Application of the BRAFO tiered approach for benefit–risk assessment to case studies on dietary interventions

Hans Verhagen a,h, Rikke Andersen b, Jean-Michel Antoine c, Paul Finglas d, Jeljer Hoekstra a, Alwine Kardinael e, Hervé Nordmann f, Gülden Pekcan g, Kristina Pentievah h, Tom A. Sanders i, Henk van den Berg j, Henk van Kranena, Alessandro Chiodinik, ⇑

⇑Corresponding author. Address: ILSI Europe a.i.s.b.l., Avenue E. Mounier 83, Box 6, 1200 Brussels, Belgium. Tel.: +32 (0) 27710014; fax: +32 (0) 27620044. E-mail address: publications@ilsieurope.be.

a National Institute for Public Health and the Environment (RIVM), 3720 Bilthoven, The Netherlands
b Technical University of Denmark, Department of Nutrition, Mørkhøj Bygade 19, 2860 Soberg, Denmark
c Institute of Food Research, Norwich Research Park, Colney, NR4 7UA, Norwich, UK
d Institute of Food Research, Norwich Research Institute (TN), Utrechtseweg 48, P.O. Box 360, Zeist, The Netherlands
e Nutrition and Food Research Institute (TNO), En Crochet 1, Apples, Switzerland
f Ajinomoto Europe, En Crochet 1, Apples, Switzerland
g Hacettepe University, Department of Nutrition and Dietetics, School of Health Technology, Sihhiye 06100, Ankara, Turkey
h Nutrition and Food Research Institute (TNO), Utrechtseweg 48, P.O. Box 360, Zeist, The Netherlands
i King’s College London, Franklin-Wilkins Building, 150 Stamford St, SE1 London, UK
k ILSI Europe, Avenue E. Mounier 83, Box 6, 1200 Brussels, Belgium

ABSTRACT

The respective examples, described in this paper, illustrate how the BRAFO-tiered approach, on benefit–risk assessment, can be tested on a wide range of case studies. Various results were provided, ranging from a quick stop as the result of non-genuine benefit–risk questions to continuation through the tiers into deterministic/probabilistic calculations. The paper illustrates the assessment of benefits and risks associated with dietary interventions. The BRAFO tiered approach is tested with five case studies. In each instance, the benefit–risk approach is tested on the basis of existing evaluations for the individual effects done by others; no new risk or benefit evaluations were made. The following case studies were thoroughly analysed: an example of food fortification, folic acid fortification of flour, macronutrient replacement/food substitution; the isocaloric replacement of saturated fatty acids with carbohydrates; the replacement of saturated fatty acids with monounsaturated fatty acids; the replacement of sugar-sweetened beverages containing mono- and disaccharides with low calorie sweeteners and an example of addition of specific ingredients to food: chlorination of drinking water.

© 2011 ILSI Europe. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Benefit–risk analysis is the comparison of the risk of a situation to its related benefits and comprises a constellation of methods, drawn from many disciplines, and addresses the question of whether a risk is acceptable. Over the past years the benefit–risk analysis in relation to foods and food ingredients has gained much attention, in Europe but also worldwide. The debate focuses mainly on how and when to conduct such analysis. So on the one hand food contains necessary and beneficial ingredients, whereas on the other hand it can also contain potentially adverse ingredients. The issue is that the beneficial and adverse potential can be in the same food or even in the same ingredient. The approaches and policies followed and measures taken to guarantee food safety may lead to suboptimal/too low levels or absence of ingredients from the perspective of benefits. Not allowing food benefits to occur in order to guarantee food safety is a risk management decision equally well as accepting some risk in order to achieve more benefits. Any choice is a choice.

As such, benefit–risk assessment (BRA) is a new area in the area of food and nutrition. It envisages comparing both risks and benefits of foods and food ingredients in one currency, thereby allowing for a qualitative and quantitative comparison of adverse and beneficial effects. The benefit–risk assessment can then be reported into policy makers to allow them to make a benefit–risk management decision.

This scientific area has only very recently been entered. Now that health risks are essentially under control, the next step can
be made: balancing benefits and risks into an overall assessment. BRA can be done on a qualitative basis. By applying value to benefits and risks more informed policy decisions could be made. Quantitative BRA can be done on an incidence basis, or by applying weighting factors to the incidences such as by using QALY’s (Quality Adjusted Life Year) or DALY’s (Disability Adjusted Life Year) or even Euro’s. In Europe, several projects are exploring this new area such as EFSA (European Food Safety Authority) (http://www.efsa.europa.eu/efsajournal/index en C15), BRAFO(http://www.qalibra.eu/), and BEPRARIBEAN(http://en.opasnet.org/w/Bepraribea). The aim of the European Funded Project BRAFO (Benefit Risk Analysis of Foods) project is to develop a framework that allows quantitative comparison of human health risks and benefits of foods and food compounds based on a common scale of measurement. This will be based on the evaluation of changes using a system that allows weighting of data quality and severity of effect, with quantification by e.g. QALY or DALY-like methodology. The framework will take into account how risks/benefits interrelate but will also consider how these relate to the same and different sub-populations, including those defined by genetic polymorphisms. It is intended that the methodology developed is sufficiently transparent to serve as a reference for the harmonization of the evaluation methods used within the European Union (EU) and more widely in international evaluation.

The objectives of Work Package 5 (WP5) are to:

- Describe in qualitative and quantitative terms the beneficial effects of dietary interventions.
- Describe in qualitative and quantitative terms the adverse effects of dietary intervention across intake levels, taking into account subgroups, severity of effects, and probability of effects.
- Identify key components and their potential for causing adverse effects.
- Assess the relationship between dietary intervention and the alteration of the nutritional properties of the food.
- Apply and adapt those evaluative methods and common core elements as developed by WP3 to undertake qualitative and quantitative comparison of benefits and risks based on a common scale of units.
- Provide guidance for WP8 by identifying key messages that need to be further communicated to stakeholders and risk managers.

The work of WP5 consists of an assessment of the number and kind of people that will perceive beneficial and adverse effects across actual intake levels, including a description of the severity and the probability of the effects occurring when consuming food subject to dietary interventions. Five examples will be addressed in this work package:

- Addition of folic acid to flour/bread.
- Replacement of saturated fatty acids by mono-unsaturated fatty acid.
- Replacement of saturated fatty acids by carbohydrate (isocalorically).
- Replacement of mono- and disaccharides by low calorie sweeteners.
- Addition of chlorine to water.

In this work package the already described BRAFO tiered approach was tested on the above mentioned case studies. In each instance, the benefit–risk approach is tested on the basis of existing evaluations for the individual effects done by others; no new risk or benefit evaluations were made.

2. Case study: folic acid

2.1. Introduction

Folate is the generic name for a number of compounds having a similar activity as folic acid (pteroylglutamic acid – PGA). Folic acid is a synthetic folate compound used in food supplements and in food fortification because of its stability, and becomes biologically active after reduction, whereas dietary folate is already in its reduced form. Folates play an important role in the transfer of C1-groups (i.e. methyl-, methylene- and formyl-groups), maintaining the methylation balance, such as in the biosynthesis of DNA and RNA bases, in amino acid metabolism and epigenetic processes like DNA and histone methylation (http://www.efsa.europa.eu/efsajournal/index en C15).

