ANSES Opinion
Request No. 2010-SA-0057

The Director General

Maisons-Alfort, 6 June 2014

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on "Assessment of the risks and benefits of consuming food products fortified with phytosterols and phytostanols"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 6 June 2014 shall prevail.

On 15 January 2010, the French Food Safety Agency (AFSSA[1]) received a formal request from the consumer association UFC – QUE CHOISIR to carry out the following expert appraisal: Assessment of the risks and benefits of consuming food products fortified with phytosterols and phytostanols.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The European Food Safety Authority (EFSA) authorises claims associating a first phrase indicating that phytosterols or phytostanols lower blood cholesterol with a second indicating that lowering blood cholesterol can reduce the risk of coronary disease. The consumer association UFC – QUE CHOISIR wished to know whether there were any studies showing a direct link between the consumption of foods fortified with phytosterols or phytostanols and cardiovascular risk. In the event that insufficient evidence were available, the association asked whether it might be necessary to reconsider the information given in the labelling of products fortified with phytosterols or phytostanols.

Furthermore, the issue of the risk associated with the consumption of foods fortified with phytosterols/stanols is based on a few scientific studies showing an increase in the plasma concentration of phytosterols following ingestion of these products (Fransen *et al.*, 2007), and on other studies associating high plasma levels of phytosterols with an increase in cardiovascular risk (Assmann *et al.*, 2006).

Moreover, people suffering from phytosterolaemia present unusually high concentrations of phytosterols in blood and tissues, leading to the development of premature atherosclerosis. It is dangerous for these subjects to consume products fortified with phytosterols or phytostanols. As a result, the association asked whether it was necessary for specific indications on this subject to be included in the labelling for these products.

[1] AFSSA and AFSSET (the French Agency for Environmental and Occupational Health Safety) have since merged to become ANSES, the French Agency for Food, Environmental and Occupational Health & Safety.

In order to address the issues raised by this request, the following points were considered and are developed in the collective expert appraisal report:

General aspects:
- Absorption and metabolism of phytosterols/stanols
- Level of consumption of phytosterols/stanols in the French population, in the normal diet and via fortified foods.

Questions concerning efficacy:
- Is the reduction in LDL-C long-lasting?
- Is there great inter-individual variability? Is it possible to quantify the proportion of individuals for whom phytosterols do not reduce LDL-C?
- The expected reduction in cardiovascular risk by phytosterols/stanols is a projection of the results observed with hypolipidemic drugs (statins), which have a different mechanism of action. Is a reduction in LDL-C by phytosterols/stanols associated with a reduction in cardiovascular risk? If so, to what extent?
- Are phytosterols/stanols effective in children?

Questions concerning risk:
- What are the toxicological risks?
- What are the risks related to a reduction in the absorption of fat-soluble vitamins (β-carotene), especially in the long-term?
- What are the risks related to high blood phytosterol levels?
- What are the risks of interactions between drugs?
- What are the risks for children, and for pregnant and breastfeeding women?
- What are the risks for subjects suffering from sitosterolaemia?

This Opinion focuses on four of the key points in this expert assessment:
- Variability of the effects of anticholesteraemic drugs
- The consequences of an increase in plasma concentrations of phytosterols
- The consequences on cardiovascular risk
- The case of particular populations.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

The Working Group based its assessment on scientific studies carried out in humans as well as those carried out on animal models and published before January 2013.

An initial bibliographic investigation was carried out at the end of 2010 in Pubmed and Scopus by cross-referencing keywords concerning phytosterols and phytostanols relating to the long-term effects on LDL-C, cardiovascular risk, phytosteroleamia, various genetic polymorphisms, drug interactions, toxicology, β-carotene and fat-soluble vitamins, consumption, and concerning children and pregnant and breastfeeding women. About 1200 articles were identified by this initial approach, about 500 of which were chosen as being related to the general question under study. A second search concerning phytosterols and phytostanols was carried out at the end of 2012 in the same databases for the period 2010-2012 in order to supplement the preceding investigation. About 150 articles were found on this occasion, 117 of which were deemed relevant for our analysis. This repository was made available to the experts as appropriate for the questions allocated to them. It was added to, where necessary, by references returned by specific bibliographic researches undertaken by the experts.

