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Benefit-risk assessment of phytosterols in margarine; a QALIBRA case study
Jeljer Hoekstra, Heidi P. Fransen, Jan C.H. van Eijkeren, Janneke Verkaik-Kloosterman, Nynke de Jong, Helen Owen, Marc Kennedy, Andy Hart

Abstract
This paper presents the benefit risk assessment of adding plant sterols to margarine using the QALIBRA method and software. Plant sterols lower cholesterol levels and consequently decrease the risk of ischemic heart disease. The also decrease β-carotene levels which in some case eventually may lead to vitamin A deficiency and nightblindness. The quantitative assessment shows that the benefits outweigh the risks.

Introduction
The market launch of functional foods forces the balancing of benefits and risks of dietary factors to be an important public health topic. In most cases it is unclear how much benefit can be achieved as the market introductions of these foods are based on a safety assurance only. This could mean that foods that introduce a small risk but a much larger benefit are kept off the market. Therefore it is of interest to know to what extent a specific food may provide population health benefits and to what extent health risks are introduced. Within the EU-funded QALIBRA project a tool is developed that can precisely do that. Benefits and risks are quantified and expressed in one common metric (DALY).

In the Netherlands, plant stanol-enriched margarines (Benecol®) and plant sterol-enriched margarines (Becel pro.activ®) are on the market since 1999 and 2000, respectively. Thus, one may assume there are only negligible risks. It is claimed there are benefits in reduction of cholesterol with the assumption that that will decrease heart diseases. We use the QALIBRA method to quantify the benefits and risks of these margarines.

The recommended daily intake of phytosterol-enriched margarines is equivalent to 2-3 g of plant sterols/stanols and is regarded as the optimal dose to reduce the LDL cholesterol levels effectively by about 9-14% (Katan et al. 2003; Law 2000). As no further LDL cholesterol reductions are achieved with intakes above 3 g/day, the former Scientific Committee on Food concluded to avoid intakes above 3 g of plant sterols/stanols per day. The cholesterol lowering effect is primarily established within a few weeks, and has been shown to remain stable for at least one year (Katan et al. 2003). Although no trials have directly tested the effects of plant sterols and -stanols on coronary heart disease (CHD) incidence, data from drug trials indicate that a reduction in LDL cholesterol level of about 10% could be expected to reduce the population incidence of ischemic heart disease by about 12% to 20% (Katan et al. 2003). Law et al. (Law et al. 1994) suggested that a reduction in serum total or LDL cholesterol of 0.6 mmol/L (about 10% for total and 15% for LDL cholesterol) would reduce mortality from ischemic heart disease by 54% at age 40 to 19% at age 80. More recent publications refer to CHD risk reductions independent of age, varying between 12-30% with a 10% to 1.0 mmol/L reduction in LDL level, respectively (Anonymous, 2001) (Baigent et al. 2005). Currently, few signals of (un)expected health effects of plant sterol/stanol have been reported. The main concern is that plant sterols/stanols decrease serum α- and β-carotene levels (Scientific Committee on Food 2002). Some data have been presented that higher plasma levels of plant sterols are associated with risk of coronary heart disease, suggesting that plant sterols may be atherogenic (Sudhop et al. 2002). There are also suggestions that the consumption of plant sterols may promote the development of stroke (Ratnayake et al. 2000) (Naito et al. 2003) or lead to the formation of unwanted hormones from β-sitosterol and have an impact on estrogenic activity (Malini and Vanithakumari 1993; Mellanen et al. 1996). An increase in the faecal concentration of cholesterol has been reported to be mutagenic in some in vitro tests (Kaul et al. 1987; Suzuki et al. 1986). Several studies have indicated an additive effect of plant sterols on LDL cholesterol lowering when combined with a statin. However, the use of
statins has also been associated with an increase of cholesterol-standardized serum plant sterol concentration, which may so induce extra atherogenicity (Miettinen et al. 2000). On a behavioural level, one might think of interference of plant sterol/stanol enriched foods in a patient’s drug therapy compliance. A patient may think that because he consumes plant sterols, taking his drugs is not so important anymore which might induce a potential downside albeit that this remains to be investigated. On the beneficial side, in addition to their cholesterol lowering properties, consumption of plant sterols/stanols may also possess anti-cancer, anti-inflammatory, anti-atherogenicity, and anti-oxidant activities (see for an overview Berger et al. 2004) but evidence for this is still speculative.

