

**Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies  
on a request from the Commission related to a  
Novel Food application from Forbes Medi-Tech  
for approval of plant sterol-containing milk-based beverages**

**(Request N° EFSA-Q-2003-075)**

**(adopted on 25 November 2003)**

## **SUMMARY**

The Scientific Panel on Dietetic Products, Nutrition and Allergies has been asked to assess the safety of Reducol™, a mixture of sterols and stanols of plant origin (tall oil), intended to be used in milk-based beverages for the reduction of plasma levels of total and LDL cholesterol.

In accordance with the previous opinions of the Scientific Committee on Food (SCF) the Panel concluded that Reducol™ can be accepted if the sterol-containing foodstuffs are not consumed in amounts resulting in total phytosterol intakes exceeding 3 g/day. In addition, the composition and purity of the phytosterol mixture should comply with the previous recommendations of the SCF. With regard to  $\beta$ -sitostanol and campestanol, higher contents of 35% and 15%, respectively, were accepted by the Panel since these compounds or their esters have been sufficiently tested toxicologically.

The Panel also reiterated the recommendations expressed in the previous SCF opinions in relation to the need for risk management measures to minimise the likelihood of a daily intake exceeding 3 g phytosterols/phytostanols, the provision of appropriate information to consumers regarding the need for regular consumption of fruits and vegetables to address the potential  $\beta$ -carotene lowering effect of the product, and the particular circumstances of phytosterolemic patients, people under cholesterol-lowering medication and of women during pregnancy and lactation.

## **KEY WORDS**

Plant sterols, plant stanols, phytosterols, phytostanols, milk-based beverages, novel food.

## **BACKGROUND**

Within the framework of Regulation (EC) N° 258/97 on novel foods and novel food ingredients, the Commission has received a request from the company Novartis Consumer Health S.A.-N.V., now Forbes Medi-Tech Inc., for authorisation to place on the market Reducol™, a mixture of sterols and stanols of plant origin (tall oil) as a novel food ingredient. The new ingredient is intended to be used in milk-based beverages, with optional addition of fruits, in order to lower the plasma levels of total cholesterol and LDL cholesterol. Although it is not explicitly stated by the applicant, for the purposes of this evaluation the Panel assumes that the target group is adults with elevated blood cholesterol levels.

The Competent Authority of Belgium concluded in the initial assessment report that the toxicological information submitted by the applicant was not sufficient to conduct a safety evaluation of Reducol™. In particular, studies on reproduction toxicity as well as detailed information on the composition of the phytosterol mixtures used as test materials in the toxicological studies were considered necessary.

The major concerns and suggestions raised by the Competent Authorities of other Member States are:

- potential risks from cumulative and long-term consumption of plant sterols from different products and the necessity to establish a safe level of consumption,
- effects on the absorption of fat-soluble vitamins and carotenoids,
- the specification of the phytosterol mixture and its stability,
- possible consumption by non-target groups, particularly children and pregnant and lactating women,
- the need for appropriate labelling.

After examination of the original dossier, the Scientific Committee on Food (SCF) requested additional information from the applicant regarding the composition and purity of Reducol™, in particular of the sterol mixtures used in the toxicological studies. The data requested have been provided as well as several new toxicological studies and information on the manufacturing process.

This opinion takes into account the information submitted by the applicant, the results of the initial assessment carried out by the Competent Authority of Belgium, the comments/objections to the initial assessment report forwarded by the Member States and the previous opinions of the SCF concerning phytosterols.

The SCF has expressed four opinions on applications for approval of plant sterol-containing foods. The first concerns the safety in the use of phytosterol esters of fatty acids in yellow fat spreads (SCF, 2000). The second opinion addresses the use of non-esterified phytosterols, containing some phytostanols, in bakery products, grain-based snack products, gum arabicum pills, frankfurters, sausages and cold cuts, and a sterol-enriched fat ingredient to be used in yoghurt, fresh cheese, margarine and fruit-milk drinks. In this opinion, the SCF made a recommendation concerning a phytosterol/phytostanol profile of up to 80%  $\beta$ -sitosterol, 15%  $\beta$ -sitostanol, 40% campesterol, 5% campestanol, 30% stigmasterol, 3% brassicasterol and 3% other phytosterols (Table 1) which it considers generally acceptable (SCF, 2003a). The third and fourth opinions concern phytosterols and phytosterol esters of fatty acids to be used in fat spreads, salad dressings, health bars, health drinks, yoghurt type products and processed meats (SCF, 2003b), and dairy products, bakery products, processed meat products, edible fats, condiment (spice) sauces and soft drinks (SCF, 2003c), respectively.

