Towards an optimal use of folic acid

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory report *Towards an optimal use of folic acid*
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Dear Minister,

On 28 January 2006 your predecessor asked the Health Council of the Netherlands to submit an advisory report on micronutrients. I am pleased to present our advisory report on ensuring optimal folate intake. A committee of experts has looked at the most recent research and assessed the implications for policy, partly in the light of new European regulations. Three standing committees within the Health Council: the Standing Committee on Medical Ethics and Health Law, on Medicine and on Nutrition, have also reviewed the findings. Advisory reports on three other micronutrients (vitamin D, iodine and vitamin A) will be produced in the course of this year.

The committee concluded that the use of folic acid supplements by women with a desire to conceive a child in the Netherlands has increased but is still insufficient to reduce the risk of bearing a child with spina bifida to the largest possible extent. This is particularly true of women with a low level of education or from a non-Western background. The most important advice is therefore to introduce preconception care (a matter that was raised in another recent advisory report by the Health Council) and to include folic acid supplementation. It would also be advisable to focus education for women whose folic acid intake appears to be insufficient, bearing in mind that the composition of this group will change all the time.

However, these measures will probably not be sufficient to reach an adequate folate status in all women who become pregnant. This is because not all pregnancies are planned, although the percentage of those that are, is fairly high in the Netherlands. The committee therefore suggests to consider the additional measure of adding folic acid to staple foods such as bread and bread substitutes.

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Manufacturers are currently permitted to add folic acid to specific foods on a voluntary basis. However, there is no guarantee that women of childbearing age will consume these particular products. There is another objection to this policy: the currently permitted level of fortification is such that children could consume too much folic acid.

Fortifying staple foodstuffs with folic acid would establish a baseline for folic acid intake by women of childbearing age. This advisory report indicates the level of fortification that the committee finds acceptable. There is one condition for the introduction of this measure: ceasing the fortification of other foodstuffs with folic acid. This would prevent children consuming too much folic acid.

However, the problem is that under current European regulations it is impossible to meet this condition. The committee recommends from the point of view of public health that regulations in this area therefore need to be reviewed.

This new advisory report on folic acid reflects the latest scientific findings and the current situation abroad. It also contains the factors that need to be taken into account when policies are considered. I fully support the committee's conclusions and recommendations.

Your sincerely,
(signed)
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Towards an optimal use of folic acid

to:

the Minister of Health, Welfare and Sport

No. 2008/02E, The Hague, February 21, 2008

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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INAHTA

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A brief outline of the advisory report

The Ministry of Health, Welfare and Sport has asked the Health Council to advise it on optimal folate intake and on the best policies to achieve this, particularly in women planning pregnancy.

Women planning pregnancy should take 400 micrograms of folic acid a day, starting before conception.

The advice for women planning pregnancy is to start taking 400 micrograms of folic acid a day at least four weeks prior to conception and to continue taking it until eight weeks after conception in order to reduce the risk of having a child with a neural tube defect. This is the advice that has been given since 1996, and the current state of scientific knowledge confirms that this dose is effective.

Information and preconception care can further increase the number of women following this advice.

Although an increasing number of women consume folic acid before conception or in the first few weeks of pregnancy, improvement is still possible. This is particularly true of women with a lower level of education and women with a non-Dutch background. The Health Council therefore recommends that information campaigns aimed at these vulnerable target groups, whose individual members are changing all the time, should be structurally expanded and that preconception care should be introduced.

Fortification of staple foodstuffs with folic acid should also be considered

These policies could be backed up by the fortification of staple foodstuffs, such as bread and bread substitutes, with folic acid. This would mean that practically all women of childbearing age would have a basic intake of about 100 micrograms of folic acid a day, although these products would still not entirely meet their requirements. At present folic acid is only added to specific foodstuffs. There is no guarantee that they would be consumed by women of childbearing age, and it is possible that children eating these products might ingest too much folic acid.

The idea of fortifying staple foodstuffs with folic acid is subject to one condition: specific foodstuffs must no longer be fortified with folic acid in order to prevent children running the risk of ingesting too much of it.

Under current European regulations it is impossible to meet this condition. From the point of view of public health, the committee therefore recommends that the regulations in this area should be reviewed.

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Executive summary

Background to this advice

Regulations and research undergo rapid development

European legislation and research in the field of vitamins, minerals and trace elements (known as micronutrients) undergo rapid development. For this reason, the Minister of Health, Welfare and Sport has asked the Health Council of the Netherlands to reconsider its policy on micronutrients. The aim of the new policy is to ensure that as many people as possible consume adequate quantities of micronutrients while, at the same time, minimising the risk that people exceed the safe upper level of intake.

This advisory report on folic acid is the first in a series of four advisory reports on micronutrients. The other reports will deal with vitamin D, iodine and vitamin A.

Folate is essential for the human body

Folate is a B-vitamin that occurs naturally in food. The synthetic form of folate added to fortified foods and supplements is folic acid. Folate is important for growth and health. Folate deficiency can cause anaemia. Taking additional folic acid around the time of conception lowers the risk of having a child with a neural tube defect.

How can folate intake be improved?

The use of a periconceptual folic acid supplement can be improved

Since 1996 there has been a rise in the number of women who, with the desire to become pregnant, take an additional 400 micrograms per day of folic acid from at least four weeks before conception until eight weeks after. Over the past 10 years there has also been a reduction in the number of foetuses with neural tube defects. Nevertheless, the percentage of women who take the recommended additional folic acid around the time of conception remains too low to achieve the full potential health benefits in this area.

At least three-quarters of women with a non-Dutch background or those with a lower level of education and about half of higher educated women with a Dutch background do not take any periconceptual folic acid supplement, or start too late. Therefore, there is clearly room for further improvement in periconceptual folic acid intake.

Folate intake in the Dutch population does not appear to be optimal

Research into food consumption suggests that the folate intake in about half of all Dutch adults is too low. However, the limited biochemical research available into folate status reveals less dramatic figures: the folate status may be suboptimal in 8 to 25 percent of adults and elderly. The status of children up to 19 years of age has only been examined in one study and seems to be good.

What is the best way to improve folate intake?

The suboptimal folate intake is no reason to change the current policy

The committee believes that supplementation or fortification should yield a clinical benefit. As it remains unclear whether the suboptimal folate status amongst Dutch adults actually causes health problems, there is no reason to improve folate intake in the general population through food fortification or through supplementation.

Improve periconceptual folic acid intake through education and preconception care

To reach the ever-changing target group, the committee recommends a structural increase in education on folic acid use from at least four weeks before conception until eight weeks after. The implementation of preconception care is also advised. These actions should be accompanied by an additional long-term investment in education and care for women with a non-Dutch background or those with a low level of education.

In addition, consider fortifying only staple foods with folic acid

It will be a long time before education and preconception care increase the periconceptual use of folic acid supplements, particularly amongst women of non-Dutch origin or those with a low level of education. In addition, these measures will not reach women with unplanned pregnancies (9 to 15 percent of all pregnancies). For this reason, the government could consider fortifying staple foods, such as bread and bread substitutes, with folic acid so that women are ensured a basic level of folic acid intake around the time of conception. Fortification does not, however, provide the full requirement. That is why the use of folic acid supplements around the time of conception remains warranted.

Currently, fortifying specific food products with folic acid is up to the food manufacturers. This is organized through exemption. The committee is, however, of the opinion that the current policy of exemption, which permits addition of 100 micrograms folic acid per 100 kilocalories to food products, should be limited in such a way that children are no longer at risk of ingesting too much folic acid. In addition, there is no guarantee that all women of childbearing age will use these specific products.

Fortification of staple foods can increase the folic acid intake of nearly all women of childbearing age. For example, the folic acid intake of women can be increased by on average 100 micrograms folic acid per day through fortification of bread and bread substitutes with 150 micrograms folic acid per 100 grams flour after preparation. The committee feels that this level of fortification is acceptable, providing fortification of specific food products is discontinued to avoid children ingesting too much folic acid.

Investigate European regulation of this matter more closely

The conditions called for by the committee when changing the current fortification policy, i.e. limiting or banning voluntary fortification, appear to be at odds with the agreement made within the European Union to avoid any obstruction of free trade. This agreement echoes the 2004 decree of the European Court which states that fortified products may only be refused if they form a specific danger to public health. From a public health point of view, the committee recommends a closer investigation of the regulations on this matter.

If nothing changes yet, create greater control over fortification and clearer labeling

Alternatively, the government could increase its control over voluntary fortification of food products through discussions with manufacturers. It is also possible to make the labeling clearer on foods which have been voluntarily fortified with folic acid so that these can be recommended to women of childbearing age through education and preconception care.

Avoid excessive folic acid intake through fortified foods at any rate

The committee emphasises that, when fortifying foods, it is essential to ensure that folic acid intake remains below the safe upper level of intake. Children are at greatest risk of exceeding the safe upper level when foods are fortified. There is very little research into the potential health risks of folic acid in children. It has also been suggested that in adults very high doses of folic acid may promote the development of cancer.

Patients with benign colorectal tumours should be warned against dietary supplements with folic acid

The committee advises doctors to warn patients with benign colorectal tumours against using dietary supplements containing folic acid. It cannot be ruled out that a high folic acid intake may accelerate the transformation of a benign tumour into a malignant one.

Monitor the potential health effects of the chosen approach

The committee recommends monitoring the effect of the chosen policy on the intake of folate and folic acid, as well as the risk of neural tube defects, the masking of vitamin B_{12} deficiency, and the incidence of colon cancer, and stroke. Where possible, this monitoring should be carried out using existing registration systems. The committee finds further research essential to determine if, and how folate and folic acid relate to the risk of colon cancer.

Evaluate the dietary reference values for folate

The committee suggests that the dietary reference values for folate should be evaluated, since biochemical data indicate that folate intake in the Dutch population may not be as bad as suggested by food consumption data.

Chapter 1

Introduction

1.1 Background to the advisory report

Folate, also known as vitamin B_{11}, occurs naturally in food. This micronutrient is important to growth and health. That is, the body needs folate for metabolism and for the division and growth of cells. Folate deficiency causes anaemia. Taking additional folic acid* around the time of conception reduces the risk of a child with spina bifida.

The Ministry of Health, Welfare and Sport (VWS) wants to develop a new policy in the context of European regulations, ensuring that the largest possible proportion of the population ingests sufficient folate and other micronutrients. However, it wants to simultaneously minimise the risk of people consuming amounts in excess of a specific safe upper level of intake.

With that aim in mind, the Minister of Health, Welfare and Sport has asked the Health Council of the Netherlands to reconsider its policy on the fortification of foodstuffs with micronutrients such as vitamins, minerals and trace elements (annex A). This advisory report is the first in a series of four advisory reports on micronutrients. The other reports will deal with vitamin D, iodine and vitamin A.

This report was drawn up by a Committee on Micronutrients specially established for this purpose, involving experts whose knowledge covers the entire

* Folic acid is the synthetic form of folate, also known as pteroylmonoglutamic acid (PGA), that can be added to dietary supplements and foodstuffs.

field of micronutrients and fortification of foodstuffs. The members of the Committee are listed in annex B. This Committee will also consider the three other micronutrients on the programme.

1.2 The original policy in the area of folic acid

Prior to 1994, there were no statutory regulations in the Netherlands on the addition of folic acid to dietary supplements. The addition of this substance to foodstuffs was prohibited until 1996.[1]

The Dutch government was forced to review its policy in the early 1990s, mainly as a result of pressure due to free trade. Other European countries had long since approved the addition of vitamins to foodstuffs. Another reason for changing the policy was that it was apparent that not all groups of the population had a habitual diet* that met their requirements for various micronutrients. It was, however, also important to prevent an excessive intake of certain micronutrients. This is particularly true for micronutrients that have a 'narrow margin', with which the dietary reference value or the recommended amount and the safe upper level of intake are close to one another.

These developments led to the adoption of the Vitamin Preparations Exemption Regulation Commodities Decree in 1994[2] and the Micronutrient Supplementation Commodities Decree in 1996.[3] The Vitamin Preparations Exemption Regulation Commodities Decree allows manufacturers of supplements to incorporate folic acid at any concentration provided that the level of the substance in the supplement is not harmful.[2] The Micronutrient Supplementation Commodities Decree continues to prohibit the fortification of foodstuffs with folic acid, but permits restoration or substitution.[3,4]

1.3 Developments that warrant revision of the policy

At present (in 2007) new developments have made it necessary to revise the policy on folic acid. Since 1996 the fortification of foodstuffs in the Netherlands has only been permitted where a nutritional need existed. Since 2004 the decision of the European Court of Justice has meant that the absence of such a need is no longer an argument that can be used to reject an application for exemption.[5] Applications for exemption from the prohibition on the addition of micronutrients can only be rejected if it can be shown that placing the product in question on the market would endanger public health.

* Unless otherwise specified, the word 'diet' is used to cover intake from foodstuffs and supplements.

The Netherlands has therefore had to abandon its absolute ban on folic acid fortification. The current exemption, which was introduced at the end of 2006 and will remain in place until such time as new European legislation takes effect, allows the addition of up to 100 micrograms of folic acid per 100 kcal of foodstuffs. Individual manufacturers can apply for exemptions if they wish to add higher quantities of folic acid.[6]

The policy on supplements and voluntary fortification of foodstuffs is due to be harmonised throughout the European Union between 2008 and 2012. The 2002 European Union directive on supplements and the European Union regulation on voluntary fortification of foodstuffs will be fleshed out around that time*.[10,11] However, in both cases the texts will take the form of framework legislation laying down the principles, but not the details. Both the regulation and the directive specify that folate may only be added to supplements and foodstuffs in the form of folic acid.

It was not yet known at the time of drafting this advisory report what minimum and maximum amounts of folic acid were to be permitted as additions to supplements and foodstuffs. The recommended daily amount to be indicated on the label had also not yet been determined. A regulation is to be adopted on this subject. It will also specify the minimum level at which the label may state that the foodstuff contains, or is rich in, folate**. The regulation deals with voluntary fortification of foodstuffs[11], which by definition does not resolve the problem of possible deficiencies. However, the regulation does allow European Union member states to maintain or introduce mandatory fortification of foodstuffs, if this is necessary on public health grounds.

Dutch policy needs to be revised, not only because of changes to European regulations but also in the light of new scientific insights. Some sections of the population would gain considerable health benefits from consuming folate in the form of folic acid at levels (well) above the current dietary reference values. However, taking the substance in these amounts could cause unwanted side effects. The risks must be weighed up against the benefits both for groups that would benefit from a higher folate intake as well as for other groups, including a comparison of the possible positive and negative effects on health.

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* The dietary supplements directive has already been incorporated into the Dietary Supplements Commodities Decree and the Dietary Supplements Regulation Commodity Decree.[7-9]

** The new European Union health claims regulation states that a label may indicate that a foodstuff is a source of a micronutrient if it contains 15% of the recommended amount of the micronutrient per 100 g, 100 ml or portion size, and that it is rich in the micronutrient if the corresponding figure is 30%. Under Dutch legislation pursuant to this regulation, manufacturers may continue to claim that a foodstuff is rich in a micronutrient if it contains more than 20% of the recommended daily amount during the transitional period laid down in the European regulation.

1.4 Several measures with the same aim

The Ministry of Health, Welfare and Sport intends to develop a policy ensuring that the highest possible proportion of the population consumes sufficient micronutrients within safe margins. It can choose from (a combination of) four policy measures[12]:

- restoration: adding micronutrients that are lost during the production process, storage and/or sale of foodstuffs. The amount added to the foodstuff restores the level of the micronutrient to the original concentration in the edible part of the foodstuff or the raw material from which it was made.
- substitution: replacing a foodstuff with a different foodstuff that is as close as possible to it in terms of appearance, consistency, taste, colour and odour, or that serves the same purpose for the consumer.
- fortification: adding one or more micronutrients to a foodstuff, resulting in a concentration higher than that which naturally occurs in the foodstuff or the raw material from which it was made in order to prevent or correct a proven deficit in one or more micronutrients in (parts of) the population. Fortification can, in theory, be voluntary or mandatory. In the case of voluntary fortification, the manufacturer decides whether or not to fortify a product, and so specific products are fortified. The government can encourage fortification in practice by consultation with manufacturers. In the case of mandatory fortification, staple foodstuffs are fortified. Mandatory fortification is not legally feasible in the Netherlands. However, the government can make arrangements for mandatory fortification via an agreement with manufacturers. The Commodities Decree specifies how much of a particular micronutrient can be added to which products.[13]
- supplementation: using a supplement containing micronutrients as an addition to diet.

1.5 Issues addressed

In its request for advice (see annex A), the Ministry first asked the Health Council to draw up an inventory of (1) essential micronutrients that were not provided in sufficiently high concentrations by a habitual diet, (2) what the optimal level of these nutrients was, and (3) the best way in which this optimal level of supply could be achieved: restoration, substitution, fortification or supplementation, taking account of possible positive and negative health effects that may be associated with each option.

Consultation between the Health Council and the Ministry of Health, Welfare and Sport led to a decision to limit the request for advice to micronutrients that may not be supplied in sufficient quantities to the entire population from a habitual diet if they are not added to the habitual diet. This is the case for vitamins A and D, iodine and folate. An active substitution policy is already in place for vitamins A and D. Limited fortification is permitted for iodine.[12,14]

Since the early 1990s there have been indications that more than half of the adult population may not be getting enough folate in their diet.[15] The policy on folic acid has not, in recent years focused, specifically on improving the folate status of the general population, though they have been encouraged to eat more fruit and vegetables. In addition women planning to have a baby have been encouraged to take folic acid supplements around the time of conception. Little clear evidence exists to indicate that the general population might be deficient in micronutrients other than those listed above.[16,17] However, this is not the case for specific population groups. The Committee will therefore look in the last of its four advisory reports at what other micronutrients should be given priority.

In this first report, the Committee has addressed the questions raised by the Minister as follows:

1 Are there any new scientific developments in the field of folate that require a revision of Dutch policy?
2 What is the intake and nutritional status of the Dutch population or sections of the population in terms of folate?
3 If supplies seem to be excessively low, how much additional folic acid can the various population groups safely consume (above that provided by a habitual diet if no folic acid is added) in order to (continue to) ensure adequate intake?
4 What is the best way of achieving this?

1.6 Methodology

The background material relevant to this advisory report has been systematically reviewed and classified according to levels of evidence (see annex C). The Committee has not restricted itself to the current state of scientific knowledge. It has looked at earlier experience with fortification and supplementation in the Netherlands and abroad, and has examined European developments. In answering the questions, the Committee has described folate supply, discussed the effects of various policy measures, and used a number of assessments (including a risk-benefit analysis) in formulating its recommendations.

1.7 Structure of the advisory report

Chapter 2 discusses the physiological role of folate in the body and the consequences of excessively low or high intake. Chapter 3 describes the current dietary reference values for folate. In Chapter 4, the Committee considers whether there are any new scientific insights regarding folate that might affect the recommendations. This chapter therefore answers the first question to be addressed in the advisory report. Chapter 5 describes current folate supply, and in doing so deals with the second question. Chapter 6 looks at policy measures adopted in other countries and their effects. Chapter 7 discusses the current Dutch policy measures, leading on to answers to the third and fourth questions. The Committee presents its conclusions and recommendations in Chapter 8.

Chapter 2

The role of folate in the body

This chapter describes the various types of folate present in food and the differences in bioavailability that are thought to exist between them. It also looks more closely at the substance's role in the body and the effects of excessively high or low intake.

2.1 Types of folate

Folate is the collective name of a group of substances with a chemical structure related to pteroylmonoglutaminic acid (PGA or folic acid). Folic acid is a stable, chemically synthesized compound that is used in vitamin preparations and is added to foodstuffs. The various types of folate are referred to as follows in this advisory report:

- Dietary folate, folate occurring naturally in food;
- Folic acid, the synthetic form of folate, that can be added to dietary supplements and foodstuffs;
- Folate, the collective name for dietary folate and folic acid.[18]

Another synthetic form of folate has recently been launched on the market in addition to PMG: L-5-methyltetrahydrofolate (5-MTHF). It is now being added to a small number of supplements. Research shows that this substance is at least as effective as folic acid in improving folate status.[19,20] As very little investigation has been done into any other positive or negative effects that 5-MTHF may

have, it is discussed only briefly in this report, in sections 2.2 (bioavailability) and 3.3 (safe upper limit).

2.2 Bioavailability

Folate occurs naturally in small amounts in foodstuffs, usually bound to a chain of glutaminic acids. The glutaminic acids are largely broken down in the small intestine, and unconjugated folate is then absorbed via active transport, and to a lesser extent via passive diffusion. The folate is converted into 5-methyltetrahydrofolate in the cells of the intestinal wall.

However, this conversion does not appear to be complete in every individual and under all circumstances. Most dietary authorities therefore conservatively estimate that the absorption (bioavailability) of dietary folate is about 50% lower than the bioavailability of folic acid,[21,22] as folic acid can be absorbed directly by the body. It is assumed that the bioavailability of folic acid from fortified foodstuffs is about 15% less than bioavailability from supplements.

This assumed difference in bioavailability is taken into account by expressing quantities of folate in the form of dietary folate equivalents. The conversion is as follows:

- 1 microgram of dietary folate = 1 microgram of dietary folate equivalents;*
- 1 microgram of folic acid from fortified food = 1.7 micrograms of dietary folate equivalents;
- 1 microgram of folic acid from supplements = 2 micrograms of dietary folate equivalents.[21,22]

The bioavailability of 5-MTHF is assumed to be comparable to that of dietary folate.

Quantities of folate are expressed as dietary folate equivalents in this report. The only exceptions are the safe upper level of intake and the supplementation advice to women around the time of conception. Both these figures relate to folic acid and are therefore, as in other advisory reports,[21-24] expressed as micrograms or milligrams of folic acid**.

Since bioavailability was determined we have gained a greater understanding of differences between folic acid and dietary folate when it comes to absorption

* The same dietary folate equivalents as drawn up by the American Institute of Medicine.[22]

** As these standards are based on folic acid from supplements, the figures must be doubled to give dietary folate equivalents: 1 milligram of folic acid from a supplement is equal to 2 milligrams dietary folate equivalents.

in the body. It has been suggested that folic acid is metabolised in the liver more than in the intestinal wall. However, the liver has only a limited ability to convert folic acid into 5-methyltetrahydrofolate. That explains why unmetabolised folic acid is found in the blood of someone taking 260 micrograms of folic acid or more a day. These new insights might in future lead to a revision of bioavailability assumptions.[25]

2.3 Consequences of too much and too little

Folate is a co-enzyme involved in the transfer of C1 fragments, a process that is vital for the synthesis of DNA and RNA, the metabolism of amino acids and methylation reactions. Because of this essential role, relatively large quantities of folate are needed in situations where rapid cell division is taking place. Examples include the development of a foetus, during growth, and also in rapidly-dividing tissues such as blood-forming organs and the epithelial tissue of the intestinal mucosa. The consequences of insufficient folate are seen first in tissues with rapid cell division. The first effect of an excessively low intake is an inadequate folate status, which can develop into deficiency.