It is recognized that the balance between risks and benefits associated with a functional food, food component or total diet should form the ultimate basis for future nutrition policy on functional foods (EFSA, 2006). The purpose of integrated risk-benefit calculations is to express the positive health outcomes of functional food consumption in relation to any negative health outcomes. The ultimate result of the risk-benefit analyses can be used in risk-benefit management. Based on the outcomes, policy makers may want to adapt the label, stimulate the consumption of a certain food or diet, may ask for additional studies or may even withdraw a product from the market. Within the 6th EU Framework Qalibra project a quantitative risk-benefit assessment has been made of the population health effects if an active policy is pursued regarding enrichment of margarines with plant sterols/stanols.

In this assessment we answer the following specific risk-benefit question: What are the public health effects if a policy is pursued regarding enrichment of 100% of margarines with plant sterols compared with no enrichment.

Method

A computer model simulation of the scenarios is performed to compute the health effects associated with different levels of plant sterol intake in the Dutch population. The health effects in the alternative scenarios where 100% of margarine is enriched with 7.5 grams of plant sterols per 100 gram of margarine are compared with the reference scenario in which margarines are not enriched. The health effects are expressed in a common metric, the DALY (Disability Adjusted Life Years) (Murray 1994 #1002). The metric incorporates morbidity and mortality. DALYs are measured as the sum of the number of years lived with the disease adjusted with a weight that represents the severity of the disease, and the number of years lost due to earlier death as a result of the disease. Figure 1 schematically shows how DALYs are calculated for one individual.
Figure 1. Schematic representation of the DALY calculation.

To compute the health effects we need the following:

- Intake distributions that describe the intake of plant sterols in the population of interest in the enrichment and in the reference scenario;
- Identification of relevant health effects that are associated with plant sterol intake;
- Characterization of the effects that result from plant sterol intake. This is dose-response functions that describe the relation between plant sterol intake and each relevant health effect;
- Disease statistics, such as severity weights and survival data to convert the simulated incidences in DALYs;

More specifically, we use the Qalibra tool to compute the difference in the annual average amount of DALYS between the reference, no enrichment and the 100% enrichment scenario. With this method the DALYs are counted if they result from incidences occurring in one year. The difference between the scenarios can be interpreted as the long-term annual effect of enrichment.

Qalibra method

The Qalibra tool (www.qalibra.eu) quantifies and weighs benefits and risks by expressing them in a common metric, the DALY. The DALYs are calculated for the current year. Incidences that occur in the current year due to the intervention result in years lived with the disease and years of live lost as a result of the disease. Assuming that we consider a long-term intervention with a demographically stable population, the outcome can be regarded as the annual health gain expressed in DALYs/year when the intervention or policy is implemented.

The calculation of a DALY is based on two components, the number of years someone suffers from a disease and the number of years someone loses if they die earlier because of the disease. The calculation of DALYs takes account of two possibilities, either someone develops the disease or does not. If someone does, three alternative outcomes are possible an individual may

- recover,
- die early as a result of the disease,
- survive with the disease until the normal life expectancy i.e. suffer chronically.
The probability that someone develops the disease depends on exposure. It is denoted by \( P_{\text{effect}} \). \( P_{\text{effect}} \) is a dose-response relationship that associates the intake of a nutrient or contaminant with the disease. Often \( P_{\text{effect}} \) depends on age and sex and possibly other individual characteristics.

The expected total DALY loss of an individual due to a single disease occurring in the current year can then be estimated as:

\[
DALY = P_{\text{effect}} \left[ p_{\text{rec}} \cdot YLD_{\text{rec}} \cdot w + p_{\text{die}} \cdot \left( YLD_{\text{die}} \cdot w + LE - CA - YLD_{\text{die}} \right) + \left( 1 - p_{\text{die}} - p_{\text{rec}} \right) \cdot \left( LE - CA \right) \cdot w \right]
\]

where
- \( P_{\text{effect}} \) probability of onset of the disease in the current year (1/year)
- \( p_{\text{rec}} \) probability of recovery from the effect (0-1)
- \( p_{\text{die}} \) probability this effect causes death (0-1)
- \( YLD_{\text{rec}} \) duration of disease for those who recover (year)
- \( YLD_{\text{die}} \) duration of disease (years lived with disease) for those who die of it (year)
- \( CA \) current age of individual in year of disease onset (year)
- \( LE \) normal life expectancy\(^1\) (year)
- \( w \) disability weight for disease (0-1)

Between brackets the unit of each parameter is given. Each term (line) in equation (1) describes one of the three possibilities, recovery, premature death, or chronic suffering. Each term is composed of a probability that it will happen, the years lived with the disease and the years lost due to early death.

Equation (1) refers to an individual with a certain age, \( CA \), a certain exposure and possibly other properties such as sex and weight etc. on which the variables in equation (1) may depend. Parameters in equation (1) can be functions of intake and other individual characteristics. At least one of the parameters should depend on intake otherwise there is no need to simulate different intake scenarios. In general \( P_{\text{effect}} \) depends on exposure. Note that \( LE \) and \( P_{\text{effect}} \) will generally differ between age and sex groups and that other parameters may do also (e.g. the severity of a disease might depend on exposure and the age at which it occurs).