Furthermore, companies marketing foods fortified with phytosterols or phytostanols, or suppliers of ingredients based on phytosterols or phytostanols, were interviewed in order to collect all scientific or technical information that could be of use for the assessment.

An analysis of the French market for products fortified with phytosterols was carried out by the Observatory of Food Quality Unit (CIQUAL-OQALI), UOQNA, using the OQALI[2] database, which is the French Food Observatory's "nutrition section responsible for questions concerning the supply and characteristics of foods".

Consumption data for phytosterols and phytostanols were obtained from data compiled by the INCA 2 survey, carried out by ANSES's "Consumption Observatory" Unit (UOCA), and data about the composition of common foodstuffs from the CIQUAL database.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. In the present case, the collective expert appraisal was carried out by the Expert Committee (CES) on Human Nutrition on the basis of work prepared by a group of seven rapporteurs. The assessment of these rapporteurs was based on a preliminary bibliographical analysis. This was examined critically by the rapporteurs and enhanced and brought up to date by the Agency's scientific coordination. The methodological and the scientific aspects of the report were discussed by the CES on Human Nutrition between 21 February 2013 and 7 March 2014. The final report, incorporating the conclusions of the CES, was adopted by the CES on Human Nutrition, with the exception of three experts who did not participate in validating the report following the analysis of their public declarations of interest.

This Opinion summarises the report and the CES's conclusions.

Declarations of interest by the experts are made public via the ANSES website (www.anses.fr).

3. PREVIOUS ASSESSMENTS AND THE REGULATORY CONTEXT

3.1 Previous assessments

Foods fortified with phytosterols and phytostanols were brought onto the market within the framework of the procedure for novel foods (Regulation EC No. 258/97) and this has resulted in both European and French assessments of the safety of these foods.

European assessments

The Scientific Committee on Food (SCF) first assessed the risk of adding a specific mixture of phytosterol esters to food in 2000. The present opinion made use of the toxicological data provided in the application. These data did not give rise to any major health concerns related to the consumption of this mixture, when free phytosterols in the product did not exceed a maximum level of 8% (SCF, 2000).

The SCF subsequently issued a more general opinion concluding that phytostanols had no toxic effect and that phytostanols and phytosterols had a similar effect on lowering plasma concentrations of LDL-C. The SCF also considered that the data could not be used to define a maximum intake limit for phytosterols. However, considering the intake levels at which phytosterols/stanols are effective, considering that beyond these levels no additional benefit was observed and considering that high intake could result in adverse effects, the SCF considered it prudent to avoid intake of phytosterols higher than 1-3 g/day (SCF, 2002a).

Several other opinions were issued within the framework of the procedure on novel foods, for the addition of mixtures of phytosterols and/or phytostanols to several vectors between 2000 and 2007, in either esterified or free forms (SCF, 2000, SCF, 2002a, SCF, 2002b, SCF, 2003c, SCF, 2003b, SCF, 2003a, NDA, 2003, NDA, 2006, NDA, 2007). The following risk elements or reservations were mentioned, however:

- subjects suffering from phytosterolaemia must be informed of the presence of phytosterols to enable them to avoid consuming products containing these;
- patients on anticholesteraemic drugs should only consume such products under medical supervision;
- the consumption of phytosterols and phytostanols interferes with the absorption of carotenoids. The reduction in plasma carotenoids seems to reach a plateau for doses of 2.2 g/day. A reduction of 33% was observed after one year of consuming margarine supplying 3 g/day (SCF, 2002a). The SCF considers that consumers should be informed of this risk (particular risk for pregnant women, breastfeeding women and children) and that the consumption of fruit and vegetables should be recommended.