Women with an inadequate folate status around the time of conception have a greater chance of having a child with a neural tube defect.[22,26]

Folate deficiency leads to anaemia. Lower folate levels in the blood cause morphological (megaloblastic) changes in bone marrow. The decline in folate levels in red blood cells then causes the red blood cells to become larger, leading to a condition known as megaloblastic anaemia. Changes also take place in the nucleus of white blood cells, with multilobar cells being formed (neutrophilic hypersegmentation). As normal red blood cells remain in the bloodstream for about four months, it can take months for people with folate deficiency to develop megaloblastic anaemia. It causes fatigue, weakness and shortness of breath.[22,26]

The most well-known adverse effect of excessively high levels of folic acid is that it can conceal vitamin B_{12} deficiency, which can lead to neurological damage if left untreated. These effects are only observed in patients with severe vitamin B_{12} deficiency as a result of an auto-immune disease (pernicious anaemia), a condition in which sufferers absorb hardly any vitamin B_{12}.[23] The vitamin B_{12} deficiency in these patients is usually much more severe than that seen in other elderly people and those following a vegan or macrobiotic diet.[21] No research has yet been undertaken to ascertain whether folic acid has adverse effects on children. The only thing that is certain is that pregnant women can take high doses of

folic acid (up to 5 mg a day) without harming the unborn child. There is no known risk to adults or children from an overdose of dietary folate.[22,23]

One further comment: along with folate, vitamins B_{12}, B_2 and B_6 also play a role in homocysteine metabolism. It is not known whether a relatively small increase in folic acid intake (100 micrograms a day) is associated with a greater requirement for other B vitamins, but the committee thinks that this is unlikely.

Chapter 3

Current dietary reference values

This chapter describes the biochemical factors (such as blood values) and health impacts that have been used as a basis for setting the dietary reference values for folate and the safe upper limit for folic acid.

3.1 Dietary reference values and their uses

The term ‘dietary reference values’ is a collective term for various reference values for energy and nutrients. The figures are intended for healthy individuals and aimed mainly at disease prevention. They are used to:

- programme food supply for healthy groups;
- create dietary guidelines for healthy individuals;
- assess intake data of healthy groups;
- assess the intake of individuals who have been shown by biochemical parameters to have a poor nutritional status;
- draft the ‘*Guidelines for a Healthy Diet 2006’*.

In the past, dietary reference values were always set by the Committee on Dietary Reference Intakes of the Food and Nutrition Council/Health Council. The recommended dietary allowance of a nutrient was derived from figures showing the average requirement of the substance. Where no such figures were available, the committee set an adequate intake. Recommended intake and adequate intake mean the same thing in practice: they both indicate the level of

intake which is desirable on health grounds. Table 3.1 describes the type of dietary reference value that is suitable for particular uses.[21]

Table 3.1 Summary of types of dietary reference values and the uses for which they are suitable.[21]

Use	Type of dietary reference value		
	Average requirement and variation in requirement	Recommended dietary allowance or adequate intake	Safe upper level of intake
Diet programming for healthy groups		+	+
Creating dietary guidelines for healthy individuals		+[a]	+
Assessing intake data of healthy groups	+		+
Assessing intake of people who have been shown to have a poor nutritional status	+[a]	+[a]	+
Drafting the *Guidelines for a Healthy Diet*		+	+

a This process can take account of diet factors, personal characteristics and lifestyle factors that affect the requirement.

3.2 Dietary reference values for folate

The Health Council's current dietary reference values for folate distinguish between children in various age groups, adults, women who are pregnant or breastfeeding and women who wish to conceive (figure 3.1 and table 3.2). Status parameters were used to set the average requirement and recommended dietary allowance of folate for adults. Data for all other groups in the population was insufficient, and the Health Council therefore referred to adequate intake.

The average requirement is sufficient to keep serum and red blood cell folate levels within the normal (physiological) range for a significant part of the population. It also appears sufficient to prevent excessively high plasma homocysteine levels ($\geq$ 15 micromoles per litre plasma) and to make up for losses via excretion of folate degradation products.

The Committee on Dietary Reference Intakes used a relatively high variation coefficient of 25 per cent when working out the recommended dietary allowance, as genetic factors also play a part in the variation of folate requirements. The committee was of the opinion that folate requirements were also dependent on MTHFR 677 C/T polymorphism*. Individuals with the 677-T/T genotype with a comparatively low folate intake have higher plasma homocysteine levels and lower serum and red blood cell folate levels than individuals with the 677-C/C or 677-C/T genotype. This means that there are actually two types of requirement distribution in the population. It was decided that when determining average requirements and adequate intakes it would be better for practical reasons to set

* 5,10-methylenetetrahydrofolate reductase (MTHFR) 677-C/T polymorphism.

one reference value with a larger variation coefficient than to set two reference values or requirement distributions.

Low blood folate levels can cause anaemia and morphological changes to the bone marrow and white blood cells. Women of childbearing age who have an inadequate folate status are also at greater risk of bearing a child with a neural tube defect. It is estimated that women who have a baby need an additional 100 micrograms of dietary folate equivalents a day throughout pregnancy and while breastfeeding. In addition to this elevated requirement during pregnancy, women who wish to conceive are also advised to take a supplement containing 400 micrograms of folic acid per day from at least four weeks prior to conception until eight weeks after conception. According to the advisory report on *Continued advice concerning folic acid use in relation to neural tube defects* drawn up by the Health Council/Food and Nutrition Council, this additional amount of folic acid can reduce the chance of having a child with a neural tube defect by at least 50 per cent. [26] The estimates of this protective effect range from 36 to 72 per cent.[27-29] The underlying mechanism is still unclear. One hypothesis is that folic acid prevents neural tube defects by stimulating the methylation reaction.[30] It is known that neural tube closure takes place in the first month after fertilisation. Women must start taking extra folic acid at least four weeks prior to conception in order to ensure that their folate levels are adequate when neural tube closure takes place.

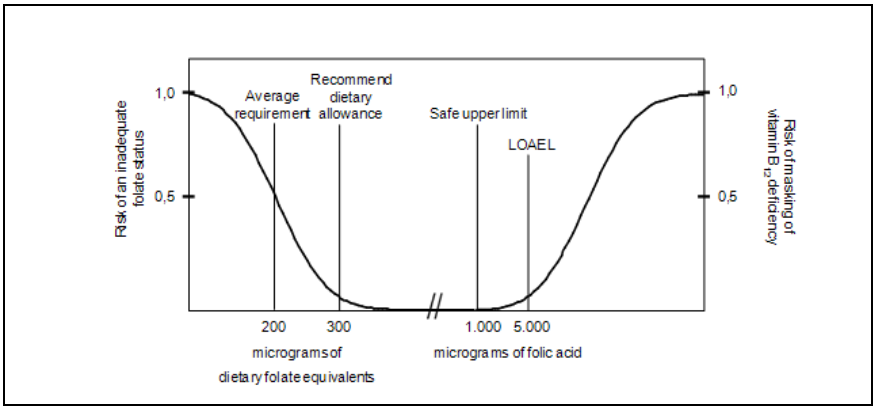

Figure 3.1 The dietary reference values for folate for adult men and women. LOAEL, lowest observed adverse effect level, the lowest level of intake at which effects of overdose are observed. The safe upper limit applies only to folic acid. One microgram of folic acid from supplements is equal to 2 micrograms of dietary folate equivalents, while one microgram of folic acid from fortified food is equal to 1.7 micrograms of dietary folate equivalents. The figure is based on figure 1.3 in the Health Council's advisory report *Dietary reference values: calcium, vitamin D, thiamin, riboflavin, niacin, pantothenic acid, and biotin.*[18]

When dietary reference values for folate were set in 2003, the indications that lower plasma homocysteine levels might protect against cardiovascular disease were not sufficiently consistent to allow definitive conclusions to be drawn.[21]

3.3 The safe upper limit

Various scientific committees have set the safe upper limit for folic acid intake at 1 milligram per adult per day. The safe upper limit for lower age groups varies according to body weight (table 3.2). As children eat more per kilogram of body weight than adults, they are at greater risk of exceeding the safe upper limit.[22-24] There is no known risk of an overdose of dietary folate.

No systematic toxicological studies into folic acid are available. For that reason the safe upper limit is based on the effects of high doses of the substance in patients with pernicious anaemia*. In these patients, a high dose of folic acid masked the haematological symptoms of vitamin B_{12} deficiency. Neurological symptoms could develop because this deficiency was not identified and so remained untreated. It has also been suggested that folic acid might itself trigger or aggravate the neurological symptoms. We do not know whether this is in fact the case, given the variation in severity and prevalence of these symptoms among patients with pernicious anaemia. However, some experiments on animals (including apes) have indicated that neurological symptoms caused by a vitamin B_{12} deficiency can be made worse by folic acid. This effect can be explained as the result of a biochemical interaction between folic acid and vitamin B_{12}, but the evidence is not yet regarded as conclusive. The safe upper limit for folic acid is derived from the lowest dose at which neurological symptoms occur in adults (*lowest observed adverse effect level*). [21-24] The American Institute of Medicine reports over a hundred well-documented cases of neurological symptoms associated with consumption of at least 5 milligrams of folic acid per day, but only ten well-documented cases associated with consumption of between 0.33 and 2.5 milligrams of folic acid per day**.[22] The European Food Safety Authority has concluded that masking of vitamin B_{12} deficiency in individuals taking less than 1 milligram of folic acid per day is very rare.[23] Both the Institute of Medicine and the European Food Safety Authority applied an uncertainty factor of five when setting the safe upper limit, resulting in a safe upper level of intake of 1 milli-

* Anaemia caused by a vitamin B_{12} deficiency.

** Six out of the ten patients with pernicious anaemia who experienced neurological damage were taking between 0.35 and 1 milligrams of folic acid a day for three to 24 months. Two patients were taking a dose of 1.25 milligrams of folic acid a day for 3.5 to 26 months, and two others were taking a dose of 1.5 to 2.55 milligrams of folic acid a day for 10 to 39 months.

gram of folic acid per day.[22,23] This safe upper limit is also used in the Netherlands.[21,24]

The Health Council's advisory report, '*Risks of folic acid fortification*', devotes quite a lot of attention to cognitive function disorders that can affect elderly people with an inadequate vitamin B_{12} status, possibly caused by folic acid supplementation.[24] This was partly in response to what were at the time 'new' insights into the frequent occurrence of an inadequate vitamin B_{12} status in elderly people.[31]

Table 3.2 The dietary reference values[a,b] for folate in micrograms of dietary folate equivalents per day unless otherwise specified and the safe upper limit[c,d] of folic acid intake in micrograms of folic acid.[2]

	Average requirement	Recommended dietary allowance	Adequate intake	Safe upper limit for folic acid
	Micrograms of dietary folate equivalents			Micrograms of folic acid
0 to 5 months			50	85[e]
6 to 11 months			60	130[e]
1 to 3 years			85	200
4 to 8 years			150	350
9 to 13 years			225	600
14 to 18 years			300	900
19 years and older	200	300[f]		1,000
Women around the time of conception			+ 400 micrograms folic acid[c,f]	
Pregnant women			400[f]	1,000
Breastfeeding women			400	1,000

a The average requirement, recommended dietary allowance and adequate intake figures relate to a combination of dietary folate and folic acid.[21]

b The safe upper limits for folic acid relate only to folic acid.[21]

c 1 milligram of folic acid from a supplement is equal to 2 milligrams of dietary folate equivalents and 1 milligram of folic acid from fortified food is equal to 1.7 milligrams of dietary folate equivalents.[21]

d The differences in safe upper limits for children between the Dutch, European and American standards are entirely due to differences in the extrapolation methods used.[21-23] Europe: 4-6 years 300 micrograms of folic acid per day, 7-10 years 400 micrograms of folic acid per day, 11-14 years 600 micrograms of folic acid per day, 15-17 years 800 micrograms of folic acid per day.[23] United States: 1-3 years 300 micrograms of folic acid per day, 4-8 years 400 micrograms of folic acid per day, 9-13 years 600 micrograms of folic acid per day, 14-18 years 800 micrograms of folic acid per day, pregnant girls aged 14 to 18 800 micrograms of folic acid per day.[22] The upper limits set by the UK Expert Group on Vitamins and Minerals are comparable to those set by the European Food Safety Authority.[23,32]

e The figure set in the Dutch dietary reference values[21] has been derived. The Institute of Medicine[22] and the European Union Scientific Committee on Food[23] have concluded that it is not possible to determine safe upper limits for children under a year old.

f Women wishing to conceive are advised to take a folic acid supplement containing 400 micrograms of folic acid from at least 4 weeks prior to conception until 8 weeks after conception in order to lower the risk of having a child with a neural tube defect.[26]

The Institute of Medicine classifies people with a vitamin B_{12} deficiency among the general population because many of them are apparently healthy. Both the Institute of Medicine and the European Union Scientific Committee on Food do however regard this group of people as at risk of excessively high folic acid intake. The Health Council's advisory report *Risks of folic acid fortification* has therefore taken a cautious approach to the matter. It states that until research results show that individuals with an inadequate vitamin B_{12} status would not suffer damage to cognitive function as a result of folic acid, this group must not be exposed to additional folic acid.[24]

The UK Expert Group on Vitamins and Minerals is of the opinion that there is insufficient data to set a safe upper limit. It has however set a guidance level for adults of 1 milligram of folic acid per person per day on the basis of the masking effect of folic acid described above.[32]

The European Union Scientific Committee on Food has set the safe upper limit for 5-MTHF, the other form of folic acid, at the same level as folic acid.[33]

Chapter 4

New scientific developments

In this chapter the committee considers what new scientific insights might need to be taken into account when drawing up its final recommendations. It looks in turn at the effects of folate on cardiovascular disease, colon cancer, impairment of cognitive function and other conditions.

4.1 Association with cardiovascular disease

The dietary reference values for folate were drawn up in 2003,[21] since when new scientific data has become available.

The impact of folate on the risk of cardiovascular disease was not taken into consideration when setting the figure in 2003 as there was insufficient evidence. As is also pointed out in the Health Council's advisory report *Guidelines for a Healthy Diet 2006*, intervention studies carried out since that time on patients with cardiovascular disease have not shown that taking 0.5 to 15 milligrams of folic acid a day reduces the risk of dying from cardiovascular disease*.[16,34-37] This conclusion was confirmed by a meta-analysis looking into the findings of individual trials.[38] A meta-analysis has greater discriminatory power than individual trials, but the total amount of data is insufficient to show a relevant effect.

* The results of the intervention study carried out by the Wageningen Center for Food Sciences are not yet available. They were to have been published in 2005, but the study was extended to 2008 because the incidence of cardiovascular disease within the study population is still too small to allow any conclusions to be drawn as to the effect of folic acid.

However, a future analysis of the outcomes of various large-scale intervention studies which are taking place at the moment should have sufficient discriminatory power to allow firmer conclusions to be drawn. The results of this future analysis should be available in 2008.[39] As these large-scale intervention studies are being conducted on patients with cardiovascular disease, it will remain uncertain whether folic acid supplementation is effective in primary prevention of these conditions.[38,39]

There are some indications that this is the case from epidemiological research and studies into the effects of genetic polymorphisms such as the MTHFR 677 C/T polymorphism.[40] Fortification of cereal products with folic acid was made compulsory in Canada and the United States in 1998. The risk of mortality from stroke decreased rapidly since then. In England and Wales, where fortification was not compulsory over the same period, this risk did not change significantly between 1990 and 2002.[41]

And a meta-analysis of seven intervention studies of healthy individuals (six studies) and patients (one study) found that folic acid supplementation had a protective effect on the risk of stroke (RR=0.82, 95% confidence interval 0.68-1.00). Secondary analyses found the protective effect to be most pronounced in studies where subjects underwent treatment for more than three years and experienced a fall of at least 20 per cent in their homocysteine levels. The effect was also greater in studies conducted in countries where folic acid fortification is not compulsory. However, none of the studies included in the meta-analysis were specially designed to examine solely the effect of folic acid supplementation on the risk of stroke. The meta-analysis was also unable to determine the effect of various doses of folic acid. It also remains unclear whether the effect of folic acid supplementation alone differs from the effect of folic acid plus other B vitamins supplementation.[42]

Another meta-analysis of 14 intervention studies found that blood vessel wall reactivity* improved in patients taking 5 to 10 milligrams of folic acid a day. Doses of 0.4 to 0.8 milligrams of folic acid a day do not seem to be effective.[43] Studies on patients with cardiovascular disease and patients who had had a venous thrombosis found that doses of 2.5 to 5 milligrams of folic acid a day for 2.5 to 5 years had no protective effect against the risk of a (further) venous thrombosis.[44,45]

In conclusion: there are some indications from epidemiological and genetic research that high folate intake is associated with a lower risk of cardiovascular

* Flow-mediated vasodilation.

disease. Intervention studies among patients with cardiovascular disease have so far been unable to confirm these indications as far as the risk of a heart attack is concerned. But there are indications that folic acid supplementation may reduce the risk of a first stroke.

4.2 Association with cancer

The UK Scientific Advisory Committee on Nutrition looked at the evidence of a link between folate and cancer in 2006. Some studies on animals suggest that folic acid may affect the development of cancer in two ways. In healthy tissue, an intake four times higher than the intake of folic acid from normal animal feed may suppress the development of cancer when compared with an excessively low intake. But where neoplasms already exist, a similar intake might accelerate the development of cancer when compared with an excessively low intake.

Exposure to levels two or three times higher than the intake of folic acid from normal animal feed was not investigated. Extremely high quantities of folic acid (20 times the amount contained in normal animal feed) might trigger the onset of cancer in healthy animals.[46,47] It is not known whether these effects also occur in humans. However, a number of epidemiological studies do point to the possibility of this dual effect.

The types of cancer that have been most widely investigated in relation to folic acid are breast cancer and colon cancer. The summary report produced by the UK Scientific Advisory Committee on Nutrition found that no single study had established a link between folic acid intake and the risk of breast cancer. Most of these studies had been carried out in the United States.

One study did show that in women with a family history of breast cancer a low folate intake was associated with a higher risk.[48] Two systematic review articles came to the same conclusion as the UK Scientific Advisory Committee on Nutrition's summary report[49,50], although one of these articles did find some indication that a sufficiently high folate intake might reduce the higher risk of breast cancer that exists among women who consume moderate or large amounts of alcohol.[50]

More recently, a French cohort study and a Swedish cohort study also found a higher risk of breast cancer among women with a low folate intake. When compared with a low intake, intake levels of 300 micrograms to 500 micrograms of dietary folate equivalents offered a protective effect*.[51,52]

* In the Swedish study a low dietary folate intake (median) was defined as 153 micrograms of dietary folate equivalents (including folic acid 160 micrograms dietary folate equivalents) and a high dietary folate intake (median) as 302 micrograms of dietary folate equivalents (including folic acid 456 micrograms of dietary folate equivalents).[51] The corresponding figures in the French study were 296 and 522 micrograms of dietary folate equivalents per day.[52]

For colon cancer, a number of prospective studies suggest that folate intake might have a protective effect on the risk of this condition.[48] The report produced by the World Cancer Research Fund concluded that there were limited indications that food containing folate or folic acid could reduce the risk of colorectal cancer (RR=0.84, 95% confidence interval 0.76-0.93 per 100 micrograms per day).[53] However, some of these studies did not correct for all possible confounding factors such as dietary fibre and alcohol intake.[54] A low folate intake might aggravate the harmful effect of high levels of alcohol consumption on the risk of colorectal cancer. But there are too few studies to confirm this.[55]

No intervention studies have been set up specifically to investigate the possible protective effect of folate intake on the risk of cancer.

Studies into high doses of folic acid in fact find that the risk is higher, which is in line with the dual-effect hypothesis.

In an American study a very high level of folic acid intake from food (> 835 micrograms per day) as a consequence of excessive supplement use was related to an elevated risk of breast cancer compared to intake in line with the recommended dietary allowance.[56] Among women who had taken part for a year in a British study into the effect of folic acid supplementation during pregnancy in 1966 or 1967, those who had taken 5 milligrams of folic acid a day tended to have a higher risk of breast cancer after 25 years than those who had taken the placebo, though the difference was not significant (RR = 2.02, 95% confidence interval 0.88 to 4.72).[57]

Cohort studies into folate and the risk of pancreatic cancer also suggest a dual effect. In individuals not taking supplements, an adequate folate status was associated with a lower risk of pancreatic cancer, while no such link existed for those who did take supplements.[58] A meta-analysis into the risk of colorectal cancer also suggests that the protective effect is more pronounced when folate is consumed as dietary folate than as folic acid.[59]

Observational studies may not have been sufficiently corrected for confounding factors. The effect of supplement use on the risk of cancer may therefore not necessarily be the consequence of excessively high folic acid intake. This is because people who take supplements often take folic acid in combination with other vitamins and minerals. High doses of some of these have been associated with an elevated risk of mortality.[60]

The UK Scientific Advisory Committee on Nutrition concluded in 2006 that the trends in the number of colon cancer cases in the United States and Canada were not evidence of a link between folic acid fortification and the accelerated growth of an existing colon neoplasm, but that they were grounds for concern.[48]

However, a more recent article published in 2007 came to the opposite conclusion.

This article stated that the number of cases of colon cancer had risen in the second half of the 1990s, reversing the previous downward trend. Case numbers started to rise in 1996 in the United States and in 1998 in Canada, peaking in 1998 and 2000 respectively. These periods coincide with the transition from voluntary to mandatory fortification, when folic acid intake was increasing. Since then there have been four to six additional cases of colon cancer per 100,000 people compared to the previous trend.[61]

Another publication drawing on the same data showed the annual percentage change in the number of cases of colon cancer among men to be -2.1 per cent between 1986 and 1996, 1.1 per cent from 1996 to 1998, and -2.6 per cent from 1998 to 2004. The corresponding figures for women were -1.8, 1.8 and -2.2 per cent. No investigation has been carried out to ascertain whether deaths from colon cancer also varied during these specific periods.[62] Mason et al. suggest that the introduction of additional folic acid to the diet in the form of mandatory fortification may be associated with an acceleration in the transformation of benign growths into cancer. However, it cannot be ruled out that this outcome may be due to chance.

Two studies have been conducted into the effect of folic acid on the occurrence of adenomas in patients who had previously had adenomas of the colon or rectum.

A British intervention study found that taking 0.5 milligrams of folic acid a day for three years had no effect on the risk of adenoma (RR=1.07, 95% confidence interval 0.85-1.34) or advanced adenoma with a greater risk of becoming malignant (RR=0.98, 95% confidence interval 0.68-1.40).[63]

An American intervention study in which patients took 1 milligram of folic acid a day or placebo for three years also found no difference in the risk of adenoma after three years (RR=1.04, 95% confidence interval 0.90-1.20) or in the second check-up three to five years later (RR=1.13, 95% confidence interval 0.93-1.37). Folic acid supplementation was associated with a 67 per cent increase in the risk of advanced adenoma with a greater chance of becoming malignant at the second check-up (RR=1.67, 95% confidence interval 1.00-2.80) and more than double the risk of having at least three adenomas (RR=2.32, 95% confidence interval 1.23-4.35).[64] This finding is open to two interpretations: the first is that only long-term use of a folic acid supplement leads to increased risk, and the second is that the risk-elevating effect only occurs after a latency period of about three years.[63]

Some intervention studies with risk of cancer as a secondary endpoint also found that folic acid supplementation has no protective effect. In the *Heart Outcome Prevention Evaluation* (HOPE) 2 study, taking 2.5 milligrams of folic acid a day for five years was associated with a 36 per cent greater risk of colon cancer (RR=1.36, 95% confidence interval 0.89-2.08) among patients with vascular disease or diabetes. The habitual level of dietary folate intake was not reported. We do know that 72 per cent of the participants live in countries where folic acid fortification is mandatory.[36] But in the *Norwegian Vitamin* (NORVIT) study there was no difference in the risk of cancer* among patients who had had a heart attack and were taking either 0.8 milligrams of folic acid a day or placebo for three and a quarter years. Folic acid fortification is not mandatory in Norway. The risk was lower among patients taking vitamin B_6.[35] These findings might therefore point to the dual effect of folic acid referred to above, but do not provide a definite answer.