2.2. Pre assessment and problem formulation

Folic acid/folate have been associated with a large variety of positive and negative health effects. The most well known of these are the well-established prevention of neural tube defects (NTD) and the masking of vitamin B12 deficiency, but there are many more (potential) health effects of folic acid. Because of its proven role in the prevention of the incidence of neural tube defects, in many countries flour and flour products are fortified with folic acid, either on a mandatory or on a voluntary basis. In this case study the benefits and risks of fortification of bread with folic acid will be described in the light of the BRAFO project.

The potential benefits are:

- A reduced incidence of neural tube defects affecting the next generation.
- A reduced incidence of megaloblastic anaemia due to folate deficiency affecting the population at large.
- A reduced incidence of stroke in people without a history of the disease.
- A reduced incidence in colorectal cancer.

The potential risks are:

- An increased incidence of neurological damage due to masking of vitamin B12 deficiency affecting elderly persons and strict vegetarians.
- An increase in the incidence of colorectal cancer in people with pre-existing polyps by accelerated progression to colorectal cancer (excessive amounts of folate only).

Table 1 summarises the most relevant health effects associated with folic acid/folate.

As concerns potential benefits and risks, three health effects with a convincing level of evidence were identified (Hoekstra et al., 2008): (1) the effect of folic acid on the prenatal development of NTD (Czeizel and Dudas, 1992), (2) the prevention of megaloblastic anaemia caused by folate deficiency (Streiff, 1970) and (3) the masking of hematological symptoms of vitamin B12 deficiency by folic acid (Dickinson, 1995). Upon the paper by Hoekstra et al. (2008), with regard to the prevention of NTD’s the evidence from ecological studies summarised in a recent review by Heseker et al. (2009) indicated that not all NTD’s can be prevented by increasing the intake of folic acid, thereby adjustments for the beneficial effects should be accounted for.

The discussions about a possible association between high dose folic acid supplementation and (colorectal) cancer risk are still ongoing (Helman, 2010). In 2009 the most recent reports of European Food Safety Authority (EFSA) Scientific Cooperation
Working Group (2009) and the UK Scientific Advisory Committee on Nutrition (2009) concluded that there is still uncertainty about this association (ESCO, 2009; SACN, 2009). However, it should be noted that two other publications are strengthening the concern that high doses of folic acid may accelerate the progression of colorectal cancer. The first is an ecological study from Chile that noted that two other publications are strengthening the concern that high doses of folic acid may accelerate the progression of colorectal cancer (also strict vegetarians).

Table 1
Application of tiers 1 and 2 of the BRAFO methodology to the case study on folic acid.

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Health effect</th>
<th>Change</th>
<th>Quality of evidence</th>
<th>Population affected</th>
<th>Health impact (beneficial/ adverse/none)</th>
<th>References to the quality of evidence</th>
<th>Effect severity (w = 0–1)</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural tube defects</td>
<td>Decrease</td>
<td>High</td>
<td>Next generation</td>
<td>Beneficial</td>
<td>EFSA (2006a,b), Hoekstra et al. (2008), Wang et al. (2007), Marti-Carvajal et al. (2009), Heseker et al. (2009)</td>
<td>0.59</td>
<td>–83</td>
<td></td>
</tr>
<tr>
<td>Megaloblastic anaemia due to folate deficiency</td>
<td>Decrease</td>
<td>High</td>
<td>Total population</td>
<td>Beneficial</td>
<td>EFSA (2006a,b), Hoekstra et al. (2008), Wang et al. (2007), Marti-Carvajal et al. (2009)</td>
<td>0.01</td>
<td>–2425</td>
<td></td>
</tr>
<tr>
<td>Neurological effects due to masking of vitamin B12 deficiencies</td>
<td>Increase</td>
<td>Low</td>
<td>Elderly &gt;65 y</td>
<td>Adverse</td>
<td>EFSA (2006), Hoekstra et al. (2008), Wang et al. (2007), Marti-Carvajal et al. (2009)</td>
<td>0.064</td>
<td>+53</td>
<td></td>
</tr>
<tr>
<td>Change in incidence colorectal cancer</td>
<td>Change (cancer cases)</td>
<td>Moderate</td>
<td>Total population</td>
<td>Adverse</td>
<td>EFSA (2006a,b), Hoekstra et al. (2008), Wang et al. (2007), Marti-Carvajal et al. (2009)</td>
<td>0.32</td>
<td>–405b</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Decrease</td>
<td>Moderate</td>
<td>Only people without a history of disease</td>
<td>Beneficial</td>
<td>(Not calculated)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Data for The Netherlands; based on Hoekstra et al. (2008).
b Net effect of increases and decreases in colorectal cancer, no effects on accelerated progression of polyps at this concentration of 70 μg/100 g flour.
c Low relates to the neurologic effects not to the well established masking of vitamin B12 deficiency.

Table 2
The most relevant effects associated with folic acid/folate in terms of number of individuals affected, severity of effects, life years with disease, life years lost and DALY's.

<table>
<thead>
<tr>
<th>Tiers 3–4</th>
<th>Health effect</th>
<th>Effect severity (w = 0–1)</th>
<th>Number of individuals</th>
<th>Years lived with disease, per affected person (YLD)</th>
<th>Change in DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural tube defects</td>
<td>0.59</td>
<td>83</td>
<td>32</td>
<td>–5474</td>
<td></td>
</tr>
<tr>
<td>Megaloblastic anaemia due to folate deficiency</td>
<td>0.01</td>
<td>2425</td>
<td>1</td>
<td>–24</td>
<td></td>
</tr>
<tr>
<td>Neurological effects due to masking of vitamin B12 deficiencies</td>
<td>0.064</td>
<td>53</td>
<td>16</td>
<td>+53</td>
<td></td>
</tr>
<tr>
<td>Change in incidence colorectal cancer</td>
<td>0.32</td>
<td>405b</td>
<td>(Intake-dependent)</td>
<td>–2217b</td>
<td></td>
</tr>
<tr>
<td>Decrease in incidence of stroke</td>
<td>0.61–0.89d</td>
<td>Not calculated</td>
<td>Not calculated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall change</td>
<td></td>
<td></td>
<td></td>
<td>–7662</td>
<td></td>
</tr>
</tbody>
</table>

a Data for The Netherlands; based on Hoekstra et al. (2008).
b Net effect of increases and decreases in colorectal cancer.
c Positive numbers are representing benefits i.e. DALY's prevented/gained, whereas negative numbers correspond to an adverse effect i.e. DALY's lost.
d Range based on two meta-analyses, RR = 0.61 from Wang et al. (2007) and a RR = 0.89 from Lee et al. (2010).

2.3. Reference and alternative scenario

For the problem formulation a reference and an alternative scenario as well as target population are formulated as follows:

Reference scenario: No fortification.

Alternative scenario: Fortification of bread with folic acid at 70 μg/100 g. Target population: European population at large.

