

Plant Sterols and Blood Cholesterol

Scientific substantiation of a health claim related to plant sterols and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006¹

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2008-085)

Adopted on 11 July 2008

PANEL MEMBERS

Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

SUMMARY

Following an application from UNILEVER PLC (United Kingdom) and UNILEVER N.V. (Netherlands), submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Sweden, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to “Plant sterols and lowering/reducing blood cholesterol and reducing the risk of coronary heart disease”.

The scope of the application was proposed to fall under a health claim referring to a reduction of a disease risk.

In the context of this application, the term plant sterols (present as free sterols or esterified) refers specifically to plant sterols from natural sources with a composition as specified in the Commission Decisions authorising the placing on the market of food products with added plant sterols under Regulation (EC) No 258/97. The Panel considered that the plant sterols for which the health claim is proposed have been sufficiently characterised.

Elevated low-density lipoprotein (LDL) blood cholesterol is one recognised risk factor for coronary heart disease (CHD). CHD is an important cause of mortality and morbidity. Lowering LDL-cholesterol by dietary intervention has been shown to reduce the risk of coronary heart disease. The Panel considers that the claimed effect of lowering LDL-cholesterol is beneficial to human health.

¹ For citation purposes: Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from Unilever PLC/NV on Plant Sterols and lower/reduced blood cholesterol, reduced the risk of (coronary) heart disease. *The EFSA Journal* (2008) 781, 1-12.

The applicant has provided evidence supporting the cholesterol-lowering effect of plant sterols added to fat-based foods such as fat spreads and low-fat foods such as milk and yoghurt. A meta-analysis of 41 trials showed that an intake of 2 – 2.4 g/day of sterols added to margarine (or to mayonnaise, olive oil or butter in 7 trials) reduced average LDL-cholesterol by 8.9%. The applicant also provided a still unpublished meta-analysis showing that an average intake of 2.15 g/day of plant sterols when added to fat-based foods or low-fat foods such as milk and yoghurt lowers LDL-cholesterol by 8.8%. On the basis of the data presented, a clinically significant LDL-cholesterol effect of about 9% can be achieved by a daily intake of 2 – 2.4 g of phytosterols in an appropriate food (e.g. plant sterols added to fat-based foods and low-fat foods such as milk and yoghurt). The magnitude of the cholesterol-lowering effect may differ in other food matrices. The Panel concludes that a cause-effect relationship has been established between the consumption of plant sterols and lowering of LDL cholesterol, in a dose-dependent manner.

With respect to the association of LDL-cholesterol lowering with reduction in the risk of coronary heart disease the Panel considers that there is evidence that the risk of CHD can be reduced by cholesterol-lowering therapy including dietary intervention strategies. However, there are no studies demonstrating that plant sterols have an impact on population-based CHD morbidity and mortality rates.

The Panel considers that products to which phytosterols are added should be consumed only by people who need and want to lower their blood cholesterol and that patient on cholesterol-lowering medication should only consume the product under medical supervision.

The Panel discussed the wording proposed by the applicant and considers that the following wording reflects the available scientific evidence: “Plant sterols have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease”.

Key words: Plant sterols, coronary heart disease, phytosterols, blood cholesterol, novel food ingredient(s)

Table of Content

Panel Members	1
Summary	1
Background	4
Terms of reference.....	4
EFSA Disclaimer.....	4
Acknowledgements	5
1. Information provided by the applicant	6
1.1. Food/constituent as stated by the applicant	6
1.2. Health relationship as claimed by the applicant.....	6
1.3. Wording of the health claim as proposed by the applicant.....	6
1.4. Specific conditions for use as proposed by the applicant	6
1.5. Similar claims as proposed/authorized by other entities.....	7
2. Assessment	7
2.1. Characterisation of the food/constituent	7
2.2. Relevance of the claimed effect to human health	7
2.3. Scientific substantiation of the claimed effect	7
2.4. Panel's comments on the proposed wording.....	9
2.5. Conditions and restrictions of use.....	9
Conclusions	9
Documentation provided to EFSA	10
References	10

BACKGROUND

Regulation (EC) No 1924/2006² harmonises the provisions that relate to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. Health claims are prohibited unless they comply with the general and specific requirements of that Regulation and are authorised in accordance with this Regulation and included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 14 to 17 of that Regulation lay down provisions for the authorization and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of that Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to European Food Safety Authority (EFSA).

