carotenoid levels. For example in the study by Noakes *et al*., (2002) the addition of one extra serving of a high carotenoid fruit or vegetable per day when consuming phytosterol-ester containing spreads maintained plasma carotenoid levels. In another recently published study no changes in serum carotenoid concentrations were observed when spreads containing phytosterol and phytostanol-esters were taken as part of a controlled diet (Raeini-Sarjaz *et al.,* 2002).

As the health benefits of carotenoids have not been established it cannot be assumed that a modest reduction will have any significance for public health.

7. MICROBIOLOGICAL ASPECTS

The stability of milk is dependent on the temperature and time processing parameters (e.g. Pasteurisation or UHT) and the type of packaging into which it is added (e.g. aseptic).

The stability of yoghurt is dependent on the pasteurisation of milk prior to inoculation with yoghurt cultures and maintaining the pH.

The microbiological stability of ‘milk’ and ‘yoghurt’ type products containing phytosterol-esters is governed by the same principles as conventional products.

Formulation and process rules currently used to ensure design safety of conventional milk and yoghurt products are equally applicable to the new products made with phytosterol-esters and have been used in setting formulations. The accepted principles of Good Manufacturing Practice (GMP) used for conventional milk and yoghurt products will be used to control quality and safety during manufacture.

‘Milk’ and ‘yoghurt’ type products containing phytosterol-esters have been tested for their microbiological and chemical stability over time, including the impact of pasteurisation, and these have been found to be similar to standard products.

8. TOXICOLOGICAL INFORMATION

There is a history of safe consumption of phytosterols within the normal dietary intake of between 200-400mg/day. However, it was estimated that the use of phytosterol-esters in Yellow Fat Spreads would lead to a five to ten fold increase in the consumption of phytosterols that required a thorough toxicological evaluation. Hence, a comprehensive safety testing programme was carried out to address the following:

- mutagenicity,
- absorption,
- sub-chronic toxicity,
- reproductive toxicity (including oestrogenicity), and
- tolerability of high doses in humans.

The conclusions from these studies were as follows:

- No evidence of genotoxicity (Wolfreys and Hepburn, 2002)
- Absorption is very low (Sanders *et al*., 2000)
- No evidence of subchronic toxicity – NOAEL of 4.1g phytosterols/kg/bodyweight/day in a 90 day rat feeding study (Hepburn *et al.,* 1999)
- No effect on the reproductive system, and no oestrogenic activity (Baker *et al*., 1999; Waalkens-Berendsen., 1999)
- High doses produced no adverse physiological effects in humans (Weststrate *et al*., 1999; Ayesh *et al.,* 1999)

A full toxicological assessment of phytosterol-esters using the above studies and data available from the literature was carried out as part of the previous Novel Foods submission (Unilever documents D97/042, D98/002 and D98/028).

Based on this assessment the EC Scientific Committee on Foods concluded that the use of phytosterol-esters in Yellow Fat Spreads at a maximum level corresponding to 8% free phytosterols is safe for human use.

Other information on long term use of high doses of phytosterols

From the 1950's through to 1982 β-sitosterol (actually mixtures of phytosterols) was marketed in the USA as a treatment for hypercholesterolaemia under the trade name Cytellin by Eli Lilly. Its use was discontinued by the FDA at the request of the Company (Federal Register, 1985). The reason for withdrawal was lack of palatability (and hence compliance) and the availability of more effective hypocholesterolaemic drugs (especially statins). Cytellin preparations contained unesterified phytosterols suspended in a variety of vehicles, the main ones being

methylcellulose and vegetable oils. The source of phytosterols also changed during the lifetime of the drug; initially soyabean and cottonseed oils were used but tall oil (derived from pine trees) was introduced later.

Initially a daily dose of 6-12g of phytosterols was recommended, but later the maximum effect in adults was achieved with 3g phytosterols per day. In clinical trials much higher doses had been used, for example in one study reported by Lees *et al.,* (1977) 9-24g/day were given for between three months and three years. Between 1952 and 1954 the amount of sitosterol in preparations ranged from 0.3 to 53g/day, although doses between 1 and 10g/day were used in half the studies (Pollak and Kritchevsky, 1981).

In their review of the vast number of clinical studies conducted on β-sitosterol, Pollak and Kritchevsky (1981) concluded that there were no adverse effects or side effects of sitosterol, even when taken for a long time.

The study by Riley and Steiner (1957) is an example of one of the studies where very high doses of β-sitosterol were given. Patients were treated with a 20% liquid suspension of Cytellin. The substance was administered orally before each of the three daily meals in divided dosages totalling 19 to 52g per day to 13 patients with coronary atherosclerosis. The period of sitosterol administration varied between one to six months per patient. There was no effect on liver function parameters and there was no mention of any adverse effects.

In summary, a thorough toxicological evaluation of phytosterol-esters has not identified any adverse health effects up to the maximum dose levels that it is possible to test. Also, human trials using involving large daily intakes of phytosterols have not reported any adverse health effects.

9. RISK ASSESSMENT

9.1 *Determination of the no-observed adverse effect level*

The acceptable daily intake (ADI) is set on the basis of the highest no-observed adverse effect level (NOAEL) in animal studies (JECFA, 1987). The NOAEL for phytosterol-esters was established by the 13-week rat feeding study. It is the study of longest duration with phytosterol-esters and conducted according to OECD guidelines that require intensive and extensive examination of the animals. In this study, rats received phytosterols (as phytosterol-esters) in their diet at levels of 0, 0.1, 1, 2, or 5%. A dietary level of 5% is generally recognised as the maximum level required for the testing of non nutritive components without having to modify the diet to maintain nutritional balance (Food and Drug Administration, 1982). There were no adverse effects at the highest concentration and therefore it can be used as the NOAEL. Mean daily intake of phytosterols over the 13 weeks was 3900mg/kg body weight/day in males and 4200mg/kg body weight/day in females. The mean value (4.1g/kg body weight/day) will be used in the risk assessment.

This NOAEL is supported by the lack of adverse effects in the two-generation rat reproduction study when phytosterols comprised 5% of the diet (1.54-5.62g phytosterols/kg body weight/day).

9.2 *Determination of the safety factor*

In the traditional assessment of safety of micro-food additives, an appropriate safety factor is applied to the NOAEL in the study using the most sensitive animal species and/or the study giving the lowest NOAEL. A 100-fold safety factor is typically applied to micro-food ingredients to take into account possible differences in susceptibility between humans and the test species and possible individual susceptibilities within the human population, although higher and lower values may be used depending on the specific material in question (Renwick, 1991). However, for macro-ingredients, where the human intakes are considerably larger than what is usually encountered for micro-food additives and where animal studies cannot create exposures high enough to elicit toxicity, it may not be possible to apply a safety factor of 100. If such substances are free from toxicity when tested in animals at the maximum inclusion levels without causing nutritional or physiological disturbances, then smaller safety factors may be appropriate especially if additional data are available to support safety. Such data include chemical structure suggesting low probable toxicity, adequate and reliable human clinical data, a history of safe intake of the ingredient from traditional foods, and studies that indicate that additional exposures are unlikely to result in adverse effects (Rubery *et al*., 1990; Borzelleca, 1992).

A safety factor less than 100 is appropriate for phytosterol-esters because phytosterols are poorly absorbed from the gastrointestinal tract (generally <10%), are rapidly eliminated, and do not accumulate in the mammalian body. There is an absence of structural alerts for toxicity. The material was not genotoxic in a series of *in vitro* mutagenicity and cytogenetic studies. There was no indication of toxicity or any toxicological or histopathological changes in the 13-week feeding study in rats or in the two generation reproduction study. Carcinogenicity studies on a structurally related compound, γ-oryzanol (a mixture of ferulic acid esters of phytosterols including β-sitosterol), in both rats (Tamagawa *et al*., 1992a) and mice (Tamagawa *et al*., 1992b) at doses of up to 2000mg/kg body weight/day failed to elicit any treatment-related adverse effects or increase in tumour incidence. Chronic studies with sitosterols in rats, rabbits, and dogs conducted suggest no adverse effects (Shipley *et al*., 1958). Phytosterols inhibit the carcinogenicity of known carcinogens (Raicht *et al*., 1980; Yusakawa *et al*., 1991; Janizec and Rao, 1992) and have been associated epidemiologically with decreases in colon cancer (Nair *et al*., 1984; Hirai *et al*., 1986). Extended human testing of phytosterols involving high doses has been conducted for decades without any reported adverse health effects. These are supported by recent clinical trials on phytosterol-esters showing a lack of adverse effects (see Unilever document D01-033).

Renwick (1991) provides a technique to estimate a safety factor using pharmacokinetic and mechanistic data for an ingredient. He subdivides each of the two main parts of the general safety factor (a factor of ten for extrapolation from animal data to man, and a factor of ten for human heterogeneity) into kinetic and dynamic (mechanism of action), and then provides a way to estimate how each contributes to the total safety factor. Using this method, a safety factor well below 100 is appropriate. Renwick also shows that safety factors less than 100 are not uncommon for food constituents.

For these reasons, based on the totality of analytical, animal, and human data summarised in this document (structural analysis, the numerous well conducted clinical trials in a wide variety of subjects, pharmacokinetic information and the lack of observed toxicity in any species), and using the approaches to estimating a safety factor outlined by Borzelleca (1992) and Renwick (1991), a safety factor of 30, a half-log unit between 10 and 100, was used to calculate the acceptable daily intake (ADI).

9.3 *Calculation of the acceptable daily intake*

The ADI is calculated as the NOAEL/safety factor (JECFA, 1987). For free phytosterols this would be:

4.1g/kg/day / 30 = 137mg/kg/day.

For a 70kg adult this is 9.6g/person/day. For a 20kg child this is 2.7g/person/day.

These are considered to be conservative estimates as there were no adverse toxicological findings at the highest dose level tested (equivalent to 5% phytosterols) and an effect level could not be determined due to the nutritional limitations of testing higher doses. The NOAEL could be significantly higher than the level established here.

9.4 *Determination of the estimated daily intake*

If the use of phytosterol-esters in the products is as follows:

- 1g (free) phytosterols in12.5g spread
- 1g (free) phytosterols in 125g/150g yoghurt
- 1g (free) phytosterols in 250ml milk

and the products are used as recommended on the labelling then the intake will be 2 to 3g (free) phytosterols/day.