All the intervention studies described above were carried out with folic acid, not with dietary folate. It is still unclear how far folic acid is reduced and methylated by intestinal cells to form 5-methylenetetrahydrofolate.[25] We do know that unmetabolised folic acid can be detected in the blood at oral doses of 260 micrograms of folic acid and above.[48,65] An American study among post-menopausal women found a negative relationship between the presence of unmetabolised folic acid in plasma and the cytotoxicity of natural killer cells,[66] which play a role in the destruction of tumour cells and are important to a normal immune function.[67,68] However, there is no evidence of a link between the cytotoxicity of natural killer cells and the risk of cancer. There is not enough data to allow the long-term effects of exposure to unmetabolised folic acid in the bloodstream to be ascertained.

One factor that complicates research into effects of folate on cancer is that other B vitamins may also be involved. A case-control study found that the combination of low vitamin B_2 intake and high folate intake was associated with a higher risk of colon and rectal adenomas. High vitamin B_2 intake was associated with a lower risk of adenomas, especially in individuals who also had a high folate intake.[69]

Folate also has a role to play in the treatment of cancer. Tissues in which blood cells are created are very sensitive to folate deficiency. That is why children suffering from leukaemia or lymphomas are often treated with folate antagonists. However, insufficient research has been carried out to ascertain whether folate intake has an influence on the efficacy of the treatment in humans.[23,70]

* The various types of cancer were not investigated separately.

In conclusion: experiments on animals show that a high folic acid intake is associated with a lower risk of cancer developing in healthy tissue and with a higher risk of cancer where neoplasms are already present. Both effects start to occur at exposure levels four times the amount of folic acid in normal animal feed. No investigation has been done into the effect of exposure at two or three times the level in normal feed. Even healthy animals developed neoplasms when their folic acid intake was 20 times the amount contained in normal animal feed or more.

Epidemiological and intervention studies have found indications that both an excessively low folate intake (150-300 micrograms of dietary folate equivalents) and intake levels of 0.8 to 2.5 milligrams of folic acid from supplements may increase the risk of cancer, especially colon cancer, when compared to an intake of 300 to 500 micrograms of dietary folate equivalents. The possibility that high doses of folic acid may accelerate the transformation of benign growths into malignant tumours cannot therefore be ruled out. However, the findings are not yet strong enough to enable any conclusions to be drawn as to the role of folate in the onset, growth or treatment of cancer.

4.3 Association with cognitive function and interaction with vitamin B_{12} status

Observational studies suggest that in elderly people a higher level of plasma homocysteine is associated with poorer cognitive function and the risk of dementia.

However, the results of studies into folate and/or vitamin B_{12} intake and status and cognitive function are not clear. Most randomised placebo-controlled trials have not shown folic acid or vitamin B_{12} to have any effect on cognitive function among elderly people. This might be due to various causes: a too small study population, too short a duration of treatment, or an insufficiently specific test for identifying relatively small changes in cognitive function.[16,48,71-73]

There is one exception: a study conducted among elderly people aged 50 to 70 with elevated plasma homocysteine levels and adequate vitamin B_{12} status, which meant that their folate intake was low*.[74] Unlike other studies in this area, these investigators did use a number of specific cognitive tests. Ingestion of an additional 800 micrograms of folic acid per day for three years had a beneficial effect on memory and information-processing functions. These areas of cognitive function are sensitive to ageing.

* An elevated plasma homocysteine level is defined as a total homocysteine level of 13 to 26 micromols per litre and a normal vitamin B_{12} status is defined as a serum cobalamin level of 200 picomols per litre or more.

In contrast to the aforementioned positive effect of folic acid on the cognitive function of elderly people with an adequate vitamin B_{12} status, it has been suggested that folic acid may have a negative effect on cognitive function among elderly people with an inadequate vitamin B_{12} status. This possible negative effect was the main reason for the Health Council to advise against folic acid fortification in 2000.[24] As a result of the limitations described above, intervention studies in this area have not shed any more light on this issue.[16,48,71,75,76]

Three American epidemiological studies have also looked at the effect of vitamin B_{12} and folic acid on cognitive decline (table 4.1). The American National Health and Nutrition Examination Survey (NHANES) conducted among people aged over 60 between 1999 and 2002 found very high serum folate levels to have a beneficial effect on the cognitive function of elderly people with an adequate vitamin B_{12} status. However, a negative effect was observed among elderly people with an inadequate vitamin B_{12} status. [77] In contrast, the decline in cognitive function over six years among people aged 65 or over taking part in the Chicago Health and Aging Project was found to be slightly greater in people with a high folate intake than among those with a low intake. However, the authors do not provide any information on the possible influence of vitamin B_{12} intake.[78]

A third cohort study, of elderly Mexican-Americans, found no link between the folate content of red blood cells and the risk of dementia or cognitive decline without dementia. However, this is another study that did not look at the effect of vitamin B_{12} status on the relationship between folate status and cognitive function.[79] So we are still no nearer to knowing whether folic acid can aggravate neurological symptoms in people with inadequate vitamin B_{12} status.

Experts are now more aware than was previously the case of the possibility that vitamin B_{12} deficiency may lie behind neurological symptoms. It has been suggested that folic acid fortification might expose individuals with vitamin B_{12} deficiency to a greater risk of developing neurological symptoms, though no research has been carried out so far. As folic acid can mask anaemia caused by a vitamin B_{12} deficiency, these individuals feel well and will not consult their GP until they develop neurological symptoms.[80] Another factor is that their neurological symptoms, such as depression and a tingling sensation, can be very vague. Other authors take the view that patients with vitamin B_{12} deficiency who do not suffer from anaemia will in fact consult a doctor sooner than patients who experience lethargy brought on by anaemia.[81,82]

Table 4.1 Studies into the effect of vitamin B_{12} and folic acid on cognitive function.

Study	N, age	Vitamin B_{12}	Folic acid	Effect on cognitive decline	Study limitations
NHANES[a,77]					
Cross-sectional	N=1,459, 60 years	Inadequate vitamin B_{12} status[b] Adequate vitamin B_{12} status[b]	Serum folate > 59 nmol/l versus ≤ 59 nmol/l	OR=2.6 (1.1-6.1) OR = 0.4 (0.2-0.9)	One cognitive test. The study was carried out after the introduction of mandatory fortification.
Chicago Health and Aging Project[78]					
Cohort, 6-year follow-up	N=3,718, 65 years	Vitamin B_{12} intake had no effect on cognitive decline, even after correcting for folate. A higher vitamin B_{12} intake was related to a fall in cognitive decline only among participants aged 80 or over.	20% of the population with the highest folate intake (median 742 micrograms per day) versus the 20% with the lowest intake (median 186 micrograms per day)[c]	Raw data: - 0.01 (P=0.15) standardised units After correction for confounding factors: - 0.02 (P=0.002) standardised units	Intake determined only once, in 86% of participants prior to the introduction of mandatory fortification; no distinction between the bioavailability of dietary folate and folic acid.
Sacramento Area Latino Study on Aging[79]					
Cohort, 4.5-year follow-up	N=1,779, 60 years	The relationship between plasma vitamin B_{12} and cognitive decline followed a U-shaped curve and was not affected by folate status.	Folate content of red blood cells (average 1,144 ± 363 nmol/l)[c]	HR=0.85 (0.57-1.24) for developing dementia or cognitive decline without dementia	The study was carried out after the introduction of mandatory fortification.

a National Health and Nutrition Examination Survey.

b Inadequate vitamin B_{12} status is defined as a serum cobalamin level of 148 pmol per litre or less or a plasma methylmalonic acid level of 120 nmol per litre or more. Vitamin B_{12} status is regarded as good if the serum cobalamin level is 148 pmol per litre or more and the plasma methylmalonic acid level is between 60 and 120 nmol per litre.

c The effect of vitamin B_{12} on the relationship between folate and cognitive decline was not investigated.

In conclusion: not enough research has been done into whether additional folic acid might influence certain areas of cognitive function that tend to worsen as we get older. The effects might be positive in the case of elderly people with an adequate vitamin B_{12} status or negative in the case of elderly people with an inadequate vitamin B_{12} status.

The committee thinks it unlikely that folic acid fortification would put people with inadequate vitamin B_{12} status at greater risk of neurological symptoms than people with severe vitamin B_{12} deficiency, on whom the safe upper level of intake is based. The committee therefore takes the view that the safe upper level of intake of 1 milligram of folic acid per day also applies to people with inadequate vitamin B_{12} status.

4.4 Association with other conditions

Additional folic acid has been associated not only with a lower risk of giving birth to a child with a neural tube defect but also with a lower risk of other congenital abnormalities and a greater risk of multiple pregnancies. It has also been suggested that folate is involved in depression and folic acid in fractures and hearing loss.

A systematic meta-analysis of 41 studies into the effect of a multi-vitamin supplement containing folic acid on the outcome of pregnancy found that taking additional folic acid around conception was associated with a lower risk of bearing a child with congenital heart or limb abnormalities. Women who took a multi-vitamin supplement containing folic acid were also at lower risk of having a child with a hare lip, either as a single condition or in combination with cleft palate, urine tube defects or hydrocephalus. However, these effects were of a significant extent only in the meta-analysis of case-control studies, not in the meta-analysis of cohort studies and intervention studies.[83] As it would now be unethical to prevent women from taking extra folic acid around the time of conception, these effects cannot be verified in an experimental study among women. Additional evidence for these results will remain restricted to data from epidemiological studies, experiments on animals and in-vitro research.

There is some concern that folic acid supplementation may increase the likelihood of multiple pregnancies. It has been suggested that taking folic acid around the time of conception increases the risk of bearing twins (OR=1.25, 95% confidence interval 0.91-1.73).[84] A high folic acid intake may increase the risk of multiple pregnancy in women undergoing in-vitro fertilisation with several embryos being re-implanted.[48]

There is insufficient evidence from intervention studies and cohort studies to indicate whether folate reduces the likelihood of depression. Not enough research has been done to ascertain whether folic acid has a preventive effect on fractures either. [48] One study of 728 men and women aged between 50 and 70 with elevated homocysteine levels found that additional folic acid had a protective effect against hearing loss, but it was too small to be audible to the human ear.[85]

In conclusion: there are indications that taking additional folic acid around the time of conception is associated with a lower risk of giving birth to a child with a congenital abnormality other than a neural tube defect. There are also indications that high folic acid intake may increase the risk of multiple pregnancies. Further-

more, there is no clear evidence from cohort or intervention studies of a link between folate and depression. Finally, too few high-quality intervention studies have been performed to allow any conclusions to be drawn as to a possible protective effect of folic acid against fracture and hearing loss among elderly people.

4.5 Conclusion

New research findings have become available since the dietary reference values for folate were published in 2003. The most significant of these relate to the link between folic acid and the risk of cardiovascular disease, colon cancer, and other problems such as fracture and the effect of folic acid on cognitive function (table 4.2).

Research among patients with cardiovascular disease does not show additional folic acid to have any protective effect against cardiovascular disease. But there are recent indications that folic acid supplementation may reduce the risk of stroke. The same applies to the risk of giving birth to a child with a congenital abnormality other than a neural tube defect. However, the committee is of the opinion that this evidence is too weak to be taken into account when weighing up risks and benefits.

Experiments on animals suggest that, compared to an excessively low intake, a folic acid intake that is four times as high as intake from normal animal feed may counteract the development of cancer in healthy animals but promote it in animals which already have a neoplasm. Epidemiological studies and intervention studies appear to back up this suggestion to some degree.

There are suggestions that both a low intake of folate (150-300 micrograms of dietary folate equivalents) and a high intake of folic acid from supplements (0.8-2.5 milligrams of folic acid a day) are associated with a higher risk of cancer, especially colon cancer, compared to an intake of 300 to 500 micrograms of dietary folate equivalents. The possibility that high doses of folic acid may accelerate the transformation of benign growths into malignant tumours cannot therefore be ruled out. However, the committee takes the view that the findings are not yet strong enough to enable any conclusions to be drawn as to the role of folate in the onset, growth or treatment of cancer. They were therefore excluded from the risk-benefit analysis.

Table 4.2 Summary of the levels of evidence of new scientific developments, showing the desired effects and adverse effects (see annex C for a description of the classification and codes).

Level of evidence	Desired effects	Adverse effects
Convincing	Folic acid supplementation reduces the risk of bearing a child with a neural tube defect A1[29]	
Probable	Optimal dietary folate intake is associated with a lower risk of colon cancer and breast cancer. B1[48,59], B2[51,52]	A high folic acid intake increases the risk of multiple pregnancies among women who conceive as a result of in-vitro fertilisation. B1[48]
	Folic acid supplementation reduces the risk of stroke (primary prevention). B1[42]	
	Folic acid supplementation around the time of conception reduces the risk of bearing a child with a congenital abnormality other than a neural tube defect, such as heart and limb abnormalities. B1[83]	
Insufficient	Folic acid reduces the risk of cardiovascular disease among patients with cardiovascular disease (secondary prevention). A1[38]	A high folic acid intake can accelerate the progression of colon, rectal and breast cancer. C[48], A2[64], B2[56]
	Taking additional folic acid protects elderly people against depression. B1[48]	Very high folic acid intake has a negative effect on cognitive function among elderly people with inadequate vitamin B_{12} status and a positive effect on cognitive function among elderly people with adequate vitamin B_{12} status. B2[77]
	Folic acid supplementation improves cognitive function among elderly people with elevated homocysteine levels. A2[74]	Folic acid supplementation around the time of conception increases the risk of twin pregnancies. B1[84]
	Taking additional folic acid protects elderly people against fractures. B1[48]	
	Taking additional folic acid protects elderly people against hearing loss. A2[85]	

The committee concluded that, in spite of new research results, it is still unclear whether high folic acid intake may have a negative effect on cognitive function among individuals with inadequate vitamin B_{12} status. These possible effects were the main reason why the Health Council's advisory report *Risks of folic acid fortification* came out against folic acid fortification. The committee thinks it unlikely that folic acid fortification would put people with inadequate vitamin B_{12} status at greater risk of neurological symptoms than people with severe

vitamin B_{12} deficiency, on whom the safe upper level of intake is based. The committee therefore takes the view that the safe upper level of intake of 1 milligram of folic acid per day also applies to people with inadequate vitamin B_{12} status.

Chapter 5

Folate intake in the Netherlands

This chapter discusses levels of folate intake among the Dutch population (folate supply). The committee first looks at how this was assessed, and then examines the values which have been recorded. It also describes the main sources of folate in the Dutch diet, considering the use of folic acid supplements by women wishing to conceive as a separate issue. Finally it considers the extent to which an excessively high folic acid intake occurs in the Netherlands.

5.1 Methods used to determine folate supply

Three steps are involved in deciding whether the folate supply is adequate. The first is to collect intake data: what do people in the Netherlands eat and drink, and how much folate is there in this accumulation of food sources and supplements? The second step is to compare the findings with dietary reference values stating how much folate people of varying genders and ages need for health. This allows us to determine whether the folate intake of individual groups is excessively low, excessively high, or just right. The third and final step should give a definitive answer to the estimate arrived at in step two: investigating the folate status* of a specific group of individuals. It may also be necessary to investigate conditions which may be connected to an excessively high or low intake.

* Folate and homocysteine concentrations in the blood.

5.1.1 *Intake data*

Most of the intake data on which this advisory report is based comes from food consumption surveys. Until 2000 this intake data was collected on two consecutive days. Data of this kind is therefore not independent, but does give an insight into day-to-day variation. We can correct for this variation. The term 'observed intake' relates to the raw intake data, while the term 'habitual intake' relates to corrected data. The average of the habitual intake is similar to the average of the observed intake, but the variation is smaller.[86] Data relating to habitual intake is preferred when determining the number of people whose intake is excessively low or excessively high.

5.1.2 *Comparing intake data and dietary reference values*

Two quantitative methods can be used to estimate the percentage of people in a population that are at risk of an undesirable level of intake: the threshold method and the probability method. The threshold method provides information about the percentage of the population whose intake is above or below a specific dietary reference value. The probability method combines the distribution of the habitual intake and the distribution of the requirement in a population group in order to arrive at an estimate of the percentage of the population whose intake is below the requirement. This makes the estimate more accurate.

However, the probability method uses two assumptions which mean that the outcomes must be interpreted with caution. The first is an average folate requirement for children derived from that applied to adults. The problem is that the probability method can only be used if the distribution of the requirement is known, i.e. if both an average requirement and a recommended dietary allowance have been determined. But in the case of children, only an adequate intake figure has been set for folate, because the Health Council was previously of the opinion that there was insufficient data to allow an average requirement to be set for children. Secondly, the outcome of the probability method is strongly dependent on the assumed variation in requirements, which the Health Council has only been able to establish as a broad figure. It was decided that a single requirement distribution with a relatively large variation coefficient should be established so as to include the requirement of people with the MTHFR-677-T/T genotype as well.[21,87,88]

5.2 The Dutch population's folate supply

5.2.1 Folate intake data

Food consumption surveys indicate that dietary folate intake fell by 3.5 per cent between 1988 and 1998.[89-91] The threshold method found that in the third food consumption survey (1997/98) and the food intake survey of young children (2002) the average intake among all population groups, apart from children under 4, was well below the recommended dietary allowance or adequate intake (table 5.1).[87,90-92]

Intake calculations were not corrected for differences in bioavailability between dietary folate and folic acid. This problem has little or no impact on estimates of intake for most population groups as hardly any foodstuffs fortified with folic acid were available prior to 2003. One exception to this is the intake of folic acid by infants and young children aged between 9 and 18 months who are being fed with follow-on formula milk,[92] which contains 11 to 13 micrograms of folic acid per 100 millilitres.[93] The folate intake of subjects taking part in the young adults food consumption survey (2003) and the MORGEN survey (1993-97) are comparable to intake data from the third food consumption survey (1997/1998)* (table 5.2).[94,95]

The probability method was used to produce an estimate of the number of people whose folate intake is below the average requirement. This estimate is based on data from the third food consumption survey (1997/1998). As described above, this estimate is heavily dependent on the requirement distribution (variation coefficient), which the Health Council was only able to set at a global level. Using the probability method, it was estimated that the proportions of individuals in various age groups with an intake below the average requirements were:

- 10 per cent of children aged 1 to 3;
- 31 per cent of children aged 4 to 8;
- 48 per cent of children aged 9 to 13;
- 61 per cent of teenagers aged 14 to 18;
- 40 to 68 per cent of adults.[87]

* As no folic acid fortified products were available between 1993 and 1996, and hardly any were yet on the market around 2003, it is assumed that the estimated intake in micrograms is equivalent to the intake in micrograms of dietary folate equivalents.

Table 5.1 Average and percentile figures for habitual folate intake in micrograms of dietary folate equivalents per day in the third food consumption survey (1997/98) and the food consumption survey of young children (2002).[a,87,92]

	Average intake (standard deviation)	P1	P10	P25	P50	P75	P90	P99
Infants, 9 months	123 (26)	74	92	104	120	138	157	195
Infants, 12 months	126 (23)	81	98	110	124	140	156	188
Infants, 18 months	114 (26)	63	82	95	111	129	148	184
Children, 1-3	113 (33)	39	66	83	106	131	154	217
Children, 4-8	129 (35)	46	75	97	121	151	184	293
Children, 9-13	158 (39)	68	98	117	148	187	226	330
Children, 14-18	182 (46)	56	108	132	169	212	260	373
Men, 19-50	216 (61)	79	126	157	202	249	306	508
Women, 19-50	173 (50)	59	97	123	161	205	253	388
Men, 51-65	221 (59)	91	135	164	203	254	324	434
Women, 51-65	182 (49)	71	107	132	168	213	272	390
Men, > 65	202 (61)	70	113	150	189	236	298	438
Women, > 65	178 (53)	65	99	126	167	207	251	409

a The estimated intake relates to total folate intake from food, i.e. both dietary folate and folic acid. It does not include folic acid intake from supplements. However, it is not corrected for differences in bioavailability between folate and folic acid. This led to an underestimation of the folate intake of infants being fed on follow-on milk. The additional folic acid intake from follow-on milk is 59 micrograms of dietary folate equivalents for infants aged 9 months, 36 micrograms of dietary folate equivalents for infants aged 12 months and 4 micrograms of dietary folate equivalents for infants aged 18 months.[93] As follow-on milk was practically the only foodstuff fortified with folic acid that was available on the market until 2003, the fact that figures were not corrected for bioavailability has no consequences for intake estimates for other population groups.

Table 5.2 Folate intake by adults in the food consumption survey of young adults (2003) and the MORGEN study in dietary folate equivalents.

Study	Gender, age	Average folate intake (standard deviation)
Food consumption survey among young adults 2003[a,b]		
	Men, 19-35	223 (60)
	Women, 19-35	155 (36)
MORGEN cohort[a,c] 1993-1997[94,95]		
	Men, 20-65	239 (73)
	Women, 20-65	192 (54)

a Intake of folic acid from supplements was not determined.
b Habitual folate intake.
c Observed folate intake.

5.2.2 Data on folate status

The Health Council used various thresholds to determine folate status. Serum folate levels below 10 nmol/l are an early sign of the development of folate deficiency. Levels below 7 nmol per litre are associated with neutrophilic hypersegmentation, as are red blood cell folate levels below 325 nmol per litre. DNA damage to lymphocytes can also be seen at this threshold. Homocysteine levels above 15 micromols per litre are regarded as excessively high.[21]

The limited amount of data from studies into folate status weakens indications pointing to excessively low intake. Most of the status data is derived from studies whose participants did not necessarily have to be a good representation of the Dutch population or of a particular population group.

A study among white children from the Nijmegen region ranging in age from birth to 19 years old found that they all had blood folate levels above the lower limit of 10 nmol per litre*.[96]

In studies among adults, the percentage of people with an inadequate folate status ranged from 8 to 25 per cent (table 5.3).[15,95,97] The figure for men of Moroccan origin was astonishingly high, at 40 per cent.[98] The percentage of elderly people with inadequate folate status varied from 2 to 23 per cent, with elderly people who were not living independently or who were in a fragile state being at greatest risk of inadequate folate status.[75,99,100,101]

It is difficult to compare the various percentages as the biochemical parameters and thresholds used varied and the methods of determination were of mediocre quality.[102-106] The committee is unaware of any reports of anaemia as a consequence of folate deficiency among the Dutch population.

5.2.3 Conclusion

Intake data gives some indication that the folate intake of large parts of the Dutch population is excessively low. So far a limited amount of status research has been carried out that dilutes these indications. What little research has been done shows the following results. One study found that the folate status of children aged up to 19 seemed to be adequate. Approximately 8 to 25 per cent of Dutch adults have inadequate folate status, a condition that is more prevalent among men than women. This figure seems to be much higher in people of Moroccan

* The 2.5% lower threshold of the confidence interval relating to plasma folate levels was lowest in the 15-19 age group, at 14 nmol per litre.

Table 5.3 Prevalence of inadequate folate status among adults.

Study	N, gender, age	Inadequate folate status Definition	%
General Health Monitor study, Amsterdam 2004[98]			
	210 Dutch men aged 18 or over	Serum folate < 7 nmol/l	25
	189 Turkish men aged 18 or over		20
	181 Moroccan men aged 18 or over		40
	289 Dutch women aged 18 or over		12
	212 Turkish women aged 18 or over		13
	145 Moroccan women aged 18 or over		24
MORGEN cohort 1993-1996[97,98]			
	2 015 men and women aged 20-65	Plasma folate < 4.5 nmol/l	8-23[a]
	1 490 men aged 20-65	Total plasma homocysteine > 15 micromol/l	31
	1 513 women aged 20-65		20
Brussaard 1997[b,15]			
	74 men aged 20-49	Plasma folate < 7 / < 13.6 nmol/l	11 / 79
	74 men aged 50-79		8 / 74
	74 women aged 20-49		13 / 71
	75 women aged 50-79		6 / 60
Eussen 2006[75]			
	195 men and women aged 70 or over[c]	Red blood cell folate level < 305 nmol/l	6
Manders 2006[100]			
	men and women aged 65 or over[d]	Serum folate level < 6.8 nmol/l	23
De Jong 2001[101]			
	130 men and women aged 70 or over[e]	Red blood cell folate level < 337 nmol/l	21

a Inadequate folate status was observed in 8% of individuals with the MTHFR 677C/C genotype, 11% of individuals with the C/T genotype and 23% of individuals with the T/T genotype.
b The method used to determine serum folate levels was not sufficiently standardised at the time of this study.
c With inadequate vitamin B12 status.
d Elderly people not living independently.
e Frail elderly.

origin. However, it is unclear whether this inadequate folate status has any health implications.