Steps taken by EFSA:

- The application was received on 11/10/2007.
- The scope of the application was proposed to fall under a health claim referring to a reduction of a disease risk.
- During the check for completeness³ of the application, the applicant was requested to provide missing information on 30/10/2007.
- The applicant provided the missing information on 14/03/2008.
- The application was considered valid by EFSA and the scientific evaluation procedure started on 15/04/2008.
- During the meeting on 11/07/2008, the NDA Panel, after having evaluated the overall data submitted adopted an opinion on plant sterols.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue a scientific opinion on the scientific substantiation of a health claim related to: "Plant sterols and lowering/reducing blood cholesterol and reducing the risk of (coronary) heart disease".

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of phytosterols, a positive assessment of its safety, nor a decision on whether phytosterols is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim and the conditions of use as proposed by the applicant may be subject to changes pending the scientific

² European Parliament and Council (2006). Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

³ In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

evaluation by EFSA, and ultimately pending the outcome of the authorization procedure foreseen in Article 17 Regulation (EC) No 1924/2006.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group for the preparation of this opinion: Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Hannu Korhonen, Ambroise Martin, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

1. Information provided by the applicant

Applicant's name and address: UNILEVER PLC/NV ; Unilever PLC: Port Sunlight, Wirral, Merseyside, CH62 4ZD, UK and Unilever NV: Weena 455, Rotterdam, 3013 AL, Nederland

1.1. Food/constituent as stated by the applicant

The plant sterols concerned in the present application are those defined in the various commission decisions on authorizing, under the Novel Foods Regulation EC 258/97, the placing on the market of products with added plant sterols (Decision 2000/500/EC, 2004/333-336/EC, 2004/845/EC, 2006/58-59/EC).

1.2. Health relationship as claimed by the applicant

“Plant sterols” (presented as free sterols or esterified) are the substance, “blood cholesterol” the risk factor and “coronary heart disease” (CHD) the human disease.

1.3. Wording of the health claim as proposed by the applicant

“Plant sterols have been proven to lower/reduce blood cholesterol significantly. Blood cholesterol lowering has been proven to reduce the risk of (coronary) heart disease”.

“Plant sterols are proven to lower/reduce blood cholesterol significantly. Blood cholesterol lowering is proven to reduce the risk of (coronary) heart disease”.

“Product x contains (added) plant sterols proven to lower/reduce blood cholesterol. Blood cholesterol lowering reduces/has been proven/shown to reduce the risk of (coronary) heart disease”.

1.4. Specific conditions for use as proposed by the applicant

With respect to the specified conditions of use, it is stated that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products making the proposed reduction of disease risk claim. This includes among other information, information on the target group, on who should avoid using the food, on portion communication and on maximum levels of consumption:

- Statement that the product is intended exclusively for people who want to lower their blood cholesterol;
- Statement that patients on cholesterol lowering medication should only consume the product under medical supervision;
- Statement that the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years;
- Definition of a portion of the food with a statement of the plant sterol amount that each portion contains;
- Statement that the consumption of more than 3g/day of added plant sterols should be avoided.

The applicant proposes that the claim can be made if the product(s) provide(s) a minimum daily intake of 2 g of added plant sterols. Furthermore it is proposed that the claim can be made for

products with added plant sterols as authorized to date by Commission Decisions 2000/500/EC, 2004/333-336/EC, 2004/845/EC and 2006/58-59/EC (yellow fat spreads; milk type and yoghurt type products; salad dressings; fermented milk type products; soya drinks; cheese type products; spicy sauces and rye bread) and subsequent products authorized under Regulation (EC)

No 258/97 authorizing the placing on the market of products with added plant sterols.

