Health Council of the Netherlands

Towards an adequate intake of vitamin A

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of the advisory report *Towards an adequate intake of vitamin A*
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Dear Minister,

On 26 January 2006, your predecessor asked the Health Council of the Netherlands to reconsider the policy on micronutrients. I hereby wish to present to you the advisory report on one of these nutrients: vitamin A. Earlier this year, the Health Council of the Netherlands already informed you about folic acid, vitamin D and iodine. A concluding advisory report about other micronutrients will appear in the first half of 2009.

In order to advise you about the optimal intake of vitamin A, a Committee of experts has evaluated the recent literature and the implications for the current policy, also taking new European legislation into consideration. Two of the Health Council's Standing Committees – the Standing Committee on Medicine and the Standing Committee on Nutrition – reviewed the findings.

The Committee concludes that a good and varied diet should be sufficient to give us the vitamin A that we need. There is also no danger of an intake that is too high. Specific additional recommendations can be made for several groups. The Committee upholds the previous advice that pregnant women should not eat liver and liver products, or use vitamin A supplements, as these can be harmful to their unborn child. The recommendation to smokers is new: in addition to the advice to stop smoking, they should avoid supplements containing more than 20 mg of beta-carotene per day. Studies have shown that these supplements can further increase the already elevated risk of lung cancer in smokers.

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It is not clear whether this forms the be-all and end-all of vitamin A intake in our country. Whether the current level of intake is sufficient is still a matter for discussion, but hard data are lacking. More research is essential in order to obtain clarity on this matter. The results could lead to additional recommendations in the future.
I fully support the Committee's conclusions.

Yours sincerely,

(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2008/26E, The Hague, December 16, 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 and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. 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.

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A brief outline of the advisory report

You need to make sure you are getting enough vitamin A, yet not too much

Adequate intake of vitamin A is important for reproduction, growth and development in humans and for a strong immune system to fight illness. Vitamin A is also necessary for good vision in low light conditions. However, it is not a case of 'the more, the better', as an intake that is too high can result in liver damage. In pregnant women, a dose that is too high increases the risk of a child with congenital abnormalities.

A good and varied diet is enough to ensure sufficient intake

Only food products of animal origin naturally contain vitamin A. It is also added to margarine, low-fat margarine and products used for baking and frying. The body is also able to produce vitamin A from pro-vitamin A carotenoids, which are found in dark green leafy vegetables and in certain yellow and orange fruits and vegetables. This means that a good, varied diet generally provides sufficient vitamin A, without causing a risk of excessive intake.

Smokers are advised to avoid supplements containing a high dose

The recommendation to smokers is new: in addition to the advice to stop smoking, they should avoid supplements containing more than 20 mg of beta-carotene per day. Studies have shown that the use of these supplements increases the risk of lung cancer in this group that is already at increased risk.

Pregnant women are advised to avoid liver and supplements

Pregnant women are also at risk of excessive intake of vitamin A, not because it is harmful to them but because it is harmful to their unborn child. Therefore, they should avoid liver, liver products and supplements containing vitamin A.

Other recommendations depend on additional research

Whether the current level of intake is sufficient is still a matter for discussion, but hard data are lacking. Further research is required for this. Any additional recommendations can only be made once these results are known.

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Executive summary

Background to this advisory report

Regulations and research undergo rapid development

European legislation, regulations and research in the field of vitamins, minerals and trace elements, known as micronutrients, undergo rapid development. That is why the Minister for Health, Welfare and Sport has asked the Health Council of the Netherlands for advice in connection with a review of policy in this area.

The aim of the 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.

In this advisory report, a specially appointed committee indicates what is necessary in the case of vitamin A.

Vitamin A is essential for the body

Vitamin A is a fat-soluble vitamin that is important for sight at low light levels, for reproduction, the immune system, growth and development. Too much vitamin A can cause problems in the functioning of the liver and, in the case of pregnant women, in foetal development. That is why pregnant women should avoid liver, liver products and supplements containing vitamin A.

There are various sources of vitamin A

Only foods of animal origin contain vitamin A: liver and liver products contain large amounts. It is also added to margarine, low-fat margarine and products used for baking and frying (except oils), in the same proportions as are naturally found in butter. The body can also produce vitamin A itself from provitamin A carotenoids. The main sources of these provitamins are dark green leafy vegetables and some yellow and orange varieties of fruits and vegetables. Dairy fat and egg yolk also contain these substances.

What are the main scientific developments?

A high intake of beta carotene from supplements increases the risk of lung cancer among certain groups

Experimental research has shown that the use of supplements containing at least 20 milligrams of beta carotene a day increases the risk of lung cancer in smokers and asbestos workers.

A high vitamin A intake may be associated with a greater risk of osteoporosis

Observational research indicates that a high intake of vitamin A from foods and supplements may be associated with a greater risk of osteoporosis.

What is the situation with regard to vitamin A intake?

It appears that both excessively high and excessively low vitamin A intake occur

Data on vitamin A intake reveals that 20 to 30 per cent of the Dutch population may have an excessively low vitamin A intake. On the other hand, almost 10 per cent of children aged two or three may have an excessively high intake, consuming up to 600 microgram retinol activity equivalents (RAE) too much of vitamin A.* This excessively high intake is related mainly to consumption of large amounts of liver, liver products and supplements containing vitamin A. Further research is needed to ascertain whether this poses a real problem.

* There is only a tolerable upper level of intake for retinol and not for provitamin A-carotenoids.

How can vitamin A intake be improved?

A good, varied diet provides enough vitamin A

A good, varied diet provides enough vitamin A without exposing people to the risk of excessively high intake. The latter point is not true in the case of women who are pregnant or who plan to conceive: the Committee is of the opinion that these groups should still be advised to avoid liver, liver products and dietary supplements containing vitamin A during pregnancy in order to reduce the risk of congenital abnormalities in the child.

Smokers should be advised against taking supplements with high doses of beta carotene

Smokers and asbestos workers should be advised (besides the advice to give up smoking) to avoid taking supplements containing 20 milligrams of beta carotene or more a day.

What other aspects need to be investigated?

Research into whether an excessively low intake of vitamin A really causes vitamin A deficiency

The Committee recommends that research using stable isotopes be conducted into the vitamin A status of people who do not consume margarine, low-fat margarine or non-oil products used for baking and frying. The results of this research should indicate whether vitamin A intake is really inadequate in these individuals.

Research into whether an excessively high intake of vitamin A among children is really a problem

In order to ascertain whether excessively high vitamin A intake among young children is really a problem, research should be conducted into the link between vitamin A intake and the activity of liver enzymes in the blood, the children's vitamin A status and the extent of vitamin A accumulation in the liver.