2.4. BRAFO tiered approach

A recent in-depth benefit–risk assessment of folic acid fortification was used as a starting point for testing the BRAFO tiered approach: Hoekstra et al. (2008) evaluated the effects of fortification of flour for making bread was across several levels of fortification (from no fortification, and 70, 140, 280 and 420 μg folic acid per 100 g of bread). This detailed study is based on incidences in the population of the Netherlands, which has a relatively small population (ca. 16.5 million), albeit that this does not have any consequences for the BRAFO tiered approach. Only the absolute size of the population health effects may differ, unlike the relative public health effects.
We did not update the recent data on stroke, colorectal cancer, and NTD’s (Heseker et al., 2009) in the models of Hoekstra et al. (2008), because the aim of this WP is to test the BRAFO tiered approach instead of having the most recent literature updates at hand. For the actual benefit–risk calculations we used the original results as presented in Tables 4 and 5, and we speculated how incorporation of this new data would alter the outcome. As compared to Hoekstra et al. (2008), the beneficial NTD effect should be considered slightly weaker because less cases can be prevented by folic acid fortification, but another beneficial effect, prevention of stroke in a subpopulation (see above) should be added. Furthermore the strength of the evidence is increased for the adverse effect, increase in colorectal cancer incidence for high doses of folic acid, but the size of the effect is still as uncertain as in Hoekstra et al. (2008). Therefore it seems rather unlikely that incorporation of these new data would alter the overall conclusions for the ruggedness of the BRAFO tiered approach. The overall uncertainty about the evidence per se and the size of the colorectal cancer effect still dominates the outcome.

In tier 1, it is concluded that the alternative scenario versus the reference scenario involves potential health benefits as well as potential health risks. Hence this case is a genuine benefit–risk question (tier 1 passed).

In tier 2, a qualitative evaluation of benefits and risks is made. With respect to severity of effects, there is large variation ranging from \( w = 0.01 \) (megaloblastic anaemia) to \( w = 0.59 \) (neural tube defects). There are health effects that rank high in severity (neural tube defects, colorectal cancer), moderate (neurological effects due to masking of vitamin B_{12} deficiency) and low (megaloblastic anaemia). The number of individuals affected varies over 1–2 orders of magnitude (from \( n = 53 \) to \( n = 2425; \) data for the Netherlands). On the basis of this evaluation, it is concluded that there is a significant variation with respect to the number of individuals affected as well as the severity of effects. As a consequence no definite answer can be given whether or not the alternative scenario dominates the reference scenario or vice versa. Hence this case qualifies for tiers 3 and 4 (see Table 2).

In tiers 3 and 4, the number of people perceiving benefits of prevention of neural tube defects is in the same order of magnitude as the number of individuals perceiving the adverse effects in terms of neurological disorders due to masking of vitamin B_{12} deficiency. As concerns (colorectal) cancer, at the presented low dose of fortification (70 μg/100 g of bread), the overall incidence for colorectal cancer is a decrease, whereas at this dose levels also a reduction in the number of cases with neural tube defects and megaloblastic anaemia is seen. The adverse effect at this dose level (increase in neurological disorders due to undiagnosed vitamin B_{12} deficiency) affects about the same number of persons as the number of cases of neural tube defects prevented. The number of life years with disease as well as the severity-weighting factor for neural tube defects and colorectal cancer are the largest. Since both are reduced in incidence at this level of fortification, the overall DALY value indicates a significant overall change at a modest (minus) 7000 DALY’s prevented (compared to a yearly loss of ca. 4.5 million DALY’s in the Netherlands).

2.5. Conclusions

The overall effect of fortification of bread with folic acid at 70 μg/100 g is a significant benefit (>7000 DALYS), versus an adverse effect of 53 DALYS (data for the Netherlands), viz. the net health benefit outweighs the net health risk by about two orders of magnitude. Hence the benefit–risk evaluation can actually stop at tier 3. In this evaluation it must be emphasized that there are large uncertainties in the actual estimates but that the overall evaluation points into a direction of net health benefits associated with fortification: the alternative scenario dominates the reference scenario. This example illustrates the BRAFO tiered-approach to be applicable down to tiers 3/4.

Whereas the benefit–risk evaluation can stop at tier 3, it is a risk-management decision whether or not to implement such an evaluation. It must be a policy decision to weigh the adverse effects of neurological disorders in elderly persons (and strict vegetarians) and the high-dose related (colorectal) cancer risk versus the benefits in the other population groups. Moreover, there can be other ways of increasing the intake of folic acid intake in target groups like females of child-bearing age (e.g.) In the Netherlands, the minister of Health has recently decided for another approach to prevent neural tube defects by folic acid: educating the target group of young females to take folic acid in the form of a food supplement (Netherlands Ministry of Health, Welfare and Sport, 2010). It should however also be noted that this approach was not successful in the UK (SACN, 2009).

3. Case studies: saturated fat versus mono-unsaturated fat and versus carbohydrates

3.1. Introduction

Diet-related diseases are major causes of morbidity and mortality in both developed and developing countries. Cardiovascular disease (CVD) is the major contributor to the global burden of disease (GBD) among the non-communicable diseases (WHO/FAO, 2003; WHO, 2004). The prevalence of heart disease has been linked to the adoption of a sedentary lifestyle and the increased dietary dependence on saturated fats from animal sources and the intake of refined foods. The relationship between dietary fats and CVD, especially coronary heart disease, has been extensively investigated with strong and consistent associations both from animal and human studies (Kris-Etherton, 1999; Kris-Etherton et al., 2001; Mann et al., 2007). The increase in the quantity and quality of the fats in the diet is an important feature in the diets of developing countries. Prospective studies examined the correlations between saturated fat intake and risk of coronary heart disease (CHD), and some studies have found a positive or a weak positive association. A major problem has been that the methodology to measure saturated fatty acids intakes has often depended on unreliable methods of dietary assessment.

Coronary heart disease (CHD) is the leading cause of death in Europe. The underlying pathology involves atherosclerosis, which develops over a long-time period without symptoms, but clinical events usually occur as a consequence of thrombosis triggered by the rupture of an atherosclerotic plaque. Elevated blood pressure and raised serum cholesterol are regarded as the major reversible risk factors for developing the disease. Large variations in plasma total and Low-Density Lipoprotein (LDL) cholesterol concentrations between populations and this are related to population risk of CHD. Keys and Willis (1966) in the Seven Countries Study estimated that two-thirds of the variation in median serum cholesterol concentrations between countries in Europe could be explained by differences in Saturated Fatty Acid (SAFA) and cholesterol intake. This led to a series of systematic studies demonstrating that saturated fatty acids C12–C16, but not C18, raised serum cholesterol (Keys and Willis, 1966). Studies within-populations have demonstrated a strong relationship between total serum cholesterol and risk of cardiovascular disease (Lewington et al., 2007). The absolute risk of cardiovascular disease associated with serum cholesterol appears to have no threshold but the absolute risk increases markedly with age. Risk is amplified by cigarette smoking, high blood pressure and the presence of type 2 diabetes. While total cholesterol concentration is positively associated with increased risk, High Density Lipoprotein (HDL) cholesterol concentration is inver-
sely associated with risk. Observational studies within populations indicate that the ratio of total/HDL cholesterol is twice as informative of individual risk than total cholesterol (Lewington et al., 2007). In contrast to between population studies, only a relatively small proportion of the variation in total and LDL cholesterol can be explained by differences in SAFA and cholesterol intake within populations.

Carbohydrates and fats are the principal energy source in the diets of most people and have a special role to play in energy metabolism and homoeostasis. The joint WHO/FAO Expert Consultation recommended that total carbohydrate should provide 55–75% total energy and that free sugars should provide less than 10%. Recommended intake of fruits and vegetables was 400 or more g per day, excluding tubers. Precise amounts of Non-starch Polysaccharides (NSPs) or dietary fibre were not recommended. However, it was considered that appropriate intakes of fruits, vegetables, legumes and regular consumption of wholegrain cereals would provide in excess of 20 g/day of NSP and over 25 g of total dietary fibre (WHO/FAO, 2003). Current dietary guidelines in general also recommend a diet that contains 15–30% (or ≤30%) of energy as fat and ≤10% of total energy as saturated fatty acids (WHO/FAO, 2003; Kris-Etherton et al., 2001). The classic studies of Keys and Willis (1966) have shown that saturated fatty acids (i.e. those with a carbon chain length of C12:0 to C16:0) raise total and low-density lipoprotein (LDL) cholesterol levels.