1.5. Similar claims as proposed/authorized by other entities

The US Food and Drug Administration (FDA), the Swedish Nutrition Foundation and The Netherlands Nutrition Centre have already approved health claims for plant sterols which are similar to those proposed in this application.

The applicant also lists various international and national organisations which endorse the consumption of 2g/day of plant sterols to lower LDL-cholesterol: International Atherosclerosis Society (2003); National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) (USA); American Heart Association (AHA) (USA); Heart Foundation of Australia; Lipid Management Guidelines of Australia (endorsed by, among others, National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand, Australian Atherosclerosis Society, National Stroke Foundation, Internal Medicine Society of Australia and New Zealand, The Royal Australian College of General Practitioners); and The Flemish Dietetic Association (Belgium).

2. Assessment

2.1. Characterisation of the food/constituent

Plant sterols are naturally occurring compounds structurally similar to cholesterol. Around 300 plant sterols have been identified so far. In the context of this application, the term, plant sterols (present as free sterols or esterified), refers specifically to plant sterols from natural sources with a composition as specified in the Commission Decisions authorising the placing on the market of food products with added plant sterols under Regulation (EC) No 258/97 (Commission Decisions 2000/500/EC, 2004/333-336/EC, 2004/845/EC and 2006/58-59/EC) and subsequent products authorised under Regulation (EC) No 258/97 for the placing on the market of products with added plant sterols. The Panel concluded that the particular plant sterols for which the health claim is proposed have been sufficiently characterised.

2.2. Relevance of the claimed effect to human health

Coronary heart disease (CHD) is a leading cause of mortality and morbidity in European populations with over 1.9 millions deaths in the European Union and over 4.35 million deaths in Europe each year (Petersen et al., 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002).

It has been shown that blood cholesterol can be reduced by drugs and by dietary and lifestyle changes (Denke, 2005; Gordon, 2000; Katan, et al., 2003; Law, 2000; Ornish et al., 1998; van Horn et al., 2008). The Panel considers that the claimed effect of lowering LDL-cholesterol is beneficial to human health.

2.3. Scientific substantiation of the claimed effect

The review of the human data made by the applicant was considered as comprehensive and pertinent data have been identified and included in the application.

LDL-cholesterol lowering effect

There are many human studies, showing that phytosterols in the form of supplements or enriched conventional food products can lower blood total- and LDL-cholesterol concentrations and the body of evidence has been previously reviewed and published (Berger et al., 2004; Katan et al., 2003; Law, 2000; Moreau et al., 2002).

The review by Katan et al. (2003) is a meta-analysis of 41 randomised placebo-controlled, double-blind clinical trials (RCT) showing that the daily intake of 2 to 2.4 g/d of plants sterols or stanols added to margarine (or to mayonnaise, olive oil or butter in 7 trials) reduced on average low-density lipoprotein (LDL) blood cholesterol levels by 8.9% (95 CI: 7.4-10.5). The dose-response relationship seems to level off at doses higher than 2.5 g/d and the average maximum effect was estimated to be 11.3% (95% CI: 10.2-12.3). Testing doses of 0.7 to 1.1 g/day resulted in an average LDL cholesterol lowering effect of 6.7% (95% CI: 4.9-8.6). The effect of the sterols and stanols on LDL-cholesterol is primarily established within a few weeks and seems to remain stable in studies lasting one year. No adverse effect on HDL-cholesterol has been observed.