Research as to whether an excessively high intake of vitamin A increases the risk of osteoporosis

The Committee believes that further research is needed into the indications that high vitamin A intake is associated with lower bone density and a greater risk of bone fracture.

Evaluate the dietary reference values for vitamin A

The dietary reference values and safe upper levels of intake for vitamin A were drawn up in 1989. In this advisory report the Committee has moved on from these values, using instead dietary reference values based on those established by the American Institute of Medicine, in which Dutch growth curves have been incorporated. It has also used the safe upper levels of intake established by the EU Scientific Committee on Food.

Chapter 1

Introduction

Vitamin A – or retinol – is a fat-soluble vitamin that occurs in food products of animal origin. Plant-based food products can also contribute to the intake of vitamin A: they contain certain carotenoids that can be converted to vitamin A by the body. Carotenoids are also found in certain food products of animal origin, such as milk and eggs. Vitamin A is important for vision at low light intensity, gene expression, reproduction, embryonic development, immunity and growth.[1]

The Ministry for Health, Welfare and Sport wants to develop a new policy in the context of European regulations, ensuring that as many people as possible in the population have an adequate intake of vitamin A and other micronutrients. However, it wants to simultaneously minimise the risk of people consuming amounts in excess of the established safe upper level of intake. With that aim in mind, the Ministry has asked the Health Council of the Netherlands for advice in the context of reviewing its policy on the fortification of food products with micronutrients, such as vitamins, minerals and trace elements (Annex A).

This advisory report is the fourth in a series of five. The previous advisory reports – on folic acid[2], vitamin D[3] and iodine[4] – have already been published. Other micronutrients will be discussed in an advisory report that is still to be published.

1.1 The original policy on vitamin A

Until 1994, the addition of vitamin A in the form of retinol to food supplements was not regulated in the Netherlands. Permission to add this substance to food products was very limited.[5] For example, retinol could only be added to margarine, low-fat margarine and products used for baking and frying. It was prohibited to fortify other food products with vitamin A.

In the early 1990s the Dutch Government felt the need to revise its policy. The most important reason was pressure from the free market. Other European countries had already allowed the addition of vitamins to food products for some time. Another reason for changing the policy was that the habitual diet* appeared to be inadequate for providing all the necessary micronutrients. In contrast, there was the risk that people would consume too much of a certain micronutrient. This had to be prevented. This risk applies mainly to micronutrients with a 'narrow margin', where the dietary reference value or the recommended dietary allowance and the safe upper level of intake are relatively close together.

These developments resulted in the implementation of the Commodities Act Regulation on the Exemption of Vitamin Preparations in 1994 [6] and the Commodities Act Decree on the Addition of Micronutrients in 1996.[7] The Commodities Act Regulation on the Exemption of Vitamin Preparations sets a limit on the amount of vitamin A – in the form of retinol – that can be added to vitamin preparations.[6] The Commodities Act Decree on the Addition of Micronutrients continues to ban the fortification of food products with retinol, but does still allow for restoration or substitution.[7,8] The government signed an agreement in 1999 with the manufacturers of margarine, low-fat margarine, and products used for baking and frying to fortify these alternatives to butter with at least 75 percent of the legal limit of 800 micrograms RAE retinol per 100 grams. This agreement remains valid until new European legislation about fortification comes into force.[9]

1.2 New developments

Between 2008 and 2014, the policy on supplements and the voluntary fortification of food products will be harmonised within the European Union. By this time, a supplement guideline by the European Union from 2002 and a

* Unless specified further, diet refers to the intake from food products and supplements. Definitions are listed at the end of the text in Annex E.

regulation by the European Union about voluntary fortification of food products from 2006 will have been worked out*.[13,14] However, both cases relate to so-called framework legislation in which the principles have been set out, but not the details. It has already been set out in the regulation and the directive that vitamin A – in the form of retinol, retinyl acetate, retinyl palmitate and beta carotene – may be added to supplements and food products**.

During the drafting of this advisory report, it was not yet known what the minimum and maximum doses of vitamin A that may be added to supplements and food products would be. The recommended dietary allowance shown on the label also had not been set. A regulation will be put in place to define this, as well as the minimum dose at which the label may state that the food product contains vitamin A or is rich in vitamin A***. The regulation concerns voluntary fortification of food products, which does not necessarily mean that the problem of shortages will be solved.[14] However, the regulation does give the European Union member states the option of maintaining or introducing mandatory fortification of basic food products, if this is necessary in the interests of public health.

1.3 Several measures for the same goal

There are various measures to ensure that the largest possible portion of the population receives enough micronutrients, within safe limits. Foremost is the consumption of a varied diet. If this is not sufficient, one or a combination of the following additional measures can be considered: restoration, substitution, fortification and suppletion.[16]

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* The guideline for nutritional supplements and the directive on fortified food products have already been included in the Commodities Act Decree on Nutritional Supplements and the Commodities Act Regulation on Nutritional Supplements.[10-12]

** In 2007, in a change in the Commodities Act decision on the Addition of micronutrients to food products, the list of permitted substances was expanded to include carotene mixtures with pro-vitamin A activity.[15]

*** The new European claims directive stipulates that the label may state that a food product is a source of a certain micronutrient when the product contains 15 percent of the recommended dietary allowance of the micronutrient per 100 g or 100 ml or per portion pack and that it is rich in the micronutrient at a level of 30 percent. According to Dutch legislation concerning this directive, the claim that a food product is rich in a micronutrient may still be used if the product contains more than 20 percent of the recommended dietary allowance per daily portion, for the duration of the interim period that has been set by the European directive.

- Restoration: adding micronutrients that are lost during the production process, storage and/or sale to foods. The amount added to the food restores the level of the micronutrient to the previous concentration in the edible part of the food or the raw material from which it was made.
- Substitution: Replacing a food with a different food that corresponds as close as possible in terms of appearance, consistency, taste, colour and aroma, or that serves the same purpose for the consumer.
- Fortification: Adding one or more micronutrients to a food, resulting in a concentration higher than that which is naturally occurs in the food 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 makes the decision to fortify the product or not and therefore only specific products will be fortified. In practice, the government can also consult with the manufacturer to stimulate voluntary fortification. In the case of mandatory fortification, basic food products are fortified. Mandatory fortification is not legally feasible in the Netherlands. The government can arrange mandatory fortification via an agreement with manufacturers, as is the case for the addition of iodine to baking salt. The Commodities Act specifies how much of a particular micronutrient can be added to which products.[17]
- Supplementation: Using a supplement containing micronutrients as an addition to the diet.