If the labelling recommendations are **not** followed and it is assumed that the intakes of phytosterol-ester products will be equivalent to that of unfortified products then the potential intakes of free phytosterols has been estimated based on dietary survey and consumer purchase data. From these estimations the highest potential daily intake of free phytosterols (g/person/day) for each country (irrespective of the source of the data) is estimated to be as follows:

Table 7. Highest potential daily phytosterol intakes (g/person/day) estimated from the dietary survey and consumer purchase data

	Consumers of at least one product type		***Consumers of all three products***	
	Median (age group)	95th percentile (age group)	Median (age group)	95th percentile (age group)
UK	1.6 (65+)	5.0 (65+)	2.7 (45-64)	5.8 (45-64)
Finland	3.0 (50-64)	6.8 (50-64)	3.5 (50-64)	7.7 (65+)
Germany	1.7 (60+)	4.9 (60+)	2.3 (60+)	7.2 (60+)
France	1.5 (60-64)	4.5 (60-64)	2.1 (60-64)	5.6 (60-64)
Netherlands	-	-	4.6 (46-65)	8.2 (6-16)

These intakes are considered to be a worst case situation as:

- The Post Launch Monitoring data has shown that the individual median and 95th percentile intakes of phytosterols is less than might be predicted by comparisons with unfortified products.

- Consumer purchase data from the UK and Finland where a range of comparable phytostanol-ester products are available also indicates that intakes are not as high as might be predicted from intakes of unfortified products.

- Consumer purchase data for the UK and Finland also suggest that few households buy more than one product type from the range of phytostanol-ester products available.

9.5 *Safety assessment*

If the products are used as recommended the intake will be in the range of 2-3g free phytosterols/day. This level of intake does not exceed that originally expected from the use of Yellow Fat Spreads containing 8% phytosterol-esters approved by the EC.

There is no evidence to suggest that consumers will not follow the advice provided on the labelling and supporting literature regarding recommended intakes particularly as this states that there is no additional cholesterol-lowering benefit from eating more than the recommended amount of 2-3g phytosterols/day.

However, if the products are **not** used as recommended the potential intakes of free phytosterols has been estimated based on consumption patterns of unfortifed foods. In reality, it is unlikely that all spread, 'milk' and 'yoghurt' type product consumption would be replaced by products containing phytosterol-esters. Even if this were the case then the data indicate that all intakes, including the 95th percentile intakes would be below the acceptable daily intake of 9.6g free phytosterols/day.

9.6 *Post Launch Monitoring*

The EC approval of Unilever's application for the use of phytosterol-esters as a Novel Food ingredient in Yellow Fat Spreads included a condition on the company to establish a surveillance programme to accompany the marketing of the products. This was carried out during the first year of launch. The findings of the Post Launch Monitoring were submitted to the EC in January 2002.

It has proved to be a valuable exercise confirming usage by target groups and giving valuable insight into actual intake levels by consumers. Further Post Launch Monitoring will be carried out, using the same methodology, to confirm that the range

of products is being consumed by the target groups, to assess intake levels of phytosterols and the monitoring of any potential adverse health events.

9.7 Conclusion from the risk assessment

There is no evidence to suggest that an expansion of the range of cholesterol lowering products containing phytosterol-esters available in the EU will lead to an over consumption of phytosterol-esters that would result in adverse public health effects.

Post Launch Monitoring will continue.

10. OVERALL CONCLUSIONS

Post Launch Monitoring of Yellow Fat Spreads containing phytosterol-esters has shown that the intake of phytosterols is less than predicted in the Novel Foods Submission. This indicates that there is an opportunity to offer consumers alternative or additional products to deliver optimal cholesterol-lowering benefits without increasing the intake of phytosterols above the level already approved by the EC. It will also provide consumers who do not eat spreads the cholesterol-lowering benefits of phytosterol-esters in other foods. 'Milk' and 'yoghurt' type products are considered to be suitable additional/alternative products as they are eaten on a regular basis as part of a healthy diet.

Suitable labelling will ensure that the intake of phytosterol-esters remains within the range required to provide optimal cholesterol reduction. Therefore, extension of the range of phytosterol-ester products available in the EU to include 'milk' and 'yoghurt' type products in addition to Yellow Fat Spreads will not lead to over-consumption of phytosterols resulting in adverse public health effects.

11. REFERENCES

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APPENDIX 1:

LIST OF SUBMITTED DATA

THE SUBMISSION FILE FOR THE USE OF PHYTOSTEROL-ESTERS IN YELLOW FAT SPREADS

Under Regulation (EC) No 258/97 on Novel Foods and Food Ingredients, Unilever submitted an application to European Commission (EC) seeking approval for the use of phytosterol-esters as a functional food ingredient which enhances the cholesterol-lowering activity of Yellow Fat Spreads.

The full Submission file comprises 'D' documents submitted at various stages between November 1997 and December 1998, as follows:

Document reference	***Title***	***Date***
D97-042 Volumes 1-9	'Phytosterol-esters: use in yellow fat spreads'	November 1997
D97-042 Reference volumes 1-4	'Phytosterol-esters: use in yellow fat spreads'	November 1997
D98-002 Volumes 1-5	'Phytosterol-esters: use in yellow fat spreads-Additional data'	May 1998
D98-013	'Phytosterol-esters: use in yellow fat spreads-Application for approval as a Novel Food in the EU'	May 1998
D98-014	'Phytosterol-esters: use in yellow fat spreads-Summary'	May 1998
D98-028 Volumes 1-3	'Oral two-generation reproduction study with plant sterols in Wistar rats'	September 1998
D98-029	Phytosterol-enriched spreads and impact on plasma concentrations of carotenoids and vitamin E in healthy adults: a comparison of different doses of phytosterols'	September 1998
D98-038	'A double-blind placebo-controlled trial of the efficacy of phytosterol enriched spreads to lower blood cholesterol levels in healthy adults: vitamin D and K analysis'	December 1998

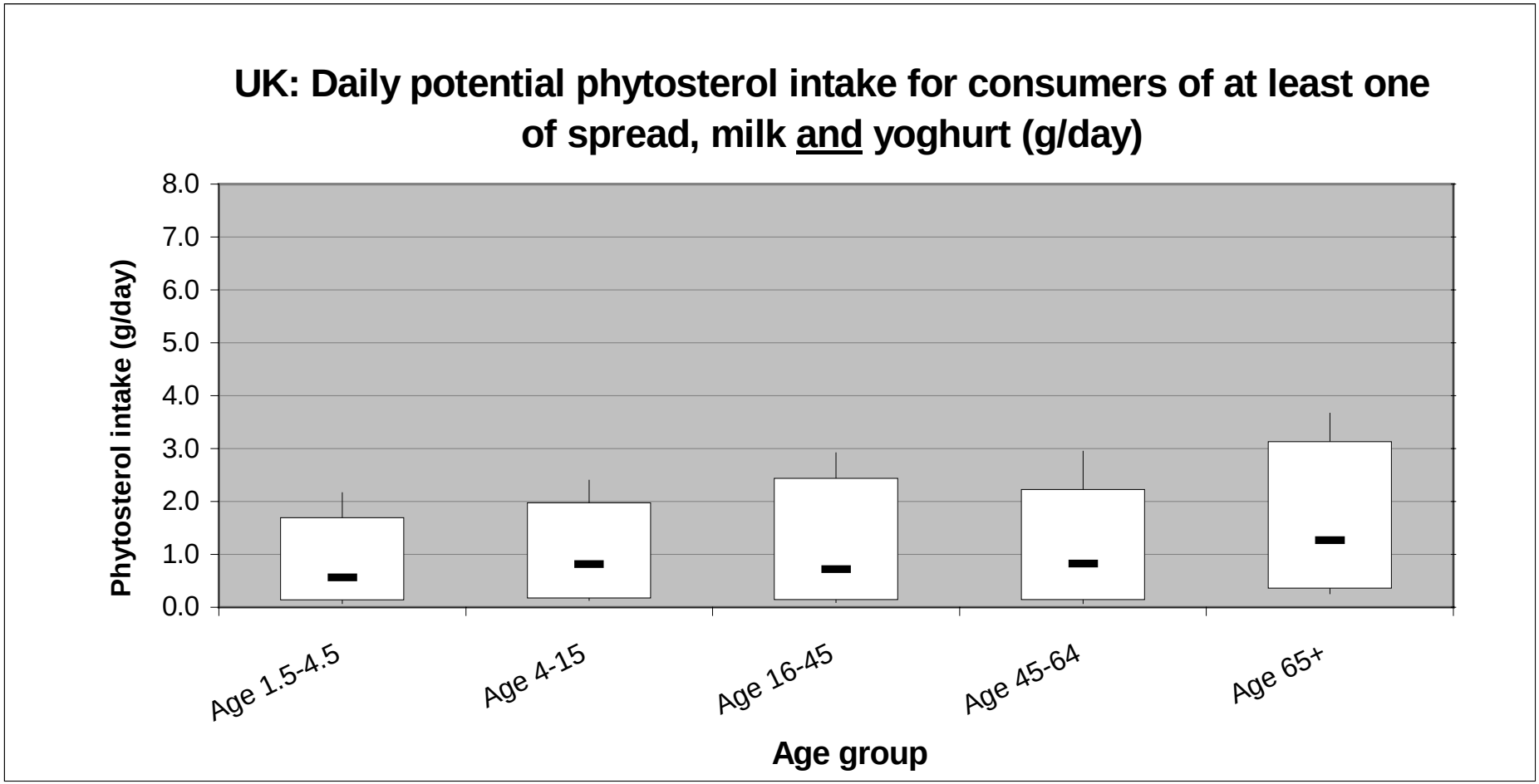
APPENDIX 2:

EXAMPLES OF THE RANGE OF PHYTOSTEROL/ PHYTOSTANOL PRODUCTS AVAILABLE IN THE EU

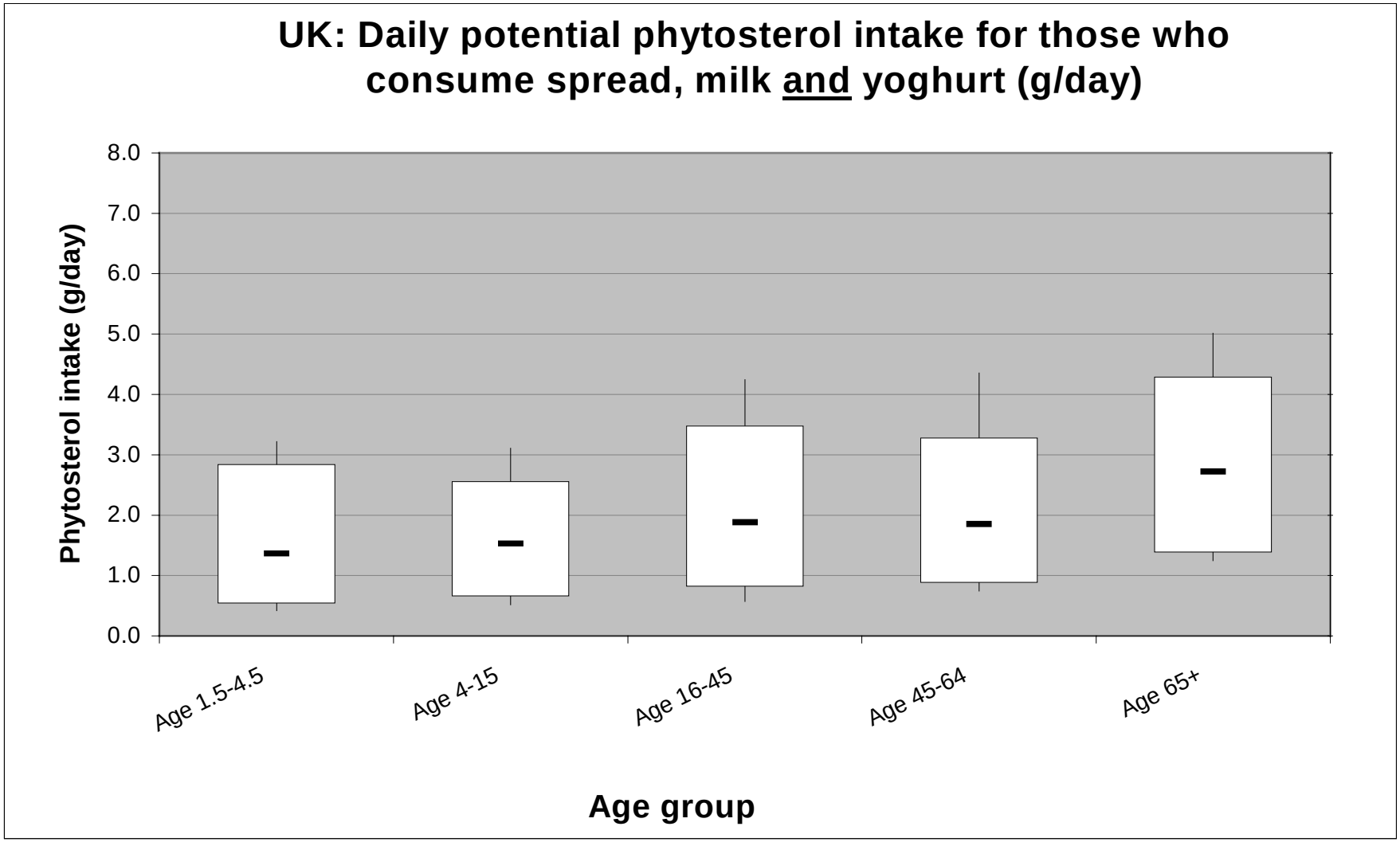
EXAMPLES OF THE RANGE OF PHYTOSTEROL/PHYTOSTANOL PRODUCTS AVAILABLE IN THE EU

APPENDIX 3:

DISTRIBUTION OF POTENTIAL INTAKES OF PHYTOSTEROLS FROM THE CONSUMPTION OF SPREAD, MILK AND YOGHURT CALCULATED USING UK AND DUTCH DIETARY SURVEY DATA



All intakes are given as free (unesterified) phytosterols



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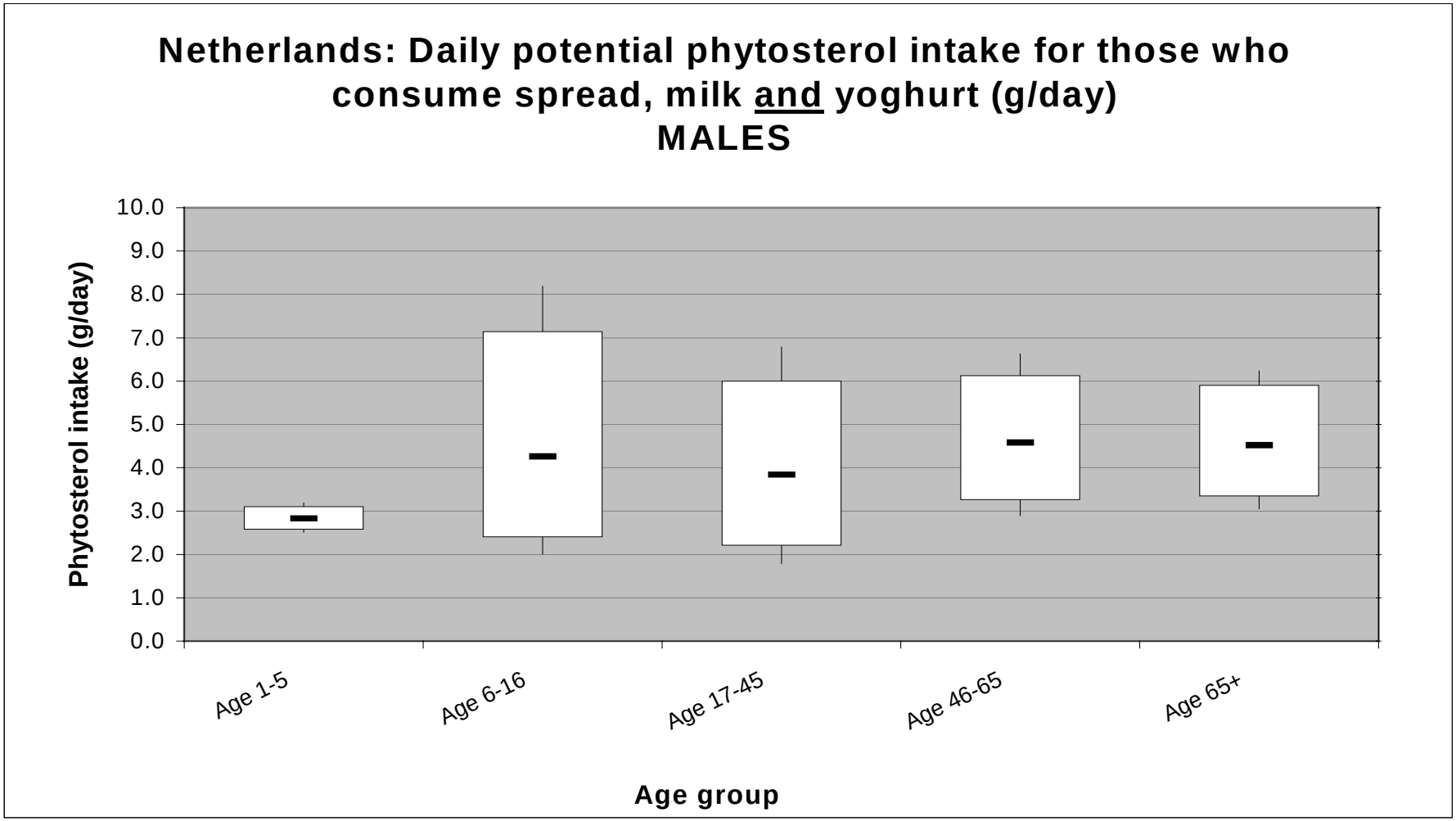

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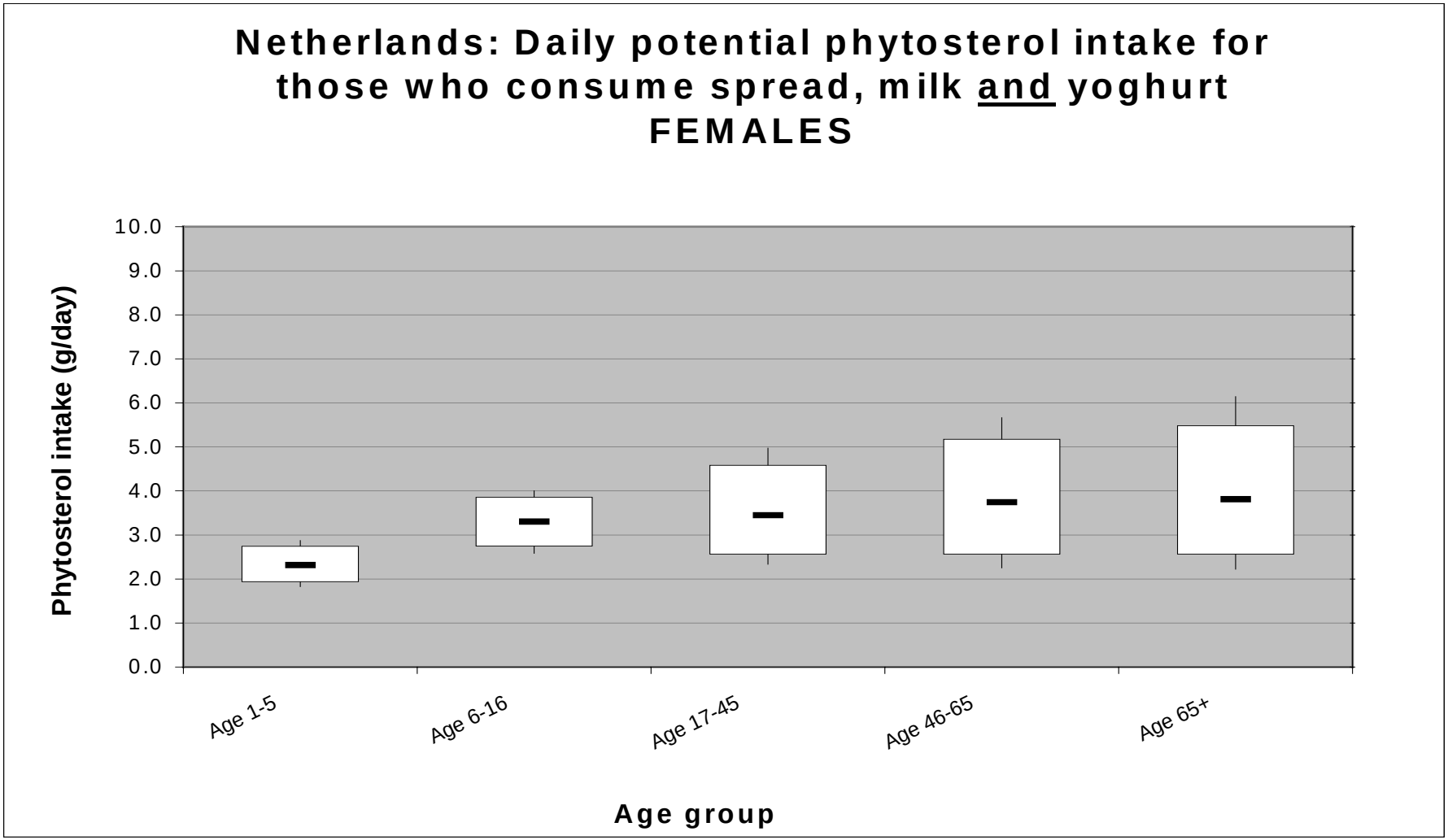


All intakes are given as free (unesterified) phytosterols

APPENDIX 4:

CALCULATING POTENTIAL PHYTOSTEROL INTAKES FROM CONSUMER PURCHASE DATA

Calculating phytosterol intake from consumer purchase data

For some countries dietary survey information is not available for use in the calculation of the distribution of phytosterol intakes from more than one product type. However consumer purchase data is available for the UK, Germany, France and Finland. These data consist of the volume of unfortified spread, milk and yoghurt products purchased per household throughout a period of 12 or 26 weeks, depending on the data being collected. In data collected from panels in the UK and Finland, information was also available on the volume of phytosterol/stanol cholesterol-lowering products purchased, such as pro.activ and Benecol margarine, Benecol yoghurt and 'other' products such as Benecol cheese and cereal bars.