SAFA intake increase plasma total and LDL cholesterol levels by decreasing LDL receptor-mediated catabolism (Mensink and Katan, 1992; Mensink et al., 2003). The saturated fatty acids myristic and palmitic acids have the greatest effect and are abundant in diets rich in dairy products and meat (WHO/FAO, 2003). However, the evidence is not consistent in this respect. The techniques used to measure platelet function are not associated with increased risk of CHD.

Therefore, the general consensus for some years for the prevention of coronary heart disease, has been that dietary intake of SAFA should be reduced. Lowering habitual intakes of SAFAs, requires substitution by other macronutrients to maintain energy balance, such as carbohydrates (Jakobsen et al., 2009) and (polysaturated fatty acids. In the context of the BRAFO project, it is relevant to perform a benefit−risk assessment of replacing 5% of dietary energy from SAFA with 5% of dietary energy from monounsaturated fatty acids and with 5% from carbohydrates, both in an isocaloric situation. All the health effects are associated with the risk of CVD.

Carbohydrates (CHO) as a group have not been intensively investigated in epidemiological studies of diet and cancer. There is a moderately large amount of data on the possible association between dietary fibre and the risk for colorectal cancer; the results of studies have varied and no firm conclusion can be drawn, but the available data suggest that high intakes of dietary fibre, provided by foods naturally rich in fibre as opposed to that added to the diet, possibly reduce the risk for colorectal cancer. Neither of these achieves the level of convincing or probable as required for the formulation of dietary guidelines as defined by WHO and World Cancer Research Fund (WCRF) and this is also reflected in Table 3.

### 3.2. Pre-assessment and problem formulation

A recent meta-analysis indicates that the estimates from between countries may have exaggerated the effect of SAFA on serum cholesterol. A meta-analysis (Mensink et al., 2003), however, confirms the raising effects on C12−C16 fatty acids on total and LDL cholesterol and showed that the major dietary MUFA (oleic acid) when substituted for SFA lowers total cholesterol and LDL cholesterol and the ratio of total/HDL cholesterol; no effect on the ratio was noted when stearic acid (18:0) was replaced by Monounsaturated Fatty Acids (MUFA). Current dietary guidelines recommend limiting the intake of SAFA to no more than 10% of the total energy intake (Elmadfa and Kornsteiner, 2009). However, there is no consensus as to how the energy derived from SAFA should be replaced and dietary reference values for MUFA are estimated by difference from total fat energy less SAFA, trans fatty acids (FA) and polyunsaturated fatty acid intake. The replacement of 5% of dietary energy from SAFA with 5% of dietary energy from MUFA in an isocaloric situation is considered.

The potential benefits, all resulting in a slowing of the progression of atherosclerosis are:

- A decrease in total cholesterol.
- A decrease in LDL-cholesterol.
- A decrease in total:HDL cholesterol ratio.

The potential risks are:

- An increase in pro-coagulant activity.
- Potentially increase risk of thrombosis in those individuals with established atherosclerosis.

The established non-existing effects are:

- A decrease in blood pressure.
- A decrease in risk of coronary heart disease.

The reference and alternative scenario are described below:

| Reference scenario: Current situation a high and a low level of intake of SAFA. |

<table>
<thead>
<tr>
<th>Table 3 Application of Tiers 1 and 2 of the BRAFO methodology to the case study on saturated fat versus mono-unsaturated fat.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 1</strong> Health effect</td>
</tr>
<tr>
<td>Total and LDL cholesterol</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
</tr>
<tr>
<td>Total:HDL cholesterol</td>
</tr>
<tr>
<td>CHD risk Factor Vilk pro-coagulant activity</td>
</tr>
<tr>
<td>CHD incidence and mortality</td>
</tr>
<tr>
<td>Overall change</td>
</tr>
</tbody>
</table>
Alternative scenario: Substitution of 5% of calories of SAFA (C12, C14 and C16), considering exclusively mono-unsaturated fatty acids, with 5% of calories of MUFA (oleic acid) in isocaloric situation.

Target population: European population.

3.3. BRAFOD tiered approach

In tier 1, the effect on coronary heart disease from dietary fats has traditionally been estimated from their effects on the biomarker total cholesterol. However, more recent analyses from the pooled results of prospective studies indicate that the ratio total/HDL-cholesterol ratio is twice as informative regarding risk of Coronary Heart Disease (CHD) than total cholesterol. Replacement of C12-C16 SAFA with MUFA would lower the total:HDL cholesterol ratio (Mensink et al., 2003). Other risk markers associated with risk of thrombosis are emerging and may be important in precipitating coronary events. High intakes of MUFA acutely increase factor VII coagulant compared with SAFA (Sanders, 2009) which may potentially influence risk of coronary events in older subjects with established atherosclerosis. There is insufficient evidence to demonstrate benefit for other risk markers such as blood pressure, markers of inflammation of endothelial function.

The biomarkers mentioned above are all intermediate markers of CHD. Since only one health effect is involved the case identifies an unidirectional question: the health effects are either beneficial, or adverse or no effect, but there is no situation of two effects that need comparison. Hence, replacement of 5% SAFA with 5% MUFA is not a genuine benefit-risk question. Hence the tiered approach stops at tier 1. However, the magnitude of the positive health effects remains worthwhile knowing in case different options need to be prioritized. Therefore, we continue with a limited benefit, if any, characterization.

An analysis from the US Nurses Study indicated that replacement of SAFA with MUFA would decrease risk of CHD. However, the Strong Heart Study and the Framingham Study indicated that MUFA intake was associated with increased risk of CHD. Nonetheless, the data are confounded by the inclusion of trans fatty acids with MUFA in some of the earlier studies. The relationship between SFA and risk of CHD and stroke in a recent meta-analysis stops at tier-1. However, the magnitude of the positive health effects remains worthwhile knowing in case different options need to be prioritized. Therefore, we continue with a limited benefit, if any, characterization.

Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize (van Dam and Seidell, 2007). Diets successful in causing weight loss can emphasize a range of fat, protein, and carbohydrate compositions that have beneficial effects on risk factors for cardiovascular disease and diabetes (Noakes et al., 2006; van Dam and Seidell, 2007; Sacks et al., 2009). Carbohydrates are among the macronutrients that provide energy and can thus contribute to weight gain when consumed in excess of energy requirements. If energy intake is strictly controlled, macronutrient composition of the diet (energy percentages of fat and carbohydrates) does not substantially affect body weight or fat mass (Mann et al., 2007; van Dam and Seidell, 2007). Most recommendations have specified that the saturated fat eliminated from the diet be replaced by carbohydrates from grains, vegetables, legumes, and fruits. This change would diversify the diet and add protective constituents from plant sources; including dietary fibre, folate, potassium, flavonoids, and antioxidant vitamins. However, as the present scenario of this review was based on the replacement of 5% of dietary energy (E%) from SAFA with 5% of dietary energy from CHO in an isocaloric situation literature based on weight-loss and the related diseases were excluded).