5.3 Contribution of various sources in diet

The principal sources of folate in diet are grains, grain products and vegetables. Folate consumption fell by 3.5 per cent between 1987/88 and 1997/98. This was mainly due to a decline in the consumption of fruit and vegetables. [89] The 2003 food consumption survey among young adults found that grain and grain products were the main source of dietary folate (25.6%), followed by vegetables (16.8%), dairy products (12.1%) and meat and meat products (9.6 %).[107]

The contribution of supplements to folate intake seems to be very limited. It is evident that only a small percentage of the Dutch population were taking folic acid supplements at the time of the third food consumption survey (1997/98) (table 5.4). The contribution made by products fortified with folic acid on a voluntary basis was not investigated. Until 2003/2004 very few products fortified with folic acid were available.

Table 5.4 Folic acid intake (micrograms per day) from supplements among people taking folic acid supplements.[108]

Study	Gender, age	% of total number of participants in the study	Average (standard deviation)	P90
Third food consumption survey (1997/1998)				
	10 children, 1-3	4	158 (172)	450
	39 children, 4-8	9	114 (86)	300
	33 children, 9-13	8	97 (43)	150
	23 children, 14-18	5	122 (72)	200
	63 men, 19-50	4	143 (127)	250
	123 women, 19-50	7	178 (147)	400
	25 men, 51-65	6	156 (124)	300
	43 women, 51-65	9	151 (121)	375
	9 men, 65 or over	3	100 (13)	125
	32 women, 65 or over	8	168 (150)	400
Young adults food consumption survey (2003)				
	44 men, 19-30 jaar	13	146 (165)	250
	92 women, 19-30 jaar	23	237 (268)	600

5.4 Contribution of folic acid supplements around the time of conception

The amount of dietary folate that women consume around the time of conception is not known. However, some data is available on the use of folic acid supplements at that time (table 5.5). For example, the European Surveillance of Congenital Anomalies (EUROCAT) study of women wishing to conceive found that between 1998 and 2000 on average only 36 per cent of women from northern Netherlands took extra folic acid in accordance with the guidelines (400 micrograms extra from at least four weeks before conception to eight weeks after conception). This is despite the fact that the majority of pregnancies in the Netherlands are planned (about 85 per cent), a one-off media campaign in 1995/1996 and an active government policy on folic acid supplementation.[109,110] There are some indications that this figure rose between 2000 and 2005.[111,112]

Table 5.5 The percentage of women taking a folic acid supplement around the time of conception before and after the information campaign in 1997/1998 and the percentage taking it according to the guidelines.

Study/location/group	Year	N	% some use of folic acid	% correct use of folic acid
Northern Netherlands - EUROCAT[a,109,117]	1994-2000			
	March 1994	485	8	0
	Autumn 1994	352	21	5
	Autumn 1996	350	38	15
	Autumn 1998	453	63	36
	Autumn 2000	461	61	36
Northern Netherlands - EUROCAT[114]	2003			
Low level of education		113	56	22
Average level of education		253	74	43
High level of education		166	88	59
Bakker, 2003[113]	1996			
Dutch background		1,174	69[b]	29[b]
Non-Dutch background		30	56[b]	9[b]
PBBS/KOALA study[a,c,112]	2000-2002	7,208	83	51
ABCD study Amsterdam[a,d,111]	2003-2004			
Dutch background		2,095	89	51
1st-generation non-Dutch background		529	23-48	8-17
2nd-generation non-Dutch background		206	44-60	16-25
Amsterdam clinics[115]	2007			
Turkish		83	43	n.m.[e]
Moroccan		135	39	n.m.
Surinamese/Antillean		33	46	n.m.

a EUROCAT European Surveillance of Congenital Anomalies, PBBS Peri-Partal Pelvic Pain Syndrome, KOALA Child, Parent and Health: Consideration for Lifestyles and Predisposition, ABCD Amsterdam Born Children and their Development study.
b Number or percentage of women who were aware of the folic acid recommendation; 41% of the women of non-Dutch background and 79% of the women of Dutch background were aware of the folic acid recommendation at the time of the one-off folic acid campaign.
c Relatively large number of female participants with a high level of education.
d 'Non-Dutch background' refers to Moroccan, Turkish or Surinamese background.
e N.m. = not measured.

The use of folic acid supplements is lower among women of non-Dutch background or a low level of education than among highly-educated women of Dutch background.[111,113-115] Studies into folate status confirm the role of ethnicity in the use of folic acid supplements. 13 per cent of women taking part in the Amsterdam Born Children and their Development study had serum folate levels below 10 nmol/l. The figures ranged from 6 per cent among women of Dutch background to 20 to 35 per cent of women of non-Dutch background. The difference in folate status is largely related to the use of supplements. The percentage of women with inadequate folate status was two to five times higher among women who did not take folic acid supplements than among those who did.[111] Women of a lower educational level were also less likely to take a supplement containing folic acid around the time of conception than more highly-educated women. This difference in use also increased markedly in the first eight years after the media campaign.[114,116]

In conclusion: over three-quarters of women of non-Dutch origin, and half of women of Dutch origin, do not take a folic acid supplement around the time of conception, or start to take it too late. Supplement use is also lower among women of a low educational level than among those with a higher level of education.

5.5 Data on excessively high folic acid intake

The safe upper limits relate only to folic acid. Data from the third food consumption survey (1997/98), the food intake study of young children (2002) and the food consumption survey of young adults (2003) did not make any distinction between intake of dietary folate and intake of folic acid. No correction was made for differences in bioavailability either (table 5.1). However, very few products fortified with folic acid were available until 2003, apart from follow-on milk for infants. The folic acid intake of infants drinking about half a litre of follow-on milk a day is below the safe upper level of intake of 200 micrograms a day. Nevertheless, plasma folate levels in white infants under 2 years old from the Nijmegen region appear to be about four times higher than among children aged between 2 and 19*.[96] But this data remains to be confirmed, as folate levels were only measured in seven infants under 2 years old. There are also indications that 10 per cent of the children aged between one and 3 who take a folic acid supple-

* The average plasma folate level was 79 nmol per litre, while among older children the figure ranged from 24 nmol per litre in children aged 2-5 to 15 nmol per litre in adolescents aged 11-19.[96]

ment obtain more than the safe upper level of intake of folic acid from it (table 5.4).[108]

It appears that only a small proportion of adults taking a folic acid supplement are consuming amounts in excess of the safe upper level of intake.[87,108] No data is available on the situation regarding women wishing to conceive.

In conclusion: there are no clear indications that consumption of folic acid in excess of the safe upper level of intake as a result of taking supplements occurs frequently among the Dutch population. No information is available as to whether this is also true of women wishing to conceive. The contribution of products fortified with folic acid on a voluntary basis to folic acid intake among the Dutch population is unknown.

5.6 Conclusion

Folate intake has fallen by 3.5 per cent among the Dutch population over the past decade, mainly as a result of a decline in the consumption of fruit and vegetables. Status studies show that folate supply may be inadequate for 8 to 25 per cent of adults and elderly people. The status of children up to the age of 19 appears to be good, though only one study has been conducted. It is as yet unclear whether inadequate folate status among a part of the adult population is causing clinical problems.

Not enough women wishing to conceive take the right amount of folic acid at the right time. Over three-quarters of women of non-Dutch origin, and about half of women of Dutch origin, do not take a folic acid supplement around the time of conception, or start to take it too late. The same is true of about three-quarters of women with a low level of education.

There are also indications that excessively high intake of folic acid occurs only occasionally among young children and adults taking a folic acid supplement. No information is available as to whether this also applies to women wishing to conceive and taking folic acid for that reason.

Chapter 6

Effects of folic acid policy in other countries

In this chapter the committee looks at the effects of various policies in other countries. It also considers plans for new policies on mandatory fortification of staple foodstuffs in various European countries, Australia and New Zealand.

6.1 Effects of information on the use of folic acid supplements

Information can boost the use of folic acid supplements around the time of conception, but only among women whose pregnancy is planned. This means that it is less effective in countries such as the United States, the United Kingdom, Ireland, Australia and New Zealand, where fewer than 50 per cent of pregnancies are planned.[48,118-120] This contrasts with countries such as Sweden and Norway where 80 per cent of pregnancies are planned.[121] Information can have a greater impact in those countries.

This does not mean that the use of folic acid supplements around the time of conception is already ideal there. For example, in the period from 2000 to 2003 a total of 10 per cent of the 22,500 Norwegian women taking part in the Norwegian Mother and Child cohort study took folic acid supplements according to the (Norwegian) guidelines, i.e. from at least a month before conception until four months after conception. This is in spite of the fact that 72 per cent of the participants did take a dietary supplement containing folic acid among other ingredients at some time before conception or during pregnancy. The women who did not take folic acid supplements, or who started to take them too late, were more

likely to have a low level of education or to have become pregnant unintentionally.[121]

This finding is in line with the results of other studies, which found that women who did not follow the recommendations also were often under 25 or under 19, of low socio-economic status, or born in another country.[122-125] The high percentage of planned pregnancies is one of the reasons why Sweden has decided not to opt for mandatory fortification but to take an active approach to women likely to benefit from preconception care.

In conclusion: information can boost the use of folic acid supplements around the time of conception among women whose pregnancy is planned. In the past, information campaigns have had less effect on women of a low level of education, low socio-economic status, who are young or who were born in another country than on other women.

6.2 Effects of voluntary fortification of specific foods

Voluntary fortification of specific foods with folic acid is permitted in Europe. A study of 441 Irish adults found that the use of products which had been fortified with folic acid on a voluntary basis was associated with better folate status. A quarter of the participants did not consume any products fortified with folic acid. Among the quarter of participants who consumed these products most frequently, the median intake figure was 208 micrograms of folic acid per day, while the maximum intake was 708 micrograms of folic acid per day.[126]

Voluntary folic acid fortification can therefore be just as effective as mandatory fortification. This outcome confirms the finding that the use of fortified breakfast cereals is associated with better folate status.[127] However, there is no guarantee that every individual will consume products that have been fortified with folic acid on a voluntary basis.

Voluntary fortification is permitted alongside mandatory fortification in various non-European countries such as the United States and Canada. This raises various questions, including the implications for the folate status of children. In many cases little data is available.

It has however been calculated that the combination of mandatory fortification of staple foodstuffs and voluntary fortification of specific foodstuffs means that 9 per cent of children aged 2 or 3 in Australia have folic acid intake levels above the safe upper level of intake. This does not take account of intake of folic acid from supplements. The extent to which the safe upper level of intake is exceeded is not indicated. However, the authors do state that no single child has

an intake close to five times the safe upper level of intake, which is the safety factor applied when setting the safe upper level of intake. The report concludes that intake in excess of the safe upper level is undesirable but probably does not entail any risk in view of the large safety margin used when setting the safe upper level of intake.[120,128]

The United Kingdom and Germany have taken a different view, deciding that mandatory fortification of staple foodstuffs could only be introduced if voluntary fortification of specific products were subjected to restrictions.[48,129] This is because otherwise children in particular would be at risk of consuming in excess of the safe upper level of intake.

The German Federal Institute for Risk Assessment takes the position that masking vitamin B_{12} deficiency, the principle on which the safe upper level of intake was based, is less relevant for children and teenagers than for adults. As the safe upper levels of intake for children and teenagers were derived from that set for adults, they are less suitable for determining the risk of a negative effect. On the other hand, hardly any data is available allowing the long-term effects of folic acid on children to be determined.[130]

In the United Kingdom there is yet another reason for advising against combining voluntary and mandatory fortification: the suggestion that a high dose of folic acid may accelerate the transformation of benign growths into malignant tumours.[131] In Germany it was decided that the maximum level of voluntary fortification should be 100 micrograms of folic acid per portion.

In conclusion: the use of specific products fortified with folic acid on a voluntary basis can improve folate status. However, there is no guarantee that women of childbearing age will use these products. The combination of mandatory fortification of staple foodstuffs with voluntary fortification of specific products can, leaving aside any supplement use, lead to excessively high folic acid intake, especially among young children.

6.3 Effects of mandatory fortification of staple foodstuffs

Over fifty countries around the world have introduced mandatory fortification of staple foodstuffs with folic acid. The United States and Canada were the first to make folic acid fortification of grain products mandatory, followed mainly by Latin American and African countries.[119,132] Women wishing to conceive who eat fortified foodstuffs obtain 17 per cent (Canada)[133] to 48 per cent (United States)[134] of the 400 micrograms of additional folic acid that they are recom-

mended to take. In Canada and the United States they are therefore advised to take a folic acid supplement and perhaps to alter their diet as well.

6.3.1 *Decline in the number of neural tube defects*

A descriptive epidemiological study looked into the efficacy of various policies on the occurrence of neural tube defects prior to 2003. This condition was becoming less common in almost all countries before the introduction of the policies. This downward trend continued in countries where women were only advised to take folic acid supplements around the time of conception or where only voluntary fortification of specific foodstuffs was permitted. The occurrence of neural tube defects is on the other hand lower than would be expected by looking at the downward trend in countries where folic acid fortification of staple foodstuffs is mandatory.[135]

Calculations produced by the American Centers for Disease Control show that the introduction of mandatory fortification is associated with a 27 per cent lower risk of bearing a child with a neural tube defect (table 6.1).[136] A combination of data from 21 American population-based records of congenital abnormalities shows that the number of new cases of spina bifida has fallen sharply since the introduction of mandatory fortification: by 19 per cent in the black population, 34 per cent in the white population and 36 per cent in the Hispanic population.[137] The difference between population groups can be partly explained by the fact that black women have a lower folate intake than white or Hispanic women.[138]

According to the Latin American Collaborative Study of Congenital Malformations, occurrence fell in Chile by 51 per cent (minimum 27% and maximum 66%). The number of new cases of anencephaly also declined both in the United States and Chile, though less sharply than the decline in the number of cases of spina bifida.[137,139]

The occurrence of neural tube defects has also fallen in Canada since the introduction of mandatory fortification. An analysis in which data from birth records from seven Canadian provinces were grouped together shows that the occurrence of neural tube defect fell by 46 per cent since the introduction of mandatory fortification (95% confidence interval 40-51%).[140] The decline varies from region to region: from 32 per cent in Quebec to 78 per cent in Newfoundland.[133,141-143]

Table 6.1 Comparison of the occurrence of neural tube defect before and after the introduction of mandatory fortification.[a,b]

Country and type of fortification	Before or after the introduction of mandatory fortification	Occurrence of neural tube defect	
		Incidence (per 10,000 births)[c]	Decline in the risk after fortification (%)[d]
UNITED STATES[136]	Before	10.6	
Mandatory: 140 micrograms of folic acid /100 grams of grain after production	After	7.6	27
CANADA			
Mandatory: 150 mcg folic acid / 100 g white flour, 200 mcg folic acid / 100 g fortified pasta	Before	15.8	
	After	8.6	46
Ontario[142]	Before	11.3	
	After	5.8	51
Nova Scotia[143]	Before	25.8	
	After	11.7	54
Quebec[141]	Before	18.9	
	After	12.8	32
Newfoundland[133]	Before	43.6	
	After	9.6	78
CHILE[139]	Before	17.5[e]	
Mandatory: 220 mcg folic acid / 100 g flour	After	8.0[e]	47[d]

a Based on tables 1 and 28 of Folate and disease prevention 2006.[48]

b In the Netherlands, prevalence between 1995 and 1998 was 11.9 children per 10,000 live births, stillbirths and elective terminations.[144]

c Unless otherwise specified, the figure includes live births, stillbirths, cases diagnosed in pre-natal tests and elective terminations.

d The reduction in risk is not always the same as the figures in the middle column because the percentage is sometimes an average of the individual reductions in risk of neonates with spina bifida or anencephaly.

e Live births and stillbirths, not including cases diagnosed in pre-natal tests or elective terminations.

6.3.2 *Perhaps greater masking of vitamin B_{12} deficiency*

Initially there were no indications that elevated folic acid intake as a consequence of mandatory fortification of staple foodstuffs has led to vitamin B_{12} deficiency being masked more often than in the past. A study conducted on all patients attending the Veterans Affairs Medical Center who had a vitamin B_{12} test between 1992 and 2000 found no clear change in the percentage of patients with inadequate to adequate vitamin B_{12} status without megaloblastic anaemia (table 6.2).[145] Another study of people aged 65 or over in Newfoundland found that in the three years after the introduction of mandatory folic acid fortification (1998-2001) their

Table 6.2 Effects of mandatory folic acid fortification on masking vitamin B_{12} deficiency.

Study	Outcome	N	Introduction of fortification Before	During	After	P-value
Veterans Affairs Medical Center[145]						
	% of patients with inadequate to adequate vitamin B_{12} status without anaemia[a]	1,573	39%	45%	38%	0.96
Rush University Medical Center[146]						
	% of patients with inadequate to adequate vitamin B_{12} status without megaloblastic cells[a]	633[b]	70%	85%	87%	<0.001
People aged 65 or over in Newfoundland[c,133]		N	Before	N	After	P-value
	Serum vitamin B_{12} (pmol/l)	202	183	186	216	<0.001
	Plasma methylmalonic acid (micromol/l)	202	0.24	186	0.26	0.229

a Inadequate to adequate vitamin B_{12} status is defined as a serum cobalamin level below 258 pmol per litre.
b N before fortification = 86, N during = 138 and N after = 409.
c Blood values that are indicative of anaemia - haemoglobin level and mean corpuscular volume - remain almost identical. Exact figures were not reported.

serum vitamin B_{12} levels had improved. Serum methylmalonic acid levels and blood values pointing to anaemia also remained more or less the same*. The individuals aged 65 or over taking part in this study did not take vitamin preparations.[133]

However, a more recent study found that in the United States the number of people with inadequate to adequate vitamin B_{12} status without megaloblastic cells increased from 70 per cent prior to the introduction of mandatory fortification to 87 per cent after the introduction of mandatory fortification.[146] There are also indications that the enzymatic functions of vitamin B_{12} decline in the presence of higher plasma folate levels in individuals with inadequate vitamin B_{12} status** but rise in individuals with adequate vitamin B_{12} status.[147]

6.3.3 *Greater occurrence of intake levels above the safe upper level of intake*

In the United States, more adults are consuming folic acid in amounts above the safe upper level of intake (1 milligram per day) since the mandatory fortification of staple foodstuffs. This is particularly true of people who are also taking a folic acid supplement (table 6.3).[133,134,138,148] For example, among adults taking part in the Framingham Offspring Cohort study, the number of people taking supplements who were consuming too much folic acid rose from 1 per cent before the introduction of mandatory fortification to 11 per cent afterwards. In addition,

* The haemoglobin content and mean volume of the red blood cell.
** Inadequate to adequate vitamin B_{12} status is defined as a serum cobalamin level of 148 pmol per litre or less.

prior to the introduction of mandatory fortification the combination of excessively high folic acid intake and inadequate to adequate vitamin B_{12} status did not occur*.

Table 6.3 Effect of mandatory folic acid fortification on the percentage of individuals with an excessively high folic acid intake or folate status.

		% consuming more than 1 mg of folic acid a day				
Study	Study population	N	Before	N	After	P-value
Framingham Offspring Cohort[134]						
	Subjects aged between 30 and 80, not taking vitamin B supplements	389	0.4	389	0.2	n.d.
	Subjects aged between 30 and 80, taking vitamin B supplements	160	1.3	160	11.3	P<0.001
NHANES[a,b, 148]						
	White men aged 65 or over	n.d.[c]	2	n.d.	4	P<0.05
	Black men aged 65 or over	n.d.	1	n.d.	3	P<0.05
	Men of Mexican-American background aged 65 or over	n.d.	6	n.d.	2	P<0.1
	White women aged 65 or over	n.d.	2	n.d.	4	P<0.01
	Black women aged 65 or over	n.d.	1	n.d.	1	P>0.1
	Women of Mexican-American background aged 65 or over	n.d.	4	n.d.	1	P<0.1
NHANES[a, 138]						
	Women aged between15 and 34	n.d.	n.d.	1,095	7.0[d]	n.d.
	Women aged between 35 and 49	n.d.	n.d.	590	4.2[d]	n.d.
Newfoundland[133]						
	Women aged between 19 and 44, not taking supplements	233	0	204	0	n.d.
	Men aged 65 or over, not taking supplements	202	0	186	0	n.d.
		% with serum folate levels > 45 nmol/l[e]				
Study	Study population	N	Before	N	After	RR (95%-CI) [f]
Ontario and British Columbia[151]						
	Women aged 65 or over with inadequate vitamin B_{12} status	4,572	0.1	11,092	0.6	RR=7 (2.6-19.2)
NHANES[a] III and 1999-2000[149,150]						
	Children aged between 3 and 5	1,742	7	361	43	n.d.
	Children aged between 4 and 11	4,627	5	1,131	42	P<0.001
	Elderly people aged 60 or over	5,051	7	1,487	38	P<0.001

a National Health and Nutrition Examination Survey.
b This percentage may be an underestimate as serum and red blood cell folate levels increased more than would be expected on the basis of intake data.[152]
c N.d. not determined.
d 1.5% of the women aged between 15 and 34 and 0.2% of the women aged between 35 and 49 had an excessively high folic acid intake from fortified foodstuffs alone.
e 45.4 nmol per litre is an arbitrary threshold for defining excessively high serum folate levels.
f CI confidence interval.

* Inadequate to adequate vitamin B_{12} status is defined as a plasma cobalamin level below 258 pmol per litre.

Following the introduction of mandatory fortification, three (1.8%) of the 160 participants who took supplements were affected by this combination.[134] Among the women taking part in the *National Health and Nutrition Examination Surveys* who were of childbearing age but were not pregnant, 5.5 per cent had an excessively high folic acid intake (over 1 milligram of folic acid a day) from fortified food and supplements combined, while 0.9 per cent had an excessively high folic acid intake from fortified food alone.[138]

The committee is not aware of any intake data for children. The percentage of children aged between 4 and 11 with a relatively high* serum folate level did increase from 5 per cent in the period from 1988 to 1994 to 42 per cent in the period from 1999 to 2000.[149] The percentage of elderly people with a relatively high serum folate level rose from 7 to 38 per cent.[150] Between 2001 and 2004 these percentages fell to 19 per cent in children and 32 per cent in elderly people. However, this study used an arbitrary figure of 45.4 nmol per litre to define what was regarded as a relatively high serum folate level.[149]

6.3.4 *Quantities of unmetabolised folic acid in blood*

Unmetabolised folic acid has been detected in blood at oral doses of 260 micrograms of folic acid and above.[48] It is not found in blood at lower doses or in individuals consuming only dietary folate. A study in which subjects ate bread and breakfast cereals that had been fortified with folic acid for five days found the threshold value of folic acid intake at which unmetabolised folic acid appears in serum was 266 micrograms of folic acid per meal.[65] In another study, unmetabolised folic acid was measured six hours after taking the supplement in the serum of subjects who had taken a supplement containing 400 micrograms of folic acid a day for fourteen weeks. This was also the case in people taking 400 micrograms of folic acid a day in fortified bread, but not when they consumed lower doses (200 or 100 micrograms of folic acid a day) in fortified bread.[153] A cross-sectional study of American post-menopausal women found unmetabolised folic acid in the plasma of 78 per cent of the participants.[66] The physiological significance of the presence of unmetabolised folic acid in blood is unknown.