Other RCT have confirmed that multiple daily intakes of phytosterols in the form of low-fat foods such as milk and yoghurt as well as single doses of 2-3 g/day phytosterols incorporated in low-fat food formats such as yoghurts and yoghurt mini-drinks significantly lower LDL-cholesterol concentrations (Beer et al., 2001; Clifton et al., 2004; Doornbos et al., 2006; Mensink et al., 2002; Noakes et al., 2005; Algorta et al., 2005; Thomsen et al., 2004; Volpe et al., 2001). A confidential unpublished meta-analysis provided by the applicant and including 84 placebo-controlled, randomized parallel or cross-over trials showed that an average intake of 2.15 g/ day of plant sterols when added to fat-based food or low-fat food such as milk and yoghurt lowers the blood LDL-cholesterol by 8.8%. (Ras and Demonty, 2008, unpublished).

There are only very limited studies on the LDL-cholesterol lowering effect of phytosterols added to other food forms such as spicy sauces and rye bread. However, the food matrix may affect the cholesterol-lowering efficacy of plant sterols significantly (Clifton et al., 2004; Katan et al., 2003). For example, Clifton et al. (2004) concluded from a randomised incomplete cross-over single-blind study, that plant sterol esters (1.6 g/day) in low-fat milk were almost three times more effective than in white bread and cereals (muesli style).

The Panel concludes that a cause-effect relationship has been established between the intake of plant sterols added to fat-based foods and low-fat foods such as milk and yoghurt and lowering of LDL cholesterol, in a dose-dependent manner. A clinically significant LDL-cholesterol lowering effect of about 10% can be achieved by a daily intake of 2 g of phytosterols in an appropriate food (e.g. fat spreads). The magnitude of the cholesterol-lowering effect may differ according to the food matrix.

LDL cholesterol and coronary heart disease

The relationship between serum LDL cholesterol levels and coronary heart disease (CHD) has been intensively studied and the applicant has provided the relevant studies. Both epidemiological studies and randomised controlled clinical trials have indicated a causal relationship between elevated LDL-cholesterol and CHD (Mensink et al., 2003; Stamler et al., 1986; Verschuren et al., 1995). Furthermore, there is evidence that the risk of CHD is reduced by cholesterol-lowering therapy (Pedersen et al., 2005), including dietary intervention strategies (Denke, 2005; Ornish et al., 1998; van Horn et al., 2008). However, there are no human intervention studies demonstrating that plant sterols reduce the risk of coronary heart disease.

The references to the non-human studies as provided by the applicant support the opinion derived from human studies. Plant sterols have been shown to consistently lower total plasma

cholesterol concentrations in more than 50 animal studies with no known adverse effects, and under a wide variety of physiological and pathological conditions. In addition, there are animal studies that provide relevant and convincing information for a beneficial effect of plant sterols in reducing the development of atherosclerosis (Plat et al., 2006).

2.4. Panel's comments on the proposed wording

Taking into account the scientific evidence presented, the Panel considers that the following wording reflects the scientific evidence:

"Plant sterols have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of (coronary) heart disease".

2.5. Conditions and restrictions of use

The Panel recommends that the products to which phytosterols are added should be consumed only by people who want to lower their blood cholesterol.

With respect to the specified conditions of use, it is suggested that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products making the proposed reduction of disease risk claim.

The scientific justification of the claim is related to a daily intake of 2 g of plant sterols added to fat-based food formats and low-fat foods such as milk and yoghurt. Other food forms should be evaluated for their cholesterol-lowering effect.

The product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years; patients on cholesterol lowering medication should only consume the product under medical supervision.

Relevant studies performed under free living conditions have been provided by the applicant showing the feasibility of consuming the recommended level of plant sterols (2 g/day) via various foods. Thus, the panel considers that the beneficial effect described by the proposed claim can be reasonably achieved through consumption of foods with added plant sterols that form part of a balanced diet.

CONCLUSIONS

Based on the data presented, the Panel concludes the following:

- Plant sterols for which the health claim is proposed have been sufficiently characterised.
- Elevated blood LDL-cholesterol is one risk factor for coronary heart disease. Coronary heart disease is an important cause of mortality and morbidity. Lowering LDL cholesterol by dietary intervention has been shown to reduce the risk of coronary heart disease.
- A cause-effect relationship has been established between the consumption of plant sterols and lowering of LDL cholesterol, in a dose-dependent manner.
- A clinically significant LDL-cholesterol lowering effect of about 9 % can be achieved by a daily intake of 2 – 2.4 g of phytosterols in an appropriate food (e.g. plant sterols added to fat-based foods and low-fat foods such as milk and yoghurt). The size of the cholesterol lowering effect may differ in other food matrices.