Table 4 summarises the most relevant effects associated with replacement of SAFA with CHO intakes. The main effect is on

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health effect</td>
<td>Change</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>Decrease</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Decrease</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Decrease</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Increase</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>None</td>
</tr>
<tr>
<td>CVD</td>
<td>Decrease</td>
</tr>
<tr>
<td>Coronary deaths</td>
<td>None</td>
</tr>
<tr>
<td>Overall change</td>
<td>None</td>
</tr>
</tbody>
</table>
cardiovascular disease (CVD) and the underlying biomarkers are indicating beneficial as well as adverse effects, however, all biomarkers are related to the same endpoint: cardiovascular disease.

The potential benefits are:

- A decrease in total cholesterol.
- A decrease in LDL-cholesterol.

The potential risks are:

- A decrease in HDL cholesterol.
- An increase in fasting triglycerides.

The established non-existing effects are:

- Total/HDL cholesterol ratio.
- Risk of coronary heart disease and coronary deaths.

The reference and alternative scenario are described below:

Reference scenario: Current situation.
Alternative scenario: Replacement of 5% of dietary energy from SAFA with 5% of dietary energy from carbohydrates in isocaloric situation.
Target population: Europe.

4.2. BRAFO tiered approach

In tier 1, the effect on coronary heart disease from dietary fats have traditionally been estimated from their effects on the biomarker LDL cholesterol, however, it also seems to have an effect on HDL cholesterol and total/HDL cholesterol ratio. In a fairly recent meta-analysis of 60 mostly short term controlled trials (Mensink et al., 2003), estimates the effect on the biomarkers when saturated fats is replaced with carbohydrates in an isocaloric situation (5% of dietary energy, 5E%). Estimated regression coefficients for mean changes in serum lipids and lipoproteins (Mensink et al., 2003) shows that when replacing SAFA with CHO in an isocaloric situation, LDL and total cholesterol decreases (which are beneficial effects), but that also HDL cholesterol decreases and fasting triglycerides increase (which are adverse effects).

There is no significant effect on the ratio total/HDL cholesterol. For LDL and HDL cholesterol and fasting triacylglycerol well validated, easy applicable and generally accepted biomarkers exist (Mensink et al., 2003). The relationship between diet-related changes in LDL cholesterol and disease risk is well established, but HDL cholesterol and triacylglycerol are markers sensitive to dietary factors, however, it is not clear to what extent changes in these markers reflect enhanced function and reduction of disease risk (Mensink et al., 2003). The results of Mensink’s meta-analysis, appeared to offer a strong message, that regardless of the source of the fat displaced, an increase in total carbohydrate was associated with an increased ratio of total to HDL cholesterol. However, although these studies paid careful attention to ensure that the comparison were carried out under isoenergetic conditions and food intake was thoroughly controlled, there was less consistency with regard to the source and class of carbohydrate that was used as fat replacement (Mann et al., 2007).

The biomarkers mentioned above are all intermediate markers of the same disease: cardiovascular disease. This is similar to the previous case study. Since only one health effect (cardiovascular disease) is involved the case identifies an unidirectional question: the health effects are either beneficial, or adverse or no effect, but there is no situation of two effects that need comparison. Hence, replacement of 5E% SAFA with 5E% CHO is not a genuine benefit–risk question. Hence the tiered approach stops at tier-1.

Even though this is not a genuine benefit–risk question, it is still unanswered whether replacement of 5E% SAFA with 5E% CHO is leads to a beneficial or an adverse effect on cardiovascular disease. Two papers replace SAFA with CHO in an isocaloric situation and have cardiovascular disease as an endpoint instead of biomarkers (Hu et al., 1997; Jakobsen et al., 2009). Jakobsen et al. (2009) a pooled analysis of 11 cohort studies concluded that a 5% lower energy intake from SAFA and concomitant higher intake from CHO leads to a small increased risk of coronary events (Hazard Ratio- HR; 95% CI: 1.07; range: 1.01–1.14), and the risk of coronary deaths was not significant (HR; 95% CI: 0.96; range: 0.82–1.13). Jakobsen et al. (2009) argue that the estimated HR’s for CHO may reflect that the type of carbohydrate was not taken into consideration (e.g. dietary fiber content, extent of processing, glycemic index). Hu et al. (1997) indicated that after 14 years of follow-up of the Nurses’ Health Study Cohort the effect of total dietary fat and specific major types of fat was examined and the effect of substituting carbohydrates for saturated fats was estimated. It was found that each increase of 5% from SAFA, as compared with equivalent energy intake from CHO, was associated with a 17% increase in the risk of coronary disease (Relative Risk – RR; 95% CI: 1.17; range: 0.97–1.41; P = 0.10). So a (borderline) beneficial effect of replacing SAFA with CHO is possible. Therefore, the effect of replacing SAFA with CHO on CVD is still unclear, but it is outside the scope of this project to decide this.

4.3. Conclusions

It is concluded that in case study 3, the alternative scenario versus the reference scenario does not involve a true benefit–risk problem, since only one health effect (CVD) is involved. Going through tier 1, it became clear that the main effects are related to one disease only, and that even though the underlying biomarkers are indicating beneficial as well as adverse effects; there is still only one health effect involved (CVD) irrespective of whether the effect is positive, negative or neutral. Hence this case is not a genuine benefit–risk question as tier 1 passed and the benefit–risk analysis stopped at this level. It is not relevant to go through tiers 2, 3 and 4 in this case, since there is only one disease endpoint, and therefore there is not a genuine benefit–risk problem.

5. Case study: low calorie sweeteners

5.1. Introduction

Sugars, mono- and/or disaccharides, occur widely in foods such as fruits, some vegetables, milk and milk products, i.e. as naturally occurring ‘intrinsic sugars, or as ‘extrinsic’ sugars, added to foods such as (carbonated) beverages and sweets. Data from dietary surveys in Europe indicate that in children and adults between 16 and 36E% (% of total daily energy intake) comes from (total) sugars (EFSA, 2010).

Sugars are part of the glycemic carbohydrates, and a source of energy, but not an indispensable nutrient for the human body.

With respect to potential risk, frequent consumption of sugar-rich foods, but not the amount consumed as such, is associated with increased caries risk, especially when oral hygiene and fluoride prophylaxis are insufficient. High intakes of sugars, especially in liquid form, such as sugar-sweetened beverages, have been associated with a positive energy balance, i.e. weight gain. There are also some reports with respect to the relation between sugar in-
take and the risk of diabetes, cardiovascular disease, cancer, and gout.

Since the World Health Organization (WHO) Report on Diet, Physical Activity and Health of 2004, the food industry is heavily engaged in finding solutions to manufacture less dense food. The report is suggesting reducing free sugar intake from present 14–15% to 10% of calorie intake. This could be possible if substitution of free sugar in liquids would be massively recommended and advertised.

The intakes of low calorie sweeteners have been submitted to a previous systematic review, which evaluated all published data up to 1997 (Renwick et al., 2003). At that time it was clear that the average intakes of all intense sweeteners were below the relevant Acceptable Daily Intake (ADI) values. The intakes by the highest consumers of sweeteners other than cyclamate were also well below their ADI values. The highest estimated intakes of cyclamate by diabetics and children were close to or slightly above the ADI.

