The role of plant sterols/stanols in life-long management of blood cholesterol - from science to claims

Prof Dr Elke A. Trautwein, Senior Scientist Cardiovascular Health, Unilever, on behalf of the International Plant Sterols and Stanols Association (IPSSA)
Established in 2015; based in and operating from Brussels, Belgium

Founding (and current) members are leading international companies in plant sterols and stanols
- Arboris, BASF, Cargill, Raisio, Unilever

IPSSA covers all aspects of the plant sterols and stanols sector
- B2B (producers of plant sterols, plant stanols, and their esters)
- B2C (producers of foods with added plant sterols and stanols)

IPSSA has a global focus
IPSSA – Our mission

1. To educate the **media** and the **public** about the role of a healthy diet and lifestyle in reducing the risk of heart disease.

2. To demonstrate in a clear and concise manner how plant sterols and stanols have been **scientifically proven to lower blood LDL-cholesterol**.

3. To inform **policymakers** about the safety of plant sterols and stanols as well as their efficacy in lowering blood LDL-cholesterol and thus, their contribution to reducing the risk of heart disease.
CVD is the leading cause of death in adults worldwide

In Europe, CVD accounts for 45% of all deaths*

Major burden on health care costs to EU economy with estimated costs of 210 billion Euro per year

Elevated blood LDL-cholesterol is causal risk factor of atherosclerotic cardiovascular disease (ASCVD)**

Lowering LDL-cholesterol ⇒ \textit{The lower the better; the earlier the better!}

Diet and lifestyle are the cornerstone in CVD prevention

With adequate changes, at least 80% of (premature) CVD mortality may be prevented**

Introducing foods with added plant sterols and stanols as part of a healthy diet will contribute to blood cholesterol management of individuals

*European Cardiovascular Disease Statistics; 2017 Edition
**Ference et al, Eur Heart J 2017
Plant sterols and stanols are found in foods of plant origin, e.g. grains, seeds, vegetable oils, nuts, legumes, fruit and vegetables.

Average daily intake with habitual diets:
- 200 to 300 mg/day of naturally occurring plant sterols
- ~50 mg/day of naturally occurring plant stanols
- Up to 600 mg with vegetarian/vegan-type, plant-based diet

Plant sterols and stanols are structurally similar to cholesterol with both different side chain configurations and lack of double bonds.

- Cholesterol
- Campesterol
- Sitosterol
- Sitostanol
Plant sterols/stanols - most thoroughly studied dietary ingredients for blood cholesterol-lowering

- Long history of knowing their cholesterol-lowering effect
- Since mid/late 1990s, foods with added plant stanols/sterols commercially available, with wide range of different food formats and food supplements

- Vast evidence for cholesterol-lowering effect
  - >120 **human studies** showing that plant sterols/stanols lower total and LDL-cholesterol without affecting HDL-cholesterol*
  - Plant sterols/stanols also modestly lower triglycerides (TG) esp. in individuals with high basal TG levels**

*Ras et al, Br J Nutr 2014
**Rideout et al, J AOAC International 2015
Building scientific evidence - basis for Health Claim authorisation

- Several **meta-analyses** summarising evidence for the dose-dependent cholesterol-lowering effect of plant sterols and stanols

- Numerous humans studies addressing aspects, like
  - Efficacy of different food formats and food supplements
  - Efficacy in specific target groups
  - Factors that influence efficacy, e.g. intake occasion and frequency
  - Interaction with cholesterol-lowering drugs
  - Understanding of underlying mechanism of action

Cholesterol-lowering of plant sterols and stanol across different dose ranges

Meta-analysis based on 124 studies with 201 study arms; 9,692 study participants; variety of food formats, e.g. margarine, milk, yoghurt, food supplements

Plant sterol/ stanol intakes of 1.5 - 3 g/day dose-dependently reduce LDL-cholesterol by 7 - 12.5%

Ras et al, Br J Nutr 2014
LDL-cholesterol lowering of plant sterols and stanols demonstrated under various conditions

Cholesterol-lowering efficacy demonstrated in different populations

- Individuals with
  - Diabetes Mellitus
  - Familial hypercholesterolemia (FH)
  - Metabolic syndrome

- In combination with lipid-lowering drugs (statins, fibrates, ezetimibe)

Plant sterols/stanols are effective with different background diets

- As part of a typical (habitual) diet
- Additive to cholesterol lowering effect of a low-fat diet
- As part of a whole diet (dietary pattern)
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. 

