Integrated risk–benefit analyses: Method development with folic acid as example

Jeljer Hoekstra *, Janneke Verkaik-Kloosterman, Cathy Rompelberg, Henk van Kranen, Marco Zeilmaker, Hans Verhagen, Nynke de Jong

National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

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Abstract

With the introduction of novel and functional foods, there is increasing need for an integrated quantitative risk–benefit assessment of foods. Consensus about a quantitative risk–benefit assessment mirroring the risk assessment approach has been reached during a recent EFSA workshop. In line, we propose a risk–benefit model that consists of: (1) hazard and benefit identification, (2) hazard and benefit characterization through dose–response functions, (3) exposure assessment, and (4) risk–benefit integration. The DALY, which combines morbidity and mortality serves as common health measure.

The overall health impact of bread fortified with folic acid in the Netherlands has been simulated. The case study showed how the risk–benefit approach may assist a policy maker in decisions on food fortification programs. It illustrates general problems regarding the data demands, the assumptions and uncertainties. A simple sensitivity analysis showed which assumptions were most crucial. Modest fortification (140 μg/100 g bread) seems reasonable to improve public health but the results hinge on the assumptions one makes for the association between colorectal cancer and high folate intake. A precautious policymaker may very well decide against folic acid fortification. The often debated increase in masked vitamin B12-deficiency appears negligible compared to the health gain resulting from prevented neural tube defects.

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1. Introduction

With the introduction of an increasing number of foods that carry nutritional or health claims, the balancing of risks and benefits of dietary factors becomes an important public health topic as potential population safety issues cannot be ruled out. For policy makers but also for scientists, food industries and consumers, it is of interest to know what kind and to what extent specific food strategies may provide population health benefits beyond the benefits of a regular or traditional diet without introducing health risks. Nevertheless, in most cases it is both unclear how much health benefit can be achieved and which health hazards should be taken into account. Until recently, risk assessment and benefit assessment have been largely separate processes with different approaches. Currently, the market introduction of many new foods and supplements is based on the assurance of safety only (Coppens et al., 2006). Since 1995 a generic risk (safety) assessment model for food standards issues had been agreed upon (FAO/WHO Expert Consultation, 1995). In short, risk assessment is a systematic means to evaluate the probability of the occurrence of adverse health effects in humans due to (excess) exposure and can be divided into several steps, i.e. hazard identification, hazard characterization, exposure assessment, and risk characterization. The term hazard describes “The potential of a risk source to cause an
adverse effect(s)/event(s)”, and risk describes “The probability and severity of an adverse effect/event occurring to man or the environment following exposure, under defined conditions, to a risk source” (Scientific Steering Committee, 2000). Generally, risk depends on the fraction of the population exceeding any defined upper limit and mainly accounts for the most sensitive hazardous effect. It is increasingly recognized that a similar paradigm can – and should – be constructed for the benefit assessment or rather in an integrated risk–benefit assessment approach (EFSA, 2006). Consequently, risk–benefit assessment can be divided into four analogous steps, i.e.: (1) hazard and benefit identification, (2) hazard and benefit characterization through dose–response functions, (3) exposure assessment, and (4) risk–benefit characterization through integration of risks and benefits. To perform an integrated risk–benefit assessment new elements have to be developed. Both, hazardous and beneficial effects need to be taken into account and potential risks and benefits must be balanced by use of a common measure such as disability-adjusted-life-years (DALYs), quality-adjusted-life-years (QALYs), or healthy-life-expectancy (HALE) (Ezzati et al., 2003; Ponce et al., 2000). In the case of cost benefit analysis health state is often expressed in a monetary value such as Willingness To Pay (WTP) or Willingness To Accept (WTA). Ponce et al. (2001) and Wong et al. (2003) provide a general review of such metrics. Risk–benefit assessment of dietary factors may have different levels of aggregation. Firstly, the total diet may be taken into account as demonstrated by van Kreijl et al. (2006), who calculated for example the population health gain if the population would meet five dietary recommendations. Secondly, a specific food such as fish might be the focus by weighing the effects of xenobiotics versus nutrients (Ponce et al., 2000; Mozaffarian and Rimm, 2006; Cohen et al., 2005; Foran et al., 2005). Thirdly, a risk–benefit assessment may focus on a single food component like a micronutrient, which may evoke both beneficial and hazardous effects, depending on the intake level. Regarding the latter, a first attempt has been described by Renwick et al. (2004), who introduced a theoretical model in which they presented the results as incidence of risk and incidence of benefit. Also Meltzer et al. (2003) describe how a risk analysis model can be applied to food fortification. Unfortunately, they did not proceed with any balancing of risks and benefits using a common health measure.

Here, we present a general model for integrated risk–benefit assessment of dietary factors, including the weighing of beneficial versus hazardous effects by means of calculating DALYs as a composite health measure which takes both incidences of disease and severity of health effects into account. To illustrate the model we have simulated the intake of bread mandatory fortified with different levels of folic acid in the Dutch population as a case study. We have calculated the overall health impact of fortification relative to the situation in which folic acid fortification is not allowed.

2. Risk–benefit model

Schematically, our model for an integrated risk–benefit assessment is presented in Fig. 1. At the start, the prevailing risk–benefit question that needs to be answered should be defined (Step 0). Step 1 (hazard and benefit identification) includes the identification of both beneficial and hazardous health effects and the corresponding benefiting population or population at risk for the micronutrient of interest. Step 2 (hazard and benefit characterization) includes the establishment of a dose–response relation for the identified beneficial and hazardous health effects. In Step 3 (exposure assessment) relevant intake scenarios are established. The scenarios include a reference scenario (e.g. intake based on the current situation) and some relevant simulated scenarios (e.g. micronutrient intake following the introduction of a new fortified food). For each scenario, the habitual intake distribution at a population level is estimated for the micronutrient of interest. Finally, in Step 4 (the risk–benefit characterization) Steps 2 and 3 are combined and the overall health impact is calculated using a common metric e.g. the DALY. Below we describe each step in detail using folic acid as an example.

2.1. Step 0: definition of the risk–benefit question

In our opinion, there is a minimal set of items that should be addressed in the formulation of a clear risk–benefit question. These are:

- What is the reference situation in the population with respect to demographics, intake and health parameters of interest?
- Whose intake will potentially be changed (affected population)?
- How does this intake change (scenarios of intake distributions)?
- What is the health gain or loss resulting from the change in intake?

As an example, we defined the following risk–benefit question for folic acid:

What will be the overall health effect of mandatory fortification of bread with folic acid for the Dutch population in comparison to the current situation (no mandatory folic acid fortification of bread)?