[2] http://www.oqali.fr/oqali/

Subsequently, EFSA assessed the scientific basis for the claims regarding phytosterols and phytostanols, within the general framework of Regulation (EC) No.1924/2006, Article 14 (NDA, 2009a, NDA, 2009b, NDA, 2008a, NDA, 2008b). EFSA considered that the following terms reflect the available scientific proof:

- "Plant sterols have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease";
- "Plant stanol esters have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease";
- "Phytosterols have been shown to lower/reduce blood cholesterol. High blood cholesterol is a risk factor in the development of coronary heart disease".

In these opinions, EFSA also indicated that a daily intake of phytosterols or phytostanols of 1.5 g to 2.4 g can lead to a reduction in LDL-C of 7 to 10.5%. EFSA considered that this reduction has biological significance in terms of a reduction in the risk of coronary heart disease.

National assessments

In 1999, the French High Council for Public Health (CSHPF) issued a first opinion on a food fortified with phytosterols (CSHPF, 1999). In this opinion, the CSHPF considered that fortifying foods with phytosterols could be of benefit to subjects with high cholesterol levels. However, it considered that these products were not appropriate for consumption by subjects presenting low or normal levels of cholesterol, with a low risk of cardiovascular disease. The CSHPF also asked for proof of the very long-term safety of this fortification, and asked that the reality of benefit to cardiovascular condition be established.

Subsequently, several opinions were issued on a variety of food products fortified with different mixtures of phytosterols or phytostanols.

In 2002, the French Food Safety Agency (AFSSA) advised against the consumption of foods fortified with phytosterols for pregnant and breastfeeding women and children, as a result of a lack of data on the long-term safety in these populations (AFSSA, 2002). It warned against the risk of overconsumption related to the increasing number of fortified foods and asked producers to monitor consumption. It also indicated that the effective dose of phytosterols to obtain a reduction in plasma concentrations of LDL-C is approximately 2 g/day, from all sources.

In 2003, the Agency recommended that information on the importance of consuming fruit and vegetables to mitigate reduced plasma concentrations of β-carotene be displayed on the labels of products fortified with phytosterols (Afssa, 2003).

In 2005, the Agency reiterated that the long-term effects of high intake of phytosterols, bearing in mind the cumulative effect, was still poorly understood, and recommended medical surveillance in the event of prolonged use (Afssa, 2005).

In Germany, the BfR (Bundesinstitut für Risikobewertung) asked in its opinion of 1 December 2011, that EFSA again assess the risk related to the consumption of products fortified with phytosterols, on the basis, firstly, of a new study in humans suggesting increased cardiovascular risk related to the consumption of these products, and secondly, of recent data on consumption in Germany and Belgium (BfR, 2011). These data indicate that among consumers of these products there is a non-negligible proportion of children and that only 58% of adults consuming these products are aware of their own cholesterol levels. The BfR concluded that information on labelling was insufficient to ensure that these products are consumed by their target population.

3.2 Regulations

Following these European and national assessments, a first decision to grant marketing authorisation for a food fortified with phytosterol esters was issued on 24 July 2000, under the terms of Regulation (EC) No. 258/97 governing the sale of novel foods. It concerned "yellow fat spreads" (Decision 2000/500/EC). Ten other Decisions[3] followed, authorising the placing on the market of other food vectors such as other spreads, milk-based drinks or salad dressing. European Commission Regulation No (EC) 608/2004 concerning labelling specifically requires that labels include:

- information as to whether the product contains added plant sterols or plant stanols;
- the amount of added phytosterols/stanols in the product;

[3] Decisions 2008/36/EC, 2007/343/EC, 2006/58/EC, 2006/59/EC, 2007/343/EC, 2004/845/EC, 2004/336/EC, 2004/335/EC, 2004/334/EC, 2004/333/EC

- a statement that the product is intended exclusively for people who want to lower their blood cholesterol level;
- a statement that patients on cholesterol lowering medication should only consume the product under medical supervision;
- a warning stating that the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years;
- advice that the product is to be used as part of a balanced and varied diet, including regular consumption of fruit and vegetables to help maintain carotenoid levels;
- a statement that the consumption of more than 3 g/day of added plant sterols/plant stanols should be avoided;
- a definition of a portion of the food or food ingredient concerned (preferably in g or ml) with a statement of the plant sterol/plant stanol amount that each portion contains.