The incidence of a disease in the current year is estimated by summing \( P_{\text{effect}} \) over all individuals in the population.

\[
\text{inc} = \sum P_{\text{effect}}
\]

(2)

In order to obtain an appropriate estimate for the average annual DALY loss of a whole population, the calculation in equation (1) needs to be repeated and summed for each disease and for each characteristic individual in the population. Characteristic individuals are constructed in proportion to the age structure, the intake distribution (potentially per age and sex group) and other properties of the population. Our model population consists of 1000 model individuals, representative for the Dutch population in terms of age and sex.

In a risk-benefit assessment the focus is on evaluating the net health impact of a dietary change or intervention, in essence a change in intake. This is represented as the change from a reference scenario to an alternative scenario. Thus, the net health impact of an intervention in DALYs is calculated as:

\[
\Delta DALY = \sum DALY_{\text{alt}} - \sum DALY_{\text{ref}}
\]

where \( \sum DALY_{\text{ref}} \), sum over all individuals and all health effects of DALY losses for the reference scenario

\( \Delta DALY \) is the net health impact in DALYs of the intervention. It can be positive or negative indicating a net health benefit or harm, respectively.

\(^1\) Note: life expectancy is sometimes defined as the number of years of life remaining, but here it is defined as the expected age at death.
\[ \sum DALY_{alt} \], sum over all individuals and all health effects of DALY losses for the alternative scenario

The following paragraphs describe the scenarios i.e. population and intake and every variable from equation (1) which is necessary to simulate the health effects of the scenarios.

**Exposure assessment: Scenarios of plant sterol intake in the Netherlands**

The scenarios describe the public health effects in the Dutch population when 0% (reference scenario) or 100% (alternative scenario) of margarines is enriched with 7.5 grams of plant sterols/100 gram margarine?

We assume that every individual in the population will consume the same amount of margarine in each scenario. This is the amount that follows from the Dutch National Food Consumption Survey (DNFCS) intake database depending on age and sex. So, we assume that subjects will not alter their margarine consumption when margarines are enriched

**Population**

The scenarios were simulated with a population of 1000 individuals representing the Dutch population. The Dutch population age distribution for both sexes in 2007 was obtained from CBS-Statline. From this distribution (see figure 2) 1000 individuals were randomly drawn. When random sampling a subject from the population, the cumulative frequency is employed to determine the subjects age. Whether the subject would be a male or female is determined by the age dependency of the probability of a subject being a female. Finally, 1000 model individuals represent the Dutch population, i.e. the distribution of age and sex in the model population is the same as in the Dutch population.

![Figure 2. The age distribution of men and women in the Dutch population](image)

**Margarine intake**

Data of the most recent population wide Dutch National Food Consumption Survey (DNFCS) were used to simulate several scenarios of plant sterol intake. This DNFCS was conducted in 1997-1998. The respondents (N=6250, aged 1-97 yrs) recorded their food intake via dietary records on two consecutive days (Hulshof 2003). In the period this DNFCS was conducted, plant sterol enriched
foods were not yet introduced on the market. The Dutch food composition table does not contain information about plant sterols naturally occurring in foods. However, it is expected that plant sterol intake from enriched margarines surpasses the intake from natural sources. For example, Hearty et al. (2008) report a mean background exposure for plant sterols of 287 mg/day. An average slice of bread contains about 6 grams of margarine, corresponding to 450 mg of plant sterols using the current enrichment level of 7.5 g/100 g. Thus, plant sterol intake through enriched margarine consumption by far outweighs plant sterol intakes from natural sources. Therefore, background intake was ignored in the scenarios.

From the DNFCS for each subject the mean (low-fat) margarine intake over two days was calculated. The (low-fat) margarine intakes during hot meals were excluded. Subjects with a mean intake of zero grams over the two days were considered non-consumers of the product group. From the DNFCS data the fraction of non-consumers is established and an intake distribution for margarine consumers is established, depending on age and sex. The distributions are illustrated in the graph in figure 3. The two clusters that can be identified in the graph are ‘men’ and ‘women’. The graph shows that men tend to eat somewhat more margarine than women.

![Graph showing margarine intake distribution](image)

Figure 3. A cumulative distribution of margarine intake in the Dutch population stratified for age and sex

Phytosterol intake
In the policy scenarios it was assumed that every (low-fat) margarine was enriched with plant sterols and that these enriched products were used by the margarine consumers. For the reference scenario we assumed that no margarines were enriched with plant sterols. For (low-fat) margarine the intake from hot meals was not taken into account, as plant sterol enriched (low-fat) margarines are intended to be used as bread spread only. In the scenarios (low-fat) margarine was simulated to be plant sterol enriched with a level of 7.5 g plant sterols per 100 grams margarine.