- There are no human intervention studies demonstrating that plant sterols reduce the risk of coronary heart disease.
- The recommended amounts and patterns of consumption required to lower blood LDL cholesterol can reasonably be achieved as part of a balanced diet.
- The Panel recommends that the products to which phytosterols are added should be consumed only by people who want to lower their blood cholesterol.
- The Panel considers that the following wording reflects the available scientific evidence: “*Plant sterols have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease*”.
- With respect to the specified conditions of use, it is suggested that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products bearing the proposed reduction of disease risk claim.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on plant sterols and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006 (claim serial No: 0004_SE). March 2008. Submitted by Unilever PLC & Unilever N.V.

REFERENCES

- Algorda Pineda J, Chinchetru Ranedo MJ, Aguirre Anda J, Francisco Terrero S, 2005. Hypocholesteremic effectiveness of a yogurt containing plant stanol esters. *Rev. Clin. Esp.* 205, 63-66.
- Beer MU, Pritchard PH, Olesen M, Black R, 2001. Phytosterols from tall oil delivered in low fat food matrix successfully lowers plasma cholesterol. *Ann. Nutr. Metab.* 45, 99
- Berger A, Jones PJ, Abumweis SS, 2004. Plant sterols: factors affecting their efficacy and safety as functional food ingredients. *Lipids Health Dis.* 3, 5.
- Cleghorn CL, Skeaff CM, Mann J, Chisholm A, 2003. Plant sterol-enriched spread enhances the cholesterol-lowering potential of a fat-reduced diet. *Eur. J. Clin. Nutr.* 57, 170-176.
- Clifton PM, Noakes M, Sullivan D, Erichsen N, Ross D, Annison G, Fassoulakis A, Cehun M, Nestel P, 2004. Cholesterol-lowering effects of plant sterol esters differ in milk, yoghurt, bread and cereal. *Eur. J. Clin. Nutr.* 58, 503-509.
- Commission Decision 2000/500/EC of 24 July 2000 on authorising the placing on the market of ‘yellow fat spreads with added phytosterol esters’ as a novel food or novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council. (OJ L 200, 8.8.2000, p.59).
- Commission Decision 2004/335/EC of 31 March 2004 on authorising the placing on the market of milk type products and yoghurt type products with added phytosterols esters as novel food ingredients under Regulation (EC) No 258/97 of the European Parliament and of the Council (*notified under document number C(2004) 1245*). (OJ L 105, 14.4.2004, p.46).
- Commission Decision 2006/58/EC and Commission Decision 2006/59/EC of 24 January 2006 authorising the placing on the market of rye bread with added phytosterols/phytostanols as novel foods or novel food ingredients under Regulation (EC) No 258/97 of the European Parliament and of the Council. (OJ L 31, 3.2.2006, p. 18-21).