The new Regulation (EU) No.1169/2011 on the provision of food information to consumers amends these labelling statements, via the Delegated Regulation No. 78/2014 of 22 November 2013, regarding the third point (concerning the target population), replacing it as follows: “a statement that the product is not intended for people who do not need to control their blood cholesterol level”.

Regarding claims, Regulation (EU) No. 384/2010 of 5 May 2010 approves the claim proposed by EFSA: “Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High blood cholesterol is a risk factor in the development of coronary heart disease", as long as consumers are informed “that the beneficial effect is obtained with a daily intake of 1.5-2.4 g plant sterols/stanols”.

4. ANALYSIS AND CONCLUSIONS OF THE CES ON HUMAN NUTRITION

Phytosterols or plant sterols are natural compounds found in plants, especially nuts and oil seeds. They have a structure similar to that of cholesterol but differ in their C24 side chain and/or the position and configuration of the double bond. Phytostanols are the product of the hydrogenation of phytosterols.

No reference intake has been defined for these substances, which are not essential molecules for the body to function.

These compounds compete with cholesterol in terms of intestinal absorption and thus limit the absorption of cholesterol.

Phytosterols are absorbed less than cholesterol and their plasma concentration is about 200 times lower than that of cholesterol, but it increases with phytosterol intake. Phytostanols are even less well absorbed and their plasma concentrations are lower than those of phytosterols.

4.1 A cholesterol-lowering effect for only a fraction of the population

The CES on Human Nutrition confirms the earlier assessments of AFSSA and EFSA, i.e. that phytosterols and phytostanols, at an intake of 1.5-2.4 g/day, lower total blood cholesterol levels and concentrations of LDL-C by about 10% over periods ranging from a few weeks to one or two years. However, it is important to emphasise that there is considerable individual variability in the response to phytosterols: it has been estimated that in 30% of subjects, the non-responding subjects, there is no reduction in concentrations of LDL-C. In particular, response to phytosterols varies according to the subjects’ capacity for synthesising cholesterol: subjects that do not respond to phytosterols/stanols have a higher capacity for synthesising cholesterol.

To our knowledge, there is no information about the variability of individual response to phytostanols.

The degree of the reduction in LDL-C also depends on the initial concentration of LDL-C. Studies having investigated this particular point found that reductions seemed to constant in terms of percentage, with higher absolute values in subjects presenting a higher initial concentration of LDL-C.

Regarding genetic influence, the few studies of heterozygous subjects on a mutation of the genes ABCG5/G8 (which causes homozygous sitosterolaemia) show a similar reduction in LDL-C following the consumption of food fortified with phytosterols or phytostanols in both heterozygous subjects and in subjects not carrying this mutation.

Tests to measure the influence of genetic polymorphism on the variability of the response to phytosterols or phytostanols are inconclusive: in the case of polymorphism in the apolipoprotein E, studies do not concur; in the case of the ABCG5/G8 transporter, there seems to be no major influence; and in the cases of the

NPC1L1 transporter, the CETP transfer protein and the CYP7A1 enzyme, influence of polymorphism remains to be confirmed.

4.2 An increase in concentrations of phytosterols with poorly understood consequences

The consumption of foods fortified with phytosterols at a dose of 1.6 g/day increases plasma concentrations of phytosterols by about 30%, while the consumption of phytostanols at a dose of 0.6 g/day reduces plasma concentrations of phytosterols but increases concentrations of phytostanols by 170%. There have been several observation studies on the consequences of high plasma concentrations of phytosterols on cardiovascular risk, but none have investigated any association between concentrations of phytostanols and cardiovascular risk.