From the intake distributions of the policy scenario mentioned above, age- and sex-specific margarine intakes were drawn and multiplied by the level of plant sterols in enriched (low-fat) margarine (i.e. 7.5 g/100 g) to calculate the total plant sterol intake from enriched foods.
Benefit identification and characterization

Katan et al. (2003) present summary estimates from randomized placebo-controlled trials of the relative reductions in LDL cholesterol (%) to plant sterol/stanol dose (g/d). Demonty et al. (2009) found a similar relationship between LDL cholesterol decrease and plant sterol intake. In addition, Law et al. (1994, 2003) present an age dependent relationship between absolute LDL cholesterol reduction (mmol/L) and decrease in IHD events (%).

Based on these two (internal and external) dose–response relationships, we develop a combined (external) dose-response relationship between intake of sterols (g/d) and decrease in the probability of an IHD event, that is dependent on the LDL cholesterol level at the start of the intervention. The combination of this dose-response relationship together with age dependent relations between serum LDL cholesterol level and IHD incidence allows for estimating absolute IHD probability in dependence on plant sterol dose and age ($p_{\text{effect,IHD}}$).

Plant sterols and IHD effect, $p_{\text{effect,IHD}}$

The relationship between plant sterol intake and reduction of IHD incidence ($p_{\text{effect,IHD}}$) combines several calculation steps:

1) plant sterol intake (grams/day) → relative LDL cholesterol reduction,
2) relative LDL cholesterol reduction (%) → Absolute LDL cholesterol reduction (using baseline LDL cholesterol data)
3) Absolute LDL cholesterol reduction → relative reduction of the probability of an IHD event
4) relative IHD probability → Absolute IHD probability (using baseline IHD incidence)
5) IHD incidence → DALY

1) plant sterol intake versus relative LDL cholesterol reduction

Data presented in Katan et al. (2003) figure 2, summarizing estimates from randomized placebo-controlled trials of the percentage reductions in LDL related to dose were modelled following equation (4).

$$\%\_\text{Reduction\_LDL} (d) = R_{\text{max}} \cdot \left( 1 - \exp \left( -\ln(2) \cdot \frac{d}{d_{1/2}} \right) \right)$$

(4)

where $R_{\text{max}}$ is the maximally attained reduction (%), $d$ is sterol dose (g/d) and $d_{1/2}$ the half maximum LDL reduction dose. The corresponding confidence interval boundaries were estimated by fitting equation (1) through the 2.5 and 97.5 percentiles.

While fitting equation (1) to the data in Katan et al. (2003) figure 2, the last data at about 4 g/d was omitted (in accordance with the summary in Katan et al. (2003) table 3) because of its great uncertainty and thus avoiding a dose–response relationship that might be too optimistic. When fitting the 2.5 and 97.5 percentiles, the value for the half dose $d_{1/2}$ was fixed at is value found when fitting the mean. The estimated model parameter values for the mean, 2.5 and 97.5 percentile are tabulated in Table 1.

Table 1. Estimated parameter values for the relative LDL serum level decrease (%) versus sterol dose (g/d) model equation (4). The estimates of Demonty et al. (2009) are shown between brackets.

<table>
<thead>
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<th>$R_{\text{max}}$ (%)</th>
<th>$d_{1/2}$ (mmol/L)</th>
</tr>
</thead>
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<tr>
<td>2.5 percentile</td>
<td>10.1 (9.99)</td>
<td>0.803 (0.62)</td>
</tr>
<tr>
<td>mean</td>
<td>11.9 (12.68)</td>
<td>0.803 (1.12)</td>
</tr>
<tr>
<td>97.5 percentile</td>
<td>13.7 (15.38)</td>
<td>0.803 (1.63)</td>
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According to the dose-response relationship (eq. (1)), the predicted relative LDL cholesterol lowering effect of the recommended daily dose of plant sterols (2 g) would be 9%, similar to the estimate of Demonty et al. (2009).

2) Converting relative LDL cholesterol reduction to absolute LDL cholesterol reduction using baseline LDL cholesterol

Relative LDL cholesterol values can easily be converted in absolute values when baseline absolute levels are known. Data on LDL cholesterol levels in dependence on age and sex were obtained from [Goto, 1984; Verschuren, 2008]. Data in [Goto, 1984] suggested a constant level for ages till about 20 years and a steady increase thereafter. So, the following model was applied:

\[
LDL(Age, s) = \begin{cases} 
C(s) & \text{Age < 20} \\
C(s) + (M(s) - C(s)) \left(1 - \exp \left(-\log(2) \frac{Age-20}{Age_{1/2}(s)} \right) \right) & 20 < Age
\end{cases}
\]

(5)

where LDL is the baseline LDL cholesterol level, \(M\) is an asymptotic maximum LDL-cholesterol level (that need not be representative of LDL levels encountered in practice), \(Age_{1/2}\) the half age at which LDL level is halfway in between \(C\) and \(M\) and \(s\) corresponds to sex category, male or female.