* A high folate level is defined as a serum folate level of at least 45.4 nmol per litre. This arbitrary figure is the highest concentration of folate that can be measured by the Bio-Rad Quantaphase II assay in undiluted samples.

6.3.5 *Risk of over-fortification*

A large proportion of fortified products in the United States appear to contain more folic acid than is required by law, as a result of which folic acid intake has increased by more than was anticipated beforehand. In the case of breakfast cereals, folic acid content was sometimes as stated on the label but often three times higher or more. Half of the breakfast cereals contained folic acid in concentrations one and a half times higher than stated on the label.[154] Manufacturers over-fortify their products in order to compensate for any loss of folic acid during storage. They can therefore be sure that when the product is coming to the end of its shelf life it still contains as much folic acid as is stated on the label. Over-fortification has meant that folic acid intake in the United States is twice as high as was anticipated (190 to 240 micrograms of folic acid a day compared to 100 micrograms)*.[134,155] However, there are indications that over-fortification has declined since 2001.[156]

6.3.6 *Consequences of fortification*

There appears to be a clear benefit in countries where mandatory fortification of staple foodstuffs with folic acid has been introduced: this measure is associated with a 30 to 50 per cent decline in neural tube defects. No strong evidence that mandatory fortification with folic acid has harmful consequences has been found in these countries.

The findings of research into the question of whether increased folic acid intake as a consequence of mandatory fortification has led to increased levels of masking of vitamin B_{12} deficiency are unclear. Some studies found no change, while others found an increase. It is true that since the introduction of mandatory fortification some people are at risk of consuming too much folic acid, especially adults who take a folic acid supplement. This is particularly the case since as a result of over-fortification the levels of folic acid intake are unintentionally higher than was initially calculated, particularly in the United States.

However, there are indications that most adults who do not take a supplement remain below the safe upper level of intake. Not enough research has been done to ascertain the percentage of children under the age of 15 in these countries who

* It is true that NHANES studies show that folic acid intake has risen only by 76 to 100 micrograms, but this is probably an underestimate because blood values show a different picture. In fact, since fortification was introduced plasma folate levels are 136% higher and red blood cell folate levels are 57% higher than they were before.[148,152]

consume too much folic acid. We still do not know how unhealthy it is for them to take too much folic acid. Unmetabolised folic acid is found in the blood of people who take oral doses of 260 micrograms of folic acid a day.

6.4 Plans for the introduction of mandatory fortification in Europe and elsewhere

6.4.1 Ireland

Ireland was the first European country to make the fortification of bread with folic acid mandatory. In doing so the government was following the advice of Ireland's National Committee on Folic Acid Fortification. This committee recommended that when mandatory fortification was introduced a small number of less popular types of bread and flour sold in shops should be excluded from fortification. The proposed level of fortification is 120 micrograms of folic acid per 100 grams of bread. This level of fortification only meets part of the folate requirement of women around the time of conception. That is why the committee also advised that a national campaign be set up, in consultation with all parties concerned, to maintain awareness among the Irish population of the importance of women taking extra folic acid around the time of conception. The Irish committee also recommended that the effect of mandatory fortification with folic acid on folate intake, folate status, the occurrence of neural tube defects and other congenital abnormalities should be monitored. On the issue of products fortified with folic acid on a voluntary basis, the committee referred to the European debate on minimum and maximum levels of addition of folic acid to foodstuffs and supplements.[119]

6.4.2 United Kingdom

In 2007 the British Food Standards Agency advised the British government to make the fortification of bread or flour with folic acid mandatory. It was anticipated that mandatory fortification would lead to a decline in the occurrence of neural tube defects and improve the folate status of the population as a whole. The advisory report also recommended limiting voluntary fortification of specific products and giving clear advice on the use of folic acid supplements. This should help prevent excessively high consumption of folic acid.

It should be pointed out that this recommendation is in line with the advice of the UK Committee on Carcinogenicity that a cautious approach should be taken when considering the introduction of mandatory fortification.[131] This advice was

given on the basis of new publications referring to a possible link between high folic acid intake and elevated risk of colon cancer.[157] In October 2007 British ministers asked whether the Scientific Advisory Committee on Nutrition would review new publications on the link between folic acid fortification and the risk of colon cancer.[61,64] At the time of drafting our advisory report it was still not clear what the committee's view was and whether folic acid was going to be added to bread or flour.

The UK recommendation is based on various sources of information, including a report by the Scientific Advisory Committee on Nutrition and a public consultation.[158] The Scientific Advisory Committee on Nutrition's report concludes that fortification of flour with folic acid could be made compulsory on two conditions. The first is that the government must take action to reduce intake of folic acid from specific foodstuffs that are fortified on a voluntary basis. The purpose of this is to ensure that the number of people consuming more than the safe upper level of intake does not rise. The second condition is that the government must monitor the situation to ascertain whether long-term consumption of folic acid above the safe upper level of intake causes negative health effects such as neurological damage, cardiovascular disease or cancer. The UK committee also recommends in-depth deliberations to ascertain how over-fortification with folic acid can be restricted. It also suggests reviewing the possible positive and negative effects of folic acid fortification after five years.

The Scientific Advisory Committee on Nutrition is also of the opinion that even if mandatory fortification of flour with folic acid is introduced, women should continue to take an extra 400 micrograms of folic acid a day around the time of conception. It estimates that if no products that have been fortified with folic acid on a voluntary basis are on the market, and the extent of over-fortification with folic acid is limited, the optimal level of fortification of flour is 300 micrograms of folic acid per 100 grams (equivalent to 225 micrograms per 100 grams of flour in the final product). In this case 0.2 per cent of the population would have an excessively high intake. More than half of these (72,000) would be children between the ages of 4 and 10. But this percentage is lower than the current figure because it is assumed that voluntary fortification with folic acid will be subjected to considerable restrictions. The risk of bearing a child with a neural tube defect would decline further at higher doses, but at the same time this would mean that more people, especially children between the ages of 4 and 10, would have an intake above the safe upper level of intake. The UK committee advises making fortification with folic acid mandatory. It suggest that the eventual level of fortification, and the types of products affected, should be decided in the light of various factors including the use of vitamin supplements and the

extent to which over-fortification and products that are fortified with folic acid on a voluntary basis can be restricted.[48]

Table 6.4 summarises the advantages and disadvantages of various fortification strategies for the British population. The UK committee's advisory report also sets out in detail the costs of each measure, calculated on the basis of DALYs due to neural tube defect, production costs and healthcare savings*.[159] It calculates that the net benefit to the UK of introducing mandatory fortification at a level of 300 micrograms folic acid per 100 g of flour would be € 20.1 million (£ 13.7 million) a year if no products fortified with folic acid on a voluntary basis were available. The figures are slightly different if the requirement does not apply to wholemeal flour (€ 18.5 million (£ 12.6 million)). These estimates are based on the most pessimistic estimate of the number of children with a neural tube defect that can be prevented.[160]

Table 6.4 Summary of the advantages and disadvantages to the British population of fortification of flour with folic acid. The figures between brackets show the effects if it is assumed that only white flour would be fortified and wholemeal flour would not.[159]

Fortification level in micrograms of folic acid per 100 grams of flour before processing (after processing)	Estimated number of children a year in whom a neural tube defect is prevented	Estimated number of people aged 65 or over with inadequate vitamin B_{12} status and an intake of > 1 mg of folic acid per day	Estimated number of people consuming folic acid in excess of the safe upper level of intake
Includes both dietary folate and folic acid from foodstuffs fortified on a voluntary basis and supplements.			
0 (0)	-	900	127,000
100 (75)	47-99 (42-93)	1,700	241,000 (225,000)
200 (150)	91-198 (82-180)	2,800 (2,000)	460,000 (404,000)
300 (225)	126-285 (114-261)	3,300 (2,500)	907,000 (773,000)
450 (338)	175-378 (163-369)	9,000 (6,300)	2,535,000 (2,200,000)
Voluntary fortification with folic acid is not permitted. Includes only dietary folate and folic acid from supplements.			
0 (0)	-70	800	18,000
100 (75)	-7 (-14)	800	38,000
200 (150)	42-90 (35-63)	900	52,000
300 (225)	84-189 (77-162)	900	119,000 (115,000)
450 (338)	140-315 (126-279)	1,400 (900)	660,000 (559,000)

* The calculations assume that one DALY is equivalent to a little over € 44,000 (£ 30,000).

6.4.3 Germany

The German Federal Institute for Risk Assessment has advised that if Germany were to introduce mandatory fortification of staple foodstuffs with folic acid, the voluntary fortification of other, specific foodstuffs should be limited to a maximum of 100 micrograms of folic acid per portion. This should prevent excessive intake of folic acid by the population, especially children. It also recommended that fortification of soft drinks with folic acid should be prohibited. The aim of mandatory fortification is to improve the folic acid supply for the entire population, not only women wishing to conceive. The institute points out that mandatory fortification cannot meet the entire requirement of women around the time of conception. Women are therefore advised to take a folic acid supplement from before conception until the end of the first trimester of pregnancy.[129]

The advice given by the Federal Institute for Risk Assessment is based on a study into the effects of supplementation and various fortification strategies on the folic acid intake of German children and adults.[130] It concluded that simply advising women to take a folic acid supplement around the time of conception is not sufficient as around half of pregnancies in Germany are unplanned. By definition, women whose pregnancy is unplanned cannot start taking folic acid supplements in time.

A second option for increasing folic acid intake is the use of partially fortified flour. However, there is no guarantee in this case that women of childbearing age would actually consume the flour. It is therefore unclear whether this would improve their folate status.

Mandatory fortification of flour with folic acid is a third option. This would certainly have an effect on women of childbearing age. The study calculated that fortifying flour at a level of 150 micrograms of folic acid per 100 grams of flour would markedly improve the folate status of the German population without resulting in too many people consuming amounts above the safe upper level of intake. But mandatory fortification can only be introduced if specific products that are fortified with folic acid on a voluntary basis do not contain more than 100 micrograms of folic acid per portion and if fortification of soft drinks is prohibited. That is because the study contains some indications that the combination of mandatory fortification and a high level of voluntary fortification (200 micrograms of folic acid per 100 grams) would lead to more children and adults consuming folic acid at levels in excess of the safe upper level of intake than the combination of mandatory fortification and a low level of voluntary fortification (100 micrograms per 100 grams). Furthermore, there are indications that in chil-

dren consumption of specific products fortified on a voluntary basis (200 micrograms of folic acid per 100 grams) makes a greater contribution to consumption of folic acid in excess of the safe upper level of intake than consumption of staple foodstuffs fortified on a mandatory basis.[130]

6.4.4 *Australia and New Zealand*

At the time that this advisory report was being drawn up, Australia and New Zealand had decided to introduce mandatory folic acid fortification for flour intended for breadmaking. Consequently, as from 2008 flour intended for breadmaking in these countries will have to be fortified with 200 to 300 micrograms of folic acid per 100 grams of flour. There will be a transitional period of two years.[161] The current system whereby specific products can be fortified with folic acid on a voluntary basis will remain in place.[120,162]

It has been calculated that at this level of fortification the positive health impacts clearly outweigh the costs. The calculation compared the benefits of preventing neural tube defects in children and the costs of mandatory fortification. The addition of folic acid to flour intended for breadmaking will result in a net gain of € 64 million a year ($ 122 million a year) in Australia and € 25 million a year ($ 41 million a year) in New Zealand as a result of the prevention of live births and stillbirths of children with a neural tube defect. The net benefits are lower if the calculation only takes account of the number of live children born with a neural tube defect and if folic acid is added at a later stage of the breadmaking process*.

This mandatory fortification will lead to 9 per cent of children aged 2 or 3 in Australia having a folic acid intake above the safe upper level of intake. This figure takes account of intake of folic acid from specific products that are fortified on a voluntary basis but not from supplements. The extent to which the safe upper level of intake is exceeded is not indicated. [120,128]

6.5 Conclusion

Information can boost the use of folic acid supplements around the time of conception, but only among women whose pregnancy is planned. Information campaigns have less impact on women with a low level of education or a low socio-

* If the calculations for New Zealand are re-worked, leaving out the benefits of preventing abortions and stillbirths but including the lower limit of the effect of folic acid on preventing neural tube defects, the costs would outweigh the benefits by € 1 million a year ($ 2 million a year).

economic status, and women who are young or who were born in another country.

Specific products fortified with folic acid on a voluntary basis can improve folate status, but there is no guarantee that women of childbearing age will consume them. The situation with mandatory fortification of staple foodstuffs is different: that would have an impact on this group, improving their folate status and reducing the likelihood of a child being born with a neural tube defect.

There are indications that the introduction of mandatory folic acid fortification in the United States, Canada and Chile – countries with a relatively high percentage of unplanned pregnancies – has been associated with a reduction of on average 30 to 50 per cent in the occurrence of neural tube defects in foetuses.

Table 6.5 Summary of levels of evidence of the effects of policies adopted in other countries (see annex C for a description of the classification and codes).

Level of evidence	Desired effects	Adverse effects
Convincing		Unmetabolised folic acid is found in the blood of people who take oral doses of at least 260 micrograms of folic acid a day. A1[65,153]
Probable	Consumption of specific products fortified with folic acid on a voluntary basis is associated with better folate status. B2[126,127]	Information campaigns on the use of folic acid supplements around the time of conception have had less impact on women of a low level of education, low socio-economic status, young women, women whose pregnancy was not planned and women who were born in another country. B2[121-125]
	Mandatory fortification of staple foodstuffs with folic acid in combination with advice on supplements reduces the risk of bearing a child with a neural tube defect compared to supplement advice alone or in combination with voluntary fortification of specific products. B1[136,137,139,140]	Since the introduction of mandatory fortification of grain products with folic acid in America, some people are at risk of having an excessively high intake, especially adults who take a folic acid supplement. B1[134,138,148]
		Over-fortification leads to an unintentionally higher intake of folic acid than was anticipated. B1[134,155], C[154]
Insufficient		Children who take a folic acid supplement are at particular risk of excessively high intake in countries where folic acid fortification of staple foodstuffs is mandatory. C[120,128,160]
		Masking of vitamin B_{12} deficiency occurs more frequently since the introduction of mandatory fortification than before this measure was introduced. B1[133,145,146]

It is unclear whether the prevalence of masked vitamin B_{12} deficiency in the United States has increased since the introduction of mandatory folic acid fortification. However, excessively high intake of folic acid does occur more frequently among adults and elderly people, especially among people taking supplements. It is not clear whether folic acid intake among children exceeds the safe upper level of intake in countries where fortification is mandatory.

Scenario calculations suggest that children are at greater risk than adults of consuming too much folic acid from fortified products (table 6.5). That is why in some countries governments have been advised to combine any introduction of mandatory folic acid fortification of staple foodstuffs with restrictions on voluntary folic acid fortification of specific products (the United Kingdom and Germany). Another cause of excessively high intake of folic acid is the marked degree of over-fortification. Folic acid intake in the United States is twice as high as anticipated as a result of over-fortification.

In Europe, Ireland has made the folic acid fortification of bread compulsory, but a number of types of bread may not be fortified. The UK Food Standards Agency has also advised introducing mandatory folic acid fortification.

Chapter 7

Effects of Dutch folic acid policy

In this chapter the committee discusses the effects of information on the use of folic acid supplements. Higher folic acid intake around the time of conception reduces the risk of bearing a child with a neural tube defect. Excessively high intake of folic acid can mask vitamin B_{12} deficiency in elderly people; the committee looks at both conditions. It then discusses the current exemption policy relating to voluntary fortification of specific products with folic acid. Finally the committee examines three calculations of the possible effects of fortifying staple foodstuffs with folic acid.

7.1 Effects of information on the use of folic acid supplements

In 1993 the Health Council advised women wishing to conceive to take a dietary supplement containing 400 micrograms of folic acid a day from at least four weeks before conception to eight weeks into the pregnancy.[26] On the basis of this advice, a one-off national education campaign was held in 1997/1998 to highlight the importance of taking additional folic acid around the time of conception. Following the information campaign the number of women who had heard of folic acid rose from 41.7 per cent just before the campaign to 77.3 per cent one year after the campaign. Correct use of additional folic acid around the time of conception rose from 4.8 to 21.1 per cent, while the use of folic acid during part of the recommended period rose from 25.1 to 53.1 per cent.[163]

So far, efforts to provide information in the Netherlands have had the greatest impact on highly-educated women of Dutch background (table 5.5).[109,111-116,164] About half the women in this category use a folic acid supplement correctly around the time of conception, one of the highest percentages in the world.[164] The figures for women of non-Dutch background and women with a low level of education are much lower. The percentage ranges from 8 to 25 among women of non-Dutch background and is 22 per cent among women with a low level of education. Experience from information campaigns conducted in other countries has also shown that it is difficult to reach women who were born in another country or who have a low level of education.[164]

The main reason why women do not take extra folic acid around the time of conception is because they are not aware of the importance of doing so. This lack of awareness is closely related to inability to understand Dutch or a low level of education.[113,115,165,166] This finding is in line with the Health Council's observation in 2006 that mass-media campaigns can only be effective if they are combined with other targeted activities.[167]

Information campaigns cannot ensure that all women take extra folic acid around the time of conception correctly, as some pregnancies are unplanned. It is estimated that 9 to 15 per cent of pregnancies in the Netherlands are unplanned. The EUROCAT study found that approximately 15 per cent of pregnancies in the Netherlands were unplanned.[109,110] Another study conducted at the time of the high-profile media campaign in 1996 found that 24 per cent of pregnant women of non-Dutch background and 8 per cent of pregnant women of Dutch background had not planned to become pregnant, giving an average of 9 per cent.[113] The Amsterdam Born Children and their Development study asked indirectly whether the pregnancy had been planned. In reply, 7.5 per cent of the 8,153 women said that they agreed, or agreed completely, with the statement that they had not actually wanted to become pregnant (again)*. In addition, around 2 to 9 per cent (the exact figure varies according to the respondents' ethnic background) of women who had not taken a folic acid supplement around the time of conception said that they had become pregnant earlier than planned.[165]

Some women who knew about folic acid supplements did not use them in spite of their awareness.[112] There are women who are opposed to taking any supplements during pregnancy. Among the women taking part in the Amsterdam Born Children and their Development study, this figure varied according to ethnic background from 1 to 8 per cent.[165]

* Personal communication, M. van Eijsden, M.Sc., 2 May 2007.

There has only been one national information campaign. Since then, information has tended to be provided via intermediaries* who come into contact with women who want to conceive or are already pregnant. However, a survey conducted by the Nutrition Centre in 2003 found that this method of supplying information is not always ideal. The intermediaries are fully aware that many women receive information too late because they do not talk about their wish to conceive with the intermediary. Preconception care in the Netherlands is at a very early stage of development.[168] In its advisory report on the subject, the Health Council concluded that an integrated approach to preconception care was the best way of giving women information about risks, how to look after their health, and what procedures they might have to undergo before and during pregnancy.[169]

A study into preconception care at GP clinics found that 86 per cent of women receiving preconception care took folic acid supplements at the right time around the time of conception, compared with 53 per cent in the group receiving standard care. Women who were born in the Netherlands accounted for a higher proportion of the group receiving preconception care (95 per cent compared to 88 per cent in the other group). The same slight imbalance is found in the percentage of women with a high level of education (45 per cent compared to 38 per cent).[170]

The government set up a folic acid working party in 2005, aiming to ensure that by 2010 70 per cent of women take a folic acid supplement correctly around the time of conception. During the campaigns held in 2006 and 2007 the focus lay on women of non-Dutch background and women of low socio-economic status. The working group's activities include various information projects delivered by pharmacists, obstetricians and child health centres, and the 'Folic Acid Umbrella, Encouraging Preventive Use of Folic Acid' project run by the Stichting Erfocentrum, a foundation working in the field of hereditary diseases. One of the features of this project is a website, 'slikeerstfoliumzuur.nl', which highlights the importance of taking folic acid to women wishing to conceive.[171]

7.2 Number of neural tube defects

7.2.1 Prevalence among babies born alive and stillborn babies

The national records kept by obstetricians and neonatologists show that 152 children were born with a neural tube defect in the Netherlands in 1998. The average

* GPs, obstetricians, gynaecologists, nutritionists, doctors working at child health centres or youth health centres, pharmacists and chemists.

prevalence of a neural tube defect between 1995 and 1998 was 7.6 per 10,000 live births and 11.9 per 10,000 live births and stillbirths.[144] These records cover about 90 per cent of all pregnancies from sixteen weeks gestation onwards in the Netherlands. However, they are less extensive than those of the European Surveillance of Congenital Anomalies (EUROCAT records).[172]

The EUROCAT records for northern Netherlands show slightly lower figures for the period from 1981 to 2004. They indicate the prevalence of neural tube defects as being 5.8 per 10,000 live births and 9.9 per 10,000 live births and stillbirths. These figures include pregnancies which were terminated because the foetus had a neural tube defect.

The lower figures for northern Netherlands may be attributable to the fact that they do not include neural tube defects caused by chromosomal or monogenetic abnormalities or miscarriages occurring before 24 weeks. This is because the investigators were interested in the effect of folic acid on the occurrence of neural tube defects and assume that it can only reduce the occurrence of other kinds of neural tube defects, i.e. those with a multifactorial causation. Another reason might be that this data was collected with the consent of the parents and the voluntary cooperation of doctors and obstetricians.[172]

Between 2000 and 2004, prevalence of neural tube defect was 6.6 per 10,000 live births and stillbirths*. On the basis of this figure, it has been estimated that 124 babies were born or stillborn with a neural tube defect in 2005**.

7.2.2 *Trends*

The occurrence of neural tube defects fell in the first ten years after the 1995 information campaign. EUROCAT records show a statistically significant fall in the occurrence of neural tube defects over the past decade. As figure 7.1 shows, the decline started in 1996 and has continued since then. This may be partly due to the increase in consumption of additional folic acid around the time of conception, but other factors may also be involved. Data from recent years is not complete, as in some cases abnormalities are not reported until years after birth.[172] Another study based on data from three perinatal databases, the Netherlands Paediatric Surveillance Unit and a patients' association found that there had been no fall in the occurrence of neural tube defects in the first three years after the information campaign.

* Personal communication by Dr. H.E.K. de Walle 22-11-2007.

** The numbers of live births and stillbirths (from 28 weeks gestation onwards) in 2005 were 187,910 and 760 respectively. The prevalence estimates for 2005 may be a slight underestimate because miscarriages between 24 and 28 weeks gestation are included in the numerator but not in the denominator.[191]

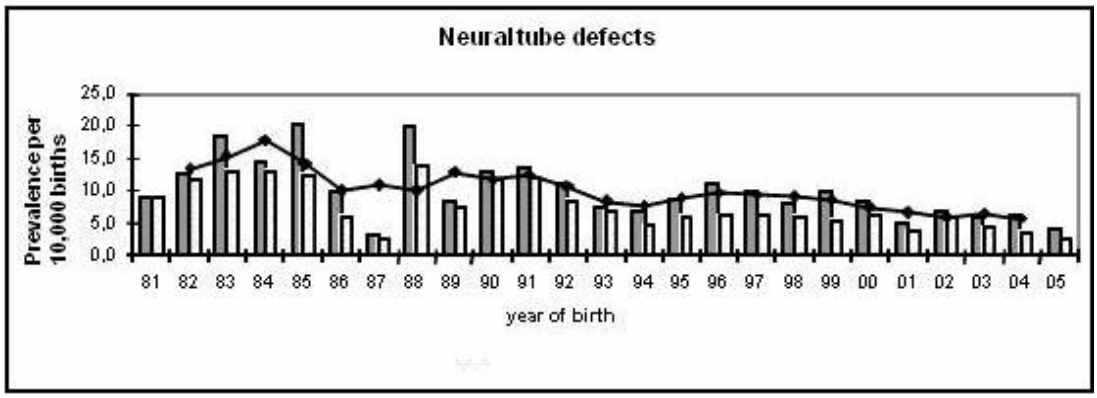

Figure 7.1 The occurrence of neural tube defects in foetuses between 1981 and 2005 as shown by the EUROCAT records (prevalence per 10,000 births). The shaded columns show the total number of children with a neural tube defect (live births, stillbirths and terminated pregnancies), and the blank columns show the total number excluding terminated pregnancies. The trend line shows the three-year average of occurrence in the year in question, the year before and the year after. This chart was taken from reference [172].