- Denke MA, 2005. Diet, lifestyle, and nonstatin trials: review of time to benefit. *Am. J. Cardiol.* 96, 3F-10F.
- Doornbos AM, Meynen EM, Duchateau GS, Van der Knaap HC, Trautwein EA, 2006. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur. J. Clin. Nutr.* 60, 325-333.
- Gordon DJ, 2000. Cholesterol lowering reduces mortality. The Statins. In Cholesterol-Lowering therapy. Evaluation of Clinical Trial Evidence. Grundy SM (ed.) Marcel Dekker Inc., pp. 299-311.
- International Atherosclerosis Society Executive Board. International Atherosclerosis Society Harmonised Clinical Guidelines on Prevention of Atherosclerotic Vascular Disease. March 2003.
- Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R for the Stresa Workshop Participants, 2003. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin. Proc.* 78, 965-978.
- Law M, 2000. Plant sterol and stanol margarines and health. *B.M.J.* 320, 861-864.
- Mensink RP, Ebbing S, Lindhout M, Plat J, Van Heugten MM, 2002. Effects of plant stanol esters supplied in low-fat yoghurt on serum lipids and lipoproteins, non-cholesterol sterols and fat soluble antioxidant concentrations. *Atherosclerosis.* 160, 205-213.
- Mensink RP, Aro A, Den Hond, E, German JB, Griffin BA, Ter Meer H-U, Mutanen M, Pannemans D, Stahl W, 2003. PASSCLAIM - Diet-related cardiovascular disease. *Eur. J. Nutr.* 42 (suppl. 11), 1/6-1/27.
- Moreau RA, Whitaker BD, Hicks KB, 2002. Phytosterols, phytostanols and their conjugates in foods: structural diversity, quantitative analysis, and health-promoting uses. *Prog. Lipid Res.* 41, 457-500.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP-ATP III), Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002. 106, 3143-4321.
- Noakes M, Clifton PM, Doornbos AM, Trautwein EA, 2005. Plant sterol ester-enriched milk and yoghurt effectively reduce serum cholesterol in modestly hypercholesterolemic subjects. *Eur. J. Nutr.* 44, 214-222.
- Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, Sparler S, Armstrong WT, Ports TA, Kirkeeide RL, Hogeboom C, Brand RJ, 1998, erratum in 1999. Intensive lifestyle changes for reversal of coronary heart disease. *J.A.M.A.* 280, 2001-2007, erratum 281, 1380.
- Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendixsen FS, Lindahl C, Szarek M, Tsai J, 2005. Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *J.A.M.A.* 294, 2437-2445.
- Petersen S, Peto V, Rayner M, Leal J, Luengo-Fernandez R, Gray A, 2005. European cardiovascular disease statistics. British Heart Foundation (ed).

- Plat J, Beugels I, Gijbels MJJ, deWinther MPJ, Mensink RP, 2006. Plant sterol or stanol esters retard lesion formation in LDL receptor-deficient mice independent of changes in serum plant sterols. *J. Lipid Res.* 47, 2762-2771.
- Ras RT and Demonty I, 2008. The Effect of Phytosterol Intake on Low-Density Lipoprotein (LDL) Cholesterol Concentrations: a Meta-Analysis of Randomized Controlled Trials. Unilever R&D Vlaardingen. Unpublished Report.
- Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. (OJ L 43, 14.2.1997, p. 1–6).
- Stamler J, Wentworth D, Neaton JD, 1986. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356, 222. Primary screenings of the Multiple Risk Factor Intervention Trial (MRFIT). *J.A.M.A.* 256, 2823-2828.
- Thomsen AB, Hansen HB, Christiansen C, Green H, Berger A, 2004. Effect of free plant sterols in low-fat milk on serum lipid profile in hypercholesterolemic subjects. *Eur. J. Clin. Nutr.* 58, 860-870.
- Van Horn L, Mc Coin M, Kris-Etherton PM, Burke F, Carson JA, Champagne CM, Karmally W, Sikand G, 2008. The evidence for dietary prevention and treatment of cardiovascular disease. *J. Am. Diet Assoc.* 108, 287-331.
- Verschuren WMM, Jacobs DR, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedeljkovic S, Nissinen A, Toshima H, 1995. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. *J.A.M.A.* 274(2), 131-136.
- Volpe R, Niittynen L, Korpela R, Sirtori C, Bucci A, Fraone N, Pazzucconi F, 2001. Effects of yoghurt enriched with plant sterols on serum lipids in patients with moderate hypercholesterolaemia. *Brit. J. Nutr.* 86, 233-239.
- WHO (World Health Organisation), 2002. World Heart Report - Reducing Risks, Promoting Healthy Life.