Data on the relationship between plasma concentrations of phytosterols and cardiovascular risk do not converge. More precisely, case studies in humans diverge, some suggesting a positive association between plasma levels of phytosterols and cardiovascular risk, and others an absence of association or even a negative association. Of the five cohort studies carried out, four report a significant positive association between plasma concentrations of phytosterols and the risk of cardiovascular events, while the fifth, on a small number of subjects, finds the opposite effect. A recent meta-analysis of all these studies concludes an absence of association between plasma concentrations of phytosterols and cardiovascular risk, but the very high heterogeneity between the studies (I^2 = 84%, P = 0.002), of which in any case there are comparatively few, could explain this absence of association.

In addition to this heterogeneity between the results of the studies, there is a further difficulty related to interpretation of plasma concentrations of phytosterols. These vary in proportion to their dietary intake but also to individual capacity to absorb sterols (cholesterol and phytosterols). Since some studies show a positive association between the capacity to absorb sterols and cardiovascular risk, the increase in cardiovascular risk reported in some studies may be related to high intake of phytosterols, or to a high capacity for absorbing sterols. A third element to be taken into account when interpreting the results lies in the fact that these studies were carried out on subjects who were not consuming food fortified with phytosterols, and their plasma concentrations can be assumed to be lower than those of regular consumers of fortified foods supplying 1.6-1.7 g of phytosterols per day.

To conclude, none of the available data demonstrate cardiovascular risk related to plasma levels of phytosterols, but nor can such a risk be ruled out.

Concerning phytostanols, to our knowledge there has been no study on a link between plasma concentrations and cardiovascular risk.

4.3 What is the result on cardiovascular risk?

Atherogenesis, which is at the origin of many cardiovascular diseases, is a complex process involving cholesterol deposits in the arteries, phenomena of oxidation, inflammation, cell proliferation and migration and a reorganisation of vessel walls. It is a multifactorial physiopathology for which the French High Authority for Health (HAS) recognises the following risk factors: age, smoking, the presence of a family history of early-onset cardiovascular events, permanent high blood pressure, type 2 diabetes, microalbuminuria and dyslipidaemia (high LDL-C, low HDL-C).

No conclusion can be reached from studies on the effects of phytosterols and phytostanols on certain parameters associated with cardiovascular risk (circulating lipids, oxidation processes, arterial elasticity) regarding the effects of dietary phytosterols and phytostanols on reduced cardiovascular morbidity and mortality. Moreover, the only epidemiological study on cardiovascular events does not provide sufficient evidence to conclude that they provide any benefit.

Furthermore, there is a lack of data for determining the cardiovascular consequences of an increase in phytosterols absorption resulting from the consumption of food fortified with phytosterols. Although the opposite association is found between plasma levels of carotenoids and cardiovascular risk, it is not possible to conclude that lower plasma levels of carotenoids resulting from the consumption of foods fortified with phytosterols has any consequence on cardiovascular risk.

Concerning phytostanols, the available data suggest a similar effect to that of phytosterols on fats and plasma carotenoids, but to our knowledge there are no studies on inter-individual variability of any cholesterol-lowering effect nor on any association between plasma concentrations of phytostanols and cardiovascular risk.

In the absence of data from intervention studies, it is not possible to take a position on the effect of phytosterols and phytostanols on cardiovascular morbidity and mortality, in agreement with the conclusions of the European Atherosclerosis Society (EAS) (Gylling *et al*., 2014).

4.4 Case of particular populations

Children

Most studies on phytosterols in children were carried out with children suffering from familial heterozygous hypercholesterolaemia. The consumption of food fortified with phytosterols/stanols is clinically well tolerated in children. In hypercholesterolaemic children, it can bring about a significant short and medium-term reduction in LDL-C, but has no proven effect on arterial function.

In children, as in adults, the consumption of phytosterols leads to a rise in plasma concentrations of sitosterol and campesterol. Lower plasma concentrations of β-carotene are also observed following consumption of phytosterols and phytostanols. Paediatric studies do not permit any conclusion about the possible consequences of their consumption on the absorption of the other fat-soluble vitamins.