Although there is no information regarding the number of adults or children in each household, within each data set there is information on the total number of members, age group of primary shopper, and whether or not that household has children. Other than the total volume of each product purchased during the survey there is no further break down of the purchases by week. Therefore the estimated intakes of phytosterols could not be calculated in the same way as when dietary survey data is available.

Intakes of phytosterols per one member households

These calculations were carried out using only the information from one member households. In order to calculate the phytosterol intake per household the volume consumed daily is calculated by assuming the volume consumed each day is an equal proportion of the total volume purchased, e.g.

$$\text{Daily consumption of product per household} = \frac{\text{Total volume purchased}}{\text{no. of days in survey}}$$

From this the daily phytosterol intake can be calculated as:

Daily phytosterol intake per household = Daily consumption of product * phytosterol fortification

A distribution of phytosterol intakes for the survey population can be produced.

Distributions were produced for the following:

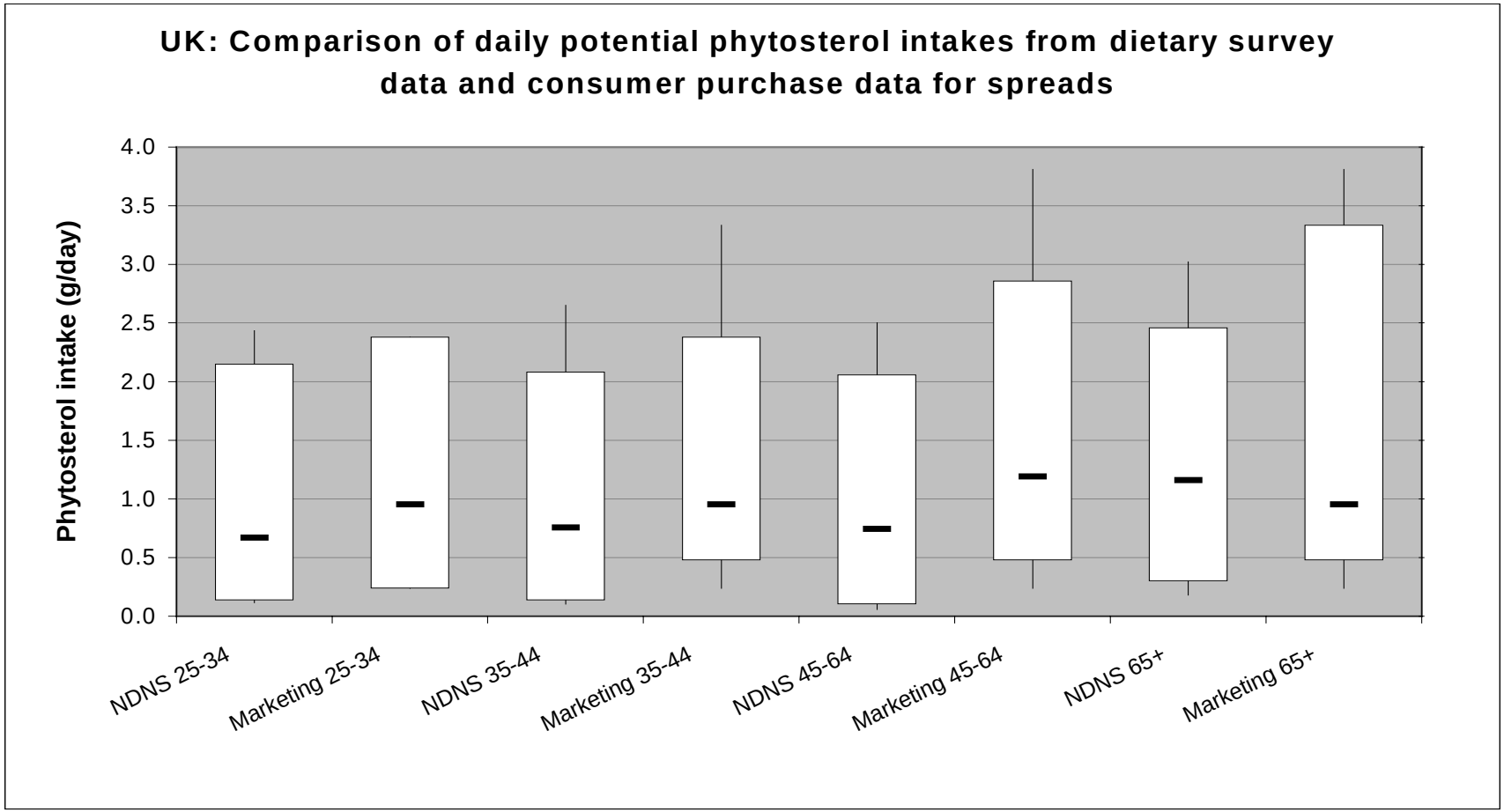
- Each of spread, milk and yoghurt separately
- The total intake from those households that bought at least one of the three products
- The total intake from those households that bought all three products

Intakes from phytosterol/stanol cholesterol-lowering products

Similar distributions were produced for the phytosterol/stanol cholesterol-lowering products in the UK and Finland. The intake calculations are the same as described above, except that intakes are shown per household (irrespective of the number of memebers) as well as for one member households. Intakes are only shown for households that bought at least one of the cholesterol-lowering products (spread, yoghurt or 'other'). In both the UK and Finland, there were insufficient households buying all three product types to make any meaningful estimates of intake.

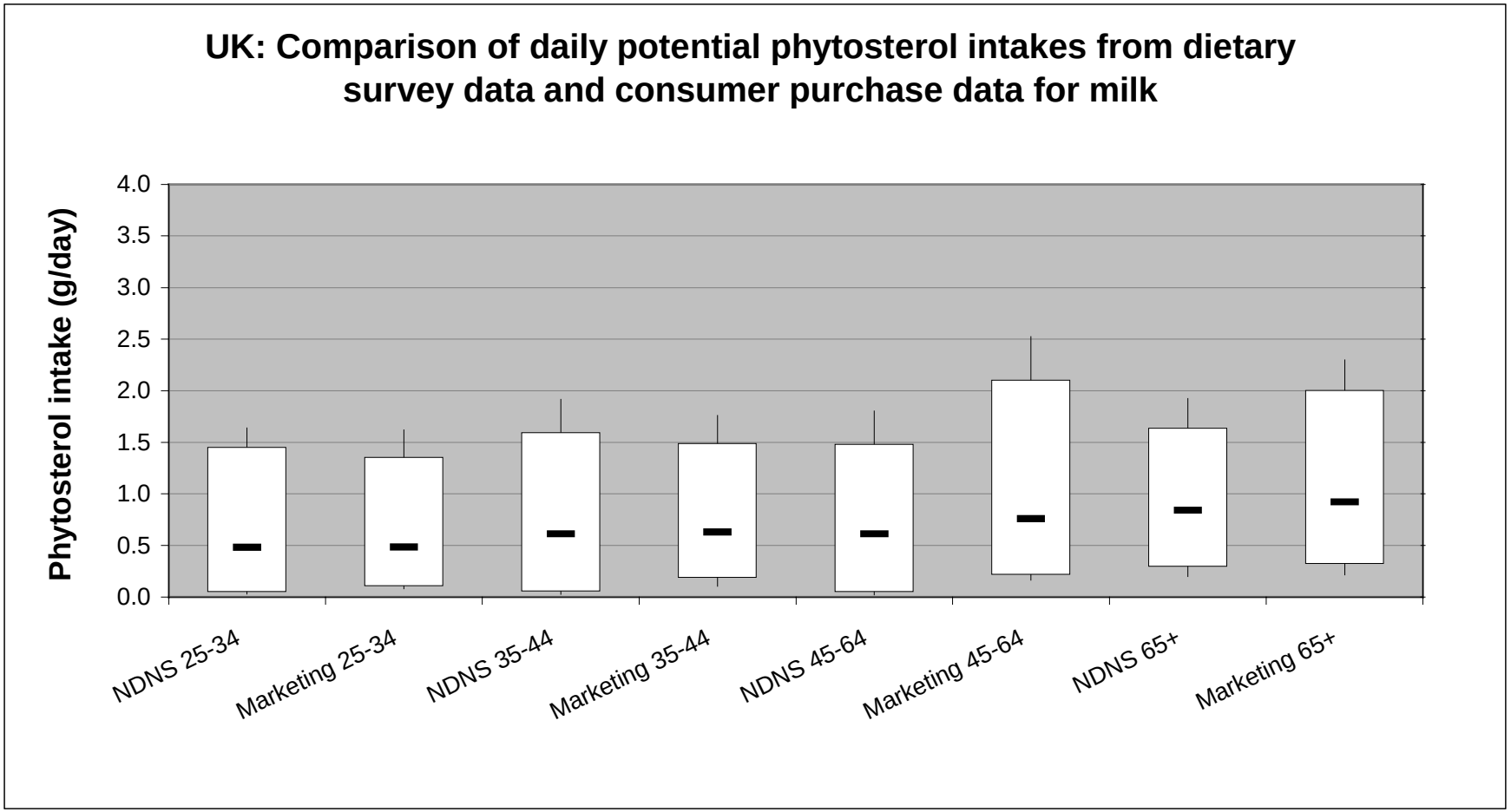
APPENDIX 5:

DISTRIBUTIONS OF POTENTIAL PHYTOSTEROL INTAKE CALCULATED FROM UK DIETARY SURVEY DATA AND FROM UK CONSUMER PURCHASE DATA



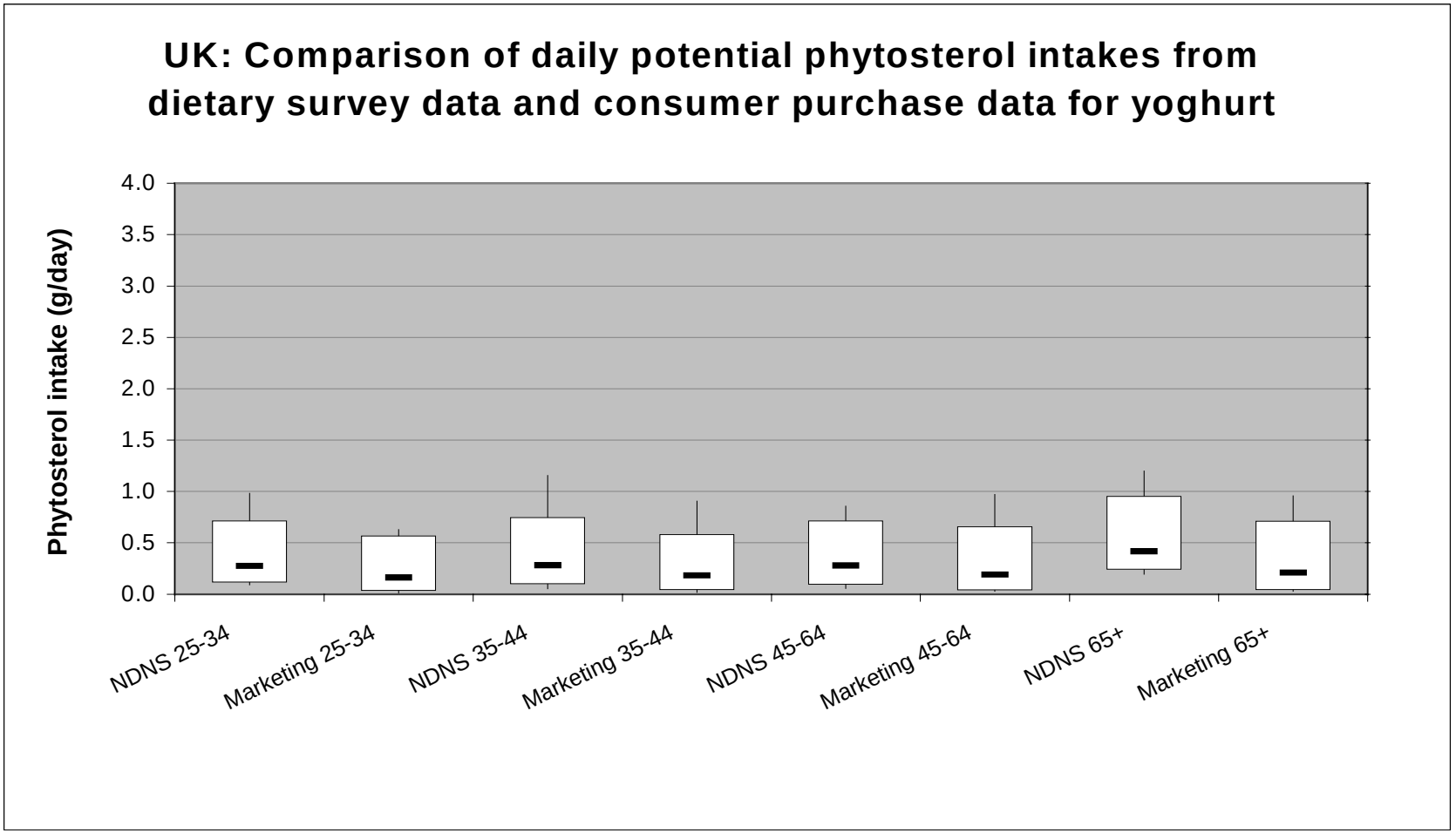
NDNS = National Diet and Nutrition Survey
Marketing = Consumer purchase data (one member households)

All intakes are given as free (unesterified) phytosterols



NDNS = National Diet and Nutrition Survey
Marketing = Consumer purchase data (one member households)

All intakes are given as free (unesterified) phytosterols

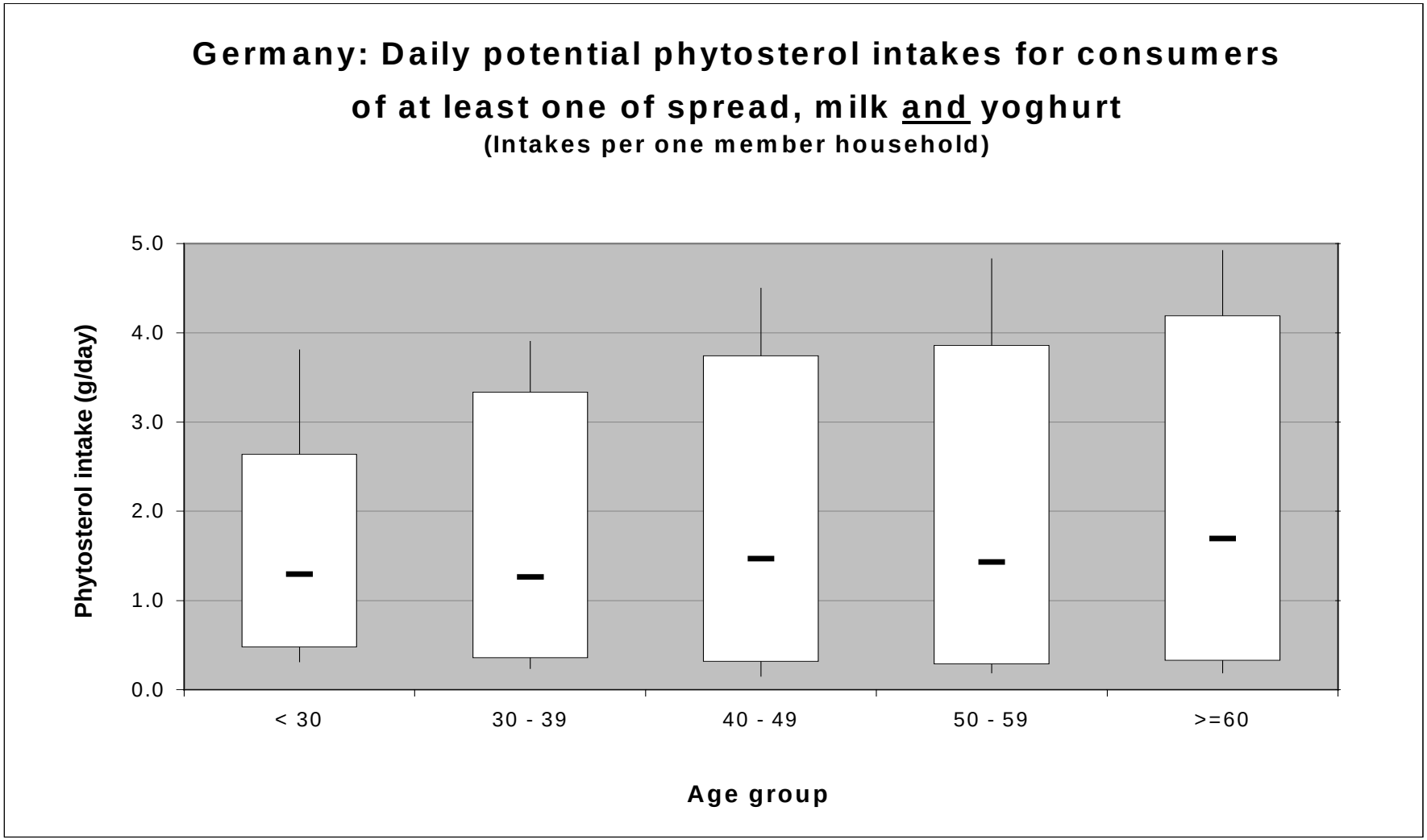


NDNS = National Diet and Nutrition Survey
Marketing = Consumer purchase data (one member households)

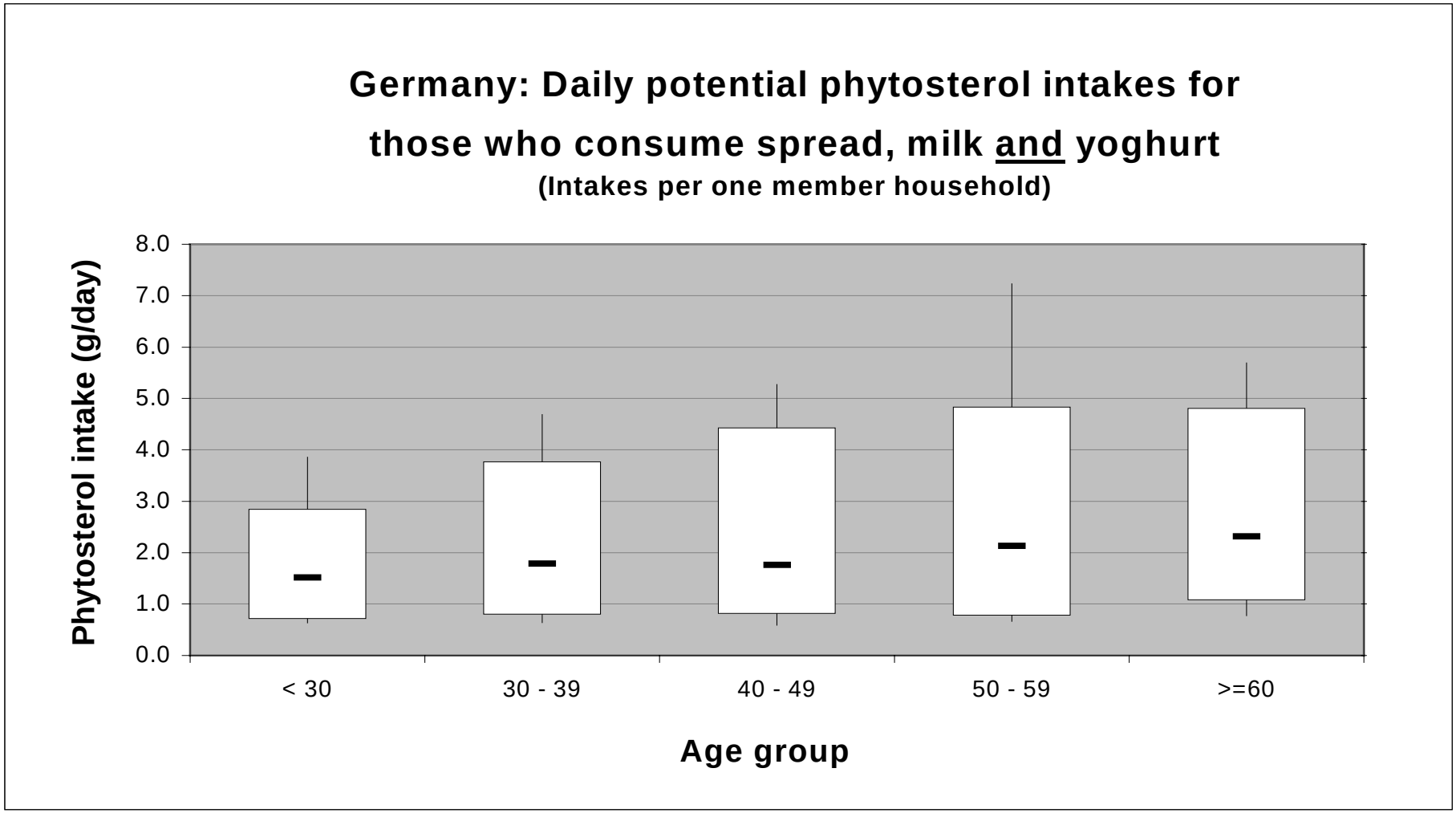
All intakes are given as free (unesterified) phytosterols