In addition, the SCF has expressed a general view on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources. The Committee concluded that a numerical upper level for the total daily intake of phytosterols could not be established on the

basis of the data available. In consideration of the dosages found to be effective for cholesterol-lowering, without evidence of additional benefit at higher intakes and the possibility that high intakes might induce undesirable effects, it was considered prudent to avoid plant sterol intakes exceeding 3 g/day (SCF, 2002a).

Furthermore, in the evaluation of the first application concerning plant sterols in yellow fat spreads, the SCF required that the applicant should establish a surveillance program accompanying the marketing of the product to obtain data on consumption and for further investigation of possible health effects, including among others the effects on plasma  $\beta$ -carotene levels. The results of this task have also been assessed by the SCF in its opinion on a report on post-launch monitoring of yellow fat spreads with added phytosterol esters (SCF, 2002b).

## TERMS OF REFERENCE

With reference to the initial assessment carried out by the authorities of Belgium, taking into account the relevant comments/objections presented by Member States and pursuant to Article 11 of Regulation (EC) N<sup>o</sup> 258/97, the European Food Safety Authority is asked to assess the safety, from the point of view of consumer health, of Reducol<sup>TM</sup>.

## ASSESSMENT

The applicant has classified the product in class 1.1 (pure chemicals or simple mixtures derived from non-genetically modified sources; the source has a history of food use in the EU) as defined in the SCF recommendations concerning the assessment of novel foods and novel food ingredients (Commission Recommendation 97/618/EC). Regarding the type of information provided, the application followed the procedure recommended for this product class.

### Production process

The phytosterol mixture Reducol<sup>TM</sup> is obtained from tall oil soap, a by-product of the pulping process used for coniferous trees in North America and Europe. Tall oil soap is the lipid layer that forms at the top of the digestion tank when the conifer chips are digested in an alkaline medium to liberate the wood fibres.

Originally, tall oil soap was extracted with water and a mixture of organic solvents (hexane and acetone). Crude phytosterols were obtained from the organic phase by removal of the solvents, complexation of the sterols in the extract with calcium chloride in methanol, separation of the sterol-complexes by centrifugation, dissociation of the complexes by heating in water and removal of the water. The crude phytosterols were further purified by crystallisation from isopropanol.

According to the additional information provided by the applicant, a new production process is now used to produce Reducol<sup>TM</sup>. The tall oil soap is first subjected to fractional distillation which removes volatile compounds. The resulting residue (tall oil pitch) containing sterols in esterified form is treated with alkali to liberate these sterols. After neutralisation, the material is subjected to a two-stage distillation process. The distillate is then dissolved in

methanol/methylethylketone solvent and the sterols crystallising from this solution are obtained by filtration, washed with solvent and dried. Compared with the original process, this procedure leads to a lower stanol and a higher sterol content of the phytosterol mixture. Furthermore southern conifers, which have a naturally lower stanol content compared with the originally-used northern conifers, are now used as the primary source of the tall oil soap. Therefore stanols (obtained by catalytical hydrogenation of the phytosterol mixture) are added before the crystallisation step in order to maintain the original stanol/sterol ratio.

## Compositional data

### *Phytosterol profile*

According to the proposed specification in the original dossier, the total phytosterol content of Reducol™ produced by the original process was >95%, including 36-79% β-sitosterol, 6-34% β-sitostanol, 4-25% campesterol and 0-14% campestanol. For these four major sterols a content of >86% was specified (Table 1).