1.4 Issues addressed

The request for an advisory report from the Ministry for Health, Welfare and Sport to the Health Council of the Netherlands (see Annex A) initially asked for an inventory of (1) essential micronutrients that are not obtained sufficiently from the habitual diet, (2) the desired level of supply of these nutrients and (3) the best way in which this desired level of supply can be achieved: restoration, substitution, fortification or supplementation, taking into consideration any associated beneficial or adverse health effects.

Consultation between the Health Council of the Netherlands and the Ministry for Health, Welfare and Sport resulted in this request for an advisory report being limited to the micronutrients for which supply from the habitual diet may be insufficient for the entire population in the situation where no micronutrients are added to the habitual diet. This is the case for the vitamins A and D, iodine and folic acid. An active substitution policy has already been implemented for the

vitamins A and D. Limited fortification is permitted for iodine.[16,18] There have been indications since the early 1990s that the nutritional status of more than half the adult population may be insufficient where folic acid is concerned.[19] There are no clear indications for the other micronutrients that the general population receives inadequate quantities.[20,21] This is a different matter for specific population groups. Therefore, in the last advisory report in a series of five, the Committee (Annex B) will indicate which other micronutrients should be given priority.

For this advisory report, the Minister's questions for vitamin A were operationalised as follows:

- Are there any new scientific developments that warrant a re-evaluation of the Dutch policy?
- What is the intake and nutritional status of the Dutch population or population groups for vitamin A?
- If the supply is inadequate, how much extra – or less – vitamin A can the various population groups safely consume to ensure (a lasting) adequate intake of vitamin A?
- What is the best way of achieving this?

1.5 Methodology

For this advisory report, the relevant background information was systematically evaluated and categorised according to the level of evidence (see Annex C). The Committee has also taken into consideration previous experiences in and outside the Netherlands of supplementation and fortification and of European developments. In order to answer the questions, the vitamin A supply was described, the effects of various policy measures were discussed and the current available data and the data actually required to formulate the recommendations were weighed.

The Committee submitted its advisory report for review to the Standing Committees on Nutrition and Medicine of the Health Council of the Netherlands.

1.6 Structure of the advisory report

Chapter 2 discusses the physiological role of vitamin A and the consequences when intake is too low or too high. Chapter 3 describes the dietary reference values for vitamin A. In Chapter 4, the Committee analyses whether there are any new scientific insights into vitamin A that could influence its

recommendations. Therefore, this Chapter answers the first question of the request for an advisory report. Chapter 5 describes the current vitamin A supply. This addresses the second part of the request. Chapter 6 focuses on the current Dutch policy measures and the benefits and disadvantages of any changes to this policy and describes international policy measures. The third and fourth parts of the request can be answered based on this information. The Committee presents its conclusions and recommendations in Chapter 7.

Chapter 2

Introduction on vitamin A

This Chapter describes the various ways in which vitamin A can be obtained and the various units in which it can be expressed. This Chapter also discusses the role of vitamin A in the body, the effects of too little and too much vitamin A and the various sources of vitamin A.

2.1 Nomenclature

Vitamin A – or retinol – can be obtained in two different ways: from retinol (retinyl esters) and from the pro-vitamin A carotenoids alpha-carotene and beta-carotene and beta-cryptoxanthin. Retinol occurs in the form of esters in food products from animal origin. The most common is retinyl palmitate. Both the esters and free retinol can be found in nutritional supplements and food products. The retinyl esters and pro-vitamin A carotenoids are converted to retinol in the body.

In this advisory report, the various forms of vitamin A and precursors are indicated as follows:

- vitamin A: collective term for vitamin A derived from retinol and pro-vitamin A carotenoids
- retinol: vitamin A derived from animal food products, margarine, low-fat margarine, products for baking and frying and supplements

- pro-vitamin A carotenoids: carotenoids obtained from plant-based food products, milk and egg yolk, which can be converted to vitamin A in the body.

2.2 Units

In this advisory report, vitamin A, retinol and pro-vitamin A carotenoids are expressed in retinol activity equivalents (RAE), except in the description of the original dietary reference values from 1989 and intake data prior to 2003. There they are expressed as retinol equivalents (RE) (see also 4.1 Bio-efficacy).

2.3 Function

Vitamin A is involved in various biochemical and physiological processes. Functions for which vitamin A is essential are vision at low light intensity and reproduction. Vitamin A is also involved in, among others, cellular differentiation required for the maintenance and proper functioning of epithelial tissue*, gene expression, immunity and growth.[1,22]

2.4 Consequences of a deficiency and an overdose

A shortage of vitamin A can result in night-blindness, changes to the skin – such as hyperkeratosis – elevated susceptibility to infections and anaemia. A long-term, severe deficiency can result in blindness (xerophthalmia).[1,22] Vitamin A deficiency is mainly a problem in developing countries.

An intake of retinol exceeding 3,000 micrograms RAE can have teratogenic effects.[23] This is the reason that pregnant women and women who want to become pregnant are advised to avoid liver, liver products and nutritional supplements containing retinol.[24] An intake exceeding 7,500 micrograms RAE retinol has led to hepatotoxic effects. In postmenopausal women, a retinol intake of 1,500 micrograms RAE or more may be associated with an elevated risk of osteoporosis and bone fractures.[23]

A tolerable upper level of intake has not been set for beta-carotene. However, intervention studies have shown that a supplement of 20 milligrams beta-carotene (10 milligrams RAE) per day increases the risk for smokers of developing and dying from lung cancer. Animal experiments have provided possible mechanisms that could explain this effect in the lungs. In rats, beta-

* Internal and external surface tissue.

carotene interfered in the bio-transformation system and in ferrets it affected certain nuclear receptors. It may also be able to change into a pro-oxidant as a result of the relatively high partial oxygen pressure in the lungs.[23]

2.5 Sources

In the western world, retinol from animal products provides a more significant portion of the intake of vitamin A than pro-vitamin A carotenoids. The most important sources of retinol are animal products, such as milk, butter, cheese, egg yolk, liver and certain types of fatty fish. In addition, vitamin A is added to margarine in the same amount found naturally in butter.[1,22] Liver is very rich in retinol. When consuming a sandwich with margarine (5 grams) and liver sausage (15 grams), 40 micrograms RAE retinol is obtained from the margarine and 660 micrograms RAE from the liver sausage. A comparable amount of liver pâté provides 1,110 micrograms RAE.[25] Other animal products contain significantly less retinol. The most important sources of pro-vitamin A carotenoids are dark green leafy vegetables and some yellow and orange fruits and vegetables. Milk fat and egg yolk also contain pro-vitamin A carotenoids.[1,22]

Chapter 3

Dietary reference values from 1989

This Chapter explains what dietary reference values are, what they are based on and which upper and lower limits are used.