Prevalence in 1998 was one of the lowest in the period from 1988 to 1998.[163] The difference in findings between the two studies may be due to the fact that the latter study covered a shorter period.

7.2.3 Ethnic variations

Women of Mediterranean background may be at greater risk of bearing a child with a neural tube defect than women of Dutch background. A five-year cohort study based on data from national records of obstetricians and neonatologists covering the period from 1996 to 2000 found that women with a Mediterranean background had a 40 per cent greater chance of this outcome (OR=1.38; 95% confidence interval 1.12-1.69)*.[173] This may be because women with a Mediterranean background are less likely to take a folic acid supplement around the time of conception.

7.3 Masking vitamin B_{12} deficiency

People with inadequate vitamin B_{12} status are at risk of having this deficiency masked if they take too much folic acid. This invisible deficiency can lead to irreversible neurological conditions. That is why some organisations and authors

* Personal communication by Dr. S. Anthony 02-08-2007.

have recommended adding vitamin B_{12} to foods fortified with folic acid.[174-177] However, the committee doubts whether this would be beneficial.

There are indications that around 12 to 25 per cent of elderly people have an inadequate vitamin B_{12} status (table 7.1)*.[31,75,100,101,178,179] Vitamin B_{12} deficiency does not seem to affect only elderly people. The Amsterdam Health Monitor Study found that approximately 14 per cent of participants had vitamin B_{12} deficiency**. Vitamin B_{12} deficiency was most common among men and women of Turkish origin.[98] However, these figures and the figures from some of the studies on elderly people [100,101,178] may overestimate the real number of people with vitamin B_{12} deficiency because the diagnoses were based only on serum vitamin B_{12}. Additional measurements of methylmalonic acid and homocysteine levels produce a more specific diagnosis.[180]

Vitamin B_{12} deficiency in vegans and people who follow a macrobiotic diet is caused by an excessively low intake of vitamin B_{12}. In elderly people, the cause is usually a decline in the absorption of vitamin B_{12} from food: they can absorb crystalline vitamin B_{12}, but little or no vitamin B_{12} that is bound to dietary protein. The Health Council's 2003 advisory report *Dietary reference intakes. Vitamin B_6, folic acid and vitamin B_{12}* advised elderly people with serum cobalamin levels at the low end of the normal range and elevated methylmalonic acid levels to take a supplement containing at least 2 micrograms of crystalline vitamin B_{12} a day.[21] However, the standard treatment for patients with anaemia caused by severe vitamin B_{12} deficiency consists of injections of 1 mg of vitamin B_{12} every one to three months, or taking an extra 300 to 1000 micrograms of vitamin B_{12} a day.[23]

A dose-response study carried out in 2005 found that doses of at least 650 micrograms of crystalline vitamin B_{12} a day were needed to normalise plasma methylmalonic acid levels among elderly people with mild or severe vitamin B_{12} deficiency*** within a period of sixteen weeks. Daily doses of 2.5 to 250 micrograms of crystalline vitamin B_{12} led to small but significant reductions in plasma methylmalonic acid levels, but did not restore normal values within sixteen weeks.[181] Another study conducted on elderly people with impaired dietary vitamin B_{12} absorption who were given an extra 80 micrograms of vitamin B_{12} a day for thirty days found the same results.[182] There has not yet been sufficient

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* There are no fixed cut-off points determining the line between an inadequate vitamin B_{12} status and a mild vitamin B_{12} deficiency. This is why the status parameters used to determine marginal B_{12} status or mild B_{12} deficiency overlap.

** Vitamin B_{12} deficiency is defined as a serum cobalamin level below 150 pmol per litre.

*** Mild or severe vitamin B_{12} deficiency is defined as a serum cobalamin level of between 100 and 300 pmol per litre and a plasma methylmalonic acid level above 0.26 micromols per litre.

research into the long-term effects of relatively low doses on the vitamin B_{12} status of elderly people with impaired dietary vitamin B_{12} absorption.

The amount of vitamin B_{12} needed to improve the vitamin B_{12} status of elderly people with impaired absorption is therefore around 200 to 900 times as high as the adequate intake or recommended dietary allowance of vitamin B_{12} for children and adults*. [21] The committee considers that this dose is too high to be achieved by means of vitamin B_{12} fortification. It is true that no safe upper level of intake has been set for vitamin B_{12} as there are no indications that a high dose of vitamin B_{12} is harmful. However, insufficient research has been carried out into the possible effects of such a high dose (0.6-1 mg of vitamin B_{12} a day) on children, for example.[23]

Table 7.1 Prevalence of inadequate vitamin B_{12} status among adults.

		Inadequate vitamin B_{12} status	
Study	N, gender, age	Definition	%
General Health Monitor study, Amsterdam 2004[98]			
	210 Dutch men aged 18 or over	Serum cobalamin < 150 pmol/l	13
	189 Turkish men aged 18 or over		16
	181 Moroccan men aged 18 or over		6
	289 Dutch women aged 18 or over		10
	212 Turkish women aged 18 or over		32
	145 Moroccan women aged 18 or over		11
Van Asselt 1998[31]			
	105 men and women aged 74-80	Plasma cobalamin < 260 pmol/l & methylmalonic acid > 0.32 micromol/l	24
Van Asselt 2001[178]			
	189 men and women aged 64-89	Plasma cobalamin < 150 pmol/l	15
Dhonukshe-Rutten 2005[179]			
	615 men and women aged 70 or over[a]	Serum cobalamin 100-300 & methylmalonic acid ≥ 0.30 micromol/l	18
Eussen 2006[75]			
	896 men and women aged 70 or over	Serum cobalamin 100-200 or ≥ 200-300 & methylmalonic acid ≥ 0.32 micromol/l & creatinine ≤ 120 micromol/l	25
Manders 2006[100]			
	43 men and women aged 65 or over[a]	Serum cobalamin < 160 pmol/l	12
De Jong 2001[101]			
	130 men and women aged 70 or over[b]	Serum cobalamin < 221 pmol/l	44

a Elderly people not living independently.
b Frail elderly.

* Adequate intake of vitamin B_{12} for children up to the age of 14 varies with age from 0.7 to 2.0 micrograms a day, while the recommended dietary allowance for people aged 14 and over is 2.8 micrograms a day.

7.4 Effects of voluntary fortification

A decision handed down by the Court of Justice of the European Communities in 2004[5] means that the Netherlands can no longer refuse requests for exemption for folic acid fortification on the basis that there is no nutritional need. Consequently, a general exemption exists for the addition of up to 100 micrograms of folic acid per 100 kcal to specific foods.[6] This exemption was introduced in March 2005 and will remain in place until new European legislation takes effect. Manufacturers may apply for individual exemptions if they wish to add higher amounts of folic acid. The general exemption is temporary and does not restrict the amount of folic acid per portion.

The formula used to calculate the exemption figure was based on the safe upper level of intake for adults. It did not take account of the safe upper level of intake for children, which varies with age from 200 to 600 micrograms of folic acid a day. It would not otherwise have been possible to grant an exemption for the addition of folic acid to food. The reason given for not taking the upper limits for children into account is that these limits are derived from the safe upper level of intake for adults, based on masking of vitamin B_{12} deficiency. This condition does not seem to affect children to any significant extent. Furthermore, the European Commission's directive on cereal-based processed food and baby food for infants and young children limits the folic acid content of these products to 50 micrograms per 100 kcal.[183]

The exemption was also calculated on the assumption that 15 per cent of energy intake would be fortified, and that the worst-case scenario for folic acid intake from supplements would be 300 micrograms a day for children and 600 micrograms a day for adults.

The new European regulation that took effect in 2007 allows nutritional claims* to be made on products that meet the ‘nutritional profile’. This nutritional profile has yet to be determined and is expected to contain thresholds for a limited number of nutrients, such as fat, sugar and salt. Manufacturers are also permitted to make a nutritional claim on products that meet the profile for all except one nutrient, provided that they make this exception clear on the label next to the claim. It is therefore possible that manufacturers may add extra folic acid to products that meet the profile or meet the profile for all nutrients except one. This could be the case for fruit juice or soft drinks, for example. If a fruit drink or soft drink is fortified to the maximum extent, 100 ml (= 44 kcal) will already

* For example, ‘contains folic acid’ or ‘rich in folic acid’.

contain approximately the adequate folate intake for children aged 1 to 3 (85 micrograms of dietary folate equivalents), and drinking 450 ml would take a child above the safe upper level of intake of folic acid for this age group. Children aged 4 to 8 would cover their folate requirements (150 micrograms of dietary folate equivalents) with about 175 ml of fruit drink or soft drink. Drinking 800 ml would take them above the safe upper level of folic acid intake.

It appears likely that many manufacturers will add less than the maximum permitted amount of folic acid. They need less of the recommended dietary allowance - 15% (30 micrograms of folic acid per 100 g) or 30% (60 micrograms per 100 g) - in order to make a nutritional claim on the label. However, there are already some products on the Netherlands market that already supply a quarter to a half of this amount in a single portion.

At present there is not enough data to allow the intake of folic acid from specific products that have been fortified on a voluntary basis to be assessed and the effects of this on the folate supply of various groups of the population to be determined.

Nevertheless, the committee thinks it likely that children may persistently exceed the safe upper level of intake simply by consuming specific products that have been fortified with folic acid on a voluntary basis.

7.5 Possible effects of mandatory fortification of staple foodstuffs

7.5.1 Scenario calculations

In 2005 the Netherlands Organization for Applied Scientific Research TNO performed various scenario calculations to determine folic acid intake levels if bread and bread substitutes were to be fortified.[184] These calculations do not take account of intake of dietary folate. One of the reasons for this was that a safe upper level of intake has been determined only for folic acid, not for dietary folate.[21] The calculation assumed concentrations of 200 micrograms of folic acid in 100 g of flour made from grains after processing or in the final product. It was assumed that concentrations of folic acid in breakfast cereal would not exceed 50 micrograms per 100 kcal, which is the statutory maximum for infants and young children. These scenario calculations are based on data from the third food consumption survey (1997/98) and the food consumption survey of young adults (2003). The five scenarios investigated ranged from fortification of bread to fortification of bread and bread substitutes in combination with breakfast cereals that are eaten cold and/or hot.

The various scenarios produced average habitual intake figures of 165 to 169 micrograms of folic acid a day for girls aged 14 to 18, and 154 to 159 micrograms of folic acid a day for women aged 19 to 50. In all scenarios the additional intake of folic acid was highest among boys aged 14 to 18: 214 to 232 micrograms a day based on median figures (annex D, table D.1).

In calculations based on the assumption that the fortified foods are the only source of folic acid, the number of children aged between 1 and 3 with a habitual intake above the safe upper level of intake does not exceed 2 per cent. In this case, no other groups have an intake above the safe upper level of intake. If it is assumed that all children are also taking a folic acid supplement, then the percentage of children aged 1 to 3 who have an intake above the safe upper level rises to up to 10 per cent. The calculation assumed that the amount of folic acid consumed in the form of supplements would be 50 micrograms a day for children aged up to 8 and 100 micrograms a day for people aged 9 or over. The extent to which intake exceeds the safe upper level is marginal in all the scenarios. Without supplementation, the habitual intake of children aged 1 to 3 is no more than 4 to 10 micrograms of folic acid a day above the safe upper level of intake. With supplementation this rises to up to 54 to 60 micrograms a day.

The percentage of children with an intake above the safe upper level is an overestimate in the scenarios with supplementation, as they were worked out on the assumption that all children would be taking a folic acid supplement. In fact, far fewer children actually take a supplement containing folic acid; the third food consumption survey (1997/1998) found that the figures varied from 4 to 9 per cent.[108] On the other hand, the extent to which the intake of children who do take a supplement would exceed the safe upper level might be an underestimate as the assumed level of folic acid from supplements is too low. If the recommendations on folic acid supplement packaging are followed, the daily dose should be 100 micrograms for children and 400 micrograms for adults.[185]

The habitual intake of folic acid in other groups does not exceed the safe upper level of intake (table 7.2). The scenario calculations do not take account of any folic acid consumed in specific foods that are fortified on a voluntary basis.[184]

The Dutch National Institute of Public Health and the Environment (RIVM) has taken these scenario calculations and worked out the effects on the extent to which the safe upper level of intake would be exceeded if the fortification level was 150 micrograms of folic acid per 100 grams of flour for bread and bread substitutes rather than 200 micrograms. At this level, folic acid intake appears to rise in girls aged between 15 and 17, reaching 126 micrograms a day. The figure for women between 18 and 50 is 117 micrograms. In addition, the extent to which

Table 7.2 Scenario calculations of the percentage of people with an intake above the safe upper level of intake in various fortification scenarios, both with and without consumption of folic acid supplements. The safe upper level of intake is not exceeded in the other population groups.[184]

Population group (N)	Children aged 1 to 3 (254)		Children aged 1 to 3 (254)	
Safe upper level of intake (micrograms per day)	200		150[a]	
Supplementation	No		Yes	
Intake data	Observed	Habitual	Observed	Habitual
Scenario 1 (%)[b]	0.4	n.c.[c]	5.1	n.c.[c]
Scenario 2 (%)[b]	0.4	n.c.[c]	6.7	n.c.[c]
Scenario 3 (%)[b]	0.4	n.c.[c]	7.5	n.c.[c]
Scenario 4 (%)[b]	2.4	2	11.8	10.3
Scenario 5 (%)[b]	2.4	2	12.6	10.3
Population group (N)	Children aged 4 to 8 (431)		Boys aged 9 to 13 (197)	
Safe upper level of intake (micrograms per day)	300[a]		400[a]	
Supplementation	Yes		Yes	
Intake data	Observed	Habitual	Observed	Habitual
Scenario 1 (%)[b]	0	0	0	0
Scenario 2 (%)[b]	0.2	0	0.5	0
Scenario 3 (%)[b]	0.2	0	0.5	0
Scenario 4 (%)	0.2	0	0.5	0
Scenario 5 (%)[b]	0.2	0	0.5	0

a Safe upper level of intake, taking account of any folic acid consumed from supplements. The daily folic acid intake figures for children up to 8 years old and for boys aged 9 to 13 are 50 micrograms and 100 micrograms respectively lower than the safe upper level of intake.

b Scenario 1: fortification of bread; scenario 2: fortification of bread and bread substitutes, scenario 3: fortification of bread, bread substitutes, and breakfast cereals that are eaten cold; scenario 4: fortification of bread, bread substitutes, and breakfast cereals that are eaten hot; scenario 5: fortification of bread, bread substitutes, and breakfast cereals that are eaten hot or cold. The fortification level is 200 micrograms of folic acid per 100 g of processed flour.

c N.c., not calculated, as it was impossible to convert the figures into a normal distribution.

the safe upper level of intake is exceeded by children aged 1 to 3 is half the level compared to fortification at 200 micrograms of folic acid per 100 grams of flour (annex D, table D.2).[185]

7.5.2 *Risk-benefit analysis*

The starting point for the risk-benefit analysis is that the anticipated positive effect of the policy chosen must outweigh any adverse effects that might occur. This analysis takes careful account of any positive and negative health effects associated with a policy. The key point is the question of whether the need of a particular population group for additional folic acid may be harmful to another population group, and what policy can achieve the best balance between positive

and negative effects. These effects are difficult to compare because they are expressed in different units.

In a quantitative risk-benefit analysis this is overcome by expressing the positive and negative effects in disability-adjusted life years, DALYs*.[186] These units indicate how many years of healthy life are lost due to premature death and the burden of illness in the years when people are living with the disease. The severity of a condition is converted into a weighting factor in this process. A risk-benefit analysis can only take account of any positive and negative health effects for which a dose-effect relationship is known. It cannot take account of health effects that are plausible but for which not enough data is available to quantify an effect.

The RIVM has linked a risk-benefit analysis to scenario calculations looking at the effect of various levels of folic acid fortification of bread and bread substitutes on the intake of this substance. The fortification levels used in the model are expressed in micrograms of folic acid. They correspond to an increase in intake of 100 to 150 micrograms of folic acid by women of childbearing age.

The risk-benefit analysis shows the effects of fortifying bread with various concentrations of folic acid on four different outcomes expressed in DALYs. They are risk of:

- a neural tube defect in the foetus,
- folate deficiency (megaloblastic anaemia)**,
- masking of vitamin B_{12} deficiency and
- colorectal cancer. As the committee is of the opinion that data on colorectal cancer is insufficiently reliable (the same applies to data on strokes), this data is not included in table 7.3.

The RIVM's risk-benefit analysis calculates that, expressed in DALYs, the increased risk of masking vitamin B_{12} deficiency associated with fortification is very small compared to the decline in the risk of a child with a neural tube defect. The estimated gain is approximately 1400 to 2100 DALYs smaller for a fortification level of 150 micrograms folic acid per 100 grams flour in the final product compared to higher fortification levels (175 and 200 micrograms folic acid per 100 grams in the final product).[185]

As the risk-benefit analysis does not take account of current consumption of folic acid supplements, the positive health effects will probably turn out to be smaller and the negative effects greater than shown in the analysis. That is

* DALYs were developed by the World Health Organisation.
** Intake of folic acid and dietary folate were combined only for determining the risk of folate deficiency.

Table 7.3 The quantified health effects of fortifying bread and bread substitutes with different levels of folic acid compared to no fortification. The health effects are expressed as absolute and relative changes in occurrence and as changes in DALYs for neural tube defect, folate deficiency (megaloblastic anaemia), masked vitamin B_{12} deficiency and total change in DALYs.[a, 185]

	Level of fortification in micrograms of folic acid per 100 g of flour in the final product		
	150	175	200
Neural tube defects			
Absolute change in occurrence (persons/year)	-10	-32	-48
Relative change in occurrence (%)	-5	-16	-25
Change in DALYs	-661	-2,074	-3,159
Folate deficiency			
Absolute change in occurrence (persons/year)	-2,692	-2,869	-3,018
Relative change in occurrence (%)	-48	-51	-54
Change in DALYs	-27	-29	-30
Masking vitamin B_{12} deficiency			
Absolute change in occurrence (persons/year)	33	38	44
Relative change in occurrence (%)	1	1	1
Change in DALYs	33	38	43
Total change in DALYs	-655	-2,065	-3,146

a The effects of folic acid fortification on colorectal cancer are not included in this table because they are not sufficiently clear.

because there are indications that the preventive effect of folic acid is greater when intake rises from 0 to 100 micrograms per day than when it increases from 400 to 500 micrograms per day.[27,28,187]

7.5.3 *Advantages and disadvantages of various policies*

The committee has devised an estimate of the occurrence of foetal neural tube defects for various levels of folic acid fortification and supplementation. The estimate was carried out in two ways in view of the uncertainties in the available data. The approach taken by the UK *Scientific Advisory Committee on Nutrition* was followed.[48] The first approach, referred to below as the Daly method after the lead author of the article, is based on 1. a linear interpolation between observed changes in the risk of a child with a neural tube defect and changes in the folate content of red blood cells, and 2. the effect of an increase in folic acid intake on the folate content of red blood cells.[27,187] The second approach, referred to below as the Wald method after the lead author of the article, is based on serum folate levels, using data from the same observational study[27,187] but performing a more extensive statistical analysis.[28] A number of different scenarios were compared to produce the calculations:

- Supplementation with 400 micrograms of folic acid a day, with 35, 50, 70 or 80 per cent of women taking the supplement correctly.
- Fortification of staple foodstuffs at a level leading to an increase in folic acid intake of 100 micrograms a day on average.
- The combination of these scenarios.

The calculation assumed that 145 children with a neural tube defect would be born each year in the Netherlands if additional folic acid is not taken in the form of a supplement or specific foods fortified with folic acid on a voluntary basis (see annex E for the calculation) and no pregnancies are terminated on the grounds of this condition. It is also assumed that 15 per cent of the pregnancies are unplanned, so that in theory 22 of the 145 children with a neural tube defect are the result of an unplanned pregnancy.[109,113]

The calculations are designed to compare the effects of the various policies. They do not take account of incorrect use of folic acid supplements around the time of conception, consumption of multi-vitamins containing folic acid or specific foods fortified with folic acid on a voluntary basis as this would introduce too much uncertainty. In reality, these factors may help prevent neural tube defects. This means that the estimate of the effect of fortification and supplementation set out below is probably an over-estimate.

The calculations show that if 50 per cent of women follow the advice to take a supplement containing 400 micrograms of folic acid a day from at least four weeks prior to conception until eight weeks into their pregnancy, 7 to 9 fewer children will be born with a neural tube defect each year than is the case at the moment, with 35 per cent of women taking the substance correctly (table 7.4). The reduction would be 16 to 20 a year if 70 per cent of women followed the advice, which is the target of the current information campaigns.

It is estimated that if fortification of staple foodstuffs is introduced in the current situation, 15 fewer children will be born with a neural tube defect each year.

The calculation shows that the effects of the two policies cannot simply be added together: if consumption of folic acid supplements improves to 50-70%, then fortification of staple foodstuffs reduces the number of children born with a neural tube defect by 13 and 10 a year respectively.

Table 7.4 Comparison of the effects of various policies on the occurrence of foetal neural tube defects.

Policy	Folic acid intake from supplements	Correct use	Folic acid intake from fortified foodstuffs	Exposed	Neural tube defects			
					Wald (2001)[a]	Reduction from the current situation	Daly (1995/1997)[b]	Reduction from the current situation
	micrograms per day	%	micrograms per day	%	N per year	%	N per year	%
Supplementation	400	0	0	0	145	n.a.[c]	145	n.a.
	400[d]	35[d]	0	0	130	0	125	0
	400	50	0	0	123	5	116	7
	400	70	0	0	114	12	105	16
	400	80	0	0	110	16	99	21
Fortification of staple foodstuffs	0	0	100	100	126	3	113	10
Supplementation and fortification of staple foodstuffs	400	35	100	100	115[e]	11	n.a.	n.a.
	400	50	100	100	110	15	n.a.	n.a.
	400	70	100	100	104	20	n.a.	n.a.

a Effects on the basis of the approach taken by Wald et al.[28]
b Effects on the basis of the approach taken by Daly et al.[27,187]
c N.a., not available.
d Current situation.
e This effect is achieved if 35% of women take a folic acid supplement as recommended around the time of conception and 100% of women have a folic acid intake from fortified staple foodstuffs of 100 micrograms a day.

7.6 Ethical considerations

Various ethical considerations play a part in answering the question of which policy is best able to improve folic acid intake by women around the time of conception in order to reduce the risk of bearing a child with a neural tube defect. The considerations relate to welfare (helping women who wish to have a child to have a healthy child), respect for autonomy (no unjustified interference in peoples' private lives) and not doing harm (preventing damage to health due to the measure in question).

The government could consider expanding information campaigns and introducing preconception care in order to reduce the risk of women having children with neural tube defects. If as a result 80 per cent of women take a folic acid supplement around the time of conception in accordance with the recommendations, there will be a 16 to 21 per cent fall in the number of children born with a neural tube defect (a decrease of 20 to 26 children a year).