**Table 1.** Composition of Reducol™, specification proposed by the applicant and phytosterol profile accepted by the SCF (values in %)

	Reducol™ (old process)		Reducol™ (new process)		SCF, 2003a
	Composition	Specification	Composition	Specification	
Total phytosterols	98.1	min. 95	99.7	min. 97	min. 99 <sup>3</sup>
Major phytosterols	88.7	min. 86	92.7	min. 88	
β-Sitosterol	49.1	36-79	59.8	36-79	max. 80
β-Sitostanol	19.9	6-34	23.2	15-34	max. 15
Campesterol	15.0	4-25	6.5	4-25	max. 40
Campestanol	4.7	0-14	3.1	0-14	max. 5
Stigmasterol	Not provided*		Not provided*		max. 30
Brassicasterol					max. 3
Other phytosterols	9.3 incl.* stigmasterol		7.0 incl.* stigmasterol		max. 3

<sup>1</sup> Average of 17 samples; <sup>2</sup> Average of 15 samples; <sup>3</sup> For tall oil-derived phytosterol mixtures.

\* According to additional analyses the content of stigmasterol was below 1%.

The applicant has provided analytical data to show how the composition of Reducol™ produced by the new production process differs from that of Reducol™ obtained with the original method. The contents of the four major phytosterols were determined by gas chromatography with flame ionisation detection (GC-FID; column SAC-5, 30 m x 0.25 mm, 0.25 μm, samples not silylated) using standards for these phytosterols. According to the applicant, the other (minor) phytosterols are for the most part not detectable by GC-FID but can be detected by gas chromatography-mass spectrometry (GC-MS) using the same type of column as indicated above. As no standards were available for the minor sterols, their contents were estimated from GC-MS scans assuming that the response factors for major and minor phytosterols are uniform.

In these analyses Reducol™ obtained by the new production process (15 samples) was found to have higher contents of total and the four major phytosterols, on average 99.7% and 92.7%, respectively, compared with 98.1% and 88.7%, respectively, for Reducol™ from the original process (17 samples). On the basis of these data, the applicant has revised the specification with regard to total phytosterols, now >97%, major phytosterols, now >88% and sitostanol, now 15-34%. In addition, Reducol™ obtained by the new process was found to have a lower average content of minor sterols including stigmasterol, 7.0% (3.4-9.8%) compared with 9.3% (4.6-14.7%) for Reducol™ obtained by the original process (Table 1).

In addition, Reducol™ (2 samples from the original and 3 from the new process) was compared with the phytosterols present in fat spreads which are already on the market, namely Unilever (2 samples) and Benecol (4 samples), and also to vegetable oil-derived phytosterols used by the company ADM (1 sample) which have recently been evaluated by the SCF (SCF, 2003b). Using GC-MS (VA-5MS column, 30 m x 0.25 mm, 0.25 µm) a total of 24 phytosterol compounds were identified in Reducol™.

It should be noted, however, that the numerical values determined in this study for the samples tested, differed in part considerably from the values obtained in the GC-FID and GC-MS analyses mentioned above. For example, the average content of total minor sterols in the two Reducol™ samples from the original process was found to be much higher, 17.8% vs. 9.4%, whereas in the three Reducol™ samples from the new process it was found to be much lower, 1.5% vs. 8.3%. According to the author of the study report, accurate quantification would require the use of pure standards for each compound detected, which are currently not available for all the minor phytosterols. Therefore, the GC-MS analysis should be considered as semi-quantitative.

Reducol™ was further compared with a tall oil-derived phytosterol mixture obtained from the company Teriaka Ltd. which has recently been evaluated by the SCF (SCF, 2003a). Using GC-FID (HP1 column, 25 m x 0.2 mm, 0.11 µm, silylated samples), the contents of major and minor sterols in Reducol™ obtained by the new process (4 samples) and the Teriaka product (1 sample) were found to be similar, 93.0-95.0% vs. 93.4% and 2.3-2.6% vs. 2.0%, respectively. In addition, approximately 2% unidentified materials were detected in all samples, which, according to the applicant, were probably contaminants from the GC system.

The same samples were analysed with a different GC-FID method (HP-1 column, 6 m x 0.53 mm, 0.15 µm, samples silylated) and found to have a total phytosterol content of approx. 99.7%. This is the same degree of purity as that of a tall oil-derived phytosterol mixture obtained from the company Teriaka Ltd. which has recently been evaluated by the SCF (SCF, 2003a).