2.2. Step 1: hazard and benefit identification

2.2.1. Step 1a: selection of beneficial and hazardous health effects

In most cases, intake of folate and folic acid (pteroyl-monoglutamic acid (PGA) present in fortified foods and supplements) are thought to have similar effects. Both terms will be used in this article. In the calculations, folate and folic acid are both expressed in folate equivalents.
For our case study, we have performed a computerized literature search to find every beneficial and/or hazardous health effect of folate or folic acid observed in human and/or animal studies and described in the public domain through Medline. We have used more than 30 key words, including: "folate", "folic acid", "neural tube defects", "cancer progression", "cardiovascular disease", "stroke", "vitamin B_{12}", "masking", "megaloblastic anemia", and "colorectal cancer". The search has been limited to papers written in English or Dutch, and emphasis has been placed on studies from industrialized countries. The studies have been grouped according to the criteria for strength of evidence as proposed by the WHO (2003). The strength of evidence is qualified as ‘convincing’, ‘probable’, ‘possible’ or ‘insufficient’. According to these criteria, the most convincing evidence is substantiated by multiple randomized controlled intervention trials of sufficient size, duration and quality in a population representative for the target population showing consistent effects. Also human studies were screened for non-convincing but biologically

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Fig. 1. Integrated risk–benefit model for micronutrients.
plausible evidence for effects that may have a potentially large human health impact. Furthermore, animal studies were screened for other potential risks and benefits that have not or insufficiently been studied in humans but which may have a high impact on general health. As a result, six health effects have been selected (see Table 1).

Three health effects with a convincing level of evidence were identified. Effect 1: the effect of folic acid on the prenatal development of neural tube diseases (NTD) (MRC Vitamin Study Research Group, 1991; Czeizel and Dudas, 1992). Effect 2: the prevention of megaloblastic anemia caused by folate deficiency (Streiff, 1970) and effect 3: the masking of hematological symptoms of vitamin B₁₂-deficiency by folic acid (Scientific Committee on Food, 2000; Institute of Medicine, 1998; Dickinson, 1995; Health Council of the Netherlands, 2003). In addition, three effects concerning the possible role of folate in carcinogenesis, notably for colorectal cancer have been identified. The level of evidence for these effects is not convincing (see Table 1) but the potential impact on the population is high because colorectal cancer is a serious and often fatal disease that occurs relatively frequently. Even a small change in incidence will affect many people. These effects on carcinogenesis are: a protective effect of high folate intake on colorectal cancer risk (Kim et al., 1996, 2001; Sanjoaquin et al., 2004) (effect 4), but also the opposite effect, i.e. an increased cancer risk at very high intake levels (Bashir et al., 2004; Kim, 2004) (effect 5). And finally, an increased risk of cancer progression once (pre)neoplastic lesions have been developed (Farber et al., 1948; Kim, 2003) (effect 6). Effects 5 and 6 are probably due to the same biological mechanism. But because effect 5 affects morbidity and effect 6 affects mortality, they have been separated for modeling reasons.

2.3. Step 2: hazard and benefit characterization

Step 2 involves the determination of a quantitative relation between the exposure, expressed as a habitual intake and the health effect, expressed as the probability to develop a particular disease. For the selected effects of folate and folic acid, dose–response functions preferably from meta-analyses or pooled cohort studies based on human data, were searched for in the literature. However, unambiguous and suitable dose–response functions based on human data are scarce. Often one has to make ad hoc assumptions to estimate dose–response functions based on the currently available scientific knowledge and data. Obviously, the assumptions and estimates have to be documented carefully and preferably a sensitivity and/or uncertainty analysis is performed. Alternatively, one can exclude an effect from the risk–benefit assessment due to lack of data. Basically, this means that the evidence for the effect is considered not convincing enough. In our case study we have ignored some effects because we thought the evidence was not compelling, e.g. for breast cancer, osteoporosis, and cardiovascular diseases. For colorectal cancer we have made assumptions and performed a sensitivity analysis to show how different assumptions, or completely excluding the effect, would change the results.

We assumed that dose–response functions described in the international literature are also applicable to the Dutch population when no specific Dutch data are available. Furthermore, we assumed that health effects are independent. In the Appendix we describe the dose–response functions for each of the selected health effects.

2.4. Step 3: exposure assessment

2.4.1. Step 3a: selection of scenarios

A risk–benefit assessment is in essence an answer to a what-if question. The if-part of the question is represented by intake scenarios. The scenarios show the intake distribution, which is foreseen when e.g. certain food intake policies are implemented. For the folic acid case, we have selected bread to be mandatory fortified. The fortification levels are roughly based on the current practice in the US with a fortification level of 140 µg folic acid per 100 g flour (Food and Drug Administration, 1996). We have created four scenarios, which represent fortification of bread with 70, 140, 280 and 420 µg folic acid per 100 g bread. As a reference scenario we chose the situation in which bread is not fortified with folic acid.

2.4.2. Step 3b: computation of intake distributions

Kloosterman et al. (2007) described thoroughly the method to compute the habitual intake distributions of the fortification scenarios. In brief, consumption data of the Dutch National Food Consumption Survey (DNFCS-3) (Anonymous, 1998) and food composition data of the Dutch Food Composition Table (NEVO) 2001 (NEVO Foundation, 2001; Jansen et al., 2002) have
### Table 1
Hazard–benefit identification: selected health effects of folate and/or folic acid

<table>
<thead>
<tr>
<th>Health effects of folate and/or folic acid</th>
<th>Level of evidence</th>
<th>Target population</th>
<th>Evidence</th>
<th>Type of data</th>
<th>References (first author and year of publication)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beneficial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Neuronal tube diseases (spina bifida, anencephaly)</td>
<td>Convincing</td>
<td>Women of childbearing age</td>
<td>Results of several trials lead to the recommendation of periconceptional use of folic acid supplements/fortified foods (often 400 μg/day). Since end of 1990’s some countries implemented mandatory folic acid fortification, this is shown to decrease the incidence of NTDs (20–70%).</td>
<td>Human studies</td>
<td>Czeizel and Dudas (1992), MRC Vitamin Study Research Group (1991), Ray et al. (2002), Williams et al. (2002), Honein et al. (2001), Institute of Medicine (1998), Health Council of the Netherlands (2003)</td>
</tr>
<tr>
<td>2 Megaloblastic anemia (caused by folate deficiency)</td>
<td>Convincing</td>
<td>Subjects with low intake/status</td>
<td>Although there are not many randomized-controlled interventions, from history it is convincing that folate is an essential nutrient in our diet and can cure some forms of megaloblastic anemia (Hoffbrand and Weir, 2001). In the 1940’s folate is discovered as a remedy to cure the hematological picture in megaloblastic anemia.</td>
<td>Human studies</td>
<td>Layrisse et al. (1976), Streiff (1970), Fishman et al. (2000), Hoffbrand and Weir (2001)</td>
</tr>
<tr>
<td>4 Colorectal cancer</td>
<td>Probable mechanism known</td>
<td>Total population</td>
<td>Folate is known as important factor in the one-carbon metabolism and contributes to DNA synthesis and replication as well as to epigenetic regulation of gene expression. Folate deficiency will result in reduced thymidine (T) synthesis and increased incorporation of uracil (U) in DNA instead of T and modulated cell proliferation. Epidemiological studies suggest that increased folate/folic acid intake is associated with prevention of (colorectal) cancer, however still inconsistency appears</td>
<td>Human studies</td>
<td>Kim et al. (2001), Sanjoaquin et al. (2004)</td>
</tr>
<tr>
<td><strong>Hazardous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Masking vitamin B&lt;sub&gt;12&lt;/sub&gt;- deficiency leading to progression of irreversible neurological symptoms</td>
<td>Convincing</td>
<td>Subjects with risk of vitamin B&lt;sub&gt;12&lt;/sub&gt;- deficiency (elderly, strict vegetarians)</td>
<td>The tolerable upper intake level (UL) of folate is based on this effect of synthetic folic acid (natural folate is not taken into account) (Health Council of the Netherlands, 2003). Folic acid is able to normalize the hematological picture of megaloblastic anemia, which can be caused by either folate or vitamin B&lt;sub&gt;12&lt;/sub&gt;-deficiency. It can however not cure the irreversible neurological symptoms of ongoing vitamin B&lt;sub&gt;12&lt;/sub&gt;-deficiency. Because diagnosing of vitamin B&lt;sub&gt;12&lt;/sub&gt;-deficiency was often based on the hematological picture, masking of this morphological change might result in delayed diagnosis, which may result in more progression of the irreversible neurological symptoms. The masking effect is convincing, however the consequential health effect of delayed diagnosis and probably more progression of the neurological symptoms is still under discussion. Although in countries with mandatory folic acid fortification, increased proportion of the population with low vitamin B&lt;sub&gt;12&lt;/sub&gt; status in the absence of anemia was not observed (Mills et al., 2003). The UL of folic acid is based on masking of vitamin B&lt;sub&gt;12&lt;/sub&gt;- deficiency, this health effect was therefore also taken into account</td>
<td>Human studies</td>
<td>Health Council of the Netherlands (2003), Institute of Medicine (1998), Scientific Committee on Food (2000), Dickinson (1995), Mills et al. (2003)</td>
</tr>
</tbody>
</table>