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 10% can be achieved by a daily intake of plant stanol esters equivalent to 2 g of plant stanols in an appropriate food (e.g. fat-based foods and low-fat foods such as yoghurt), preferably with a meal. The size of the cholesterol lowering effect may differ in other food matrices. 

A cause-effect relationship has been established between the intake of plant stanol esters and lowering of LDL cholesterol, in a dose-dependent manner.
Authorised disease risk reduction claim for plant sterols and stanols and conditions of use in EU

‘Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.’

Conditions of use

- Information to consumer that beneficial effect is obtained with a **daily intake of 1.5 - 3 g plant sterols/stanols**
- Reference to magnitude of effect may only be made for foods within the following categories: **yellow fat spreads, dairy products, mayonnaise and salad dressings**.
- When referring to magnitude of effect, the range **“7 to 10 %” for foods that provide a daily intake of 1.5-2.4 g plant sterols/stanols** or **the range “10 to 12.5%” for foods that provide a daily intake of 2.5- 3 g plant sterols/stanols** and duration to obtain the effect **“in 2 to 3 weeks”** must be communicated to the consumer.

Commission regulation (EU) No 686/2014
EFSA opinion from 2012 forms basis for increasing the cholesterol-lowering efficacy from 10 to 12.5%

On the basis of the data presented, the Panel concludes that... plant sterols and stanol esters at a daily intake of 3 g (range 2.6 g to 3.4 g) plant sterols/stanols in matrices approved by Regulation (EC) No 376/2010 lower LDL-cholesterol by 11.3 % (95 % CI: 10.0 - 12.5) and that the minimum duration required to achieve the maximum effect of plant sterols and stanols on LDL-cholesterol lowering is two to three weeks.
Examples of approved health claims for plant sterols/stanols across the globe

USA
- Foods containing at least 0.5 g per serving of phytosterols [plant sterols, plant stanols, or plant sterols and stanols] eaten with meals or snacks for a daily total intake of 2 g as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.

CANADA
- Serving size of product provides x% of the daily amount* of plant sterols shown to help reduce/lower cholesterol in adults.
- "Plant sterols help reduce (or help lower) cholesterol. High cholesterol is a risk factor for heart disease."

AUSTRALIA/NEW ZEALAND
- Food products authorized for enrichment with plant sterols, stanols, and their esters are eligible for high level health claim**, “reduces blood cholesterol”.
- Foods must contain at least 0.8 g of plant sterols/stanols for a daily intake of 2 g.

*The "daily amount" referred is 2 g. This amount is based on the evidence available concerning the amount of plant sterols shown to help reduce cholesterol in adults.

**High level health claim means a health claim that refers to a serious disease or a biomarker of a serious disease
Target population for foods with added plant sterols and stanols*

• Individuals with elevated serum cholesterol, but intermediate or low global CVD risk, who therefore do not (yet) qualify for drug treatment

• As an adjunct to drug (statin) therapy in individuals, who fail to achieve LDL-cholesterol targets, or are statin-intolerant in conjunction with other lifestyle interventions

• In adults and children (>6 yrs.) with familial hypercholesterolemia

Medical and scientific associations recognise foods with added plant sterols and stanols

Recognition of efficacy and safety of plant sterols/stanols as a dietary option for lowering LDL-cholesterol, a risk factor of CHD