### ***Potential impurities***

Applying GC-MS, Reducol™ obtained by the original (two samples) and the new process (three samples) were found to contain 9 and 4 non-phytosterol compounds, respectively. These were identified as long-chain aliphatic alcohols with chain lengths from C14 to C26. According to the applicant, these waxy materials are common components in foodstuffs of plant origin. The total content of non-sterol compounds was lower in Reducol™ obtained by the new process compared with the original procedure (0.07-0.19% versus 0.41-0.43%). Terpenes,

terpene alcohols, resin aldehydes or resin acids which are typical constituents of tall oil, as well as oxidation products of phytosterols were not detected.

Preliminary analytical study reports were submitted showing that 7 polychlorinated biphenyls (PCBs), 12 polycyclic aromatic hydrocarbons (PAH), among which 9 compounds were classified as carcinogens, and residues of 43 pesticides and herbicides were not detected in Reducol™ obtained by the new process. According to a table which summarises the results of further analytical studies, the levels of lead, cadmium, mercury and arsenic were below the detection levels of the methods applied and solvent (methanol) residues were <5000 mg/kg. The respective certificates of analyses, however, have not been provided.

The Panel notes that the methanol content of Reducol™ should comply with the maximum limit in Council Directive 92/115/EEC on extraction solvents. In addition, Reducol™ should comply with the recommendations on potential contaminants in the SCF's report on smoke flavourings (SCF, 1993).

### **Anticipated intake**

The applicant has recommended an intake of phytosterols of approximately 1.8 g/day consumed in three portions of approximately 115 mL of a milk-based beverage each, amounting to approximately 350 mL in total. Taking an estimated intake of approximately 0.2-0.4 g/day from natural sources into account, a total phytosterol intake of approximately 2.0-2.2 g/day would result.

The applicant gives examples of the intake of plant sterols in case the above recommendation was not followed. A milk-based beverage consumption of, for example, 450 mL/day would give a total intake of approximately 2.5-2.7 g phytosterols/day. If a person with a high level of consumption of milk and milk products, for example 1100 mL in total (this is the 95<sup>th</sup> percentile consumption of Swedish elderly), replaced all these products by phytosterol-containing milk-based beverages, a total phytosterol intake of 5.9-6.1 g/day would result.

### **Nutritional information**

The applicant refers to previous studies with phytosterols/phytostanols that have already been evaluated by the SCF (SCF, 2000, 2002a, 2003 a, b and c). In addition, several unpublished human studies were provided using Phytrol™ which, according to the petitioner, is another trade name for Reducol™. The test materials were produced by the original process.

In three randomised double-blind, placebo-controlled studies with a limited number of subjects approximately 1.5 g Phytrol™/day were administered in controlled diets to healthy normolipidemic or hypercholesterolemic subjects for periods of 10 or 30 days. In two of these studies statistically significant decreases in mean plasma total and LDL cholesterol levels without relevant changes in HDL cholesterol and triglyceride levels were observed compared to administration of a placebo. In the third study with hypercholesterolemic subjects there were slight or no reductions in mean plasma total and LDL cholesterol levels, respectively, in the treatment group but unexpected increases in the placebo group.

A randomised double-blind, placebo-controlled study was conducted with a total of 134 male and female free living subjects with primary hypercholesterolemia of which 113 completed the study. Study groups received either 1.8 g Phytrol™ per day (50-60%  $\beta$ -sitosterol, 16-21%  $\beta$ -sitostanol and 15-18% campesterol as main components) in a nutritional bar, divided in three doses, or nutritional bars without Phytrol™ for 8 weeks. Treatment with Phytrol™ induced statistically significant decreases of total and LDL cholesterol levels but had no effect on HDL cholesterol levels. According to the applicant, Phytrol™ did not seem to influence plasma vitamin A and E levels negatively. Data on the statistical significance, however, were not provided. There was no statistically significant difference in  $\beta$ -carotene levels between the groups which both showed a 10-15% decrease at the end of treatment.