APPENDIX 6:

DISTRIBUTION OF POTENTIAL PHYTOSTEROL INTAKE CALCULATED FROM CONSUMER PURCHASE DATA COLLECTED IN GERMANY, FRANCE AND FINLAND

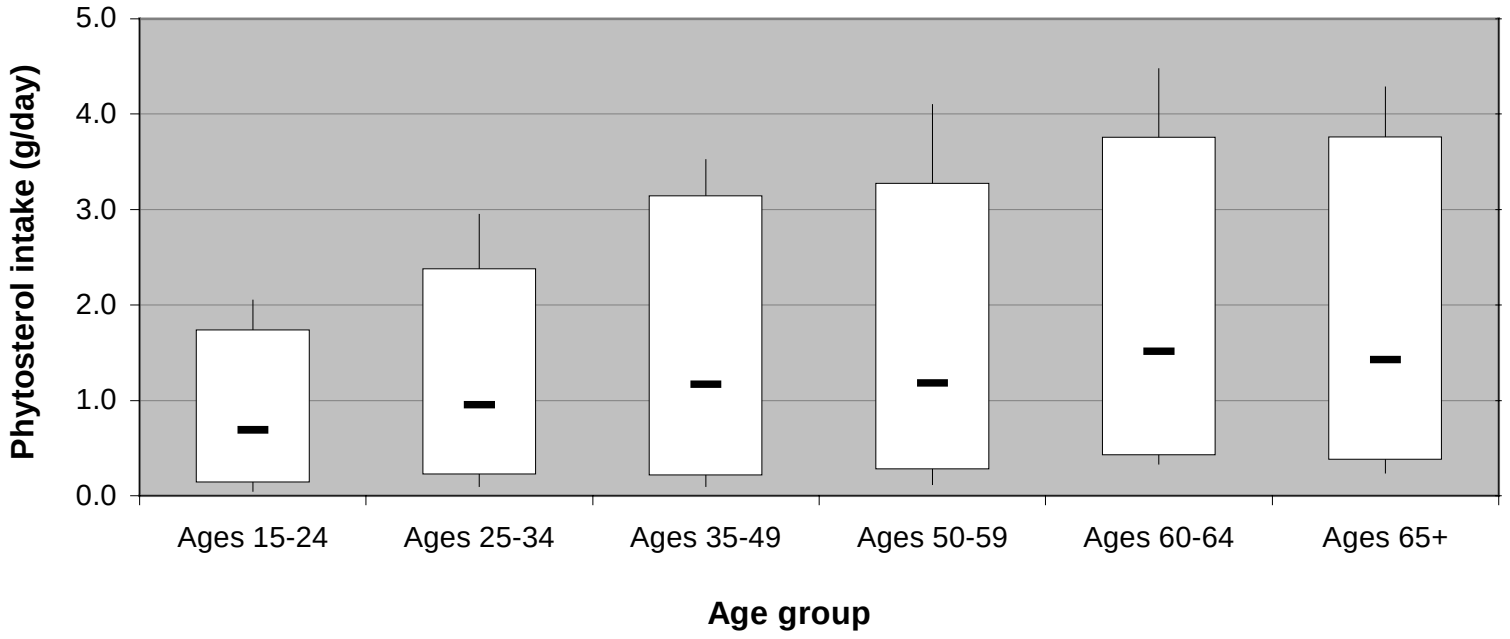


All intakes are given as free (unesterified) phytosterols

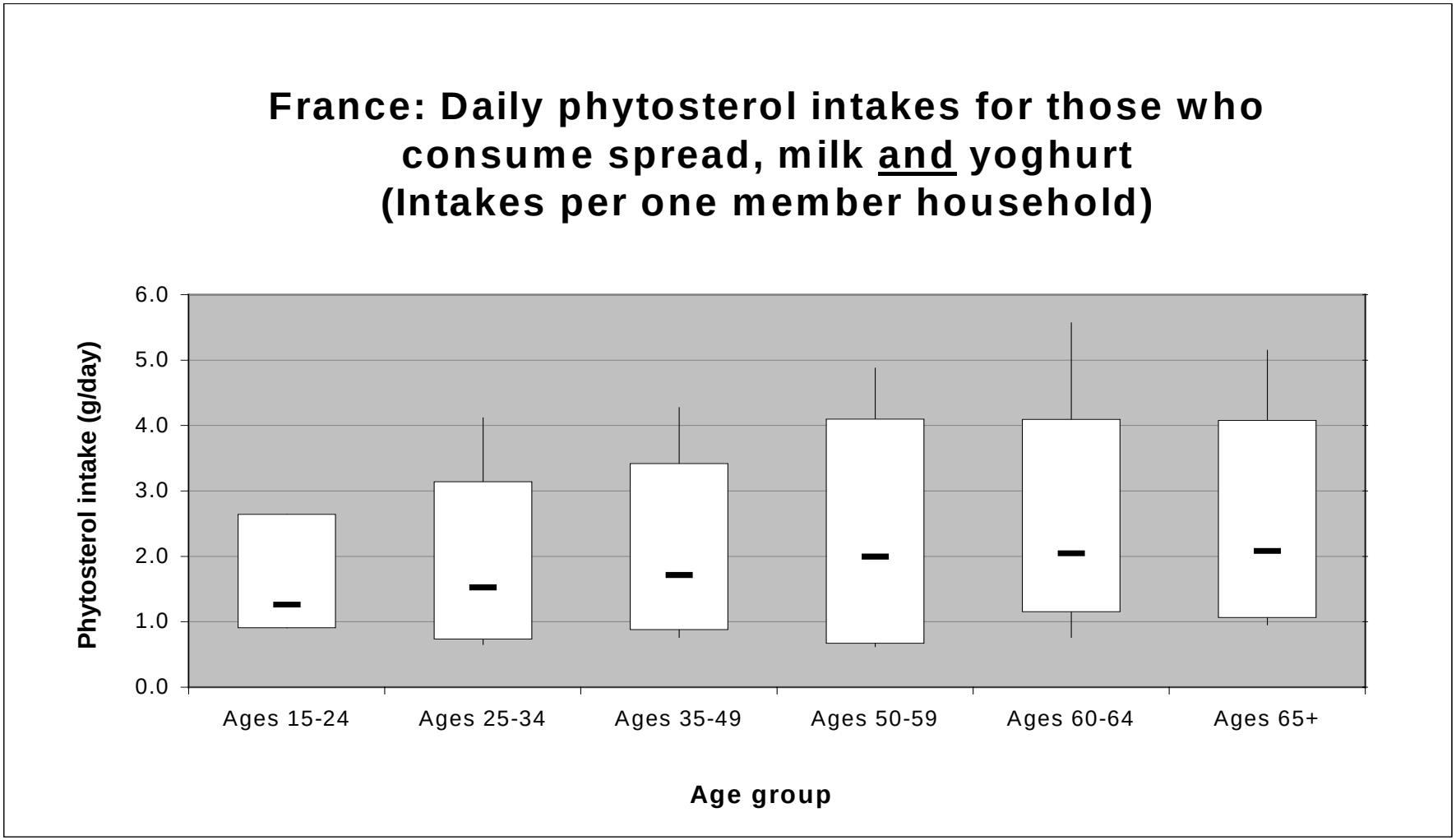


All intakes are given as free (unesterified) phytosterols

France: Daily potential phytosterol intakes for consumers of at least one of spread, milk and yoghurt (Intakes per one member household)