The model in equation (5) was fitted to the data both for men and women in [Goto1984] concerning the median (50th percentile) and the 5th and 95th percentiles of the observed distribution. The half age value, estimated for the median values data was fixed when estimating the 5th and 95th percentile data. From the model and data comparison it was decided that the model assumption is adequate. To profit from more recent data in Doetinchem [Verschuren, 2008] the model was recalibrated. This data on a Dutch sub-population may be more informative concerning current Dutch LDL-cholesterol serum levels, however was only available for ages between 30 and 80 years in age classes of ten years. It was found that the median levels of this data compared to those from U.S.A. 1984 are about 10% higher for men and 15% for women. Because of paucity of data it was decided to fix the half age value to that found for the former data. The model parameters \(C(s)\) and \(M(s)\) were corrected in accordance with the new data. Furthermore, because the data for the class 70-79 years was based on sampling only a relative small number of subjects (14 men and 27 women) these data were left out of recalibration. The final parameter values are tabulated in Table 2.

Table 2. Optimized parameter values for the LDL serum level (mmol/L) versus age (year) model equation (5).

<table>
<thead>
<tr>
<th>percentile</th>
<th>(C) (mmol/L)</th>
<th>(M) (mmol/L)</th>
<th>(Age_{1/2}) (year)</th>
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<tr>
<td>male</td>
<td></td>
<td></td>
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<tr>
<td>50</td>
<td>3.17</td>
<td>4.15</td>
<td>13.1</td>
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<tr>
<td>5</td>
<td>2.39</td>
<td>3.06</td>
<td>13.1</td>
</tr>
<tr>
<td>95</td>
<td>4.64</td>
<td>5.28</td>
<td>13.1</td>
</tr>
<tr>
<td>female</td>
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<td></td>
<td></td>
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<tr>
<td>50</td>
<td>2.91</td>
<td>9.46</td>
<td>13.1</td>
</tr>
<tr>
<td>5</td>
<td>2.18</td>
<td>7.09</td>
<td>13.1</td>
</tr>
<tr>
<td>95</td>
<td>4.03</td>
<td>11.3</td>
<td>13.1</td>
</tr>
</tbody>
</table>

\(b\): fixed to value found for calibration on (Goto, 1984) data

The relative LDL serum level decrease (%) can be combined with baseline LDL serum level to obtain absolute LDL serum level decrease:

\[
\Delta LDL(d, age, sex) = \frac{R_{max}}{100} \left(1 - \exp \left(-\ln(2) \frac{d}{d_{1/2}} \right)\right)LDL(age, sex)
\]

(6)
where $\Delta_{LDL}$ represents the absolute LDL cholesterol decrease (mmol/L).

3) **Absolute LDL cholesterol reduction → relative reduction of the probability of an IHD event**

Data presented in Law *et al.* (2003) table 7, relates expected decrease in IHD events (%) to a specified decrease in LDL-cholesterol serum level (mmol/L) based on 10 large cohort studies in a meta analysis and were fitted to equation (7) similar to equation (4):

$$\%_{\text{IHD decrease}}(\Delta, \text{Age}) = 100 \left(1 - \exp\left(-\ln(2) \cdot \frac{\Delta_{1/2}}{\Delta_{1/2}(\text{Age})}\right)\right)$$

(7)

where the age dependent decrease $\Delta_{1/2}$ (half IHD decrease LDL-cholesterol serum level) is the LDL-cholesterol decrease when IHD decrease is 50%.

To account for age dependency, we assumed a linear relationship between half cholesterol decrease and age for ages between 50 and 70 years:

$$\Delta_{1/2}(\text{Age}) = a \cdot \text{Age} + b$$

(8)

In Law *et al.* (2003) data for the three ages (50, 60 and 70 years) are tabulated, representing age classes of 45-54, 55-64 and 65-74 years, respectively. These data were simultaneously fitted to the model as defined by the equations (7) and (8). Estimated parameter values are

$$a = 0.0501 \text{ (mmol/L/year)}$$

and

$$b = -1.66 \text{ (mmol/L)}$$

(9)

The resulting model calculations are compared to those of Law *et al.* (2003). From the comparison it is evident that the modelling approach in Law *et al.* (2003) is equivalent to our approach in equation (7). Incorporation of equation (8) into the model however, allows for IHD decrease estimates for any age between 45 and 75 years. In order to estimate variability, it was observed that for the age class 55-64 year the inverse variance weighted mean of 27% of 8 investigations could as well be estimated by median polish. Therefore, the lower and upper confidence limits of the 8 investigations were median polished to obtain a confidence interval of 20 to 33%. As this range of 13% represents the 95% confidence interval of width $4\sigma$ the coefficient of variation was estimated to be $100 \times (13/4)/27 = 12\%$.