A randomised double-blind placebo-controlled study with Phytrol™ incorporated into a milk-based beverage was conducted with a total of 132 subjects with primary hypercholesterolemia of which 98 completed the study. Phytrol™ in oil was administered in a lactose-free milk preparation at three dose levels of 0.9, 1.8 or 3.6 g/day divided in three portions for 28 days. The controls received the milk preparation with Phytrol™-free oil. Among the subjects who completed the study, the groups receiving 1.8 and 3.6 g Phytrol™/day had statistically significantly reduced total cholesterol levels at the end of the treatment period compared to baseline. The differences from the placebo control group were -5.5 and -9.1%, respectively. All three treatment groups had statistically significantly reduced LDL cholesterol levels compared to baseline. The differences from the placebo control group were -7.4, -8.6 and -13.2%, respectively. There were no relevant effects on HDL cholesterol and triglyceride levels. Phytrol™ treatment did not affect the plasma levels of the vitamins A and E. Plasma levels of  $\beta$ -carotene were not different compared to those in the placebo group, however,  $\alpha$ -carotene levels were significantly lower (approx. 18%) in the highest dose group. Reductions of plasma  $\alpha$ -carotene levels as well as reductions of other fat-soluble nutrients of varying degrees were observed in several human trials. These effects were considered by the SCF in the previous evaluation of phytosterols (SCF, 2002a).

## Toxicological information

### *Studies with phytosterol mixtures produced by the original process*

In addition to previous studies already evaluated by the SCF (SCF, 2000, 2002a, 2003 a, b and c), several toxicological studies were carried out with Phytrol™ (unpublished).

Phytrol™ was negative in the mammalian microsome reverse mutation assay with *S. enterica* Typhimurium (Ames Test), a gene mutation assay with *E. coli*, the mouse lymphoma assay and the mouse bone-marrow micronucleus test. From a test on chromosome aberrations with human peripheral blood lymphocytes the petitioner did not draw conclusions concerning the clastogenic activity because the dose levels selected were not adequate. The samples tested contained 94.4% total phytosterols, including 55.4%  $\beta$ -sitosterol, 16%  $\beta$ -sitostanol, 14.6% campesterol, 3.1% campestanol and 5.3% total minor sterols (determined by GC-FID combined with GC-MS).

In a subchronic feeding study (13 weeks) groups of 24 male and female Sprague-Dawley rats received diets with 0, 1.25, 2.5 or 5% Phytrol™. In this study two batches containing 100.3/99.3% total phytosterols, 39.6/43.8%  $\beta$ -sitosterol, 30.9/25.4%  $\beta$ -sitostanol, 13.9/11.8%

campesterol, 11.3/6.1% campestanol and 4.6/12.2% total minor sterols (determined by GC-FID combined with GC-MS) were used as test materials. There was no treatment-related mortality (4 male animals from different groups died, probably as a result of a rise in temperature in the animal room to 100 °F on days 90 and 91). There were no adverse clinical signs or treatment-related effects on body weight, feed efficiency, physical, ophthalmological, hematological, serum chemistry and urine analysis parameters, organ weights and sperm concentration, motility and morphology. Gross and histopathological examinations of organs and tissues revealed no toxicologically relevant effects. The serum levels of vitamins A and E were not changed and the levels of vitamins D, K, and beta-carotene were below the limit of quantification of the assays. There were no consistent dose-related statistically significant changes in total serum phytosterol concentrations compared to the controls. The no-observed adverse effect level (NOAEL) was 5% in the diet corresponding to a dose of 4161 mg/kg body weight/day.

In an uterotrophic assay with immature female rats groups of 10 animals received daily doses of 0, 1000, 2500 and 5000 mg Phytrol™/kg body weight by oral gavage beginning on day 19 postpartum for four consecutive days. Administration of the test material did not affect absolute or relative uterine weights up to the highest dose of 5000 mg/kg body weight/day. Uterine weights were increased in a positive control group which received 17 $\alpha$ -ethinyl estradiol at a dose of 0.030 mg/kg body weight/day. The test material contained approx. 100% total phytosterols, 39.6%  $\beta$ -sitosterol, 30.9%  $\beta$ -sitostanol, 13.0% campesterol, 11.3% campestanol and 4.6% total minor sterols (one of the samples used also in the 90-day rat study).

#### ***Studies with phytosterol mixtures produced by the new process***

The following studies were carried out with Reducol™ containing 99.2% total phytosterols, including 63.5%  $\beta$ -sitosterol, 21.7%  $\beta$ -sitostanol, 6.5% campesterol, 2.8% campestanol and 4.7% total minor sterols (determined by GC-FID combined with GC-MS).