The government could also consider complementing these policies with a low level of folic acid fortification of staple foodstuffs, increasing the folic acid

intake of women of childbearing age by an average of 100 micrograms a day. The benefit of this fortification is that it would create a basic level of folic acid intake for women who cannot respond to information campaigns (because their pregnancy was unplanned) or who are likely to be reached less well than other women (because they have a low level of education or are of non-Dutch origin). Fortification of staple foodstuffs ensures that almost all women will at least have a basic level of intake. The same is not true of fortification of specific products as women cannot be forced to consume specific products that have been fortified with folic acid. The health benefit of increasing intake of folic acid by 100 micrograms a day by fortifying staple foodstuffs is the 5 to 11 per cent reduction in the risk of neural tube defect (equivalent to up to 15 cases a year).

However, fortification of staple foodstuffs does interfere with private life as practically all foodstuffs in a particular product group (such as bread and bread substitutes) would be fortified, apart from organic products. In this situation consumers would have to go out of their way to avoid purchasing fortified products. In contrast, fortification of specific products does not interfere in peoples' private lives in the same way, as consumers would still have access to unfortified products within particular product groups. The same applies to information and preconception care. The question is whether interference with private life by fortifying staple foodstuffs can be justified when it is weighed up against the health benefit of the measure.

It is also important to bear in mind that folic acid fortification of staple foodstuffs creates a risk to a part of the population that would not have any health benefit from the measure. It has been estimated that 33 elderly people would suffer irreversible neurological symptoms as a result of masking of vitamin B_{12} deficiency if staple foodstuffs were fortified with folic acid.[185]

Furthermore, the possibility that folic acid may accelerate the transformation of a benign growth into a malignant tumour cannot be ruled out.[35,36,56,63,64] The real problem is that we do not know what dose of folic acid can encourage the development of cancer, especially colon cancer. Data from intervention studies and epidemiological studies demonstrate an increase in risk at doses of 800 micrograms of folic acid a day and above.[35,36,56,63,64]

Policymakers might decide to adopt a strategy based on the precautionary principle when determining their choices on fortification as these potentially serious effects are still very unclear. Policymaking in relation to this strategy takes account of a worst-case scenario, even though evidence for the risk is not very strong*.[188]

* The Health Council will be publishing an advisory report on the precautionary principle in the course of 2008.

Policies must also take account of the fact that the more women take folic acid supplements around the time of conception, the smaller the health benefits of mandatory fortification as described above will be. Another factor that might play a part in policymaking is the question of whether information has already had enough time to achieve the optimal effect, irrespective of the effect of preconception care. Another option is to bring the importance of consuming products that have been fortified with folic acid to the attention of women of childbearing age by means of information campaigns and preconception care. These products could be highlighted by labels. It is conceivable that good preconception care might eventually almost entirely eliminate the need for fortification.

Finally, it is important that the effects of the policies which are chosen are monitored. This must involve reviewing the occurrence of foetal neural tube defects, the intake of folic acid from food by children, women of childbearing age and elderly people, and the occurrence of masking of vitamin B_{12} deficiency, stroke, and colon cancer.

7.7 Conclusion

Information campaigns have certainly brought about some improvements to the consumption of folic acid around the time of conception, particularly among highly-educated women of Dutch background. The number of foetuses with a neural tube defect has also fallen over the past decade. So far, information campaigns have not had a sufficiently strong impact on women of non-Dutch background or a low level of education. This might mean that women of Mediterranean background are at greater risk of having a child with a neural tube defect than Dutch women.

Preconception care might lead to marked improvements in folic acid intake. However, information campaigns and preconception care will never be able to ensure that all women take a folic acid supplement around the time of conception. This is because some pregnancies in the Netherlands are unplanned (about 9 to 15 per cent). Furthermore, some women are aware of the advice but do not take a folic acid supplement, or start to take one too late.

There are two forms of fortification: fortification of specific foodstuffs and fortification of staple foodstuffs. The disadvantage of fortifying specific products in an attempt to prevent neural tube defects is that it is by definition not certain whether they will reach the target group. The committee also thinks that it is likely that children could regularly exceed the safe upper level of intake in view of the current permitted level of fortification. That is because the safe upper lev-

els of intake for children were not taken into account when the exemption for folic acid fortification was calculated.

Fortification of staple foodstuffs is easier to control than fortification of specific products. Fortification of staple foodstuffs can reduce the risk of women bearing children with a neural tube defect. Scenario calculations show that this health benefit expressed in DALYs far outweighs the increased risk of masking vitamin B_{12} deficiency. In addition, there are now analytical methods for determining vitamin B_{12} status that also work in individuals with a high folic acid intake. These can be applied to individuals with neurological symptoms in order to ascertain whether they are due to vitamin B_{12} deficiency.

The harmful effects that are discounted in the DALYs (masking of vitamin B_{12} deficiency and anaemia caused by folate deficiency) are not relevant to children. That is why children do not feature in the risk-benefit analysis. Fortifying bread and bread substitutes at 200 micrograms of folic acid per 100 g of flour in the final product will cause 2 per cent of children to have folic acid intake levels of up to 4-10 micrograms a day above the safe upper level of intake. If all children were to take a folic acid supplement, which is not the case, 10 per cent of children would have folic acid intake levels up to 56-60 micrograms a day above the safe upper level of intake. In fact, only 4 to 9 per cent of children take supplements containing folic acid. Therefore, few children will have excessively high intake levels.

A third calculation shows that the combination of fortification of staple foodstuffs with supplementation would prevent more neural tube defects than either of these two policies alone. The effect of fortifying staple foodstuffs declines as the percentage of women taking folic acid supplements increases.

The committee believes that the calculations give an impression of the relative effects of various policies and fortification scenarios, but that the figures cannot be used in isolation.

Legal and ethical aspects have a part to play alongside the considerations set out above. An important question here is whether it is acceptable to expose the entire population to folic acid, bearing in mind that most people will not benefit personally because the medical advantages are relevant only for a small group. As the effects of high doses of folic acid on colon cancer are unclear, it would be advisable to choose a strategy in relation to fortification on the basis of the precautionary principle*.

* The Health Council will be publishing an advisory report on the precautionary principle in the course of 2008.

Chapter 8

Conclusions and recommendations

8.1 New scientific developments

The evidence of a link between folate and cancer is not sufficiently strong

Since the publication of dietary reference values for folate in 2003, new studies have been published into the relationship between folate and the risk of cardio-vascular disease, colon cancer and other conditions.

There are suggestions that both a low intake of dietary folate (150 to 300 micrograms of dietary folate equivalents) and a high intake of folic acid from supplements (0.8-2.5 milligrams of folic acid a day) may be associated with a higher risk of cancer, especially colon cancer, compared to an intake of 300 to 500 micrograms of dietary folate equivalents. However, the evidence is not yet strong enough to allow conclusions to be drawn as to the positive or negative role that dietary folate may play in the appearance, growth or treatment of cancer in general and colon cancer in particular.

The committee also considers the level of evidence of studies carried out into links with other conditions to be inadequate at present. It has therefore not included these new scientific insights in its risk-benefit analysis.

However, there are new indications that require further investigation. Taking folic acid around the time of conception also appears to protect the foetus against congenital abnormalities other than neural tube defect. There are also indications that high folic acid intake may increase the risk of multiple pregnancies. And

there are indications that folic acid supplementation may reduce the risk of stroke. As far as the effect of extra folic acid on elderly people is concerned, there is as yet insufficient evidence to determine whether it may have a negative impact on the cognitive function of elderly people and whether it might protect them against depression, fractures and hearing loss.

The safe upper level of intake also applies to people with inadequate vitamin B12 status

The committee assumes that the safe upper level of intake of 1 milligram folic acid a day also applies to people with inadequate vitamin B_{12} status or mild vitamin B_{12} deficiency. In its advisory report *Risks of folic acid fortification* produced in 2000, the Health Council mentioned the possible negative effects of excessively high folic acid intake on the cognitive function of people with inadequate vitamin B_{12} status. The current upper level is based on patients with neurological symptoms caused by undiagnosed severe vitamin B_{12} deficiency.

The research currently available is limited and inconclusive on this point. However, the committee thinks it unlikely that folic acid fortification would put people with inadequate vitamin B_{12} status at greater risk of neurological symptoms than people with severe vitamin B_{12} deficiency. In other words: the committee thinks that the safe upper level of intake offers sufficient protection to people with inadequate vitamin B_{12} status.

8.2 Folic acid intake in the Netherlands

The use of folic acid supplements by women around the time of conception is inadequate

The number of expectant mothers who take additional folic acid correctly - from at least four weeks before conception to eight weeks after conception - has increased over the past decade. Intake of folic acid around the time of conception is certainly among the highest in the world, particularly among highly-educated women of Dutch background. The number of foetuses with a neural tube defect has also declined over the same period. Nevertheless, the consumption of additional folic acid is still insufficient. At least three-quarters of women of non-Dutch origin or with a low level of education, and about half of women of Dutch origin, do not take a folic acid supplement around the time of conception, or start to take it too late. The risk of bearing a child with a neural tube defect is higher

among women of Mediterranean background than among women of Dutch background.

Folate intake and folate status in the Dutch population does not appear to be as good as it could be

Food consumption surveys suggest that about half of Dutch adults do not consume enough folate. The limited amount of data from status studies puts the situation in a less dramatic light, showing that folate supply may be inadequate for 8 to 25 per cent of adults and elderly people. The status of children up to the age of 19 appears to be good, though only one study has been conducted. There are no indications that a folate status defined as inadequate according to present standards causes clinical problems.

8.3 Effects of policies adopted in other countries

Information about folic acid does not reach women from vulnerable groups as well

Information can boost the use of folic acid supplements around the time of conception among women whose pregnancy is planned. Experience in other countries teaches us that women with a low level of education or of low socio-economic status, young women, and women of non-Western origin are less easy to reach in information campaigns.

Fortification of specific products is no guarantee of better folic acid supply for women of childbearing age

Specific products fortified with folic acid on a voluntary basis can improve folate status, but there is no guarantee that women of childbearing age will consume these products. Therefore, this form of fortification cannot improve the folate status of all women to such an extent that the risk of them bearing a child with a neural tube defect is reduced.

Fortification of specific products and staple foodstuffs combined can lead to excessively high intake

It has been calculated that the combination of fortification of specific products and staple foodstuffs with folic acid can lead to excessively high intake, espe-

cially among young children, irrespective of any supplement use. That is why experts in the UK and Germany have recommended that voluntary folic acid fortification of specific products should be restricted if mandatory fortification of staple foodstuffs is introduced.

Fortification of staple foodstuffs has led to a 30 to 50 per cent fall in neural tube defects

There are indications that the introduction of mandatory folic acid fortification of staple foodstuffs in the United States, Canada and Chile - countries with a relatively low percentage of planned pregnancies - has led to a reduction of 30 to 50 per cent in the occurrence of neural tube defects in foetuses. This is in line with the findings of intervention studies, which indicate that taking folic acid supplements around the time of conception reduces the risk of bearing a child with a neural tube defect by at least 50 per cent.

The possibility that fortification of staple foodstuffs may lead to more masking of vitamin B12 deficiency cannot be ruled out

Studies in the United States and Canada into the effect of mandatory fortification of staple foodstuffs with folic acid on the occurrence of vitamin B_{12} deficiency which is not picked up as a result (masked deficiency) are inconclusive. Some studies found no change, while others found an increase.

More adults who take supplements will have an excessively high folic acid intake

There are indications that excessively high folic acid intake levels have become more common among American adults since the introduction of mandatory fortification of staple foodstuffs, especially among people who take supplements. The degree of excessively high folic acid intake among women who take a supplement around the time of conception is unclear. The position with regard to children is not clear either. However, scenario calculations indicate that children are more likely to have an excessively high folic acid intake from fortified products and supplements than adults.

8.4 Effects of Dutch policies

Information and preconception care are necessary, but do not reach all women

Information has brought about some improvement in the consumption of folic acid around the time of conception. Preconception care also seems to be able to boost the use of folic acid supplements. However, neither of these measures succeeds in ensuring that all women take folic acid at the right time around conception, as 9 to 15 per cent of all pregnancies in the Netherlands are unplanned.

The present system of voluntary fortification can lead to children taking too much folic acid

The committee thinks that it is highly probable that with the current permitted level of voluntary fortification and the new European claims regulation children may consume too much folic acid solely from products that are fortified on a voluntary basis.

The committee believes that this is undesirable. It takes the view that the safe upper levels of intake for children must be taken into consideration, which was not the case when the exemption for voluntary folic acid fortification was introduced. The safe upper levels of intake for children are derived from those for adults, which are based on masking of vitamin B_{12} deficiency. This masking is not relevant for children, but very little research has been done into the possible health risks of folic acid for children. The only thing that is certain is that pregnant women can take high doses of folic acid (up to 5 mg a day) without harming the unborn child.

Restricting the folic acid content of supplements helps prevent excessively high intake among children. This is advisable not only in supplements for children but also in supplements for adults. Action to counter excessive overfortification, as has been reported in the United States, might also help restrict excessively high folic acid intake.

Health benefits can be achieved by supplementation, but also by fortification of staple foodstuffs

This advisory report has calculated that increasing the number of women who take a folic acid supplement correctly, combined with a low level of fortification

of staple foodstuffs (equivalent to 150 micrograms of folic acid per 100 grams of flour in bread and bread substitutes after processing) appears to be the most effective way of reducing the risk of neural tube defects. This conclusion is supported by a risk-benefit analysis showing that the health benefit of fortifying staple foodstuffs, expressed in DALYs, far outweighs the increased risk of masking vitamin B_{12} deficiency.

However, a risk-benefit analysis can only take account of endpoints with a known dose-effect relationship. Not enough is known about other possible health effects (the risk of colon cancer and the effects of children taking more than the safe upper level of intake) to take them into account.

Epidemiological and intervention studies suggest that both a low intake of dietary folate and a high intake of folic acid from supplements may be associated with a greater risk of cancer, particularly colon cancer, when compared to folate intake at the recommended levels.

Scenario calculations show that at a slightly higher level of fortification of bread and bread substitutes, the risk of excessively high intake and the extent to which the safe upper level of intake would be exceeded by children are limited. Mandatory fortification of bread and bread substitutes* would lead to up to 2** per cent of children aged 1 to 3 regularly having an excessively high habitual intake. It is estimated that intake would not be more than 4 to 10 micrograms of folic acid a day above the safe upper level of intake. If all children were to take a folic acid supplement, which is not the case, 10 per cent of children would have folic acid intake levels up to 54-60 micrograms a day above the safe upper level of intake. This figure of 10 per cent is a considerable overestimate, as in fact only about 4 per cent of children aged 1 to 3 take a folic acid supplement. At the lower level of fortification referred to above***, the figure would be 1 per cent, excluding supplements. These calculations ignore intake from specific fortified products.

8.5 Recommendations

Choose policies that produce health benefits

The key question in this advisory report is what policy or combination of policies is most likely to guarantee the folate supply of the Dutch population.

* 200 micrograms of folic acid per 100 grams of flour after processing.
** Depending on the scenario selected.
*** 150 micrograms of folic acid per 100 grams of flour after processing.

The committee's starting point was that both supplementation and fortification must have clinical advantages, i.e. they must produce health benefits. This is a different starting point from that used by the Dietary Reference Values Committee, which set dietary reference values for folate on the basis of clinical measurements and biochemical measurements (blood values) in order to determine the adequate level of intake. Although between 8 and 25 per cent of Dutch adults may have an inadequate folate status according to biochemical measurements, this is not in itself a reason to introduce supplementation or mandatory fortification. That is because inadequate folate status causes no known clinical problems.

Table 8.1 sets out the positive, negative and uncertain effects of various policies and indicates limitations and conditions.

Increase investment in information about supplementation and introduce preconception care

The committee recommends that information activities about the use of folic acid around the time of conception should be expanded, particularly because the individual members of the target group are changing all the time. Preconception care should be introduced as well. Investment in information and care for women of non-Dutch background or a low level of education should be increased and kept at a higher level as part of this process of expanding information activities and introducing preconception care.

This advice applies irrespective of any policies that may be adopted on fortification. The advice that women should take a folic acid supplement from at least four weeks before conception until eight weeks into their pregnancy must still remain in place.

Also consider introducing folic acid fortification of staple foodstuffs and stopping fortification of specific foodstuffs

Information can improve the use of folic acid around the time of conception to some extent, but will never be able to ensure that all women who conceive take a folic acid supplement at the right time. That is because supplementation advice relates to the early phase of pregnancy, and therefore relies on a deliberate, timely choice. But a small proportion of pregnancies in the Netherlands (9 to 15 per cent) are unplanned, and some women who are aware of the advice do not take a folic acid supplement at all in spite of it, or start to do so too late. Fortification of staple foodstuffs, such as bread and bread substitutes, could create a basic level of folic acid intake for women of childbearing age. But this would not meet

Table 8.1 Summary of the advantages and disadvantages of various policies.

Policy: exposed group	Occurrence of neural tube defect compared to the current situation[a,b]	Whether or not the safe upper level of intake would be exceeded	Risks	Uncertainties	Limitations and conditions
Supplementation: women around the time of conception	Reduction	No	Unknown	Colon cancer	9 to 15 per cent of pregnancies in the Netherlands are unplanned and so unprotected.
50% in accordance with guidelines	-5 to -7%	0			
70 % in accordance with guidelines	-12 to -16%	0			
Preconception care: women around the time of conception	Reduction	No	Unknown	Colon cancer	9 to 15 per cent of pregnancies in the Netherlands are unplanned and so unprotected.
	-16 to -21%[c]	0			
Fortification of specific products: whole population	Uncertain	Very probably by children	Masking vitamin B_{12} deficiency in elderly people	Colon cancer	No data is available on the current intake of folic acid from fortified products.
Fortification of staple foodstuffs: whole population	Reduction	Very probably	Masking vitamin B_{12} deficiency in elderly people	Colon cancer	Fortification of staple foodstuffs can only be introduced if the exemption for voluntary fortification of specific products with folic acid is withdrawn. European regulations would have to be assessed in this regard.
100 micrograms of folic acid a day	-5 to -11 %	1% of children aged 1 to 3. 20% if they also take on average 120 micrograms of folic acid a day in the form of a supplement.	33 more cases		

a At present 35% of women take a folic acid supplement around the time of conception in accordance with the guidelines.
b Between 2000 and 2004, 124 foetuses a year developed neural tube defects.
c If 80 per cent of women take a folic acid supplement around the time of conception, calculated in the same way as in table 7.3.

their entire requirement, so they would still need to take folic acid supplements around the time of conception.

Food manufacturers in the Netherlands currently only fortify specific products on a voluntary basis. This is regulated by an exemption. The committee considers that the current exemption policy, which permits manufacturers to add folic acid to foodstuffs at a rate of 100 micrograms per 100 kilocalories, should be restricted to prevent children being exposed to the risk of consuming too much folic acid. This method of fortification does not guarantee that women of childbearing age would consume these products either.

Fortification of staple foodstuffs can increase the folic acid intake of almost all women of childbearing age. One example of this is that women's intake of folic acid would increase by on average 100 micrograms of folic acid a day if bread and bread substitutes were fortified at a rate of 150 micrograms of folic acid per 100 grams of flour after processing.

The committee finds that this level of fortification is acceptable provided that folic acid fortification of specific products is stopped, as otherwise children's intake would be excessively high.

The benefit of choosing bread and bread substitutes as the products to be fortified is that the intake distribution is relatively limited compared to other products such as beverages. There are also indications that the consumption of bread and bread substitutes by young adults of Turkish or Moroccan descent is as high as or even higher than that of young adults of Dutch background. The source of the flour used to make bread and bread substitutes would need to be monitored, as would its use by the various population groups. The committee is not in favour of all flour being fortified. If this were to happen, then nutritional claims could be made for products such as biscuits and cakes that are fortified with extra folic acid, which would be confusing for consumers.

Look closely at European regulations first

The conditions for fortification advocated by the committee - that fortification of specific products would have to be restricted or eliminated - appear at present to be in conflict with the European Union agreement to refrain from creating barriers to free trade. This agreement is reflected in the judgement of the European Court in 2004, which means that fortified products can only be prohibited if they present a specific danger to public health. The committee considers that regulations in this area need to be reviewed from the point of view of public health.

It is also possible that the safe upper level of intake for folic acid set by the European Food Safety Authority might need to be re-examined in the light of new scientific findings. If this limit is changed, that might offer grounds for revising the current exemption policy.

If nothing changes, more guidance and clearer labelling should be provided

The government also has the option of managing voluntary fortification of foodstuffs through consultation with manufacturers. Foods that are fortified with folic acid on a voluntary basis could also be labelled more clearly and women of

childbearing age could be encouraged to consume them via information campaigns and preconception care.

Choose a strategy based on the precautionary principle when deciding on how to deal with fortification

Whichever option is chosen, a strategy based on the precautionary principle* is advisable, as is normal in matters where uncertainty as to serious risks makes it harder to reach a decision. Policymaking in relation to this strategy takes account of a worst-case scenario, even though evidence for the risk is not very strong.

It is vital to prevent excessively high intake of folic acid from fortified products

The committee emphasises that a fortification policy must ensure that the intake of folic acid remains below the safe upper level of intake. Children are at greatest risk of exceeding this threshold in the event of fortification. The safe upper levels of intake for children were derived from those for adults, which in turn are based on the extent to which consuming folic acid can mask vitamin B_{12} deficiency and the negative impact this can have on health. This masking may not be relevant for children, but very little research has been done into the possible health risks in this group. Research among adults also suggests that high doses of folic acid can accelerate the development of cancer, especially colon cancer.

Patients with colon adenomas should be advised not to take dietary supplements containing folic acid

The committee recommends that doctors should advise patients with benign growths in the colon not to take dietary supplements containing folic acid. This is because it is impossible to exclude the possibility that excessively high folic acid intake may accelerate the transformation of a benign growth into a malignant tumour.

The committee is also of the opinion that in general a cautious approach should be adopted to taking dietary supplements that contain more than 100% of the recommended dietary allowance of vitamins and minerals. This also applies to dietary supplements that are taken several times a day if the daily intake of vitamins and minerals from them exceeds the recommended dietary allowance.

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* The Health Council will be publishing an advisory report on the precautionary principle in the course of 2008.

Monitor the effect of the policies

The committee recommends that the intake of folic acid from food by children, women of childbearing age and elderly people should be monitored. The occurrence of foetal neural tube defects must also be kept under review.

Other conditions that need to be monitored are masking of vitamin B_{12} deficiency, cardiovascular disease and colon cancer. In all cases, as much information as possible should be taken from existing records, such as EUROCAT, food consumption surveys, cancer records and records of cardiovascular disease.

The committee believes that other forms of research, ranging from animal experiments to intervention studies, should also be carried out to determine whether, and if so how, dietary folate and folic acid affect the risk of individuals developing colon cancer. The effect on cognitive function must also be investigated. The policy may be revised in the light of the outcomes.

Evaluate dietary reference values for folate

The committee is of the opinion that the dietary reference values for folate and their biochemical basis must be assessed. That is because status data indicates that the folate supply of the Dutch population is not as bad as intake data suggests. The evaluation must consider, among other factors, variations in outcome when different methods of determination are used, new insights into the bioavailability of folate, and the suitability of reference values to asses folate intake with the probability method.