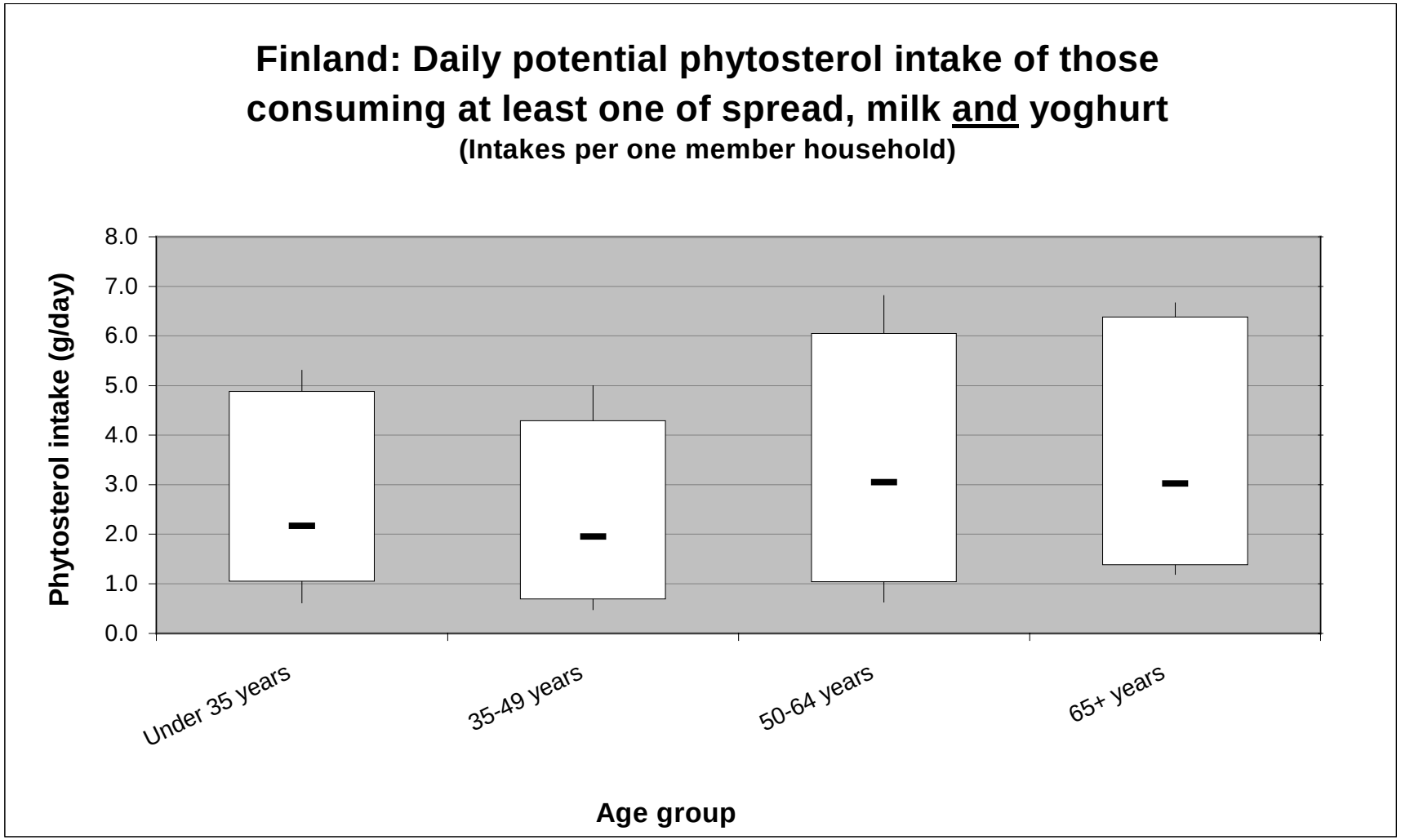


All intakes are given as free (unesterified) phytosterols



All intakes are given as free (unesterified) phytosterols

SEAC



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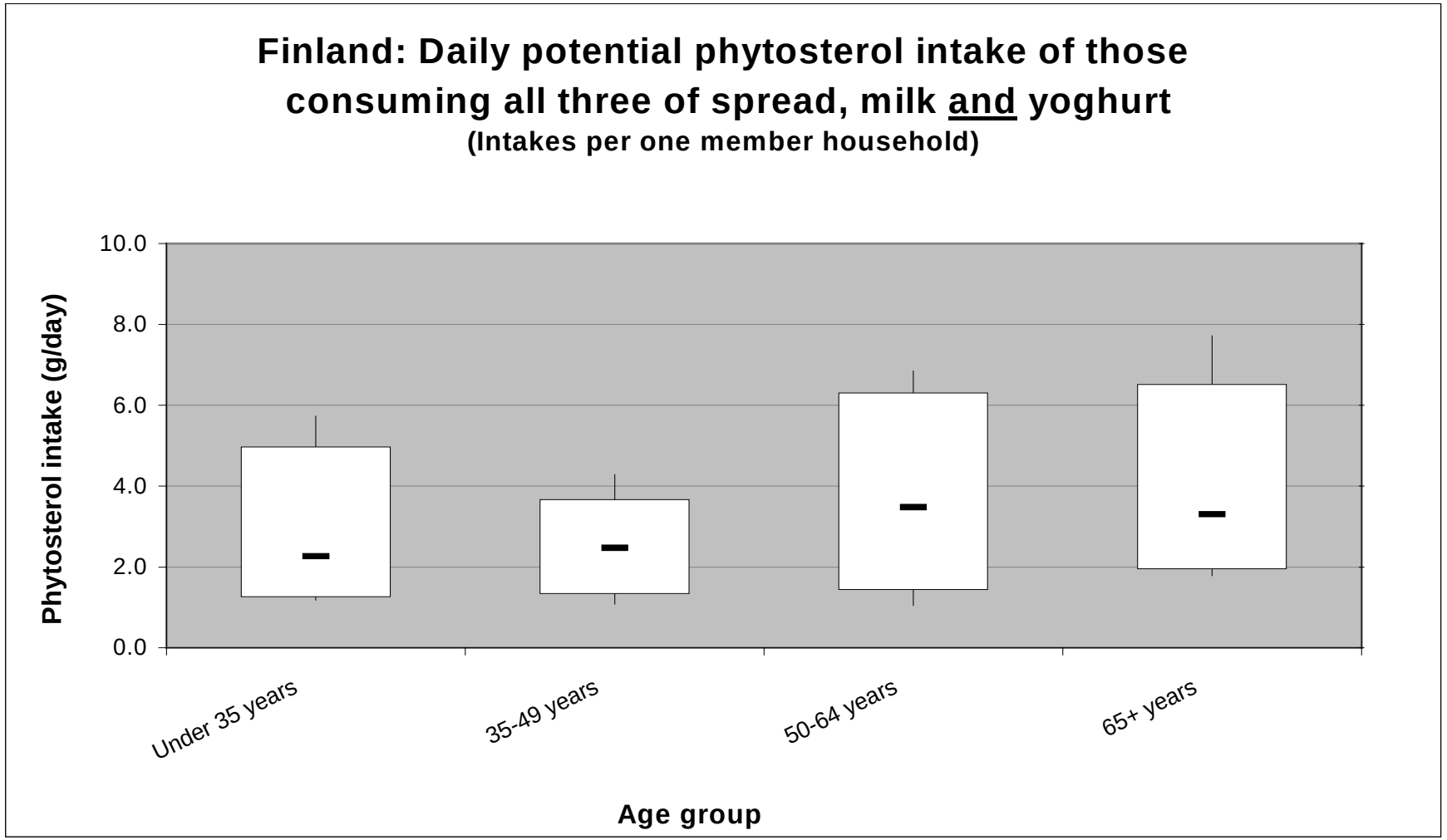
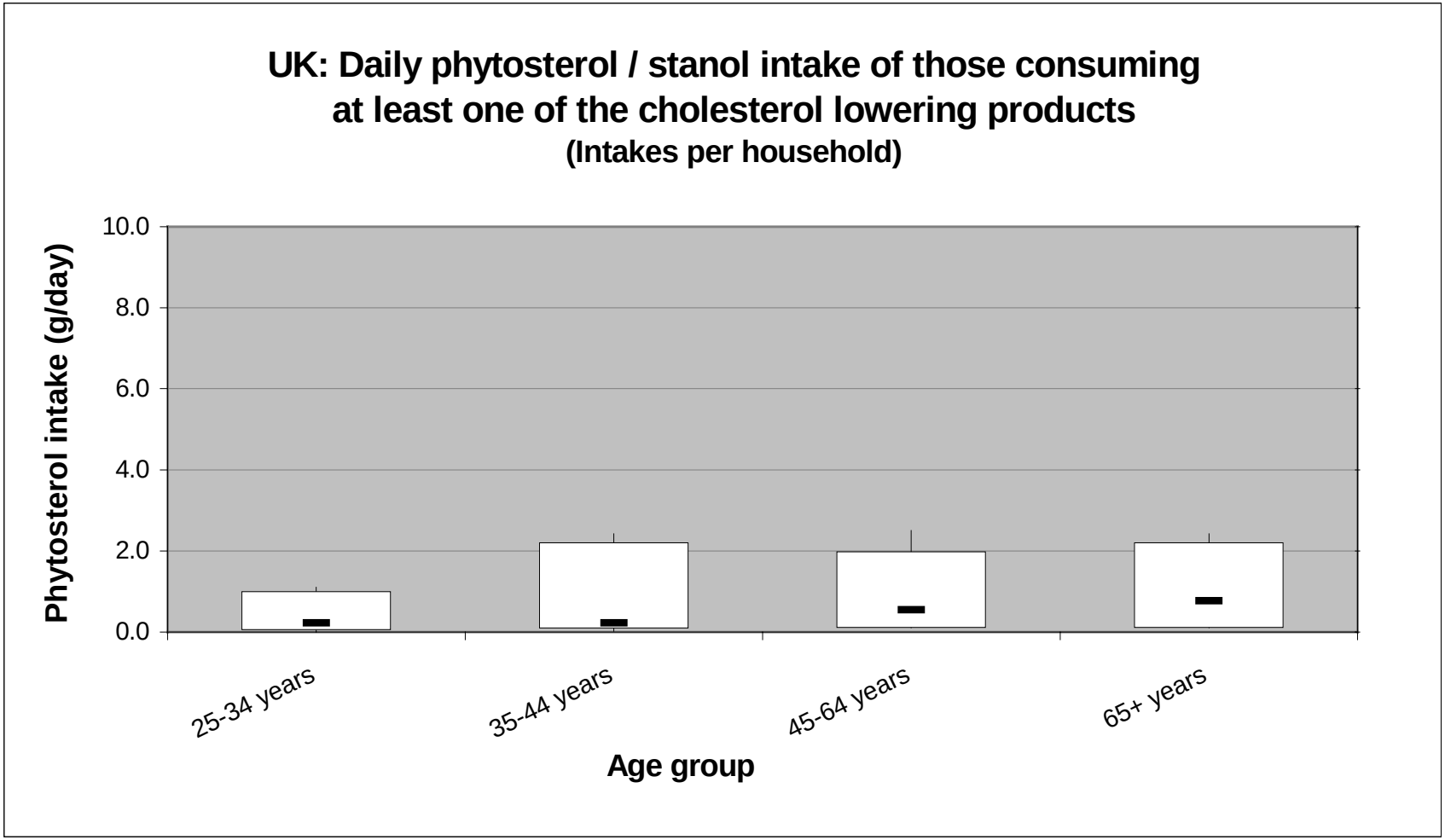


All intakes are given as free (unesterified) phytosterols

APPENDIX 7:

DISTRIBUTION OF PHYTOSTEROL/STANOL INTAKES CALCULATED FROM CONSUMER PURCHASE DATA COLLECTED IN THE UK AND FINLAND ON PHYTOSTEROL/STANOL PRODUCTS