Reducol™ was negative in the mammalian microsome reverse mutation assay with *S. enterica* Typhimurium (Ames Test) and a gene mutation assay with *E. coli*. The phytosterol mixture was not clastogenic in tests on chromosome aberrations with human peripheral blood lymphocytes.

In a subchronic feeding study (13 weeks) groups of 20 male and female Sprague-Dawley rats received diets with 0, 1.25, 2.5 or 5% Reducol™. Mortality was not observed. There were no adverse clinical signs and no relevant treatment-related effects on body weight, feed efficiency, physical, ophthalmological, hematological and urine analysis parameters and organ weights. Gross and histopathological examinations of organs and tissues revealed no toxicologically relevant effects. Apart from statistically significant increase in serum activities of the enzymes alanine aminotransferase and  $\gamma$ -glutamyltransferase in female rats receiving 2.5 and 5% as well as elevated levels of urea and non-HDL cholesterol levels in females receiving 5%, there were no notable changes in clinical chemical parameters compared to the controls. As these effects were within historical control ranges they were not considered clinically relevant. Therefore the no-adverse-effect-level (NOAEL) in this study can be regarded as 5% in the diet corresponding to doses of 4137 and 4646 mg/kg/day for male and female rats, respectively.



## Comment

Reducol™ produced by the new process was tested for genotoxicity (gene mutations in bacteria and chromosomal aberrations with human lymphocytes) and subchronic toxicity and was found not to induce effects of biological relevance. Studies on reproductive and developmental toxicity and oestrogenic activity were not provided. On the other hand, such studies have been carried out with other phytosterol mixtures having a similar composition (SCF 2000, 2002a). As in the case of other mixtures evaluated previously these studies can also be applied to assess the safety of Reducol™. On the basis of these studies the SCF concluded that phytosterol/phytostanol mixtures complying with a certain compositional profile (Table 1) are safe for consumption (SCF, 2003a, b and c).

The composition of Reducol™ does not comply fully with the phytosterol/phytostanol profile of up to 80%  $\beta$ -sitosterol, 15%  $\beta$ -sitostanol, 40% campesterol, 5% campestanol, 30% stigmasterol, 3% brassicasterol and 3% other phytosterols, based on total sterol content (w/w), which has been considered generally acceptable by the SCF (SCF, 2003a). The contents of the major sterols  $\beta$ -sitosterol and campesterol are in accordance with the accepted profile. According to the specification, however, Reducol™ can contain up to 34%  $\beta$ -sitostanol and 14% campestanol. The higher contents of these phytosterols are acceptable since esters of  $\beta$ -sitostanol and campestanol were main constituents of the stanol ester mixtures tested in studies on genotoxicity, subchronic toxicity, reproductive toxicity, developmental toxicity and oestrogenic activity (SCF, 2002a). In addition, Reducol™ samples containing relatively high amounts of  $\beta$ -sitostanol were tested for genotoxicity (up to 21.7%), subchronic toxicity and oestrogenic activity (30.9%) without inducing effects causing concerns.

According to the applicant, the content of other phytosterols in Reducol™ is below the 3% established by the SCF as the limit for the content of minor sterol constituents. The SCF came to this conclusion since esters of other sterols were only minor constituents of the phytosterol ester mixtures tested for subchronic and reproductive toxicity (SCF, 2000 and 2003a). The analytical method applied to determine the phytosterol composition of the test materials used in these studies was developed by the company Unilever (transesterification, HPLC isolation of desmethylsterols and subsequent GC-FID analysis using a 50 m column coated with a CP-SIL 13CB stationary phase, 0.2  $\mu$ m).

However, the contents of other phytosterols determined in the various analytical studies differed considerably in part depending on the methods applied. For example, one sample was found to contain 2.6% in a GC-FID analysis compared to 4.7% determined by a GC-MS method. Three samples analysed by two different GC-MS methods were found to have varying average contents of 8.3% and 1.5%.

Therefore it is important to compare and evaluate the various analytical methods used in different laboratories to determine the phytosterol composition with the objective of laying down a method that is generally accepted. The application of a defined methodology is particularly important, since phytosterol mixtures intended to be used by other manufacturers, which have already been evaluated by the SCF, were also found to have higher contents of minor phytosterols in the comparative analytical studies provided by the applicant.