(continued on next page)
been combined. DNFCS-3 was performed in 1997–1998, and comprised a random sample of 2564 households involving 6250 subjects (aged 1–97 yr). Subjects provided dietary records on two consecutive days. As long-term intake is of interest, habitual intake distributions have been estimated by correction for within-person variation using the ISU-method (Nusser et al., 1996). The habitual intake distributions of the fortification scenarios have been simulated by creating virtual food composition tables with the proposed folic acid levels (70, 140, 280, or 420 μg/100 g bread). Because folate and folic acid are assumed to have a different bioavailability, the intake of total folate is expressed as folate-equivalents using conversion factors (Institute of Medicine, 1998; Health Council of the Netherlands, 2003; Bailey, 1998; Suitor and Bailey, 2000). The reference scenario comprises the estimation of the habitual intake based on the observed intake of folate in the normal background diet with the ISU-method (Nusser et al., 1996). Separate intake distributions have been calculated for all previously defined target groups (see Table 1). For the prevention of NTDs women of childbearing age (19–50 years) were chosen as target group for folic acid fortification, for this group habitual folate-equivalent distribution was calculated. For prevention of folate deficiency total population is target group and so habitual folate-equivalent intake was simulated for the whole population. Elderly were chosen as risk group for masking of vitamin B12-deficiency, and so habitual folate-equivalent intake distribution was simulated subjects aged over 65 years. For colorectal cancer incidence figures are known per 5-year group and therefore habitual folate-equivalent intake distributions were simulated per 5-year group in the total population. As an example the intake distribution of the four simulated fortification scenarios and the reference scenario for Dutch women aged 19–50 year.

The effects include every effect for which the evidence is convincing. In addition, three effects concerning the possible role of folate in carcinogenesis which has been best studied for colorectal cancer, have been identified. The level of evidence for these effects is lower (see Table 1) but the potential impact on the population may be high.

### Table 1 (continued)

<table>
<thead>
<tr>
<th>Health effects of folate and/or folic acid</th>
<th>Level of evidence</th>
<th>Target population</th>
<th>Evidence Type of data</th>
<th>References (first author and year of publication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>Probable</td>
<td>Total population</td>
<td>High intake of folate/folic acid is suggested to be associated with a higher risk of (colorectal) cancer</td>
<td>Animal studies Human studies Patient studies Animal studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjects with existing (pro)neoplastic lesion (not diagnosed)</td>
<td>Already since its discovery in the 1940s, it is known that folate/folic acid can promote the growth of existing tumors, and therefore folate antagonists were developed as chemotherapeutics, and these are still used. Due to ethical issues, more research about timing/dose can only be performed in animal/laboratory studies. Besides it is suggested that extra-physiological doses of folic acid can increase the risk of (colorectal) cancer</td>
<td>Animal studies Human studies Patient studies Animal studies</td>
</tr>
</tbody>
</table>

![Fig. 2. Habitual intake distribution of folate-equivalents (folate and folic acid) for the reference scenario (i.e. no folic acid fortification) and four simulated folic acid fortification scenarios (70, 140, 280, and 420 μg/100 g bread), of women aged 19–50 year.](image.png)
skewed, which is the case for many fortification scenarios. Besides, this method assumes a homogeneous within-person variation within the population. Presumably, this is not the case for certain fortified foods that are infrequently consumed. As a result, we have been unable to calculate habitual intake of folic acid, because of the many observed zero intakes, skewed distribution and non-homogeneous within person variation. The intake distribution of folic acid, apart from the distribution of folate-equivalent intake, is necessary for the health effects for which the association is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency. Because total folate-equivalent intake is only studied with folic acid (e.g. dietary supplements) without taking into account the intake of natural folate from the background diet, like in the associations between folic acid and NTDs or the risk of masking vitamin B12-deficiency.

2.5. Step 4: risk–benefit characterization

2.5.1. Step 4a: calculation of prevented and/or additional incidences of diseases (combining Steps 2 and 3)

Once the dose–response function of a particular disease and the intake distribution is known, the incidence of that particular disease can be calculated in the population of interest for each intake scenario. We denote the incidence in the population by \( \text{inc} \), the folate-equivalent intake by \( F \), the dose–response function by \( p(F) \) and the cumulative distribution of habitual folate-equivalent intake by \( R(F) \). Furthermore, \( r(F) \) is the probability density function of the intake distribution, defined by

\[
r(F) = \frac{dR(F)}{dF} \tag{a}
\]

The average incidence per person year is described by

\[
\text{inc} = \int_0^\infty p(F)r(F)dF \tag{b}
\]

Often the intake scenario, \( R(F) \) is represented as a series of points, so-called percentiles. Suppose \( R(F) \) is accurately measured or simulated in \( N \) points, \( 0, F_1, F_2, F_3, \ldots, F_N \), with \( R(F_N) = 1 \). Then \( R(F) \) can be described as a piecewise linear function between the points \( F_i \). Hence, Eq. (b) becomes

\[
\text{inc} = \sum_{i=1}^{N-1} \int_{F_i}^{F_{i+1}} p(F) R(F_{i+1}) - R(F_i) \cdot dF \tag{c}
\]

Now for every scenario the incidence of each disease can be calculated. In the case of effect 4, 5 and 6, i.e. colorectal cancer, \( p(F) \) and \( R(F) \) depend on age and sex. Thus the incidence should be calculated for each age and sex separately. Then the total incidence in the population is simply the sum of all incidences weighted with their relative population size. Subsequently, the prevented or additional incidence of a disease given a fortification scenario is calculated by subtracting the incidence of the reference scenario.