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 dietary reference values are intended for healthy individuals and aimed primarily at the prevention of diseases. They are used for:

- programming the food supply for healthy groups
- creating nutritional guidelines for healthy individuals
- evaluating the intake data for healthy groups
- evaluating the intake of individuals who – based on biochemical parameters – have been shown to have a poor nutritional status
- setting up the so-called Guidelines for a Healthy Diet.

In the past, the dietary reference values have always been set by the Committee for Dietary reference values of the Nutrition Council / Health Council of the Netherlands. The recommended dietary allowance of a nutrient is derived from figures about the average requirement for that nutrient. If such figures were missing – as was the case for vitamin A in children and teenagers – the Committee limited itself to mentioning an adequate intake. The recommended

dietary allowance and adequate intake have the same practical significance: both indicate the level of intake desirable for health reasons.[26]

3.2 Minimum requirement and adequate intake

The dietary reference values for vitamin A date from 1989 (Annex D).[22] These standards provide an estimate of the adequate intake for all age categories and also an estimate of the minimum requirement for adults. The estimate is based on maintaining an adequate liver store.

In determining the dietary reference value in 1989, the following bio-availability of pro-vitamin A carotenoids was used:

1 retinol equivalent = 1 microgram retinol = 6 micrograms beta-carotene = 12 micrograms other pro-vitamin A-carotenoids.[22]

The following Chapter discusses the new scientific insights in the field of bio-availability and their effect on the dietary reference values (see Chapter 4.1 Bio-efficacy).

3.3 Tolerable upper level of intake

In the Netherlands, the tolerable upper level of intake for retinol was set in 1989 at 15,000 micrograms RE per day for adult males and 13,000 micrograms RE per day for adult females. The limit for pregnant women is 3,150 micrograms RE per day (Annex D). The assumption was that long-term intake of retinol at the level of the tolerable upper level of intake probably will not have any negative effects as a result of a vitamin A overdose (hepatotoxic or – for pregnant women – teratogenic effects).[22] Tolerable upper levels of intake that were set more recently in other countries or at a European level are significantly lower than the Dutch tolerable upper level of intake, with the exception of the limit for pregnant women (see Chapter 4.5 Foreign tolerable upper levels of intake). No tolerable upper levels of intake have been set for pro-vitamin A carotenoids.

Chapter 4

New scientific developments

In this Chapter, the Committee will indicate whether there are any new scientific insights that should be taken into consideration in the final recommendations. New insights will be discussed for: the bio-efficacy of pro-vitamin A carotenoids, the relationship between vitamin A and the risks of cancer, osteoporosis and other conditions or death and foreign tolerable upper levels of intake for retinol and beta-carotene. Based on this information, the Committee will decide whether there are any new scientific developments that it wishes to include in its final recommendation and which dietary reference values and tolerable upper levels of intake it will use in its advisory report.

4.1 Bio-efficacy

Since the publication of the dietary reference values in 1989, new insights have become available that indicate that the bio-efficacy of pro-vitamin A carotenoids from food products is lower than assumed in 1989. The bio-efficacy is the efficiency at which a pro-vitamin A carotenoid is absorbed and converted to retinol. The new insights about the lower bio-availability of carotenoids have been included in more recent foreign dietary reference values for vitamin A.[27,28]

As described in the previous Chapter, when setting the dietary reference values in 1989, the bio-efficacy of pro-vitamin A carotenoids was assumed to be as follows:

1 retinol equivalent = 1 microgram retinol = 6 micrograms beta-carotene = 12 micrograms other pro-vitamin A-carotenoids.[22]

A lower bio-efficacy for the various pro-vitamin A carotenoids from food products was assumed when setting the American dietary reference values:

1 retinol activity equivalent = 1 microgram retinol = 2 micrograms all-*trans*-beta-carotene from supplements = 12 micrograms all-*trans*-beta-carotene from the diet = 24 micrograms other pro-vitamin A carotenoids from the diet[27]

The International Vitamin A Consultative Group has adopted the abovementioned conversion factors for pro-vitamin A carotenoids with the caution that the bio-efficacy may be even lower in developing countries.[29] A conversion factor of 12:1 for all-*trans*-beta-carotene will also be used in this advisory report.

The National Institute for Public Health and the Environment (RIVM) has calculated (Table 4.1) what the Dutch standards should be when taking into consideration the Dutch growth curves and new insights into the bio-efficacy of pro-vitamin A carotenoids such as those processed in the dietary reference values of the American Institute of Medicine.[30]

Conclusion: the bio-efficacy of pro-vitamin A carotenoids from food products appears to be lower than assumed in 1989 when the dietary reference values were set. Therefore, the Committee will use dietary reference values in this advisory report that are based on the dietary reference values of the American Institute of Medicine, in which the Dutch growth curves have been incorporated. Vitamin A, retinol and pro-vitamin A carotenoids will be expressed as retinol activity equivalents in this advisory report.

4.2 Intake of vitamin A and the risk of cancer

The intake of retinol and pro-vitamin A carotenoids from the diet and supplements has been linked to the risk of various types of cancer. The World Cancer Research Fund has conducted systematic research into this.[31]

The World Cancer Research Fund deems that there is conclusive evidence that a supplement of 20 milligrams beta-carotene (10 milligrams RAE) or more increases the risk of lung cancer in individuals who smoke or have been systematically exposed to asbestos. This conclusion is based on intervention

studies. The reason for performing these intervention studies was that there were indications from observational studies that suggested that carotenoid-rich food products were associated with a lower risk of lung cancer. Explanations that have been suggested for these contradictory effects are dose discrepancies and the possibility that carotenoid-rich food products are an indicator of a healthy diet in general.[32] The EU Scientific Committee on Food concluded that the intervention studies show that heavy smokers should be discouraged from using these supplements.[23] It has not been demonstrated convincingly whether supplements with a high dose of beta-carotene also form a risk to ex-smokers or the general population.[32,33]

There are also indications from observational studies that carotenoids from food products – including beta-carotene – are associated with a lower risk of cancer of the mouth, epiglottis, throat and oesophagus.[31] These forms of cancer occur mainly in smokers. As is the case for lung cancer, intervention studies with beta-carotene show that supplements offer no protective effect against these other forms of cancer.[34,35] It is also unlikely that beta-carotene from food products or supplements decreases the risk of prostate cancer, whilst beta-carotene from supplements may increase the risk of gastrointestinal cancer.[31,36]

The level of evidence is also scant for other effects: this applies both to the finding that supplements with a high dose of retinol increase the risk of lung cancer in people who smoke, as well as to the finding that these supplements protect against a certain type of skin cancer in individuals with an increased risk of skin cancer.[31]

Conclusion: supplements with high doses of beta-carotene (20 milligrams per day or 10 milligrams RAE per day) increase the risk of lung cancer in people who smoke.