The same applies to the determination of purity. According to the SCF, tall oil-derived phytosterol mixtures must contain >99% total phytosterols/phytostanols. Although the different methods applied yielded relatively consistent values for the total sterol contents, on average 99.7%, the analytical techniques to determine the total phytosterol content have to be defined as well.

The applicant notes that subgroups of hypercholesterolemic subjects with mild hyperphytosterolaemia should be considered as a potential risk group in addition to the risk groups considered by the SCF (SCF 2000, 2002a, 2003a, b and c). The hallmark of phytosterolaemia is diagnostically elevated blood levels of plant sterols. The SCF has previously indicated that in phytosterolaemia, a rare autosomal recessive disorder, affected individuals hyper-absorb and retain not only cholesterol but also other (plant, sea fish, etc.) sterols resulting in a number of medical complications (SCF, 2002a). Studies showed that intakes around 3 g/day equally affected or minimally increased sitosterol plasma concentrations in heterozygotes compared with healthy controls (SCF, 2003c). While the studies available provide no evidence of adverse effects associated with a small increase of plasma phytosterols, more information on possible effects of long-term exposure to higher intakes of plant sterols is needed (SCF, 2002a).

## CONCLUSIONS AND RECOMMENDATIONS

In accordance with the previous opinions of the SCF, the Panel concludes that Reducol™ can be accepted provided that the sterol-containing foodstuffs are not consumed in amounts resulting in total phytosterol intakes exceeding 3 g/day. In addition, the composition of the phytosterol mixture should comply with the previous recommendations of the SCF (SCF, 2002a, 2003a, b and c).

Therefore the mixture should not contain more than 3% total other sterols in addition to  $\beta$ -sitosterol,  $\beta$ -sitostanol, campesterol, campestanol and stigmasterol. In addition, the total sterol/stanol content of this tall oil-derived phytosterol mixture should be more than 99%. With regard to  $\beta$ -sitostanol and campestanol higher levels of 35% and 15%, respectively, are acceptable since these compounds or their esters have been sufficiently tested toxicologically (SCF, 2002a).

Furthermore, the Panel reiterates the previous recommendation of the SCF that appropriate risk management measures should be developed to minimise the likelihood of a daily intake exceeding 3 g phytosterols/phytostanols, in particular from the cumulative intakes of different types of products (SCF, 2002a, 2003a, b and c).

In this application the sterols in question are intended to be solely added to (milk-based) beverages. In accordance with the SCF the Panel reiterates the general concern that with regard to the sterol intake from beverages, portion sizes are difficult to control.

The Panel also reiterates the SCF recommendations:

- that the small number of people with inborn error of phytosterol metabolism (phytosterolaemia) should be made aware of the presence of higher levels of phytosterols in the product,

- that patients on cholesterol-lowering medication should only consume the products under medical supervision, and
- that the potential  $\beta$ -carotene lowering effect should be communicated to the consumer, together with appropriate dietary advice regarding the regular consumption of fruits and vegetables.

The Panel also reiterates the conclusion of the SCF that the consequences of persistently decreased blood concentrations of  $\beta$ -carotene on human health are largely unknown and that situations where vitamin A requirements are greater than normal as in pregnancy, lactation or infancy may be of concern (SCF, 2002a, 2003a, b and c).

### **DOCUMENTATION PROVIDED TO EFSA**

Dossier on Reducol™ submitted by Novartis Consumer Health S.A.-N.V., September 2000.

Supplementary information submitted on request of the Competent Authority of Belgium, December 2000.

Additional information to the novel food dossier on Reducol™ submitted by Bioresco Ltd., on behalf of the petitioner Forbes Medi-Tech Inc., June 2003.

Additional information to the novel food dossier on Reducol™ submitted by Bioresco Ltd., on behalf of the petitioner Forbes Medi-Tech Inc., July 2003.

### **REFERENCES**

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## PANEL MEMBERS

Wulf Becker, Daniel Brasseur, Jean-Louis Bresson, Albert Flynn, Alan A. Jackson, Pagona Lagiou, Geltrude Mingrone, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Stefan Strobel and Hendrik van Loveren.

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