2.5.2. Step 4b: expressing change in incidences of a disease in a common health measure

In order to compare the health impact of several different diseases the incidence of a disease must be converted into a common integrated health measure. As in earlier reports (van Kreijl et al., 2006) we used the Disability Adjusted Life Year (DALY) because this takes into account premature death and the physical impairment in case of and due to ill health and the duration of the disease (Murray and Lopez, 1996). A DALY is a combination of years of life lost and years lived with a disability and is expressed in Eq. (d).

\[
\text{DALY}_i = (\text{YLL}_i + w_i \cdot \text{YLD}_i) \text{inc}_i \tag{d}
\]

where \( \text{DALY}_i \) is the disability adjusted life years due to disease \( i \), \( \text{YLL}_i \) the year of life lost due to disease \( i \), \( \text{YLD}_i \) the years lived with disease \( i \) inc, the incidence of disease \( i \) in person years and \( w_i \) is the disability weight of disease \( i \).

The years lived with the disability are weighted according to the severity of the disease with a factor \( (w_i) \) between 0 and 1. A more severe disease is weighted with a higher disability weight. Death is weighted with a factor 1, basically expressed through \( \text{YLL}_i \). No distinction is made between several stages of a disease. Furthermore, the severity of the disease is not discounted nor did we use age weighting. So, suffering from the disease now or in the future or by people with a different age results in the same loss of quality of life. The use of DALYs and especially age weighting and discounting is an area of open debate (e.g. Arnesen and Kapiriri, 2004; Murray and Lopez, 2000; Paalman et al., 1998; Murray and Acharya, 1997). Murray and Lopez (1996) published discounted as well as not discounted values because of the difficulties of choosing a discount rate. Arnesen and Kapiriri (2004) advocate transparency when common health measures are used. Therefore, we choose not to apply age weighting and discounting. Furthermore, we show incidences and DALY per disease along with the total number of DALYs.

The DALY value depends on the incidence of the disease. Therefore, the results of a simulation express the consequences of the (extra) incident cases in the year of the intake distribution. For a beneficial effect, compared to the reference intake (no fortification) the resulting DALY will have a negative value because less life years are lost. Subsequently, a hazardous effect is represented by a positive value. For folic acid, we calculated the DALYs per health effect and in total. The details about these calculations and the parameter values can be found in the Appendix.

Table 2 shows the change in incidence of the modelled health effects and the associated DALY values. The distinction between mild and serious health effects becomes clear when expressed in DALYs. For instance, the incidence reduction for neural tube defects is much less than for
megaloblastic anemia (e.g. scenario 70 μg/100 g bread: NTD: −83, MA: −2425). But because neural tube defects are a far more serious disease (wNTD = 0.59 versus wMA = 0.01) the resulting DALYS of megaloblastic anemia become trivial compared to neural tube defects (MA: −24, NTD: −5474).

2.5.3. Step 4c: calculation of the overall health impact

Because every health effect is expressed in the same unit (DALY), the net effect of the adverse and beneficial effects can be presented simply as the sum of all health effects in DALYs:

\[
\text{DALY} = \sum_i \text{DALY}_i
\]

2.5.4. Step 4d: results and interpretation

The overall health impact for each fortification scenario is presented in Table 2. The columns of Table 2 represent the different scenarios: bread fortified with 70–420 μg of folic acid per 100 g. The rows denote the simulated health effects per disease, expressed as an absolute and relative change in incidence and as a change in DALYs compared with the situation of no fortification. The very last row denotes the overall health effect in DALYs. The maximum change in DALYs is found at a fortification level of 140 μg/100 g bread. The simulations indicate that fortification with folic acid, up till 280 μg/100 g bread, still results in a beneficial net health effect. The beneficial effect on the prevention of NTD will not increase much more with increasing fortification levels, whereas the harmful health effect on colorectal cancer may result in a net health loss as soon as the level of folic acid fortification goes up to and beyond 280 μg/100 g bread. The masking of a vitamin B12 deficiency appears negligible in the total equation. Nor is the prevention of folate deficiency important. Even though, quite a substantial number of megaloblastic anemia cases can be prevented, the disorder is so mild that only very few DALYS can be gained.

The outcome of the calculations depends obviously on the parameters values chosen in the model. In this paper we have used point estimates of uncertain and variable parameters to do our calculations. A future development should include an (Monte-Carlo) analysis in which distributions of the parameters are used. That would add an uncertainty interval to the results and would avoid the suggestion of exactness that comes with presenting just one result. Table 3 shows the results for a different value of the uncertain parameter sl.

The final results hinge on the assumptions one makes for the association between colorectal cancer and folate intake. We performed a simple sensitivity analysis, in which the variables sl, ml, im and mml (see Appendix) have been varied independently. The sensitivity analysis revealed that the results are most sensitive for sl. This variable describes the intake level below which, folate intake protects against colorectal cancer and above which, folate intake increases the risk of colorectal cancer. If one assumes that the probability of developing colorectal cancer increases at intake levels of 500 instead of 1000 μg folate equivalents (i.e. sl = 500), then the results are quite different. The largest shifts occur between an intake of 500 and 1000 μg folate equivalents, because in the non-fortified scenario no one exceeds an intake of 500 μg folate-equivalent per day whereas with increasing fortification levels an increasing number of people exceed the 1000 μg folate-equivalent/
day limit. When bread is fortified with 280 µg folic acid per 100 g bread, the intake of 83% of the population exceeds 500 µg folate-equivalents per day and the intake of 22% of the population exceeds 1000 µg folate-equivalent per day. Table 3 shows the alternative results for \( \text{sl} = 500 \). Under this assumption a fortification level of 140 µg folic acid per 100 g of bread already results in an increase in colorectal cancer patients, the best results are obtained with a fortification level of 70 µg folic acid per 100 g bread.

### 2.6. Interpretation

The outcome is obviously very uncertain, notably because there were not enough good quality data available to estimate the dose–response function for colorectal cancer and therefore, conclusions can only be tentative. Unfortunately, colorectal cancer is a serious disease and the outcome of the total risk benefit assessment depends largely on the outcome for this disease.

One could argue that because the most important health gains result from the intake of a distinct subgroup of the population, namely women of childbearing age at the periconceptual stage and that the most important losses appear through intakes in the general population (increase in colorectal cancer (CRC) incidence) it would be advisable to address folic acid policies directly at the subgroup whose intake realises health gains without hurting some other group. However, until now that route i.e. advising folic acid supplements to women with a pregnancy wish, has been unsuccessful (Eichholzer et al., 2006). On the other hand, one could argue that fortification should be set at a level that does not negatively influences the health of the general population. Then 70 µg folic acid per 100 g of bread seems to be advisable because that would be at almost everybody’s benefit. Apart from the very few elderly people with a mild vitamin B\(_{12}\)-deficiency disorder, which could be prevented by accurate diagnosis, everyone would gain. This is exactly the kind of deliberation that a policy maker should have. We think that even an uncertain risk benefit assessment, such as we present here, could guide and assist the policy maker. Concerns about the role of folate in the development of colorectal cancer are shown to be paramount for a fortification policy. This concern is also raised elsewhere. The British Scientific Advisory Committee on Nutrition (SACN) abruptly pulled a report from the press because of the concern over a possible link between high levels of folic acid and cancer. The members of the SACN were invited to comment on time trend data on colorectal cancer incidence in North America that suggested a possible increase in colorectal cancer at around the time fortification with folic acid was introduced (Anonymous, 2006). The case study shows that the debate whether or not to fortify foods with folic acid should be about colorectal cancer not about masking of vitamin B\(_{12}\)-deficiency.