In Law *et al.* (1994) table II also one data for estimated IHD reduction of 54% at age 40 (range between 35 and 44 years) is presented inclusive a 95% confidence interval of 45 to 62%. Model calculated decrease is 70%, which shows that model based estimates are too optimistic. Therefore, estimating relative IHD reduction, for all ages below 45 year, the age of 45 year will be substituted. At least, this is a conservative approach. Moreover, the bulk contribution of IHD incidence decrease derives from ages above 45 year and therefore the resulting underestimation is expected to be irrelevant.

4) **relative IHD probability → Absolute IHD probability (using baseline IHD risk)**

Data regarding absolute baseline IHD incidence in the Dutch population in 2003 were obtained from the Nationaal Kompas Volksgezondheid [www.rivm.nl/nationaalkompas]. These data concern the two sexes and several age classes. IHD incidence is given per 1000 subjects of a given sex and age class. The data could be modelled using a hyperbolic tangent shaped function:

$$IHD(\text{age},s) = \frac{A(s)}{2} \left(1 + \tanh\left(\frac{\text{age} - T(s)}{c(s)}\right)\right) - \left(1 + \tanh\left(\frac{-T(s)}{c(s)}\right)\right)$$

(10)
where, $A$ is the asymptotic maximum, $T$ is the age at half maximum and $c$ determines the rate of increase and $s$ is the corresponding sex. $IHD$ in equation (10) should be interpreted as the baseline $IHD$ incidence ($1/1000$) of individuals of sex $s$ and age $Age$. The model equation (10) was fitted to the data for men and for women. Estimated values are presented in Table 3. Data and model are compared in Figure 4.

![Figure 4. IHD incidence per 1000 in the Dutch population in 2003 for men (blue) and women (pink). Comparison of modelling approach (straight lines) and data (symbols).](image)

Table 3. Estimated parameter values in equation (10) depending on sex.

<table>
<thead>
<tr>
<th></th>
<th>$A$</th>
<th>$T$</th>
<th>$c$</th>
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</thead>
<tbody>
<tr>
<td>male</td>
<td>29.6</td>
<td>63.8</td>
<td>15.9</td>
</tr>
<tr>
<td>female</td>
<td>21.0</td>
<td>67.1</td>
<td>13.4</td>
</tr>
</tbody>
</table>

The absolute decrease in the probability of an $IHD$ event is obtained by multiplication of the expressions in the equations (4) and (10). Consequently, the absolute probability of an $IHD$ event depending on age, sex and intake of plant sterols is given by equation (8)

$$P_{\text{effect},IHD}(d,Age,s) = \% _{IHD}(d,Age,s) \times IHD(Age,s)$$  

5) $IHD$ incidence → DALY

DALYs are computed according to equation (1). It combines mortality expressed as the number of years lost ($YLL$) and morbidity expressed as the number of years lived with the disease ($YLD$) weighted by a factor ($w$) that expresses the severity of the disease.

We assume that an individual will either live with the disease for the rest of his life, or he will die after one year. So, the probability of recovery, $p_{\text{rec}}$ and as a result $YLD_{\text{rec}}$ set to 0. In 2005, in the Netherlands, mortality of CHD-patients was 5.8% for men and 8.6% for women in the first year after hospitalisation according to Statistics Netherlands. Thus, $YLD_{\text{die}}$ is set to 1 and the probability of death, $p_{\text{die}}$ is 0.058 and 0.086 for men and women respectively. We assume mortality due to $IHD$ does not depend on plant sterol intake. The disability weight, $w$, is 0.29 (Stouthard et al., 1997).
Risk identification and characterization

The literature shows an effect of plant sterol intake on serum levels of β-carotene. LDL cholesterol is an important transport vehicle for fat-soluble vitamins. If the absorption of LDL cholesterol is lowered, for example due to the use of plant sterol enriched products, the concentration of these fat-soluble vitamins, like carotenoids, may also be affected. β-carotene is one of the carotenoids that might be affected. The effect is however controversial (Polagruto, 2006; Berger, 2004). In some plant sterol trials, decreases of β-carotene concentrations of 8-19% were found when plant sterol enriched products were consumed (Law, 2000; Katan, 2003). Other studies do not find effects on carotenoid levels. Berger et al. (Berger, 2004) has summarized these results in a review by. Some studies have shown that if the plant sterol enriched products are consumed in a healthy diet, the carotenoid levels will stay within normal levels, within the seasonal variation (Ntanios & Duchateau, 2002; Noakes, 2002). Because those studies reporting a decrease of β-carotene level are diverse with respect to quantifying units and not quantitative in relating sterol dose and serum β-carotene level decrease, a quantitative sterol dose - serum β-carotene level decrease response relation can not be obtained.