Sugar substitutes are increasingly being used as a source of sweetness in low-calorie and sugar-free foods and beverages. Low calorie sweeteners, such as aspartame, acesulfame K, cyclamates, saccharin and sucralose are typically used in table top sweeteners and beverages. Because of their intense sweetness only small amounts are needed. The European (EU) Commission, on the basis of thorough safety evaluations, approves sweeteners permitted in the EU for food use. All approved low calorie sweeteners have undergone extensive safety testing, and have acceptable daily intakes (ADIs) established. Intake of these sweeteners is monitored in the EU and shows that the average and 95th percentile intakes are below ADI values (Renwick et al., 2003), only for children intakes close, or above the ADI were observed for cyclamate in children (Mortensen, 2006). In a more recent risk benefit assessment in Norway on the substitution of all sugar sweetened by diet beverages, has been related with weight gain and overweight. Due to methodological weaknesses in the various studies, conflicting results from (few) longer term trials, etc., the evidence is, however, currently insufficient to draw conclusions (Gibson, 2008; Olson and Heitmann, 2009). In most studies the focus is on sugar intake as such, and only limited data are available with respect to the effect of substitution of sugars by low calorie sweeteners. These studies on the effect of sugar substitution, mostly by aspartame, were reviewed by de la Hunty et al. (2006). In a

### Table 5

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Health effect</th>
<th>Change</th>
<th>Quality of evidence</th>
<th>Magnitude of the effect</th>
<th>Population affected</th>
<th>Health impact (beneficial/ adverse/none)</th>
<th>References to the quality of evidence</th>
<th>Tier 2</th>
<th>Effect severity (w = 0–1)</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Decrease</td>
<td>High</td>
<td>–</td>
<td>Total population</td>
<td>Beneficial</td>
<td>Bellisle et al. (2007), de la Hunty et al. (2006)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight/ balance&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Decrease/helps to maintain energy balance</td>
<td>Moderate</td>
<td>–</td>
<td>Children/adults</td>
<td>Beneficial</td>
<td>Bellisle et al. (2007), de la Hunty et al. (2006), Gibson (2008) Olson et al. (2009), Van Baak et al. (2009)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caries</td>
<td>Decrease</td>
<td>Moderate</td>
<td>–</td>
<td>Children/adults</td>
<td>Beneficial</td>
<td>Anderson et al. (2009), Burt et al. (2001), Moynihan (2004), Van Loveren (2009)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>None</td>
<td>High</td>
<td>–</td>
<td>Total population</td>
<td>Neutral</td>
<td>Bosetti et al. (2007), Butchko et al. (2002), EFSA (2009a,b), Gallus et al. (2007)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes/ metabolic syndrome</td>
<td>None</td>
<td>Low</td>
<td>–</td>
<td>Middle aged and elderly</td>
<td>Beneficial</td>
<td>Dhingra et al. (2004); Schulze et al. (2004)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>None</td>
<td>Low</td>
<td>–</td>
<td>Middle aged and elderly</td>
<td>Beneficial</td>
<td>EPFA (2010)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>Decrease</td>
<td>Low</td>
<td>–</td>
<td>Adults</td>
<td>Beneficial</td>
<td>Choi and Curhan (2008)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Beneficial</td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Mainly based upon studies with aspartame; no (little) data available for other low-calorie sweeteners.

The potential benefits are:
- Decreased energy intake.
- Decreased caries risk.
- Decreased risk of diabetes/metabolic syndrome.
- Decreased risk of cardiovascular disease.
- Decreased risk of gout.

The potential risks are:
- Increased risk of cancer.

#### 5.2.1. Energy intake

De la Hunty et al. (2006) performed a meta-analysis of studies that examined the effectiveness of substituting sugar with aspartame, or combination of aspartame with other intense sweeteners, on energy intake. Only randomized controlled trials, which measured energy intake for at least 24 h were included in the analysis. Most of the studies included were short term (maximum 10 wk), small size (most trials 10–30 participants; one trial with 163 participants), but with variable designs (+/− energy restriction), and included different low calorie sweetened foods. On average a 10% reduction in energy intake, i.e. 0.93 MJ/day, was estimated, as compared to control (baseline diet or sucrose intake), but not with water as the control. Compensation could be calculated for some studies and was on average 32% (range 1–111%), for studies using soft drinks as the only vehicle, on average 15.5%, i.e. lower for the liquid as compared to the solid foods. No data are available for the other low calorie sweeteners.

#### 5.2.2. Body weight/weight balance

Sugar consumption, especially in liquid form, such as in sugar-sweetened beverages, has been related with weight gain and overweight. Due to methodological weaknesses in the various studies, conflicting results from (few) longer term trials, etc., the evidence is, however, currently insufficient to draw conclusions (Gibson, 2008; Olson and Heitmann, 2009). In most studies the focus is on sugar intake as such, and only limited data are available with respect to the effect of substitution of sugars by low calorie sweeteners. These studies on the effect of sugar substitution, mostly by aspartame, were reviewed by de la Hunty et al. (2006). In a

### 5.2. Pre-assessment and problem formulation

In this case study the benefits and risks of replacing sugar sweetened beverages (including tea, coffee, and tabletop sugars) by intensely sweetened beverages will be described. For the purpose of this BRAFO case study only the low calorie sweeteners are considered.
meta-analysis of data from 16 Randomised Controlled Trials (RCT) they estimated the effect of sugar substitution by aspartame on body weight. On average a weight reduction of ca. 0.2 SD was calculated, corresponding to a weight loss of 0.2 kg/wk for a 75 kg person. A comparative evaluation of other low calorie sweeteners is hampered by a lack of data.

5.2.3. Diabetes and metabolic syndrome
A beneficial effect of sugar replacement by low calorie sweeteners on diabetes risk might be anticipated, though an effect on energy balance/body weight, but data are currently insufficient to draw conclusions. In the Nurses Health Study the consumption of more than one standard serving per day of sugar sweetened beverages (SSB) was found to be associated with an increased risk for diabetes type 2 [relative ratio (RR) 1.83 (95% CI 1.42–2.36), as compared to those consuming less than one serving per month (Schulze et al., 2004). In the Framingham Offspring Study (Dhingra et al., 2004) an increased prevalence of metabolic syndrome was found to be associated with a greater intake of soft drinks (1/d or more) (95% CI 1.28–2.56). However, this effect was about similar to those consuming less than one serving per month.

Also in the Atherosclerosis Risk in Communities (ARIC) study (Lutsey et al., 2009) the consumption of sweetened beverages and diet soda was associated with a higher risk for metabolic syndrome. After adjustment for behavioural characteristics such as smoking and physical activity, this effect was only significant for diet soda (RR = 1.34 (95% CI: 1.24–1.44), but not for sweetened beverages (RR = 1.09 (95% CI: 0.99–1.19). As consumption of diet soda in this cohort was higher among diabetics than among non-diabetics reverse causality or residual confounding might, according to the authors, explain this finding, and further research is therefore warranted.

5.3. Reference and alternative scenario
For the problem formulation a reference and an alternative scenario as well as target population are formulated as follows:

Reference scenario: Sugar sweetened beverages containing disaccharides (Soft drinks and also coffee, tea, tabletop).
Alternative scenario: Substitution with intensely sweetened beverages.
Target population: Europe.

5.4. BRAFO tiered approach
In tier 1, it is concluded that the alternative scenario versus the reference scenario involves potential health benefits as well as potential health risks. Hence this case is a genuine benefit–risk question (tier 1 passed).