### 3. Discussion

#### 3.1. General

This paper describes our risk benefit methodology that aims to quantify the benefits as well as any hazards of a given food or ingredient. Although we have been able to perform the mathematics behind the quantitative risk–benefit analysis in the folic acid example, the available data or rather the lack of available data have forced us to make assumptions and educated best guesses that have resulted in outcomes accompanied with rather large uncertainties. We assume that this is generally the case, but may not always be reported explicitly. At the very minimum, uncertainties should be addressed by performing sensitivity analyses. Quantifying the uncertainties is even better but is outside the scope of this paper. In an ongoing EU 6th Framework research project, Qalibra (www.qalibra.eu), methods to quantify these types of uncertainties are currently being investigated. We demonstrated how to retrieve (population specific) beneficial and adverse health effects from the literature, how to compute current and potential intake distributions, and how to estimate and utilize dose–response curves in order to assess the net health effect on the total population. Policy makers, but also food manufacturers, scientists, nutrition education centers, and consumer organizations will be the main stakeholders who may want to know to what extent specific food strategies may provide population health benefits without introducing health risks. Below, we discuss some issues that evolved from our risk–benefit approach.
3.2. Health effects

The health effects that can be accurately incorporated in the model depend on the amount and quality of data that can be found in the scientific literature. Good quality data is needed to estimate the underlying dose–response relationships of the model.

Although an enormous pile of original studies has been described in the literature, it remains difficult to extract the specific data required for a risk–benefit approach, notably for the construction of dose–response functions. First, many of the health effects described to be associated with a certain food ingredient do not appear to be convincingly evident. This causes large uncertainties in the final outcome. Second, especially hazardous effects are often studied in animals or in vitro and not in humans due to ethical constraints. It is difficult to extrapolate the results of animal or in vitro studies to humans. Third, dose–response data are not common in the literature. Intervention studies generally use a limited number of dosages and studies are often too differently designed to easily extract a dose–response relationship by combining the available studies. Dose–response modeling and the inclusion of more dosing regimes in clinical trials, which are also described in more detail may be ways forward to partly overcome the current gaps. In addition, in cohort studies it would certainly be helpful if dose–response curves were estimated instead of a relative risk of a high intake versus a low intake. Fourth, publication bias might be relevant. Finally, when one uses a quality of life measure such as the DALY, it is important to know the duration and mortality of the disease resulting from a certain dose. Unfortunately, this is neither a common outcome of human studies nor is it in animal/in vitro studies. In human studies often early end-points or intermediate measures are taken as the finally measured outcome due to time constraints. The use of a common health measure is inevitable when a risk–benefit analysis is performed, but the choice of the common currency and whether to apply such things as age weighting and discounting is not trivial. Ethical and equity issues play a role. The choice of health measure and associated parameter values such as disability weights and discount rate give, deliberate or not, priority to one age- or disease subgroup at the expense of another. Therefore, it is important to be transparent about the choices that are made. Not only the final DALY (or other summery measure) should be presented but also intermediate variables such a incidences.

3.3. Exposure data

For a risk–benefit analysis, intake data from national food consumption surveys can be used. Ideally, the underlying database (including the food composition database) is flexible and can be used for simulation of (e.g. fortification) scenarios (Kloosterman et al., 2007). Preferably, dietary supplements should be taken into account as well since intake of e.g. micronutrients via dietary supplements may be another important source, in addition to (fortified) foods (Ocké et al., 2005). Unfortunately in many countries including the Netherlands, recent consumption data of dietary supplements and fortified foods are scarce. For folic acid, Dutch data on dietary supplement use were lacking and could not be included in our intake scenarios. Recently, a report has been published that describes how the Dutch National Food Consumption Survey (DNFCS) should be adapted to monitor intake of both (fortified) foods and dietary supplements and to obtain the total habitual intake data of micronutrients rather than reported intake data (Rompelberg et al., 2006). In the Netherlands, women with a pregnancy wish are advised to take daily a dietary supplement containing 400 μg folic acid periconceptionally to prevent NTDs. It is however not known how many women do actually take these supplements per-conceptionally. Taking into account folic acid intake from supplements will result in a higher folate-equivalent intake in part of the population. Women taking folic acid containing supplements per-conceptionally will have a more decreased risk of a child with NTD than the effect that is simulated in this model. On the other hand, in the total population also higher folate intake at the higher percentiles of the intake distribution may be expected with as result that also for the other health effects the effect is expected to be more extreme (for positive effects lower DALY, for negative effects higher DALY).

3.4. The folic acid case study

Even for a rather well-studied example as folic acid, it is difficult to make quantitative statements about the net health effect of folic acid fortification. Nevertheless, our case study reveals interesting quantitative insights. The population health impact of the masking of vitamin B12-deficiency appears to be very small, especially in comparison with the impacts of the prevention of NTDs and colorectal cancer. The low impact of masked vitamin B12-deficiency is attributable to the relatively low disability weight of the associated illness compared to a NTD. But also only very few extra cases of vitamin B12-deficiency seem to arise because at modest fortification levels only few anemia’s are masked. We base this conclusion on an overestimation of the number of masked vitamin B12-deficiencies because we assumed that no extra vitamin B12 would be added to fortified foods. Presumably, folic acid fortification will often be accompanied with vitamin B12 fortification. Additionally, we assumed that every masked deficiency is undiagnosed which is, presumably, a gross overestimation. In countries with mandatory fortification no increase in masked vitamin B12-deficiency has been shown (Mills et al., 2003; Tucker et al., 1996). This supports our finding that concern about undetected vitamin B12-deficiencies will be superfluous in the case of folic acid food fortification. Besides, health practitioners are and should be more aware of the possibility of a masked vitamin B12-deficiency in case of folic acid fortification. The
marginal contribution of masking vitamin B\textsubscript{12}-deficiency to the risk benefit equation is not a complete surprise as the introduction of mandatory folic acid fortification elsewhere in the world, did evoke a lot of discussion about this particular risk (Eichholzer et al., 2006; Health Council of the Netherlands, 2000). To the best of our knowledge this discussion was mainly based on qualitative information and the effect has never been quantified. In addition, the incidence of megaloblastic anemia is overestimated because it is taken from the general practitioner registration (Linden et al., 2004) (ICPC-code B81). In the registration, apart from megaloblastic anemia caused by folate deficiency, also pernicious anemia (vitamin B\textsubscript{12}-deficiency) is filed under the same code. Finally, every NTD is regarded as being spina bifida. This causes underestimation because encephalocele and especially anencephaly (basically a stillbirth) are more severe disabilities. So, more NTD–DALYs could be gained with folic acid fortification.