The health effects of the possible variation in blood carotenoid levels are largely unknown. It is assumed that people with higher levels of β-carotene have a lower risk for cancer and CVD (SCF, 2002), but more studies are needed to look further into this problem (Katan, 2003). As β-carotene is also an important source of vitamin A, (carotenoids can contribute to more than 40% of the vitamin A supply (ref SCF, 2002)), for this study we have chosen to look at the lowering of vitamin A levels due to lower β-carotene levels. As mentioned before, we assume that a β-carotene level decrease will result in a lower vitamin A production, leading subjects from near vitamin A deficiency into vitamin A deficiency.

Several effects are reported that are related to vitamin A deficiency, with xerophthalmia being the first visible clinical effect. This disease consists of several stages, nightblindness is the first symptom that is observed. In literature, no quantitative data that could lead to a quantitative vitamin A status - nightblindness response relation was found. Therefore, and because the conversion from β-carotene to vitamin A is according to one's needs, we chose to create an “on/off”-scenario for sterol intake and nightblindness. The model assumption is that if a person is nearly vitamin A deficient, the use of plant sterol enriched products leads inevitably to vitamin A deficiency in this person.

Sterol dose – nightblindness relation, \( p_{\text{effect,NB}} \)

Lack of clear and univocal qualitative data, let alone sufficient quantitative data, prohibited the development of a quantitative dose-response for plant sterol dose-vitamin A status and for vitamin A status-nightblindness response. Therefore, four worst-case assumptions were made to obtain a conservative but univocal population sterol dose - nightblindness relation, \( p_{\text{effect,NB}} \). These assumptions are:

1. that any amount of sterol intake (yes/no) will decrease β-carotene level;
2. that people that are supposed to possess a vitamin A level that is near deficiency are actually near deficiency;
3. that decrease of β-carotene level, considered as a provitamin A, will lead a person from near vitamin A deficiency to deficiency;
4. that a deficient vitamin A status has nightblindness as effect.

Summarizing, our model assumption is: people who have a poor vitamin A status and consume plant sterols will suffer from nightblindness. We know this is a gross overestimation of the effect of a reduced beta-carotene level due to plant sterol consumption. Not every person who is nearly vitamin A deficient will actually become deficient if their β-carotene levels decrease due to sterol intake and develop nightblindness as a result. We hypothesise that the cholesterol lowering effect of plant sterol intake outweighs the beta-carotene lowering effect. So, if a grossly overestimated beta-carotene effect is still outweighed by the cholesterol lowering effect than there is no need to be more accurate and our simple unrealistic assumptions suffice.
**Vitamin A status**

The distribution of poor vitamin A status in the Dutch population, classified on sex and age ranges, was obtained from Waijers and Feskens (2004). This distribution is based on food consumption data and the assumption that people that consume food with too low a (pro-) vitamin A (e.g. beta-carotene) content are likely vitamin A deficient or at the verge of being vitamin A deficient. The Dutch population sex and age distribution was obtained from CBS. Both distributions have been combined to obtain the vitamin A status distribution in the total population.

The population distribution of people who are supposed to be nearly deficient is shown in Table 4 (second column) as the percentage of subjects of the corresponding sex and age class. The total population age distribution is also shown in Figure 2. In effect, \( P_{\text{effect,Na}} \) for sterol intake > 0 is shown in the last column of Table 4.

Table 4. Distribution of supposed vitamin A deficiency in the Dutch population. The second column shows the distribution as percentage of the corresponding sex and age range in the first column, based on Waijers & Feskens, 2004. The third column shows the percentage of subjects in the Dutch population of the corresponding sex and age class. The fourth column shows the percentage of subjects of the corresponding sex and age class related to the total number of subjects in the population.