In tier 2, with respect to potential risks, only for cyclamate and aspartame K intakes might approach, or exceed the ADI in children with a high consumption (‘heavy users’) of beverages and foods sweetened with these compounds. So, in general, no associated risk can be anticipated in replacing sugars by low calorie sweeteners in sweetened beverages. Recent animal studies (Soffritti et al., 2005, 2006, 2007) implying a relationship between aspartame and lymphoma have been dismissed by EFSA and an international panel of experts (Magnusson et al., 2007) because methodological insufficiencies (EFSA, 2006a,b, 2009a,b). Hence, on the basis of exposure below ADI levels and in essence the absence of adverse health effects, it is concluded that only benefits, and no associated risks are anticipated for substitution of sugars in beverages by low calorie sweeteners. Therefore it is decided to stop the evaluation in this case study after tier 2. For quantitative
estimates of the potential health benefit available data are currently too limited, and (in part) contradictory.

5.5. Conclusions

Low calorie sweeteners are constantly at the forefront of risk assessment debate. The very latest in these is the risk assessment activity of EFSA (EFSA, 2011). As default, low calorie sweeteners are safe to use at the levels and in the food categories they have been assigned to by the European Directive 96/45/EEC. Cyclamate is the most critical one because in exposed sub-populations, consumption could be close to ADI (i.e. diabetic young children). It has to be considered that the ADI is not a toxic threshold and that it can be over passed during certain periods in life. With more encouragement to use products containing low calorie sweeteners it is important to regularly measure exposure in order to detect early enough major changes in consumption patterns. In this respect new methodologies, which are more accurate and less expensive, will have to be encouraged and used (Nordmann et al., 2006).

Substitution of sugar-sweetened beverages (soft drink, and coffee, tea, tabletop) by low calorie sweetened beverages might be helpful in maintaining a ‘healthy’ energy balance and the prevention of overweight, and consequently have a beneficial effect on chronic disease risk and caries incidence. However, the evidence from epidemiological studies with respect to the effect on weight balance, and subsequent effects on disease prevention, is currently inconclusive for estimation of potential benefits. Most data are available for aspartame (Renwick and Nordmann, 2007) for which analysis of data from randomized controlled intervention studies has shown a significant effect on weight. Very little specific data is available, for the other low calorie sweeteners.

6. Case study: water chlorination

6.1. Introduction

Hydration has recently been identified by EFSA as “a water intake which balances losses and thereby assures adequate hydration of body tissues is essential for health and life” (http://www.efsa.europa.eu/en/efsajournal/doc/1459.pdf). Adequate hydration can be achieved by adequate intake of water but optimal hydration is not quantifiable yet, as there is no available index to assess it. Therefore the hydration aspect is within the scope of this test case but cannot be taken into account. However, water can be contaminated by chemicals and by micro-organisms. Chemical contamination was not included in the scope of this case study focused on chlorination of drinking water and potentially associated benefits and risks.

Water chlorination is a traditional process used to clean drinkable water used for decades. William Cumberland Cruikshank used it in 1800 for the first time, and William J.L. Lyster developed in the following decade for the US army a bag technique, using calcium hypo-chloride. Chlorine in water generates hydrochloric acid and hypo-chlorous acid, which dissociates into hydrogen and hypo-chloride ions, a potent disinfectant. A well-known drawback is that chlorine can react with organic compounds found in water and generates carcinogenic compounds such as Tri-Halo-Methanes.

6.2. Pre assessment and problem formulation

The first step of the BRAFO proposed methodology is pre-assessment and problem formulation. The issue of drinking water safety has been already mentioned in the Bible when St Paul was warning Timothy not to drink water in the city of Ephesus, but to drink alcoholic drinks instead. It is still possible to see the water distribution system in Ephesus and to understand the risk of potential contamination of the local drinking water. Still today, distribution of potable water and collection of waste water in modern cities are both running side by side in tubes with a significant level of leakage, and contamination can occur at different points of the tap water aduction system. Once there is a contamination somewhere, it is practically impossible to clean every part of the distribution system including all temporary dead ends and the end faucet. The only practical way to control microbial contamination is to use a permanent disinfection procedure e.g. the classical chlorination treatment.

According to the WHO, benefit of disinfection outweighs risks of cancer due to water chlorination (Le Chevallier and Au, 2004), however there is no published comparison supporting that statement. Chlorination controls microbial contamination, which is the major risk of a drinking water distribution system. Chlorination has no effect on other water contaminants, such as chemicals.

The potential benefits of chlorination of tap water are:

- A reduced incidence of water borne diseases affecting the whole population.
- A safe distribution system delivering drinkable tap water at home.

The potential risks of chlorination of tap water are:

- An increased incidence of bladder and of rectal cancer.
- An increased incidence of stillbirth and abortion in child bearing age women.
- A reduced water intake due to the taste of residual chloride in water.

Assessment of the benefits of chlorination of tap water is not easy for three different reasons. First, the main source of information is historical epidemiology, and except for only one case report, there is no real well conducted intervention study to demonstrate the benefit of water disinfection. The second reason is that water contamination is persistent because a first contamination of a distribution system will increase the risk of new outbreak as it is nearly impossible to perfectly clean a distribution system after a first contamination. This makes each water distribution network “unique” with a specific risk of waterborne disease. That risk needs to be re-evaluated after every contamination taking into account the specificity of the pathogenic contaminant. On the other hand the longer the distribution system is clean the lower the risk of endogenous out-breaks. The third reason is that no disinfection system can protect against accidental contamination nor against resistant pathogen(s). The quantification of that risk was not possible within this assessment (EPA, 2006).

Assessment of the risks of chlorination of tap water. There are two bottlenecks: the first one is the level of chlorination by-products, which correlated with the amount of organic material in water and the concentration of chloride (Boorman, 1999) and depends on the hygienic conditions of the distribution system and cannot be extrapolated from one case study to another. Again, there is no standard value and one has to rely on available local epidemiological data. The second problem was to allocate a proper assessment of the weight of spontaneous abortion, which is not expressed in weighting factors or in DALYs in the literature. Therefore this is not indicated in the Table 6, which summarises the most relevant health effects associated with chlorination of drinking water.
6.4. BRAFO tiered approach

Every currently available sanitation procedure is known to have some side effects on human health (Boorman, 1999). The challenge is to assess whether the disinfection procedure is providing a benefit that outweighs adverse health effects. Assessment of the risk associated with no sanitation at all of drinking water can be performed using historical data from the US. Without chlorination, a permanent burden of epidemics will occur, including water transmitted typhoid fever and cholera. That burden will affect routinely from a few up to 24 per 100,000 persons like in middle Africa (Harter, 2005), down to a few hundreds cases in the entire US (Griffith et al., 2006).

This is a retrospective assessment with its methodological drawbacks, and the data cannot be directly related to the present situation. There is one quasi-experimental situation that confirmed the risk associated with the absence of drinking water disinfection. This situation occurred in Peru, when people were so concerned by the risk associated with the absence of drinking water disinfection. There is one quasi-experimental situation that confirmed this. Convincing epidemiological evidences reported an increased risk of cancer as well as an increased risk of early abortion. There are meta-analysis confirming the scientific evidence of existing risks (King et al., 2000; Morris et al., 1992; Nieuwenhuijsen et al., 2000; Villanueva et al., 2003).