Another important finding is that effects on colorectal cancer for which evidence is not yet convincing but is accumulating, have a high impact on the final outcome expressed in DALY’s. This is because of the high incidence and high mortality of colorectal cancer and the severe disability weight. Other proposed health effects of folate like osteoporosis, cognition, dementia, breast cancer, and coronary heart disease should be taken into account, if these effects are further substantiated in the future.

So far, studies have shown the risk reduction for individual health effects such as NTD. For instance, Daly et al. (1995) and Wald et al. (2001) report some 20\% reduction of the risk of NTDs for an intake of 100 \mu g folic acid per day. We have used these estimations (see Appendix) to simulate the effect of folic acid fortification on the incidence of NTDs in the total population, which has not been done before as far as we know. Let alone, to focus on several health effects in comparison. All caused by the same food fortification. Some are well-documented health effects such as vitamin B\textsubscript{12}-deficiency and some are more uncertain and based on less quantifying data such as colorectal cancer.

Since 1998 food has been mandatory fortified with folic acid in the US and Canada. Ray et al. (2002) report a decrease in NTDs since 1998 of 29\%. The fortification level was targeted at 140 \mu g per 100 g cereal product. We estimate a considerably higher decrease (53\%) for the fortification of bread with 140 \mu g folic acid per 100 g bread. This could be due to a different diet of the Canadians and the Dutch but perhaps our model also overestimates the protective effect of folic acid on incidence of NTD.

4. Conclusion

The proposed risk benefit model is useful to assist policy makers to make deliberate decisions on minimum and maximum fortification levels for foods and dietary supplements. In addition, the model assists the policy maker with decisions on, mandatory versus voluntary or no food fortification programs, or the introduction of targeted education programs. The method helps to show what the important health effects are and at which aspects, future research should be concentrated to reduce the most important uncertainties involved in food policy decision making. The particular challenge of scientific uncertainty for a policy maker has been identified earlier by Lawrence (2005).

With the growing supply of fortified foods and dietary supplements, the individual intake of vitamins and minerals will change for at least part of the population and thus the intake distribution (at population level) will change. As a result, individuals with an intake below the RDA may decrease while others may exceed the safe upper levels of intake. A risk–benefit assessment model, as demonstrated for folic acid, using intake data of national food consumption surveys will give policy makers the opportunity to obtain insight into the overall health impact of fortification of and will give them a valuable tool for making regulatory decisions on the fortification of foods. In addition, other stakeholders may be interested in a risk–benefit balance such as the food manufacturers, consumer organizations, nutrition education centers, and scientists.

There is a need for more thorough quantitative uncertainty analysis than we have provided, but our analysis has been useful to explore where some of the largest uncertainties are. As stated earlier (Ulrich and Potter, 2006; Finglas et al., 2006), further research is required on quantitative assessment of folate intake, bioavailability and especially on the role of folate in cancer development. Although lacking data has hampered a rigorous and complete analysis, our first attempt of applying the risk benefit methodology has resulted in new quantitative insights in the importance of the different health effects for folic acid and demonstrated the potential employability of this approach.

Acknowledgements

The authors would like to thank Marga C. Ocké for conceptualizing the risk–benefit topic described in this paper and Jan van Eijkeren for modeling the pharmacokinetics of folic acid. The work has been financed by RIVM (Project No. S/350610).

Appendix. Ad Step 2: hazard–benefit characterization

Below we describe how the dose–response functions have been estimated for each health effect:

Effect 1: prevention of neural tube defects

The dose–response between folic acid intake and risk of neural tube defects (NTDs) incorporates three stages. Firstly, the relationship between folic acid intake and serum folate levels has been established. Secondly, the relationship between serum folate status and the odds ratio for having a child with a NTD has been estimated. And finally...
the odds ratios have been transformed into probabilities of giving birth to a child with a NTD.

We have assumed that in the case of mandatory folic acid fortification, eventually every consumer’s serum folate level will reach an equilibrium, for which the static relation \( A.1 \) between serum folate and folate intake (expressed as folate-equivalents) can be used.

\[
SF = \alpha F \tag{A.1}
\]

where SF is the serum folate [ng/mL], \( F \) the folic acid intake [folate-equivalent mg/day] and \( \alpha \) is the conversion coefficient.

This formula has been derived from the kinetic model of Lin et al. (2004) whose aim was to quantify human folate metabolism. The kinetic model of Lin et al. has been simulated with constant folate long enough to reach equilibrium serum folate levels. The results enabled us to deduce a linear relation \( A.1 \) between equilibrium serum folate and folate intake. The conversion coefficient was estimated to be 40. This value is different from the value Wald et al. (2001) reported earlier (conversion coefficient \( = 9.4 \)). The reason for this difference is that presumably most of the subjects in their study had not reached equilibrium serum folate levels yet, because the duration of the trials was between 3 weeks and 24 months. According to the model of Lin et al. (2004) it takes about a year to reach equilibrium serum folate levels. In a study of Durga et al. (2007), subjects were given 800 \( \mu \)g of folic acid per day and had a dietary folate intake of 195 \( \mu \)g of per day. After three years their serum folate level reached 75 nmol/L. Our model (Eq. (A.1)) predicts a comparable equilibrium level of 72 nmol/L.

Wald et al. (2001) used data from a single case-control study (Daly et al., 1995) to quantify the relationship between maternal plasma folate concentration and the odds ratio of NTDs. Assuming that the serum folate concentration equals the plasma folate concentration the folate intake distribution. Subsequently, we can compute the resulting incidence expressed in one unknown, namely \( c_{\text{NTD}} \). Obviously, the computed incidence based on the current intake distribution should be equal to the measured current NTD incidence. Hence, the value of \( c_{\text{NTD}} \) is easily calculated. We used 1.15 per 1000 neonates (mean over the years 1996–2000) (Anthony et al., 2003) as an estimate for the present NTD incidence (spina bifida, anencephaly and encephalocoele) in the Netherlands, this leads to a \( c_{\text{NTD}} \) of 0.00497

Fig. A.1 shows the resulting dose–response function for the relation between maternal folate-equivalent intake and the probability of a child being born with a NTD. The habitual intake of 95% of the women between 19 and 50 years of age is less than 260 \( \mu \)g folate(-equivalent) per day and 50% has an habitual intake less than 166 \( \mu \)g folate(-equivalent) per day (DNFCS-3 1997–1998) (Anonymous, 1998). Clearly, a higher intake of folate would considerably prevent the birth of children with NTDs.

\[ p_{\text{MA}}(F) = Ae^{kF} - B \quad \text{if} \quad F \leq \text{RDI} \]
\[ = 0 \quad \text{if} \quad F > \text{RDI} \tag{A.4} \]

**Effect 2: prevention of megaloblastic anaemia (folate deficiency)**

The dose–response relationship for the prevention of folate deficiency (megaloblastic anaemia) is based on the recommended daily intake (RDI) in the Netherlands, which is 300 \( \mu \)g per day (Health Council of the Netherlands, 2003) and anaemia data from a general practitioner registration (ICPC-code B81) (Linden et al., 2004). We have assumed that if the daily intake of a subject exceeds the RDI then that subject does not develop megaloblastic anaemia. Otherwise, if a subject’s daily folate intake is less than the RDI, that subject has a probability of developing megaloblastic anaemia. This probability decreases exponentially with habitual folate-equivalent intake. The following formula describes this dose–response function:

The dose–response function contains one unknown constant, \( c_{\text{NTD}} \). This constant can be estimated using the current intake distribution (folate-equivalents) and the current incidence of NTDs in the population. Using the Eqs. \( A.3 \) and \( B.1 \) (see Section 2.5.1) in which we substitute the current intake distribution. Subsequently, we can compute the resulting incidence expressed in one unknown, namely \( c_{\text{NTD}} \).
Table A.1
Estimated parameter values of the dose-response function between habitual folate-equivalent intake and megaloblastic anaemia

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>RDI (Health Council of the Netherlands, 2003)</th>
<th>Present incidence (Linden et al., 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.75e−36</td>
<td>−0.271 day/µg</td>
<td>300 µg/day</td>
<td>0.4/1000</td>
</tr>
</tbody>
</table>

where, $F$, is the equivalent intake fraction. $A$, $B$, and $k$ are parameters that are needed to make formula (A.4) satisfy the following three conditions. (1) The probability to develop megaloblastic anaemia equals 1 for a habitual folate-equivalent intake of 0 µg/day. (2) It is 0 for a habitual folate-equivalent intake equal to the RDI. (3) The computed incidence of megaloblastic anaemia for the present habitual folate-equivalent intake distribution should equal the present incidence. The incidence of megaloblastic anaemia is estimated using Eq. (b) in Step 4a. Table A.1 shows the estimated parameter values and the dose–response function can be seen in Fig. A.2.

Effect 3: masking of the hematological picture of vitamin B_{12}-deficiency

The dose response function of vitamin B_{12}-deficiency is based on the multiplication of a series of independent probabilities. Whether a hematological picture of the anaemia will be masked depends on the degree of folic acid fortification of the consumed foods. The probability of a vitamin B_{12}-deficiency among consumers of folic acid fortified food, $p_{\text{An|B}12}$, the probability of developing megaloblastic anaemia when vitamin B_{12}-deficient, $p_{\text{ND|B}12}$, the probability of developing neurological damage when vitamin B_{12}-deficient, $p_{\text{mask}}(F)$ the probability of masking the hematological picture of an anaemia, which depends on folate intake, $p_{\text{false}}$ is the probability of a false diagnosis when doctors exclude vitamin B_{12}-deficiency because of the absence of an anaemia.

The probability $p_{\text{B}12|FF}$ depends on the amount of vitamin B_{12} consumed and the number of persons suffering from pernicious anaemia who have a difficulty to absorb vitamin B_{12}.

$$p_{\text{B}12|FF} = p_{\text{B}12}(p_{\text{pa}} + (1 - p_{\text{pa}})(1 - p_{\text{addB}12}))$$ (A.6)

where $p_{\text{B}12}$ is the probability of suffering from vitamin B_{12}-deficiency, $p_{\text{pa}}$ the probability of suffering from pernicious anaemia when suffering from vitamin B_{12}-deficiency, and $p_{\text{addB}12}$ is the probability that the parallel added vitamin B_{12} in (folic acid fortified) functional foods prevents a shortage of vitamin B_{12} in someone’s diet.

The probability of masking the megaloblastic anaemia depends on the amount of folate acid intake. Based on Bower and Wald (1995), we assume the relationship in Eq. (A.7). According to Bower and Wald, an effect was rarely shown at levels lower than 2 mg folate equivalents per day. Therefore, we conservatively estimated a linearly increasing probability from zero at no intake to 10% probability, which we considered the detection limit, at 2 mg folate equivalents per day. A 60% probability of masking megaloblastic anaemia was reported at high doses, i.e. above 10 mg folate equivalents per day. Due to lack of better data we assume a linear increase between 2 and 10 mg/day and a probability of 0.6 for any dose over 10 mg/day. This results in Eq. (A.7) for the probability of masking vitamin B_{12}-deficiency. A graph of the dose–response function can be seen in Fig. A.3.

$$p_{\text{mask}}(F) = \begin{cases} 0.05F & \text{if } F < 2r \\ 0.01 + (F - 2)0.0625 & \text{if } 2 \leq F \leq 10r \\ 0.6 & \text{if } F > 10 \end{cases}$$ (A.7)

where, $F$ is the intake of folate equivalents in mg/day

The parameter values used in (A.5) and (A.6) are shown in Table A.2. We conservatively assume that no vitamin B_{12} is added to food that is fortified with folic acid ($p_{\text{addB}12} = 0$) and that every doctor will incorrectly exclude vitamin B_{12}-deficiency from his diagnosis ($p_{\text{false}} = 1$), in the absence of an anaemia. This obviously causes an overestimation of the number of untreated patients with B_{12}-deficiency due to masking.
Thus, we propose the following dose–response function between folate-equivalent intake and the probability of developing colorectal cancer. The dose–response function depends on age and sex.

\[
p_{\text{CRC}}(F, a, s) = \begin{cases} 
   p_{0,\text{CRC}}(a, s)e^{F} & \text{if } F \leq s1 \\
   p_{0,\text{CRC}}(a, s)e^{s1(F) - s1} & \text{if } s1 < F < ml \\
   10p_{0,\text{CRC}}(a, s)e^{s1} & \text{if } F \geq ml
\end{cases}
\]

where \(p_{\text{CRC}}\) is the probability of developing colorectal cancer depends on folate equivalent intake, age and sex, \(F\) the folate equivalent intake, \(k\) the coefficient; exponential probability decrease rate, \(p_{0,\text{CRC}}\) the probability of developing colorectal cancer when folate equivalent intake is zero, depends age and sex, \(a\) the age, \(s\) the sex, \(ml\) the maximum probability of developing colorectal cancer and \(s1\) is the safe level, intake above \(s1\) causes a colorectal cancer risk increase.

The parameter \(p_{0,\text{CRC}}(a, s)\), can be computed in an analogous way to \(c_{\text{NTD}}\) in the case of NTDs, from the present incidence of colorectal cancer and intake of folate-equivalents, but now for each age (class) and sex separately. The parameter \(k\) is estimated at \(-0.00029133 (=\ln(1 - 0.11)/400; 11\%\) decrease per 400 \(\mu\)g/day see Kim et al., 2001). Fig. A.4 illustrates the dose–response function of folate-equivalent intake and colorectal cancer risk for men and women between 40 and 45-years old.