4.3 Intake of vitamin A and the risk of osteoporosis

The EU Scientific Committee on Food concluded on the basis of two epidemiological studies from Sweden and the United States that the risk of bone fractures increases with the intake of retinol in quantities obtained via the habitual diet.[23]

A systematic review article indicates that – in view of the biological plausibility* – the limited available data about a relationship between a high

intake of retinol from the total diet and an increased risk of bone fractures should be taken seriously. It was noted here that there are insufficient data to determine the relationship between the intake of retinol specifically from supplements and the risk of bone fractures.[38] Similarly, another review article concludes that negative effects can occur at an intake level of approximately 1,500 micrograms RAE per day, but that it is not possible yet to define a specific level of retinol intake above which the bone density decreases. A level of 1,500 micrograms RAE retinol per day is approximately twice the recommended intake for women.[30,39]

Other review articles state that the results of observational studies on the relationship between the intake of vitamin A or retinol or the retinol concentration in serum and the bone density or the risk of bone fractures is ambiguous. The authors provide an explanation stating that this could be partially due to the limitations in determining the intake and status of vitamin A. The intake of vitamin A is also associated with the intake of other nutrients that could affect bone density and there were differences between the studies in the part of the skeleton that was examined, the menopausal status of the participants and the variables used to correct the risk estimates.[37,40,41]

The British Scientific Advisory Committee on Nutrition reached a similar conclusion and states that the data are a cause for concern, but that it is difficult to determine a cause-effect relationship due to the observational nature of the data.[42]

A cohort study that was published after the abovementioned studies found that fifty to seventy year old Norwegian women who had used cod liver oil throughout the year during their youth had a lower bone density than women who had not used cod liver oil during their childhood. Cod liver oil used to contain a lot of retinol, the level in Norway was recently reduced by 75 percent.[43]

Conclusion: there are suggestions, but no hard evidence, that a high retinol intake is associated with a lower bone density and a higher risk of bone fractures.

* In animal experimental studies, retinoic acid reduced the activity of osteoblasts, stimulated the production of osteoclasts and decreased the ability of vitamin D to ensure a sufficient calcium concentration in the blood. All three of these effects can accelerate bone resorption, decrease bone density and increase the risk of bone fractures, which was also found with vitamin A toxicity in humans.[37]

4.4 Intake of vitamin A and the risk of other conditions and death

The intake of retinol and pro-vitamin A carotenoids from the diet and supplements has been linked to the risk of cardiovascular diseases, age-related macular degeneration and death.

Systematic review articles concluded that the intake of retinol or beta-carotene from food products or supplements has no effect on the risk of cardiovascular diseases or age-related macular degeneration.[38,44]

Whether the intake of retinol and beta-carotene influences the risk of death may depend on the dose. A systematic review seems to indicate that the use of supplements with retinol and beta-carotene is associated with an increased risk of death. The review incorporates results from 15 intervention studies on retinol and 25 studies on beta-carotene, in which the dosage in some of the studies was higher than the recommended dietary allowance or even the tolerable upper level of intake*. In studies of a good quality – which excluded studies with selenium – the use of supplements with retinol was associated with a risk of death of 1.16 (95 % confidence interval 1.10 - 1.24). The use of supplements with beta-carotene was associated with a risk of 1.07 (95 % confidence interval of 1.02 - 1.11).[45] Another systematic review article describes three studies examining 10 to 25 milligrams RAE beta-carotene per day, which all found an increased risk of death. The effect was only significant in a study among smokers. In people who were exposed to asbestos in an occupational capacity, a supplement with beta-carotene (25 milligrams RAE) and retinyl esters (5 milligrams RAE) also increased the risk of death.[38] The use of supplements with retinol or beta-carotene could therefore result in a clinical disadvantage.

Conclusion: there are no indications that retinol and beta-carotene affect the risk of cardiovascular diseases and age-related macular degeneration. There are suggestions that a high dose of retinol and beta-carotene can increase the risk of death, with the effect being most pronounced in smokers and people who were exposed to asbestos on an occupational basis.

* The dose of retinol varied in the studies from 444 to 8,333 retinol activity equivalents per day and with one outlier of 66,667 retinol activity equivalents per day and the dose of beta-carotene varied from 100 to 4,167 retinol activity equivalents per day.

4.5 Foreign tolerable upper levels of intake

According to insights obtained since the Dutch dietary reference values for vitamin A were set in 1989, the tolerable upper level of intake for retinol is lower than assumed at the time. The EU Scientific Committee on Food has based the tolerable upper levels of intake for retinol on both teratogenic and hepatotoxic effects and effects on bone density (Table 4.1). These effects were observed in

Table 4.1 The dietary reference values for vitamin A used in this study and the tolerable upper levels of intake for retinol in retinol activity equivalents (RAE) per day.

	Average requirement	Recommended dietary allowance[a]	Tolerable upper level of intake[b,c]
0 – 12 months	N/A[d]	N/A	N/A
1 – 3 years	220	300	800
4 – 8 years	300	400	1,100/1,500
9 – 13 years	440	600	1,500/2,000
Boys 14 – 18 years	600	800	2,000/2,600
Girls 14 – 18 years	510	700	2,000/2,600
Men 19 – 50 years	620	900	3,000
Women 19 – 50 years	530	700	3,000
Men 51 – 65 years	610	900	3,000
Women 51 – 65 years	530	700	3,000[e]
Men 66+ years	610	900	3,000
Women 66+ years	520	700	3,000[e]
Pregnant women	580[f]	800	3,000
Women who are breastfeeding	930[g]	1,300	3,000

[a] For the calculation of the recommended dietary allowance, it was assumed that the variation coefficient was 20 percent, in other words the recommended dietary allowance is 1.4 times the average requirement. The recommended dietary allowance was rounded off to 100 micrograms RAE retinol per day.

[b] The American and British tolerable upper levels of intake for retinol are also more recent than the Dutch tolerable upper levels of intake from 1989. United States: 0-1 years 600 micrograms RAE per day, 1-3 years 600 micrograms RAE per dag, 4-8 years 900 micrograms RAE per day, 9-13 years 1,700 micrograms RAE per day, 14-18 years 2,800 micrograms RAE per day, 18+ years 3,000 micrograms RAE per day.[27] Great Britain: guidance levels for adults 1,500 micrograms RAE per day. The Expert Group was unable to determine a guidance level for children.[46]

[c] 4-6 years 1,100 micrograms RAE per day, 7-10 years 1,500 micrograms RAE per day, 11-14 years 2,000 micrograms RAE per day, 15-17 years 2,600 micrograms RAE per day, postmenopausal women 1,500 micrograms RE per day.[23]

[d] N/A not available.