In tier 1, it is concluded that the alternative scenario versus the reference scenario involves health benefits (reduction of waterborne diseases) as well as health risks (cancers and abortions) (tier 1 passed).

In tier 2, a qualitative evaluation of benefits and risks, the question is whether benefits clearly outweigh risks or vice versa? This comes down to making estimates of the respective benefits and risks in a comparative situation.

However, it is not easy to compare on one hand the small benefit of a reduction of risks of acute outbreaks of infections with immediate health consequences for a significant fraction of the whole population, and on the other hand a low risk of long term diseases for a small percentage of the population and with a risk for a specific sub-group of the population: pregnant women.

As it is not possible at this stage to identify a clear overall benefit or risk it is concluded that tier 2 is passed and that the case progresses to tiers 3 and 4.

In tiers 3 and 4, it appears that there are many uncertainties, depending on the severity of water-borne diseases, and on the weight given to abortion and still birth. Quantification of Years Lived with Disability (YLD) and DALYs for cancer, stillbirth and abortion could be extracted from the WHO tables 2004 and from Abouzhar et al. (2000), but quantification of years lived with diseases and DALYs are more difficult for the prevention of waterborne diseases as they are strongly dependent on the pathogen(s) involved in the diseases. This is why there is a range taking into account one calculation made for a specific pathogen (Havelaar et al., 2000) and an average values calculated from published reports of outbreaks (Blasi et al., 2008; Davezac et al., 2008; Gallay et al., 2006; Koziak et al., 2009; Sandberg et al., 2006). In addition, quantification of disability weights and DALYS for abortion is disputable as it depends whether abortion was a voluntary action, with very low DALY, or whether it is a loss of an expected child in which case the DALY should be far more important. Chlorination of water increases the incidence of unwanted abortion, but it is also dependent on the level of chlorination (Nieuwenhuijsen et al., 2000). Quantification of stillbirth is not provided as the impact on the mother is consider as negligible and there is no year of life lost because the foetus is dead at birth. However this can be

---

### Table 6

Application of tiers 1 and 2 of the BRAFO methodology to the case study on chlorination of drinking water.

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Change</th>
<th>Quality of evidence</th>
<th>Magnitude of the effect</th>
<th>Population affected</th>
<th>Health impact (beneficial/ adverse/none)</th>
<th>References to the quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water-borne infections</td>
<td>Decrease</td>
<td>Medium –</td>
<td>Whole population</td>
<td>Beneficial</td>
<td>EPA (2006), King et al. (2000)</td>
<td></td>
</tr>
<tr>
<td>Abortion</td>
<td>Increase</td>
<td>High –</td>
<td>Pregnant women/child</td>
<td>Adverse</td>
<td>Morris et al. (1992)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>Increase</td>
<td>High –</td>
<td>Pregnant women/child</td>
<td>Adverse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tier 2</th>
<th>Effect severity</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(w = 0–1)</td>
<td></td>
</tr>
<tr>
<td>Water-borne infections</td>
<td>Case dependent</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>0.5</td>
<td>0.0102% incidence/ year</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>0.2</td>
<td>0.0088% incidence/ year</td>
</tr>
<tr>
<td>Abortion</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

1% of whole population.
also calculated as a whole lost life, like for unwanted abortion (Abouzahr et al., 2000).

Therefore a realistic benefit–risk assessment in tiers 3 and 4 will require a case-by-case analysis taking into account the local data, including the quality of the distribution system, the local potential pathogens, and the level of chlorination, and the weight of a baby life. Another limitation of the exercise was that many factors are not taken into account because of lack of data:

- Risk of increasing resistance of pathogens to cleaning procedures (Cooper and Hanlon, 2009; Berry et al., 2006).
- Risk due to other contaminants of the distribution systems, including the rising burden of drugs and chemicals in water supply (Emmanuel et al., 2009).
- Benefit of increased water intake due to availability of portable tap water, and improved hydration; and vice versa the risk of reduced water intake due to the disagreement of taste of the chlorinated water.

As such there are so many uncertainties in scenario's and disease estimates that this essentially renders a quantitative benefit–risk comparison impossible.

6.5. Conclusions

The rationale of BRAFO tiered approach also works in this test case, but it was not possible to compare benefits (mainly expressed as absence or reduction of risks) with risks of water chlorination. The balance is not obvious and it will trigger more precise evaluation of local scenario's and ethical consideration of adjusting weights for stillbirth and abortion.

7. Overall discussion

The objectives of WP5 have been met. As such we have been able to (1) describe in qualitative and quantitative terms the beneficial effects of dietary interventions, to (2) describe in qualitative and quantitative terms the adverse effects of dietary intervention across intake levels, taking into account subgroups, severity of effects, and probability of effects, to (3) identify key components and their potential for causing adverse effects, (4) assess the relationship between dietary intervention and the alteration of the nutritional properties of the food, (5) apply and adapt those evaluative methods and common core elements as developed by WP3 to undertake qualitative and quantitative comparison of benefits and risks based on a common scale of units.

The work of WP5 consisted of an assessment of the number and kind of people that will perceive beneficial and adverse effects across actual intake levels, including a description of the severity and the probability of the effects occurring when consuming food subject to dietary interventions. Five examples were addressed in this work package:

- Addition of folic acid to flour/bread.
- Replacement of saturated fatty acids by mono-unsaturated fatty acid.
- Replacement of saturated fatty acids by carbohydrate (isocalorically).
- Replacement of mono- and disaccharides by low calorie sweeteners.
- Addition of chloride to water.

Across these different cases we have found that the BRAFO tiered approach worked well. We have identified two early stops in the tiered approach because the benefit–risk question was not a genuine one (replacement of saturated fatty acids by mono-

unsaturated fatty acid and by carbohydrate (isocalorically). We have come across one test case in which the tiered approach stopped after tier 2 (replacement of mono- and disaccharides by low calorie sweeteners). The two other test cases progressed until tiers 3/4, where in one case a quantitative evaluation was possible (addition of folic acid to flour/bread), whereas in the other test case (addition of chloride to water) the lack of data did not allow for quantitative calculations.

This work package along with the other work packages provide guidance for WP8 by identifying key messages that need to be further communicated to stakeholders and risk managers.

Conflict of Interest

For those experts affiliated with academic institutions, the Commission of the European Communities covered, through ILSI Europe, the travel and accommodation costs related to their participation in the BRAFO project. R.A., P.F., A.K., G.P., K.P., T.S., H.B and H.K. received an honorarium for writing this paper. None of the authors declared any interest that may conflict with the provision of their solely scientific input to this manuscript.

Acknowledgements

The authors would like to thank Dr. Theo de Kok (University of Maastricht) for contributing to the development of the present paper. This study has been carried out with financial support of the Commission of the European Communities, Priority 5 Food Quality and Safety, within the Sixth Framework Programme (Contract No: 031731 BRAFO: Benefit Risk Analysis of Foods). This manuscript does not necessarily reflect the views of the Commission and in no way anticipates the future policy in this area. The preparation of this manuscript was coordinated by ILSI Europe.

ILSI Europe would like to thank all the contributors to the BRAFO Scientific Supported Action. Overall, we would like to thank the ILSI Europe Risk Assessment of Chemicals in Food Task Force members and the BRAFO Steering Committee members for their support and guidance. Finally we would like to thank the European Commission for the financial support. As a co-ordinator of the Scientific Support Action, ILSI Europe would like to express its profound gratefulness to all of them.

References