**Effect 6: effect on colorectal cancer progression**

Furthermore, there is some evidence that that the growth of existing tumors is enhanced with increasing doses of folate (Kim, 2003). This risk is assumed to result ultimately in untimely death. Enhanced growth of tumors is an effect on the severity of the disease, not on the prob-

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**Table A.2**

<table>
<thead>
<tr>
<th>Parameter values regarding the dose response function of habitual folate-equivalent intake and masking of the hematological picture vitamin B(_{12})-deficiency as used in Eqs. (A.5) and (A.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p_{\text{B12}}) (Linden et al., 2004)</td>
</tr>
<tr>
<td>0.00185</td>
</tr>
</tbody>
</table>

**Effect 4 and 5: effects on colorectal cancer risk**

The dose–response relationship between folate intake and the prevention of colorectal cancer was adopted from preliminary results of the pooled analysis of prospective studies on folate and colorectal cancer by Kim et al. (Kotsopoulos et al., 2005), in which a quantitative dose–response relation was presented. According to these data, the risk of colorectal cancer decreases with 11% every 400 \(\mu\)g of total folate intake. However, at high folate intake a potential increase in colorectal cancer incidence is shown in human and animal studies (Kim, 2004; Kim et al., 1996). Therefore, we assume that at a certain level (\(sl\)) of folate intake the risk of colorectal cancer will increase again. Until now, it remains uncertain at which dose this increased colorectal cancer risk may start. Kim (2004) reports that it could be 20 times the recommended intake for laboratory animals. Therefore, a rather arbitrary but supposedly conservative value was used (\(sl\) = 1000 \(\mu\)g folate-equivalents per day, i.e. about three times the RDI) as a kind of safe upper level above which the risk of colorectal cancer linearly worsens 10-fold to an arbitrary high intake level \(ml\) (5000 \(\mu\)g folate-equivalents per day). In this way we presumably overestimate this potential negative effect. In the final assessment we performed a sensitivity analysis to examine how the uncertainty about the parameters \(sl\) and \(ml\) influences the results of the risk–benefit analysis. In this sensitivity analysis \(sl\) is halved so that an even more conservative value for \(sl\) is used.

---

Fig. A.3. Dose–response function of habitual intake of folate-equivalents (\(\mu\)g/day) and the probability of masking the hematological picture of vitamin B\(_{12}\)-deficiency.

Fig. A.4. Dose–response function of habitual folate-equivalent intake (\(\mu\)g/day) and colorectal cancer risk for men and women between 40 and 45 years of age.

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ability of developing the disease. Therefore, it is modeled in the integration step in which incidence of colorectal cancer is converted to DALYs (see Section 2.5.1).

**Ad Step 4b: expressing change in incidences of a disease in a common health measure**

Below, we explain how we estimate the parameters (YLL, YLD, and w) that are needed to compute DALYs for each of the health effects.

**Effect 1: neural tube defect**

NTD is a non-curable birth defect. Thus, YLD_{NTD} is simply the life expectancy of someone with the disease and YLL_{NTD} is the difference in life expectancy between someone with and someone without the disease. The life expectancy is taken from Statistics Netherlands (Statistics Netherlands, 2007). The average of male and female life expectancy at birth is 78.9 year in 2004. We estimate the life expectancy of people suffering from spina bifida to be equal to that of people whose primary cause of death is NTD, which is approximately 32.5 years. This is a rough estimate indeed. It could be an underestimation because there may be people suffering from NTD who die from other causes such as heart diseases or cancer when they are well over 32.5 years old. On the other hand, one could argue that because of their weak health many NTD patients also die before the age of 32.5 due to other diseases. The disability weight, \( w_{NTD} \), is taken from the WHO burden of disease study (Murray and Lopez, 1996) for spina bifida and is 0.59.

**Effect 2: megaloblastic anaemia (folate deficiency)**

We assumed that no premature deaths occur because of megaloblastic anaemia. Hence, YLL_{MA} is 0. Furthermore, we assume that someone who suffers from megaloblastic anaemia will see a doctor within a year and will be cured consequently. Thus, YLD_{MA} is 1. A disability weight for megaloblastic anaemia was not found but it is considered to be equal to a moderate iron deficiency anaemia. So, \( w_{MA} \) is 0.01 (Murray and Lopez, 1996).

**Effect 3: masking of vitamin B_{12}-deficiency**

We assume that no premature deaths occur because of irreversible neural damage caused by masked vitamin B_{12}-deficiency, because as soon as the neural damage reveals itself the deficiency will become known. Hence, YLL_{B12} is 0. We also assumed that the neural damages will occur immediately. The elderly are chosen as the population at risk. According to Statistics Netherlands (Statistics Netherlands, 2007) the life expectancy of people who are 65 years old is 15.6. Thus, YLD_{B12} is estimated at 15.6. The disability weight, \( w_{B12} \), for injured nerve is 0.064 (Murray and Lopez, 1996).

**Effect 4, 5 and 6: colorectal cancer**

We assumed rather arbitrarily that three years after the colorectal cancer diagnosis a patient is either deceased or cured. This assumption is driven by the availability of survival data (Visser and van Leeuwen, 2005). This means that the years lived with the disease, YLD_{CRC} is set at 3 years for those who suffer from the disease. Furthermore, the years of live lost, YLL_{CRC} are equal to the live expectancy of those who die from the disease. High folate intake may enhance the tumor growth. Therefore, the duration of the disease for those that die from the disease shortens. We have approximated this effect by making the survival rate depend on the folate-equivalent intake. Also, we assumed that treatment will be less successful for people with faster tumour growth. There are no data to quantify the increased mortality among colorectal cancer patients depending on folate-equivalent intake. Therefore we assumed that the survival rate is equal to the present survival rate and linearly decreases to 0 when the folate-equivalent intake exceeds a certain high level. The following formula (A.9) describes the relationship between 3-year colorectal cancer survival and folate-equivalent intake:

\[
\text{surv}_{CRC}(F) = \begin{cases} 
  s_{CRC} & \text{if } F \leq \text{iml} \\
  s_{CRC} - \frac{s_{CRC}}{\text{iml}-\text{ml}}(F - \text{iml}) & \text{if } \text{iml} < F < \text{ml} \\
  0 & \text{if } F \geq \text{ml} 
\end{cases}
\]

(A.9)

where \( s_{CRC} \) is the present 3-year survival rate, 0.645 (Visser and van Leeuwen, 2005), \text{iml} the increased mortality level, the intake level at which survival decreases (1000 \( \mu \)g per day) and \text{ml} is the maximum mortality level, the intake level at which there is no survival (5000 \( \mu \)g per day).

The values for \text{iml} and \text{ml} are arbitrarily chosen due to lack of better information. A sensitivity analysis showed how influential these values are for the overall effect. Now that 3-year survival is expressed as a function of folate-equivalent intake, the following equation describes the effect of folate-equivalent intake on colorectal cancer expressed in DALYS:

\[
\text{DALY}_{CRC} = \sum_{a,s} \text{pop}(a,s) \times \sum_{i=1}^{N-1} \int_{F_i}^{F_{i+1}} p_{CRC}(F,a,s) \times (w_{CRC} YLD_{CRC} + (1 - \text{surv}_{CRC}(F))) \times \left( \frac{R(a,s,F_{i+1}) - R(a,s,F_i)}{F_{i+1} - F_i} \right) \, dF
\]

where \text{pop}(a,s) is the population size with age \( a \) and sex \( s \) (Statistics Netherlands, 2007), \( w_{CRC} \) the disability weight of colorectal cancer, 0.32 (Stouthard et al., 1997), YLD_{CRC} the years lived with the disease i.e. the duration of colorectal cancer, 3 years and \( LE(a,s) \) the life expectancy for age \( a \) and sex \( s \) (Statistics Netherlands, 2007). A more accurate computation of the DALY is possible when one uses multiple survival rates, for 1 year, for 2
years, etc. As this paper describes an example of an application of a risk–benefit model, we did not value this as absolutely necessary.

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