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Annexes

Annex **A**

Request for advice

Date of request: 26 January 2006

Letter reference: VGP/VV 2646726

It is important for public health that the population has an adequate supply of essential micronutrients. We know that a habitual diet does not contain enough of some of these essential micronutrients to meet the needs of (certain groups of) the population. The Ministry of Health, Welfare and Sport therefore follows an active policy with regard to these essential micronutrients. This policy covers both the use of supplements (vitamin D for young children, folic acid for pregnant women and women who want to have a baby) and fortification of foodstuffs. The addition of vitamins A and D to margarine, butter, and oil is permitted and encouraged under the Agreement on the vitamin fortification of spreadable fats. The addition of iodine to table salt (and alternative products), bread and bread substitutes (via salt used in breadmaking) and meat products (via nitrite pickle) is also permitted.

On the other hand it is important to ensure that people do not consume too much of certain essential micronutrients, as this could be harmful to health. That is why foodstuffs cannot in principle be fortified with essential micronutrients that have a ‘narrow margin’. The micronutrients in question are vitamin A, vitamin D, folic acid, selenium, copper and zinc. A ‘narrow margin’ in this context means that the recommended dietary allowance (RDA) and the safe upper level of intake are relatively close to one another, which means that people can easily run the risk of consuming too much of a certain vitamin, mineral or trace element. The addition of iodine to foodstuffs is prohibited for the same reason. There are however exceptions to these rules: iodine can be added to salt (used in breadmaking

and preparing meat products) and vitamins A and D can be added to spreadable fats. Controlled additions seek to ensure that consumers do not ingest too much or too little. As far as the other essential micronutrients that do not have a narrow margin are concerned, fortification of foodstuffs is permitted up to 100% of the recommended dietary allowance per daily intake.

Three developments are taking place at the moment leading to a need to review micronutrient policy. They are set out below.

Following the judgement of the Court (2 December 2004, EC Commission v. Netherlands, C-41 102), the Netherlands has had to give up its absolute ban on fortification with substances such as folic acid. Requests for exemption from the ban on adding micronutrients can only be rejected if it can be demonstrated that placing the specific product on the market would endanger public health. According to the Court's judgement, the absence of a nutritional need for the fortification of foodstuffs, which has in the past been an important argument used by the Netherlands in rejecting requests for exemption, no longer constitutes adequate grounds. The EU regulation on voluntary fortification of foodstuffs with vitamins, minerals and some other substances will take effect in the course of the next year or two. Policy on the fortification of foodstuffs with micronutrients will then be harmonised throughout the EU. This regulation will set minimum and maximum amounts of vitamins and minerals that can be added. The same procedure will be carried out for dietary supplements in order to minimise the risk of overdoses of micronutrients by people consuming fortified foodstuffs and taking dietary supplements. It is true that the regulation deals with voluntary fortification and therefore by definition does not resolve the problem of possible deficits in the supply of essential micronutrients. But the regulation does allow EU member states to continue or introduce mandatory fortification of foodstuffs if this is necessary on public health grounds. The question is whether the Netherlands should maintain its current system of voluntary fortification of spreadable fats with vitamins A and D and the fortification of table salt, salt used in breadmaking and nitrite pickle with iodine or whether it should move to a system of mandatory fortification. Another point is that science is producing new findings. Increasingly, researchers are discovering that the health benefits of a supply of certain micronutrients at levels (far) above the current dietary reference values. As this might also lead to a risk of excessive intake, which needs to be considered in the light of the other effects, the Ministry's policy could be based on a risk-benefit analysis. Risk-benefit analysis models are being devised. One example is the role that folic acid is thought to play in preventing cardiovascular diseases. The United States has examined the advantages and disadvantages of extra folic acid supply and has decided to introduce mandatory fortification of flour (for use in bread making and other applications). Ireland and the United Kingdom are currently considering whether to follow suit.

The challenge facing me is to devise a policy, within the context of the new European regulation, under which the largest possible proportion of the population will receive sufficient essential micron-

utrients while the smallest possible proportion of the population will run the risk of consuming more than the safe upper level of intake.

In the light of this, I am asking the Health Council to address the questions set out below.

For what essential micronutrients for which dietary reference values have been established in the Netherlands and in what situation does the habitual diet not offer sufficient guarantees that the population, or groups of the population, will have an adequate supply? Please use food consumption data, nutritional status data and other relevant scientific information when addressing this issue. What is the best way of ensuring an adequate supply of essential micronutrients in these situations? The Council is requested to look at all available policy instruments for each essential nutrient in its deliberations. What might the health benefits of an active fortification policy (whether with mandatory fortification or not) be for (groups of) our population in the light of a risk-benefit analysis for essential micronutrients such as folic acid and vitamin D (and any other relevant vitamins and/or minerals)?

I would very much appreciate receiving your advisory report around the middle of 2007.
(signed)
The Minister for Health, Welfare and Sport
H. Hoogervorst

Annex **B**

The committee

- Professor G. Schaafsma, *Chairman*
  Emeritus Professor of Food and Nutrition, Wageningen University / Former director food and health, TNO Quality of Life, Zeist
- Dr. H. van den Berg
  Nutritional expert, Nutrition Centre, The Hague
- E.N. Blok, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- Dr. H.J. Blom
  Clinical biochemic geneticist, Free University Medical Centre, Amsterdam
- Professor C.P.G.M. de Groot
  Professor of Nutritional Physiology, with a particular focus on the ageing process and elderly people, Wageningen University
- Dr. M. den Heijer
  Endocrinologist, St. Radboud University Medical Centre, Nijmegen
- Dr. K.F.A.M. Hulshof
  Nutrional expert, formerly with TNO Quality of Life, Zeist
- Professor P.T.A.M. Lips
  Professor of Endocrinology, Free University Medical Centre, Amsterdam
- Professor I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University
- Professor P.J.J. Sauer
  Professor of Paediatric Medicine, University of Groningen

- Professor P. van ’t Veer
  Professor of Nutrition and Epidemiology, Wageningen University
- Dr. T. Vulsma
  Paediatrician and endocrinologist, Amsterdam University Medical Centre
- Dr. R.M. Weggemans, *Scientific secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee’s work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other’s possible interests.

Annex **C**

Assessment of methodological quality and level of evidence

In view of the large number of subjects to be examined, the committee decided to select publications with short search actions. They were assessed on the basis of the approach used when drawing up the *Guidelines for a Healthy Diet 2006.*[16] However, the approach is presented more clearly in this advisory report as it incorporates tables in which the conclusions are classified according to their level of evidence, with a reference to the studies on which the classification is based. This is largely in line with the approach used when developing the evidence-based guideline.[189] Another feature of the approach taken in this advisory report is that it uses the SIGN grading system, granting the highest level of evidence (A1) only to systematic review articles of good quality.[190]

The aim of the assessment system used is to determine relationships between factors. It is not, or only to a very limited extent, to assess data on the folate supply of the Dutch population or the effects of current Dutch policy, and therefore was not applied to those subjects.

Table C.1 Grades of methodological quality used to classify individual studies into interventions with folic acid or the relationship between folate intake or status and the risk of various conditions.[189,190]

Grade	Type of study
A1	Systematic review articles of good quality relating to at least two grade A2 studies conducted independently of one another.
A2	Randomised, double-blind, comparative intervention study of good quality and sufficient size.
B1	Systematic review articles of good quality relating to at least two grade B2 studies conducted independently of one another.
B2	Comparative studies, but without all the features referred to under A2 or good-quality cohort studies or patient case studies.
C	Non-comparative studies.
D	Opinion of the committee.

Table C.2 Level of evidence of conclusions.[16,189]

Level	
1: Convincing	Based on 1 systematic review article (grade A1) or at least 2 grade A2 studies carried out independently of one another.
2: Probable	Based on 1 review article (grade B1) or at least 2 grade B2 studies carried out independently of one another.
3: Insufficient	Based on 1 grade A2 or B2 study or on grade C research.
4: Insufficient	Based on the committee's opinion (grade D).

Annex **D**

Intake calculations for various folic acid fortification scenarios

Table D.1 Observed and habitual folic acid intake in micrograms per day by children aged 1 to 3, 4 to 8, and boys aged 9 to 13 with fortification according to various scenarios.[a,184]

	Average	Standard deviation	Minimum	P5	P10	P50	P90	P95	Maximum
Children aged 1 to 3									
Scenario 1									
Observed	74	39	0	18	30	70	126	151	218
Habitual	n.c.[b]	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 2									
Observed	84	40	0	24	40	81	143	158	245
Habitual	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 3									
Observed	87	39	0	30	42	84	146	160	245
Habitual	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 4									
Observed	100	43	0	44	53	92	155	169	303
Habitual	102	37	33	49	59	97	151	170	210
Scenario 5									
Observed	103	42	19	47	58	96	156	172	303
Habitual	106	34	42	57	65	102	151	168	206

Table D.1 continued.

	Average	Standard deviation	Minimum	P5	P10	P50	P90	P95	Maximum
Children aged 4 to 8									
Scenario 1									
Observed	109	50	0	40	51	105	172	205	269
Habitual	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 2									
Observed	121	50	0	50	65	114	191	213	319
Habitual	126	41	46	66	77	122	179	198	240
Scenario 3									
Observed	124	51	0	51	67	117	195	216	319
Habitual	128	41	47	67	79	124	182	202	244
Scenario 4									
Observed	123	50	0	53	67	116	191	213	319
Habitual	128	41	48	68	80	124	181	200	242
Scenario 5									
Observed	125	50	0	54	68	117	196	216	319
Habitual	130	41	50	70	81	126	184	203	246
Boys aged 9 to 13									
Scenario 1									
Observed	163	69	14	57	81	156	255	296	378
Habitual	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 2									
Observed	173	71	20	72	90	165	264	314	404
Habitual	174	56	62	89	105	170	248	273	324
Scenario 3									
Observed	178	71	20	73	94	172	271	314	404
Habitual	179	57	65	93	110	175	254	279	329
Scenario 4									
Observed	175	72	20	72	92	167	271	314	404
Habitual	176	58	62	89	106	172	252	278	330
Scenario 5									
Observed	180	72	20	75	95	172	278	314	404
Habitual	182	58	66	93	110	178	258	283	332
Girls aged 14 to 18									
Scenario 1									
Observed	149	64	0	50	63	146	230	250	369
Habitual	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 2									
Observed	162	65	0	60	81	159	250	279	369
Habitual	165	44	72	96	110	163	223	242	278
Scenario 3									
Observed	164	65	0	62	82	160	250	279	369
Habitual	168	44	74	99	113	165	226	224	280

Table D.1 continued.

	Average	Standard deviation	Minimum	P5	P10	P50	P90	P95	Maximum
Scenario 4									
Observed	163	66	0	60	81	160	251	279	369
Habitual	167	45	72	97	111	165	225	244	280
Scenario 5									
Observed	165	66	0	62	82	160	251	279	369
Habitual	169	45	74	99	113	167	228	247	283
Women aged 19-50									
Scenario 1									
Observed	133	65	0	36	54	126	216	247	468
Habitual	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Scenario 2									
Observed	149	67	0	48	71	144	233	266	490
Habitual	154	50	61	82	95	149	219	243	294
Scenario 3									
Observed	153	68	0	52	72	148	238	270	490
Habitual	158	50	63	85	98	152	223	248	300
Scenario 4									
Observed	150	67	0	50	72	147	235	267	490
Habitual	155	50	62	84	96	150	220	244	295
Scenario 5									
Observed	154	68	0	54	72	150	238	271	490
Habitual	159	50	65	86	99	154	224	248	300

a Scenario 1: fortification of bread; scenario 2: fortification of bread and bread substitutes; scenario 3: fortification of bread, bread substitutes and breakfast cereals eaten cold; scenario 4: fortification of bread, bread substitutes and breakfast cereals eaten hot; scenario 5: fortification of bread, bread substitutes and breakfast cereals eaten cold or hot. The fortification level is 200 micrograms of folic acid per 100 g of flour after preparation.

b N.c. not calculated.

Table D.2 Habitual daily intake of folic acid in micrograms by the Dutch population after fortification of bread and bread substitutes[a]. [185]

	Average	Standard deviation	P1	P5	P10	P50	P90	P95	P99
Children aged 1 to 3	80	27	31	42	49	77	115	129	159
Children aged 4 to 6	91	29	33	48	56	88	129	143	172
Boys aged 7 to 10	127	32	63	79	88	125	168	182	209
Girls aged 7 to 10	105	31	45	59	67	102	145	159	186
Boys aged 11 to 14	144	47	50	73	87	140	205	228	275
Girls aged 11 to 14	118	34	46	65	76	117	162	177	207
Boys aged 15 to 17	185	43	96	121	134	182	242	261	300
Girls aged 15 to 17	126	38	46	67	79	123	176	192	223
Men aged 18 to 50	165	63	33	72	90	160	247	275	335
Women aged 18 to 50	117	39	34	59	70	114	168	186	226
Men aged 51 to 65	158	58	41	72	88	153	232	258	318
Women aged 51 to 65	109	42	26	50	62	105	163	183	234
Men aged over 65	137	54	39	62	76	130	206	235	302
Women aged over 65	107	31	42	62	71	104	146	161	194

a The fortification level is 150 micrograms of folic acid per 100 g of flour after preparation.

Annex **E**

Calculation of the number of foetal neural tube defects that would be prevented

Before the efficacy of folic acid supplementation and fortification in preventing foetal neural tube defects can be calculated, it is first necessary to work out how many children would be born with a neural tube defect if no women took a folic acid supplement correctly around the time of conception. The calculations do not take account of incorrect use of folic acid supplements around the time of conception, consumption of multi-vitamins containing folic acid or specific foods fortified with folic acid on a voluntary basis, as too little data is available on these points. It has therefore been assumed that these factors will remain unchanged.

The number of children who would have been born with a neural tube defect in 2005 if no women had taken a folic acid supplement correctly

This calculation is based on the following mathematical assumptions:

- it is estimated that 124 children were born with a neural tube defect in 2005 (the total number of live births and stillbirths in 2005 was 188,670; see section 7.2. Number of neural tube defects);
- in 2005, 35% of women took a supplement containing 400 micrograms of folic acid a day in accordance with the guidelines;[109,111,112,117]
- the number of cases of foetal neural tube defect that could be prevented by taking a supplement containing 400 micrograms of folic acid a day ranges from 36% [27,187] to 47%[28] or more.[29] The calculations below have been worked

out using the dose-response relationships described by Daly et al. and Wald et al. (table E.1).[27,28,187]

Table E.1 The effect of folic acid on the risk of bearing a child with a neural tube defect.

	Wald method[28]	Daly method[27,187]
Micrograms of folic acid a day	Reduction in relative risk [a]	Reduction in relative risk
100	13	22
200	23	41
300	30	- [b]
400	36	47
500	41	- [b]

a Baseline serum folate level is 11 nmol per litre.
b Not described.

The total number of children (N_t) who would be born with a neural tube defect if no women took extra folic acid correctly around the time of conception is as follows:

- N_t = total number of children who would be born with a neural tube defect if no women took extra folic acid correctly around the time of conception;
- N_{2005} = number of children reported with a neural tube defect in 2005;
- % without FA = % of women who did not take a folic acid supplement around the time of conception or who did not take it correctly;
- % with FA = % of women who did take a folic acid supplement correctly around the time of conception;
- RR $reduction_{x00}$ = reduction in relative risk brought about by taking a supplement containing x00 micrograms of folic acid a day according to the Wald method and the Daly method (table E.1).

$$NTD_{2005} = \%\ without\ FA \times N_t + \%\ with\ FA \times \{1 - (RR\ reduction_{xoo} / 100)\} \times N_t$$

Example:
Wald method: $124 = 65\% \times N_t + (35\% \times (1-0.36) \times N_t) = 0.874 \times N_t \rightarrow N_t = 142$
Daly method: $124 = 65\% \times N_t + (35\% \times (1-0.53) \times N_t) = 0.8355 \times N_t \rightarrow N_t = 148$

This calculation shows that if no women had taken folic acid supplements correctly, approximately 145 children would have been born with a neural tube defect in 2005.

The number of foetal neural tube defects that can be prevented by supplementation, fortification or a combination of both measures

This calculation is based on the following mathematical assumptions:

- the 145 cases of neural tube defect that would occur each year if no women were to take a folic acid supplement correctly;
- the fact that around 9 to 15% of all pregnancies in the Netherlands are unplanned and the women concerned are therefore unable to respond to supplementation advice.[109,113] The number of children born with a neural tube defect has therefore been downgraded in working out the effect of supplementation, taking the most conservative estimate for the proportion of pregnancies that are planned (85%). If all women who become pregnant intentionally follow the supplementation advice, then theoretically 85% of the 145 pregnancies in which the foetus develops a neural tube defect (123 pregnancies) would be affected;
- all women are exposed to fortification (100%);
- three scenarios are used, reflecting three different percentages of women taking a folic acid supplement correctly: 35% (the present situation), 50% and 70%.

The number of foetal neural tube defects that can be prevented by supplementation, fortification or a combination of both measures has been calculated as follows:

- N_s number of foetal neural tube defects prevented by supplementation;
- N_f number of foetal neural tube defects prevented by fortification;
- N_{ntd} number of children born with a neural tube defect.

$N_s = \%\ supplementation \times (RR\ reduction_{400} / 100) \times 123$
$N_f = RR\ reduction_{100} / 100 \times 145$
$N_{ntd} = 145 - \{\%\ with\ FA \times (RR\ reduction_{500} / 100) \times 123\} - \{\%\ without\ FA \times (RR\ reduction_{100} / 100) \times 145\}$

Example:
% with FA = 35
% without FA = 65
RR $reduction_{500}$ = 41
RR $reduction_{100}$ = 13

$N_{ntd} = 145 - (0.35 \times 0.41 \times 123) - (0.65 \times 0.13 \times 145) = 115$

This calculation shows that if 35% of women take a 400 microgram folic acid supplement correctly and 100% of women consume 100 micrograms of folic acid from food each day, the number of children born with a neural tube defect will be 115 instead of 145.

The estimated number of neural tube defects prevented is higher if the average prevalence for the period from 1981 to 2004 is used as the basis for the calculation. However, the estimated relative effects are comparable.

Annex **F**

Definitions

Adequate intake

The lowest level of intake that seems to be adequate for practically the entire population. An adequate intake is estimated if research data is insufficient to allow an average requirement and recommended allowance to be determined.[18]

Average requirement

The intake that meets the needs of half of the population for a particular nutrient. The recommended dietary allowance is derived from the average requirement, assuming normal distribution of the requirement.[18]

Diet

Unless otherwise specified, 'diet' refers to foodstuffs and supplements.

Fortification

Adding one or more micronutrients to a foodstuff, resulting in a concentration higher than that which naturally occurs in the foodstuff or the raw material from which it was made, in order to prevent or correct a proven deficit in one or more micronutrients in (parts of) the population.[12]

Probability method

The probability method estimates the percentage of people with an intake below the average requirement. This is done by combining the distribution of the habitual intake with the distribution of the require-

ment in a population group. Figure F.1 clarifies the method, showing how it can be used to work out how many people have an intake that does not meet their requirements at certain intake levels. In the fictional example used, the risk of excessively low intake for the 1,000 people with the lowest intake is 97.5%. This means that 975 of these 1,000 people have an intake that is lower than their requirement. The 10,000 people with an intake around the average requirement run a 50% risk of having an excessively low intake. So this means that 5,000 of them will have an intake that does not meet their requirement. Adding up all these estimates for all levels of intake for each population group results in an estimate of the percentage of people in the population group with an intake below their requirement.

There is no guarantee that all individuals within a particular population group will have their requirements met even if the average supply for that group is above the adequate intake or recommended dietary allowance. In this example, the risk of excessively low intake for the 1,000 people with the highest intake is 2.5%, which means that 25 people in that group will have an intake that does not meet their requirement. However, it is not possible to identify which individuals are at risk of excessively low intake on the basis of intake data.[87]

Recommended dietary allowance

The intake that meets the needs of 97.5 per cent of the population for a particular nutrient. It is assumed that this need is distributed normally.[18]

Restoration

Adding micronutrients that are lost during the production process, storage and/or sale to foodstuffs. The amount added to the foodstuff takes the level of the micronutrient back to the previous concentration in the edible part of the foodstuff or the raw material from which it was made.[12]

Safe upper level of intake

Highest level of intake at which no harmful effects are observed or are to be expected.[18]

Substitution

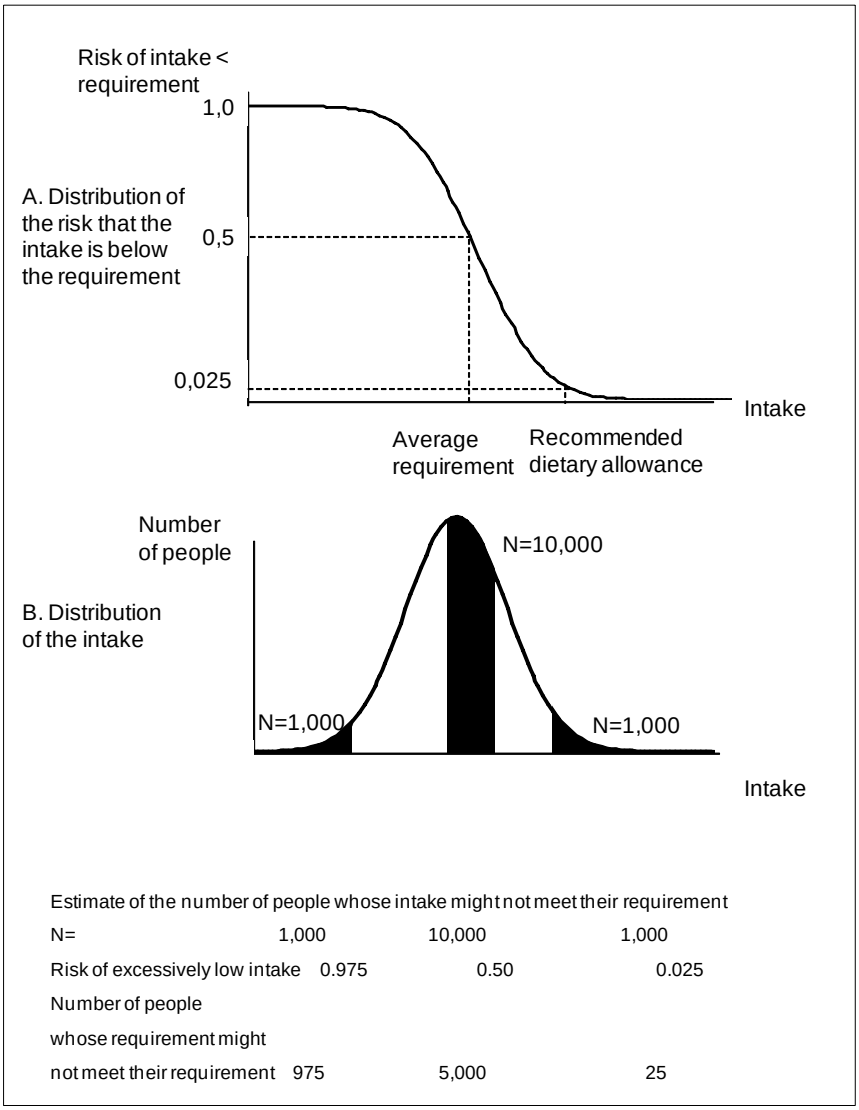
Replacing a foodstuff with a different foodstuff that is as close as possible to it in terms of appearance, consistency, taste, colour and odour or that serves the same purpose for the consumer.[12]

Supplementation

Using a supplement containing micronutrients as an addition to diet.

Threshold method

The threshold method estimates the percentage of people in a population with an intake above or below a particular dietary reference value.



Estimate of the number of people whose intake might not meet their requirement			
N=	1,000	10,000	1,000
Risk of excessively low intake	0.975	0.50	0.025
Number of people whose requirement might not meet their requirement	975	5,000	25

Figure F.1 Estimate of the number of people whose intake might not meet their requirement using the probability method based on a theoretical distribution of risk (A) and a theoretical distribution of intake (B).