[e] Because the acceptable upper limit of 3,000 micrograms RAE per day may provide insufficient protection against the possible risk of bone fractures in certain vulnerable groups, postmenopausal women – who have a higher risk of osteoporosis and bone fractures – should limit their intake to 1,500 micrograms RAE per day.

[f] The extra average requirement was set at 50 micrograms RAE per day.

[g] The extra average requirement was set at 400 microgram RAE per day.

adults. The tolerable upper levels of intake for children have been derived from those for adults, by correcting for differences in resting metabolic rate. For postmenopausal women, the EU Scientific Committee on Food states that the tolerable upper level of intake of 3,000 micrograms RAE retinol per day is inadequate to provide protection against the possible risk of bone fractures. Postmenopausal women should therefore limit their intake to 1,500 micrograms RAE retinol per day. This quantity is not a real tolerable upper level of intake, because the available data provide insufficient proof for a cause-effect relationship and are not suitable for determining a tolerable upper level of intake.[23]

The Institute of Medicine has set tolerable upper levels of intake that are reasonably similar to the European upper limits, but does not make an exception for postmenopausal women.[27]

In contrast, the British Expert Group on Vitamins and Minerals thinks that there is insufficient data available to set tolerable upper levels of intake and has therefore set guidance levels. The guidance level for adults is 1,500 micrograms RAE retinol per day and is based on hepatotoxic effects (3,000 micrograms RAE retinol per day) and the risk of bone fractures (1,500 micrograms RAE retinol per day). The Expert Group was not able to set a guidance level for children.[46]

Conclusion: recently set tolerable upper levels of intake for retinol, based on new insights into the harmful effects of retinol on the liver, the unborn child and in some cases on bone density, are significantly lower than the tolerable upper levels of intake from 1989. The Committee will use the most recent limits in this advisory report. These were set by the EU Scientific Committee on Food.

4.6 Conclusion

This advisory report will use dietary reference values that are based on those set by the American Institute of Medicine and on tolerable upper levels of intake as set by the EU Scientific Committee on Food. These more recent dietary reference values and tolerable upper levels of intake take into consideration new insights on the bio-efficacy of pro-vitamin A carotenoids from the diet and the effect of retinol on the liver, the unborn child and the bone density.

As a result of this, vitamin A, retinol and pro-vitamin A carotenoids will be expressed as retinol activity equivalents in this advisory report.

As far as other scientific insights are concerned: There is conclusive evidence that a supplement of 20 milligrams beta-carotene (10 milligrams RAE) or more increases the risk of lung cancer in individuals who smoke or have been systematically exposed to asbestos. There are also indications that there is a relationship between the intake of food products that contain carotenoids and a lower risk of cancer of the mouth, the epiglottis, the throat and the oesophagus. However, as was the case for the risk of lung cancer, intervention studies with beta-carotene supplements did not confirm these findings. Finally, there are suggestions that a high retinol intake is associated with a lower bone density and a higher risk of bone fractures (Table 4.2).

Table 4.2 Overview of the evidence of new scientific developments (see Annex C for a description of the categorisation and codes).

Convincing
Supplementation with beta-carotene increases the risk of lung cancer in people who smoke or have been exposed to asbestos. A1[31]
Likely
The intake of food products that contain carotenoids is associated with a lower risk of cancer of the mouth, the epiglottis, the throat and the oesophagus. B1[31]
Insufficient
Supplementation with beta-carotene decreases the risk of cancer of the mouth, epiglottis, throat and oesophagus. A2[34,35]
Supplementation with beta-carotene increases the risk of gastrointestinal cancer. A2[36]
Supplementation with retinol decreases the risk of a certain type of skin cancer in people at increased risk of skin cancer. B1[31]
The intake of beta-carotene from food products or supplements decreases the risk of prostate cancer. B1[31]
A high intake of vitamin A or retinol is associated with a lower bone density and a higher risk of bone fractures. B1[38], B2[37,39,40]
The intake of beta-carotene from food products or supplements decreases the risk of cardiovascular diseases. B1[38]
The intake of retinol and beta-carotene from food products or supplements decreases the risk of age-related macular degeneration. B1[38,44]
The use of supplements with a high dose of retinol or beta-carotene increases the risk of death. B1[38,45]
The intake of retinol from supplements increases the risk of lung cancer in people who smoke. B1[31]

Chapter 5

Vitamin A supply in the Netherlands

This Chapter discusses the amount of vitamin A that the Dutch population consumes, the vitamin A supply. The Committee will first discuss how this vitamin A supply is determined. They will then evaluate the values that were determined. The Committee will also describe the most important sources of vitamin A in the Dutch diet. Finally, the Committee will examine the extent to which excessive intake of vitamin A occurs in the Netherlands.

5.1 Methods for determining the supply of vitamin A

In theory, three steps are required to determine whether the vitamin A supply is sufficient: determination of intake, comparison of intake with requirement and status determination.

Firstly, data on intake are collected: what do people in the Netherlands eat and drink and how much vitamin A – in the form of retinol or pro-vitamin A carotenoids – is found in the collective food products and supplements? Most of the intake data on which this advisory report is based are obtained from food consumption surveys. Until 2000, these intake data were collected on two consecutive days. These data are not independent, but do provide an insight into the day-to-day variation. It is possible to adjust for this variation. The term ‘observed intake’ refers to the unadjusted intake data, the term ‘habitual intake’ refers to the adjusted data. The average of the habitual intake is comparable to the average of the observed intake, but the variation is smaller.[47] Data about

habitual intake are preferable when it comes to determining the number of people whose intake is too low or too high.

Step two – comparison of intake with requirement – is a comparison against the dietary reference values, which indicate how much vitamin A people of various ages and gender require for good health. Based on this information, it is possible to evaluate the intake of vitamin A for the various groups: is it too low, too high or just right? There are two quantitative methods that can be used in order to estimate the percentage of people in a population that is 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 that has an intake above or below a certain dietary reference value. The probability method combines the distribution of the habitual intake and the distribution of the requirement in a population group to create an estimate of the percentage of the population with an intake below the required level. This improves the accuracy of the estimate.

Both TNO and the RIVM have compared data about the intake of vitamin A with the dietary reference value using the threshold method. The RIVM also performed a comparison with the probability method. The approaches are described in Annex E. In both cases, intake data were expressed in micrograms RAE compared to reference values that were set by the American Institute of Medicine, adjusted according to reference weights and growth factors for the Dutch population. Most of the intake data collected until 2003 have been expressed in retinol equivalents. These were only used in this Chapter to describe changes in the intake of vitamin A over time and differences between groups.