The consumption of food fortified with phytosterols/stanols therefore seems to have the same short- and medium-term consequences in children over the age of four as in adults as regards lowered plasma concentrations of β-carotene and LDL-C and higher plasma concentrations of phytosterols in the case of fortification with phytosterols. As for adults, there are insufficient intervention studies on cardiovascular morbidity and mortality to permit a conclusion.

Current regulations require that products fortified with phytosterols/stanols carry the statement that “the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years” (Regulation (EC) No 608/2004).

On the basis of this new assessment, the CES on Human Nutrition considers that products fortified with phytosterols/stanols should not be consumed by children of any age, except on specific medical advice.

Pregnant and breastfeeding women

There are only three studies available on pregnant or breastfeeding women. On the basis of these data, the CES on Human Nutrition concludes that intake of phytosterols in breastfeeding women has an effect on the concentration of phytosterols in their milk. Furthermore, high maternal intakes are likely to cause an indirect increase in phytosterols levels in breastfed infants and to lower their plasma concentrations in β-carotene. These studies do not however permit any conclusion on a possible effect of high maternal consumption of phytosterols on the metabolism of cholesterol (synthesis versus absorption) in infants.

Current regulations require that products fortified with phytosterols/stanols carry the statement that “the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years” (Regulation (EC) No 608/2004).

Considering that phytosterols are found in breast milk and the blood of infants and that they lead to lower concentrations of β-carotene, the CES on Human Nutrition considers that products fortified with phytosterols/stanols should not be consumed by pregnant or breastfeeding women except on specific medical advice.

Heterozygous sitosterolaemic subjects

Subjects suffering from sitosterolaemia, a rare genetic disease characterised by excessively high concentrations of phytosterols (30 to 100 times higher than in the general population) must follow a diet low in phytosterols, phytostanols and cholesterol. As a result they should not consume foods fortified with phytosterols/stanols and they need to be provided with clear information on the presence of phytosterols/stanols in products.

Inversely, subjects who are heterozygous for mutations of the ABCG5/G8 genes cannot be identified in practice. In addition, in the event of consumption of products fortified with phytosterols, their cholesterol levels fall while their phytosterols levels, which have a slightly higher base rate, rises in the same proportion as for subjects not carrying the mutation. The CES on Human Nutrition therefore considers that specific information intended for these subjects does not seem appropriate.

4.5 Products fortified with phytosterols/stanols and consumption data

The French market in foods fortified with phytosterols is concentrated in three sectors; vegetable fats, fresh dairy products and salad dressing, although authorisations have been granted for other vectors. There are currently no products fortified with phytostanols on the French market.

According to the INCA 2 study, consumers of these products in 2006-2007 accounted for less than 3% of adults (70 adult subjects out of 2554 representative French individuals) and 0.7% of children (10 out of 1145). Among the adults, the age range 46-79 years, which may be considered most at risk of hypercholesterolaemia, was the most heavily represented. Mean intake levels of phytosterols in adults via ordinary foods were about 200 mg/day. Mean intake levels of phytosterols via fortified foods were 450 mg/day in subjects aged 18 to 45 and 700 mg/day in subjects aged 46 to 79 consuming fortified foods. So in subjects aged from 46 to 79, mean intake levels of phytosterols from both sources together are only 900 mg/day, which is below the dose recognised as effective by EFSA (1.5-2.4 g/day). In these subjects, the effective dose is only reached by the 90th percentile.

It is reassuring to observe that no group particularly exceeds the dose of 3 g/day, which is considered the advisable limit for adults. However, this dose was defined without taking into account the reduction in plasma β-carotene, because the mandatory statements on the labelling recommend increasing the consumption of fruit and vegetables to offset this reduction. In reality, reduced concentrations of β-carotene are observed following the consumption of fortified products providing 1.1 g/day of phytosterols. As a result, under real conditions of consumption, this potential risk cannot be ruled out.
The maximum intake level in the children surveyed was 1.1 g/day, but no comparison is possible in the absence of a defined maximum intake level. These data raise the question of the consumption of products fortified with phytosterols/stanols by children (10 children out of 80 subjects consuming these products), especially for products used to prepare family meals. However, the consumption data date from 2006-2007 and it is possible that the market for fortified products and their consumption have evolved since.