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>% of vit A deficient individuals in age and sex class</th>
<th>% of (age, sex) in population</th>
<th>% of vit A deficient individuals in the total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-3y</td>
<td>0.2</td>
<td>4.68</td>
<td>0.009</td>
</tr>
<tr>
<td>Children 4-8y</td>
<td>1.5</td>
<td>6.19</td>
<td>0.093</td>
</tr>
<tr>
<td>Children 9-13y</td>
<td>1.5</td>
<td>5.99</td>
<td>0.090</td>
</tr>
<tr>
<td>14-18y men</td>
<td>2.5</td>
<td>3.13</td>
<td>0.078</td>
</tr>
<tr>
<td>14-18y women</td>
<td>4.1</td>
<td>2.99</td>
<td>0.123</td>
</tr>
<tr>
<td>19-50y men</td>
<td>1.6</td>
<td>22.5</td>
<td>0.360</td>
</tr>
<tr>
<td>19-50y women</td>
<td>4.8</td>
<td>22.1</td>
<td>1.062</td>
</tr>
<tr>
<td>51-65y men</td>
<td>1.3</td>
<td>9.48</td>
<td>0.123</td>
</tr>
<tr>
<td>51-65y women</td>
<td>2.6</td>
<td>9.36</td>
<td>0.243</td>
</tr>
<tr>
<td>65+ men</td>
<td>0.6</td>
<td>5.74</td>
<td>0.034</td>
</tr>
<tr>
<td>65+ women</td>
<td>1.8</td>
<td>7.83</td>
<td>0.141</td>
</tr>
</tbody>
</table>

**DALY computation of nightblindness**

The resulting change in incidence in nightblindness is converted to DALYs by using a disability weight for minor visual disturbance (\( w = 0.02 \)) because no weight factor for nightblindness is available. Furthermore, sufficient intake of vitamin A will cure the disease and it is presumed that it maximally last 1 year. So, \( YLD_{\text{rec}} \) and \( p_{\text{rec}} \) are 1 and \( YLD_{\text{die}} \) and \( p_{\text{die}} \) are 0.

**Results**

The beneficial effect of using plant sterol enriched margarines is that an IHD event is prevented in the current year. The simulated adverse effect is nightblindness. So people can be affected in many ways, positively and negatively. Many people will not be affected at all, they didn’t experience an IHD event in the 0% enrichment-scenario and obviously they do not prevent that event and neither do they become nightblind. Others only experience an adverse effects, they become nightblind. The calibra method calculates the annual average DALYs that are gained. Table 5 shows the results.
Table 5. Results of the simulation of the reference scenario 0% enrichment and the 100% enrichment scenario

<table>
<thead>
<tr>
<th></th>
<th>Ischemic Heart disease</th>
<th>Nightblindness</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DALYs</td>
<td>6.56</td>
<td>0.416</td>
<td>-6.14</td>
</tr>
<tr>
<td>Incidence per 1000, Reference scenario</td>
<td>5.29</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Incidence per 1000, 100% enrichment scenario</td>
<td>4.42</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>Mortality per 1000, Reference scenario</td>
<td>0.366</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mortality per 1000, 100% enrichment scenario</td>
<td>0.303</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Enrichment of all margarines in the Netherlands would result in about 6 extra disability adjusted life years, annually per 1000 inhabitants. Assuming a stable population, the incidence and mortality of ischemic heart disease would be decreased by about 15%. Six extra health life years per 1000 people may not seem a lot but it is each year as long as margarines are enriched and represented as a 15% decrease in the incidence of a major disease changes the perspective. However, this effect is achieved only if every margarine used as bread spread is enriched with 7.5 grams of plant sterols per 100 gram. In reality, fewer margarines are and will be enriched so fewer individuals will prevent their ischemic heart disease. The results represent an upper estimate of the net effect and show the potential of margarine enrichment.

There are still some caveats that need to be made. We have ignored long term effects for which currently there is not strong enough evidence. Furthermore, people with a high cholesterol level, who have a high risk of developing IHD quite often use statins. The effect of both using statins and consuming plant sterols is not incorporated in the model. More and more products containing plant sterols are brought on the market which will enhance the effects. In the study of Law that we used to establish the relationship between LDL cholesterol reduction and IHD incidence (equation (7)) some subjects were using statins to lower their cholesterol levels. We have assumed that statins have no effect on IHD other than by lowering cholesterol. If they have the effect of cholesterol on IHD is overstated in our equation (7) and thus in the final results.

We have also slightly underestimated the effect in DALYs. When someone is simulated to develop IHD, the attributed DALYs notably the years of life lost are based on the general life expectancy not the life expectancy excluding dying from IHD.

It should be noted that the adverse effect, becoming nightblind, is a gross overestimation of the negative effect and almost nonexistent. However, because the effect is still very small it does not influence the overall results.

So given that risks are hugely overestimated, benefits are probably overestimated and the difference is large and in favour of the benefits it seems fair to conclude that the net health effect of plant sterol intake is positive.
Acknowledgement

This work was supported by the European Commission through the QALIBRA project (FOOD-CT-2006-022957): Quality of Life – Integrated Benefit and Risk Analysis. Web-based tool for assessing food safety and health benefit. [www.qalibra.eu](http://www.qalibra.eu). The UK Food and Standards Agency cofunded the research of FERA.
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