In theory, step three – the status assessment – serves to clarify the accuracy of the estimate from step two: the vitamin A status of a certain group of individuals is examined. Research is also performed on possible conditions that are suspected to be associated with an intake that is too low or too high. However, the problem is that a good status parameter is not available. The level of retinol-binding protein only decreases once the stores of vitamin A in the liver become depleted. It is possible to estimate the liver stores using a method that measures the dilution of stable isotopes. For example, the deuterated retinol dilution technique provides a good estimate at a group level of the vitamin A stores in the entire body and in the liver. The method was originally very expensive and therefore not used for population screening.[48-50] The method has since become somewhat cheaper. Finally, physiological symptoms such as night-blindness can indicate a severe vitamin A deficit.

5.2 Intake data

The intake of vitamin A in the Netherlands decreased by 10 percent between 1988 and 1998.[51]

The average habitual intake of vitamin A by 9, 12 and 18 month-old infants according to the nutrient intake study (2002) was 898, 910 and 735 micrograms RE per day respectively (Table 5.1). This study was initiated by Nutricia Netherlands B.V. and performed by TNO under the supervision of an independent advisory committee.[52]

Table 5.1 Average and percentiles of the habitual intake of retinol in micrograms RE per day.[a]

	Average intake (standard deviation) (RE)	P10	P50	P90
Infants 9 months	898 (270)	588	857	1,264
Infants 12 months	910 (285)	569	876	1,297
Infants 18 months	735 (317)	377	682	1,166

[a] Intake includes the intake of vitamin A from carotenoids and excludes the intake of vitamin A from supplements.

In the food consumption surveys of young children (2005/2006) and young adults (2003), the intake of vitamin A was expressed in retinol activity equivalents per day. The average vitamin A intake of children aged 2 to 6 years varied from 513 to 581 micrograms RAE per day. An estimated 3 to 15 percent of the children had an intake below the average requirement (Table 5.2).[53]

The habitual average intake of vitamin A for young adult men was 991 ± 1,037 micrograms RAE per day and 667 ± 627 micrograms RAE per day for women (Table 5.2).[54] The intake of vitamin A for people who did not use margarine or low-fat margarine was an average of 159 micrograms RAE lower for men and 112 micrograms RAE lower for women than for people who did use these products.[54]

The vitamin A intake for Turkish young men and women is different. In comparison to the habitual intake of vitamin A – expressed in retinol equivalents – by participants in the food consumption survey of young adults, the observed intake by Turkish young men and women and Moroccan young men was lower and by Moroccan young women was somewhat higher (Table 5.3).[55]

Table 5.2 Average, standard deviation and percentiles of the habitual intake of vitamin A in micrograms RAE per day.[a][30,52-54]

	N	Average	SD[b]	P1	P10	P50	P90	P99
Food consumption survey 2005/2006								
Boys 2 - 3 years	327	540				497		
Girls 2 - 3 years	313	581				504		
Boys 4 - 6 years	327	546				463		
Girls 4 - 6 years	312	513				474		
Food consumption survey 2003								
Men 19 - 30 years[c]	352	991	1,037		499	900	1,735	
Women 19 - 30 years[c]	398	667	627		336	600	1,151	
Food consumption survey 1997/1998								
Children 1 - 3 years	254	573	345	158	252	482	1,006	1,817
Children 4 - 8 years	431	674	488	144	259	540	1,233	2,567
Children 9 - 13 years	409	701	347	233	362	620	1,136	1,911
Boys 14 - 18 years	229	960	578	257	448	817	1,619	3,129
Girls 14 - 18 years	216	741	356	247	382	662	1,193	1,966
Men 19 - 50 years	1,437	1,096	735	291	484	899	1,910	3,942
Women 19 - 50 years	1,655	787	454	233	377	676	1,315	2,487
Men 51 - 65 years	420	1,197	775	303	510	994	2,108	4,114
Women 51 - 65 years	479	859	463	273	424	746	1,424	2,522
Men 65+ years	260	1,102	564	353	541	971	1,832	3,048
Women 65+ years	410	815	377	303	442	728	1,293	2,114

[a] Intake includes the intake of vitamin A from carotenoids and excludes the intake of vitamin A from supplements.
[b] SD, standard deviation.
[c] The average intake (standard deviation) of vitamin A by male users of margarine and low-fat margarine was 1,032 (1,012) micrograms RAE per day and that of male non-users was 873 (1,103) micrograms RAE per day. The intake by female users was 701 (635) micrograms RAE per day and by female non-users was 589 (605) micrograms RAE per day.[54]

Table 5.3 The average daily intake of vitamin A in micrograms RE of Turkish and Moroccan young adults in comparison to participants in the food consumption survey of young adults (2003).[55]

	Average vitamin A intake (standard deviation) (RE)[a]	
	Men	Women
Turkish	471 (310)	625 (574)
Moroccan	706 (509)	958 (1,255)
Participants FCS [b]2003	1,176 (1,092)	856 (714)

[a] The intake of the Turkish and Moroccan participants is the observed intake and that of the participants in the food consumption survey among young adults is the habitual consumption.
[b] FCS, food consumption survey among young adults.

Based on the third food consumption survey (1997/1998), using the probability method, it is estimated that 20 to 30 percent of the population has a vitamin A intake that is too low to maintain liver stores (see Table 5.2). The calculations also show that only a small percentage of individuals – estimated to be up to 4.8 percent of adult women – have an intake of vitamin A that is so low that the physiological requirements may not be covered.[30] These data are from 10 years ago. When compared to this food consumption survey, the median intake of vitamin A has not changed significantly in more recent food consumption surveys. Only the level for women aged 19 to 30 years was approximately 60 micrograms RAE per day lower in 2003 than in 1997/1998. The average for all groups is slightly lower in the more recent food consumption surveys, which indicates that a high intake is less common.

The percentage of vegetarians with an intake lower than the average requirement – at 7 percent – was significantly lower than the percentage amongst the general population. The variation in intake amongst vegetarians is also very small: there are very few vegetarians with a very low or very high intake.[30]

The Committee is not aware of any research on the vitamin A status in the Netherlands or of any reports about the occurrence of night-blindness due to a shortage of vitamin A in the Dutch population.

Conclusion: intake data from 1997/1998 suggest that 20 to 30 percent of the Dutch population has a vitamin A intake that is lower than the average requirement. More recent intake data appears to confirm this. There are no data about the nutritional status to verify the intake data. The Committee is also not aware of any reports about symptoms of vitamin A deficit – night-blindness – in the Dutch population.