4.6 Conclusion of the CES on Human Nutrition

This assessment confirms that the consumption of foods fortified with phytosterols/stanols at levels of 1.5-2.4 g/day lead to an average reduction in plasma concentrations of LDL-C of about 10%. However, it raises a certain number of uncertainties on the benefits and risks related to the consumption of foods fortified with phytosterols/stanols:

- the consumption of foods fortified with phytosterols does not lead to a reduction in LDL-C in about 30% of subjects;
- the consumption of these foods results in an increase in plasma concentrations of phytosterols for which the consequences on cardiovascular risks are unknown;
- in the absence of data from intervention studies, it is not possible to take a position on the effect of phytosterols and phytostanols on cardiovascular morbidity and mortality;
- the conditions under which products fortified with phytosterols/stanols are sold mean that these products are available to children, as was observed in the INCA 2 survey, despite the warnings on the labelling.

The CES on Human Nutrition therefore considers that:

- as regards public health, the available data do not make it possible to consider foods fortified with phytosterols/stanols as a suitable way of preventing cardiovascular disease;
- as regards individual health, the consumption of foods fortified with phytosterols/stanols should undergo a risk/benefit assessment on a case-by-case basis by a health professional.

It is desirable that the consumption of products fortified with phytosterols/stanols be associated with an increase in the consumption of fruit and vegetables in order to compensate for the resulting reduction in levels of plasma carotenoids.

The CES on Human Nutrition reiterates that atheromatous disease is multifactorial and that each of the factors that can be addressed by appropriate health and dietary measures should be taken into account, such as stopping smoking, increasing physical activity, reducing sedentary behaviour and improving dietary balance with particular attention to high consumption of fruit and vegetables, balanced intake of fatty acids, and moderate consumption of sugar and salt.

Lastly, as a general principle, this expert assessment reiterates that in cases of multifactorial disease, the demonstration and reduction of a single risk factor is not sufficient to conclude that there is a benefit for the risk of the disease's occurrence.

5. THE AGENCY'S CONCLUSIONS AND RECOMMENDATIONS

Phytosterols and stanols, compounds with cholesterol-lowering properties, are naturally present in food and the mean intake level of French adults through normal food is in the order of 200 mg/day.

On the French market, products fortified with phytosterols are currently concentrated in three sectors: margarines, fresh dairy products and assimilated products (yoghurts), and condiments sauces[4]). These products account for less than 4% of market share in these sectors and are consumed by about 3% of the French population. Most consumers belong to the 46-79 year-old age range, although 12.5% of consumers are children.

In 2008, EFSA recognised the effect of phytosterols on a reduction of about 10% of total blood cholesterol and levels of circulating LDL-C. However, there is considerable variability in individual response and about 30% of the population may be considered as "non-responding". In addition, this effect is observed for intakes assessed at between 1.5 and 2.4 g/day, whereas intake of phytosterols by consumers of fortified products is actually lower (in the region of 900 mg/day). There is therefore some doubt as to the capacity of these products to bring about a significant reduction in blood levels of cholesterol and LDL-C in the population as a whole.

Alongside this first cause for uncertainty, it should be emphasised that although plasma concentration of LDL-C is considered as a risk factor for cardiovascular disease, these diseases are multifactorial, involving a large number of risk factors and protective factors. As a result, a reduction in one risk factor does not necessarily lead to a reduction in the risk of the disease. ANSES considers that only a study assessing the impact of products fortified with phytosterols or phytostanols on the risk of the onset of cardiovascular events would enable an assessment of the result of all their effects on the risk of developing these diseases.

Furthermore, by acting on the plasma concentration of LDL-C, the consumption of phytosterols reduces concentrations of β-carotene and increases those of phytosterols. These modifications could increase the risk of cardiovascular disease. In this context, the use of a claim concerning phytosterols to promote fortified products must be counterbalanced in view of the uncertainties concerning these different parameters influencing cardiovascular risk (Annex 1).