International Atherosclerosis Society
American Diabetes Association
Heart Foundation Australia
ESC/EAS Guidelines
American Association of Clinical Endocrinologists
National Lipid Association
Canadian Cardiovascular Society
Austrian Atherosclerosis Society
The Association of UK Dietitians
Nederlandse Hartstichting
<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>Dose or change in intake/ habit</th>
<th>Approximate LDL-cholesterol reduction</th>
<th>Strengths of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduce and replace SAFA with unsaturated fats</strong>, (PUFA and MUFA)</td>
<td>Exchange 5% energy of SFA with PUFA Exchange 5% energy of SFA with MUFA</td>
<td>7%&lt;sup&gt;a&lt;/sup&gt; 6%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>★★★</td>
</tr>
<tr>
<td><strong>Reduce dietary cholesterol</strong></td>
<td>&lt;300 mg/day</td>
<td>3%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>★★</td>
</tr>
<tr>
<td><strong>Other LDL-lowering options</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Increase dietary fibre</strong> intake from foods rich in soluble fibre</td>
<td>≥3 g/day β-glucan</td>
<td>5-6%&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>★★★</td>
</tr>
<tr>
<td><strong>Consider plants sterols/stanols</strong></td>
<td>1.5-3 g/day</td>
<td>7-12.5%</td>
<td>★★★</td>
</tr>
<tr>
<td><strong>Consider soy protein</strong></td>
<td>≥25 g/day</td>
<td>3-4%&lt;sup&gt;f&lt;/sup&gt;</td>
<td>★★</td>
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<tr>
<td><strong>Lifestyle</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Body weight</strong></td>
<td>-10 kg</td>
<td>5%&lt;sup&gt;h&lt;/sup&gt;</td>
<td>★★</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td>3-4 sessions/week</td>
<td>2-4%&lt;sup&gt;i&lt;/sup&gt;</td>
<td>★★</td>
</tr>
</tbody>
</table>

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★★★ Level of Evidence A = Data derived from multiple randomized clinical trials or meta-analysis
★★ Level of Evidence B = Data derived from a single randomized clinical trial or large non-randomized studies

Adapted in part from 2016 ESC/EAS Guidelines for the management of dyslipidaemias
LDL-cholesterol reductions adapted from: <sup>a</sup>Mensink et al., 2003; <sup>b</sup>Weggemans et al., 2001; <sup>c</sup>Whitehead et al., 2014; <sup>d</sup>Zhu et al., 2015; <sup>e</sup>Ras et al., 2014; <sup>f</sup>Benkhedda et al, 2014; <sup>h</sup>Dattilo and Kris-Etherton, 1992; <sup>i</sup>Eckel et al. Circulation, 2013.
Conclusions

- Vast number of human intervention studies shows LDL-cholesterol lowering benefit of foods with added plant sterols and stanols
- **Intake of 1.5-3 g/day** lowers LDL-cholesterol dose-dependently by **7-12.5%**
- Plant sterols/stanols are effective in all food formats and in food supplements
- **Additive effect** to a heart healthy diet and to lipid-lowering medication
- **Authorized health claims** by e.g. EU Commission, FDA (US), Health Canada
- Included in **recommendations** for diet and lifestyle approaches for management of dyslipidaemia as an additional adjunct to a healthy diet e.g. 2016 EAS/ESC guidelines on the management of dyslipidaemias
Thank you!

For more information on plant sterols and stanols visit http://www.ipssa-association.com and follow us on Twitter @IPSSAglobal

Downloadable Infographic

Link to Voices of Lowering cholesterol campaign
Mandatory labelling requirements for foods with added plant sterols/stanols

1. ‘with added plant sterols’ or ‘with added plant stanols’ in the same field of vision as the name of the food

2. the amount of added phytosterols, phytosterol esters, phytostanols or phytostanol esters content (expressed in % or as g of free plant sterols/plant stanols per 100 g or 100 ml of the food) shall be stated in the list of ingredients

3. a statement that the food is not intended for people who do not need to control their blood cholesterol level

4. a statement that patients on cholesterol lowering medication should only consume the product under medical supervision

5. an easily visible statement that the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years

6. advice that the food is to be used as part of a balanced and varied diet, including regular consumption of fruit and vegetables to help maintain carotenoid levels

7. in the same field of vision as the statement required under point 3 above, a statement that the consumption of more than 3 g/day of added plant sterols/plant stanols should be avoided

8. a definition of a portion of the food or food ingredient concerned (preferably in g or ml) with the amount of the plant sterol/plant stanol that each portion contains

Plant sterols are authorized under EU NF Regulation
Extensive pre-market safety program basis for authorisation
Post-launch monitoring as requirement of NF authorisation shows no over-consumption in target consumers and no unwanted consumption in un-target groups (e.g. children)