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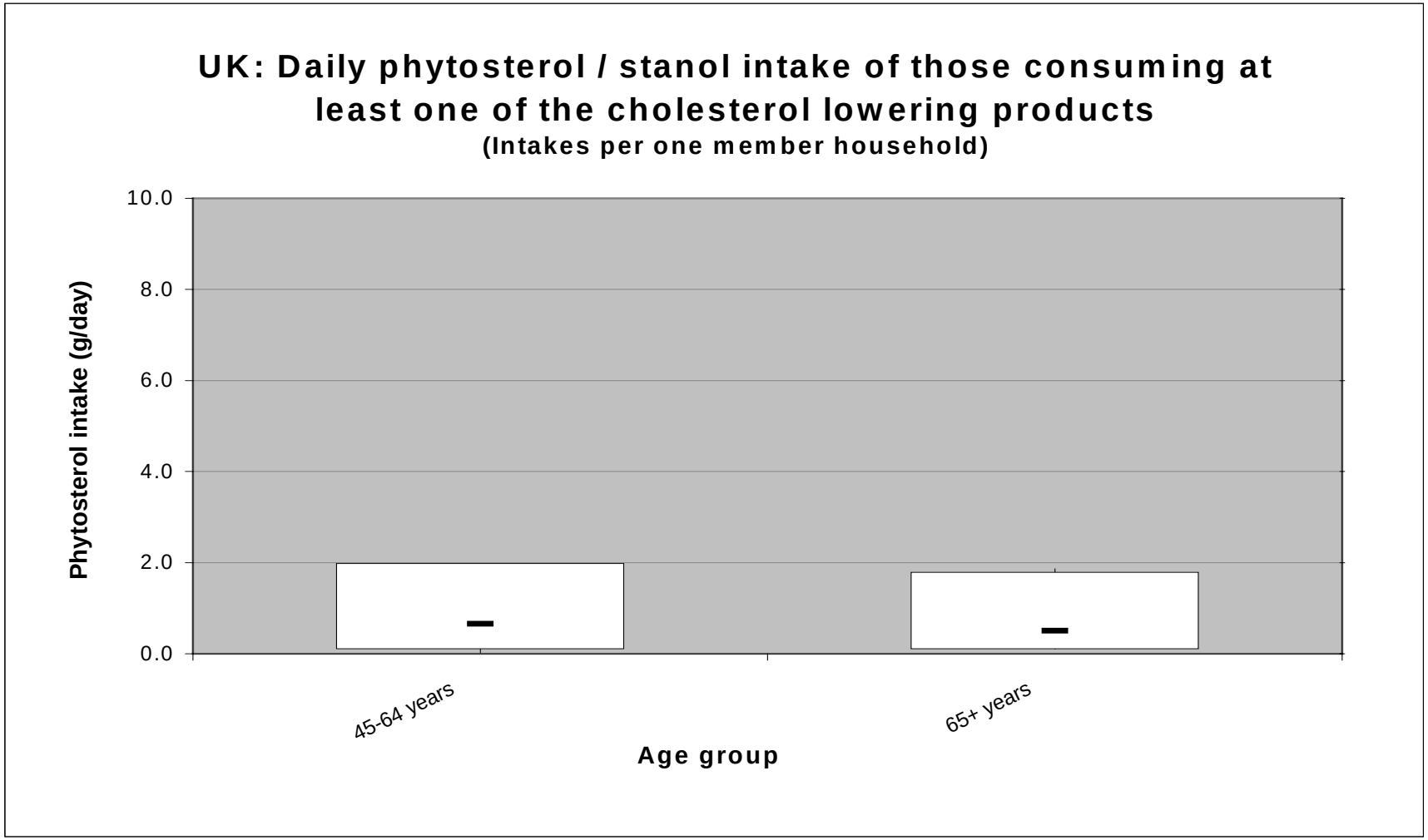

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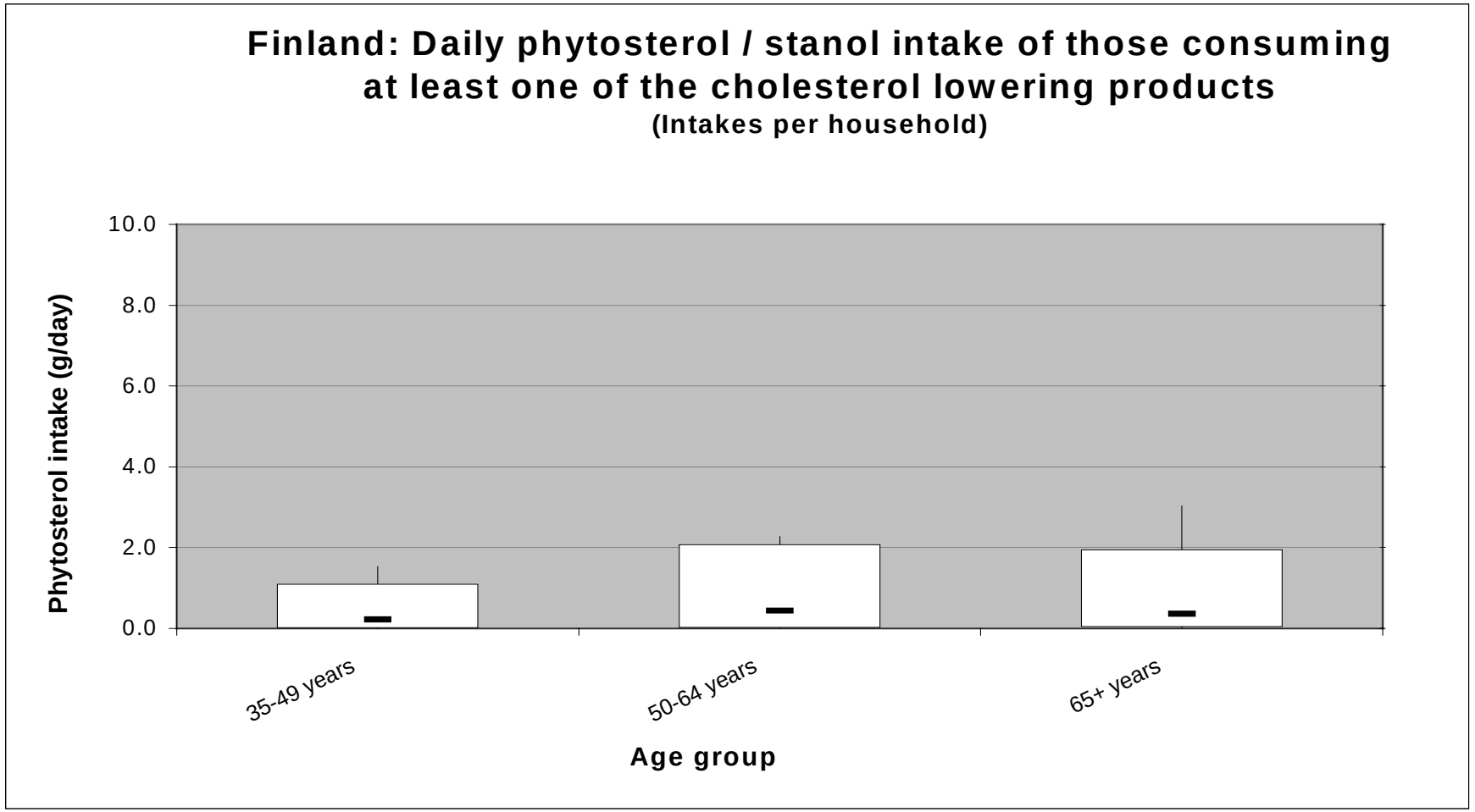

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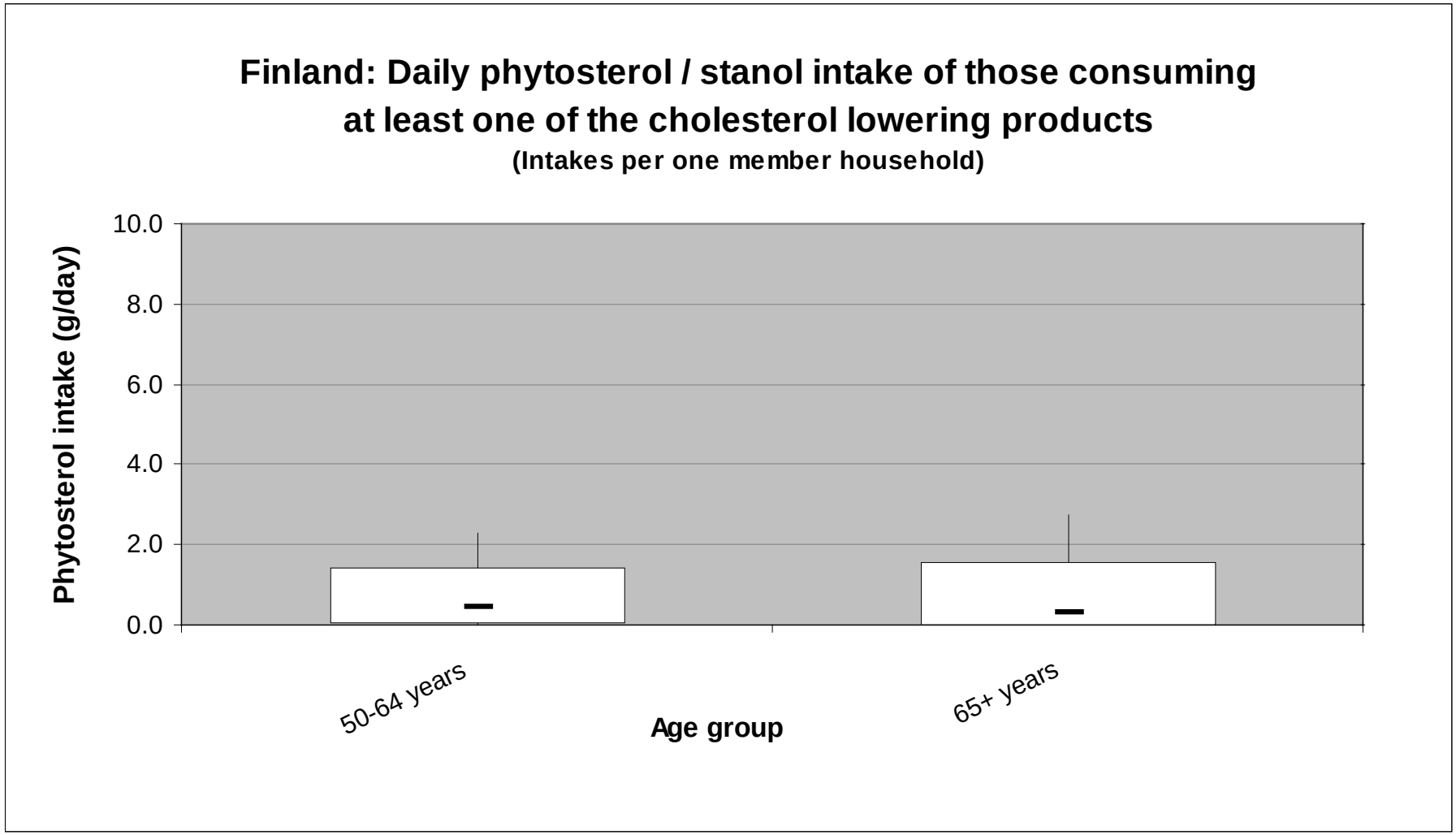

All intakes are given as free (unesterified) phyosterols/stanols