ANSES adopts the conclusions of the CES on Human Nutrition which considers that the data currently available are insufficient to conclude, at the level of public health, that foods fortified with phytosterols/stanols are an appropriate means for the prevention of cardiovascular diseases.

ANSES therefore recommends:

- that people concerned about their cholesterol levels should consult a health professional, who will be able to recommend the most suitable health and dietary measures for their situations, for maintaining normal levels of blood cholesterol: stopping smoking, increasing physical activity, reducing sedentary behaviour and improving dietary balance, taking care to consume adequate quantities of fruit and vegetables, a balanced intake of fatty acids, and moderate consumption of sugar and salt;
- that consumers of products fortified with phytosterols/stanols make sure that they consume at the very least the quantities of fruit and vegetables recommended by the French National Health and Nutrition Programme (PNNS);
- avoiding the consumption by children of products fortified with phytosterols/stanols; the Agency also emphasises that despite its previous recommendations and statements on labelling, 12.5% of consumers of these products are children;
- that pregnant and breastfeeding women avoid the consumption of products fortified with phytosterols/stanols.

Lastly, ANSES considers that it is not necessary to recommend specific statements on the labelling concerning subjects suffering from phytosteroleamia.

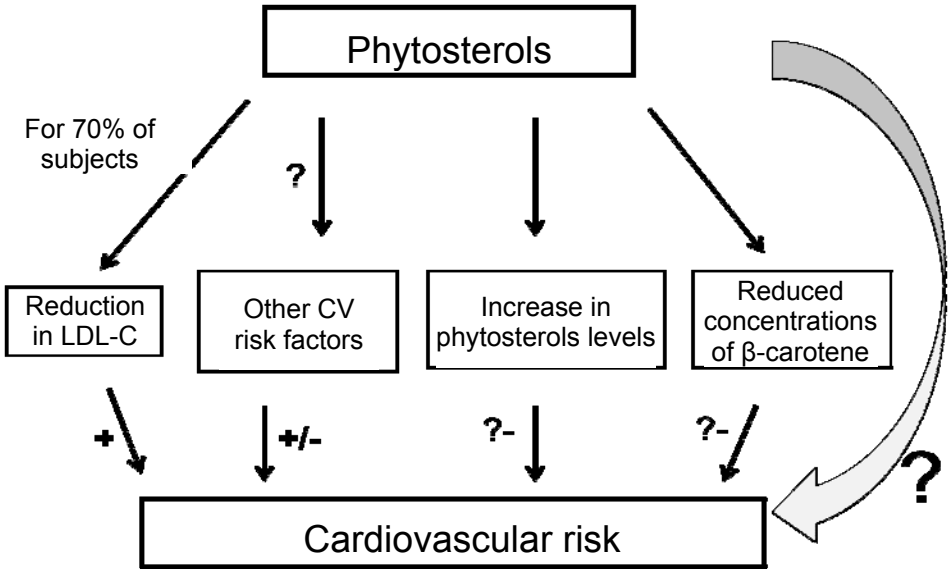
More generally, European regulation on the addition of nutrients and substances to foods is based on several distinct legal texts. As a result, benefits are assessed through a process (Regulation (EC) No

[4] Such as vinaigrette, ketchup, mayonnaise

1924/2006 on claims) which is independent from that for risks (Regulations (EC) No 258/97 and (EC) No 1925/2006). Under these conditions, it is difficult to give equal consideration to these two aspects; this expert assessment, like the one carried out in 2010 on fortified foods, illustrates the need to take benefits and risks equally into account.

Marc Mortureux

ANNEX



Annex 1. Effects of foods fortified with phytosterols on cardiovascular risk

KEYWORDS

Phytosterols, phytostanols, LDL-C, cholesterolaemia (blood cholesterol levels), sitosterolaemia, phytosterolaemia, blood phytosterol levels, risk, benefit, cardiovascular, fat-soluble vitamins, intake

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