5.3 Sources of vitamin A in the diet

The decrease in the intake of vitamin A between 1988 and 1998 is primarily caused by the lower consumption of liver, liver products, margarine and products used for baking and frying and the replacement of full-fat milk and milk products by low-fat and skimmed milk alternatives.[51] The use of the product group fats, oils and savoury sauces was virtually unchanged on balance. The decrease in the use of margarine (grams) at population level was similar to the increase in the use of savoury sauces. Compared to these changes, the increase in the use of low-

fat margarine and oil was relatively small*. Notwithstanding this fact, the number of users of low-fat margarine and oil did increase significantly in this period by 13 and 15 percent respectively.[51]

In the food consumption survey of young children (2005/2006), the product groups dairy, meat and meat products – particularly in the form of liver and liver products – and fat each contributed approximately 20 percent of the vitamin A intake, expressed in retinol activity equivalents.[53]

In the food consumption survey of young adults (2003), the product groups meat and meat products – particularly in the form of liver and liver products – (33 percent of the total RAE intake), milk products and cheese (14 percent), fats (22 percent) and vegetables (13 percent) formed the most important sources of vitamin A.[54] Compared to the participants in this food consumption survey, Turkish and Moroccan young adults consumed less meat and meat products, milk products and cheese and margarine and more vegetable-based oils.[55]

5.4 Vitamin A intake from supplements

The exact intake of vitamin A from supplements is not known.[56] Based on the retinol levels of the nutritional supplements for children available on the market, it is estimated that the use of these supplement provides an average of approximately 400 micrograms RAE per day to children.[57] In the same manner, it has been estimated that the retinol intake from use of supplements amongst young adults is about 600 micrograms RAE per day.[57]

The use of supplements with vitamins A and D is highest in young children. During the period 1987 to 1998, it was recommended to give supplements with vitamin A and D to young children. The reason for this recommendation was that – at the time – it was not technologically feasible to make a vitamin D supplement that did not contain vitamin A. Nowadays the recommendation only applies to vitamin D. In the nutrient intake study of young toddlers (2002), an average of 7.9 percent of the toddlers used a vitamin AD supplement. The use increased with age from 3.3 percent for the toddlers aged 9 months to 13.6 percent for the toddlers aged 18 months.[58] In children aged 2 to 6 years, supplements supplied 10 percent of the vitamin A intake, expressed in retinol activity equivalents.[53] Less than 2 percent of the adult population uses vitamin

* The percentage of users of margarine decreased by 22 percent, with the average consumption by the population decreasing by 10 grams. By contrast, the percentage of users of savoury sauces increased by 14 percent, with the average consumption by the population increasing by 9 grams. The percentage of users of low-fat margarine and oil increased by 13 and 15 percent respectively, whilst the average consumption by the population increased by 2 grams and 1 gram respectively.[51]

AD supplements. However, 16 percent of the young adults do use a multivitamin-mineral supplement, which usually also contains vitamin A.[56]

5.5 Excessive retinol intake

In the food consumption survey of young children (2005/2006), the percentage of children with an excessive retinol intake from food products varied from 11 percent in two and three-year-old girls to 1 percent in four to six-year-old girls. The intake of supplements was not taken into consideration.[53] There is no tolerable upper level of intake for beta-carotene.

Additional analyses show that for the 25 percent of children with the highest vitamin A intake, depending on gender and age, liver and liver products provide an average of 600 to 800 micrograms RAE retinol per day and supplements provide around 150 micrograms per day*.

A different approach confirms the abovementioned findings. The intake of retinol can be calculated from the intake of vitamin A. The relative contribution of retinol to the intake of vitamin A expressed in retinol activity equivalents is 82 percent in men and 76 percent in women (average of 79 percent).[30]

Based on this relative contribution, the intake of retinol can be estimated from table 5.2. If a relative contribution of 79 percent is used for children, then almost 10 percent of one to three-year-olds have a retinol intake that exceeds the tolerable upper level of intake of 800 micrograms, with the limit being exceeded by a maximum of about 600 micrograms of RAE retinol. An estimated maximum of a few percent of children aged 4 to 8 years and men aged 14 to 50 years have an intake that exceeds the acceptable limit. The maximum level by which the limit is exceeded is approximately 1000 micrograms RAE for the youngest boys, approximately 400 to 500 micrograms for teenage boys and approximately 100 micrograms for adult men. In the other categories, there are no indications that the tolerable upper level of intake is being exceeded.[23,30] If a tolerable upper level of intake of 1,500 micrograms RAE retinol is applied to postmenopausal women, then 4 percent of these women have an excessive intake.[59]

The Committee is not aware of any other data about the extent to which users of supplements exceed the tolerable upper level of intake for retinol intake. It can be concluded from the information above that the use of supplements that contain retinol will cause an increase both in the number of people that exceed

* Personal communication dr. C. van Rossum 01-07-2008.

the tolerable upper level of intake for intake and in the degree to which this level is exceeded.

5.6 Conclusion

Intake data suggest that 20 to 30 percent of the Dutch population has an intake of vitamin A that is too low and that nearly 10 percent of young children have an excessive intake. It is not clear whether the excessively low or excessively high intake cause health problems.

Chapter 6

Measures

In this Chapter, the Committee makes an inventory of the policy in the field of vitamin A supply. Three measures will be discussed explicitly: the substitution or margarine, low-fat margarine and products used for baking and frying, the restoration of milk products and the fortification of oil with retinol. The policy described in this Chapter mainly concerns the policy in the Netherlands. In addition, scientific advice from other countries for the policy surrounding vitamin A is studied in Chapter 6.4. These are aimed primarily at the prevention of an excessive intake of retinol.

6.1 Current Dutch policy

In the Netherlands, retinol may only be added to food products for restoration or substitution. For example, retinol is added to margarine, low-fat margarine and products used for baking and frying – substitute products for butter – to a level of no more than 8 micrograms RE per gram of product. This has been set out in an agreement, which remains valid until the new European legislation comes into force. Vitamin preparations may provide a maximum of 1,200 micrograms of RE retinol per day.[6,10]

It is not permitted to fortify products with retinol. Based on a risk evaluation, the RIVM has concluded that – apart from the addition of retinol to margarine, low-fat margarine and products for baking and frying – there is no option for adding retinol to other food products without this creating a risk of exceeding the

tolerable upper level of intake for intake by children, men from the age of 18 years and postmenopausal women. The tolerable upper levels of intake of the EU Scientific Committee on Food were used for this.[23,57]

It has also been determined that vitamin A must be declared on the label in retinol equivalents.[7,12,60] For plant-based products, this results in levels of vitamin A that are almost twice as high as the retinol activity equivalents. This is also not in agreement with the Dutch food composition table NEVO, which does express the level of vitamin A in retinol activity equivalents.[25]

6.2 Restoration of milk and milk products

Restoration is the addition to food products of micronutrients that were lost during the production process, storage and/or sale. In 2003 TNO calculated the effect on the intake of vitamin A when low-fat and skimmed milk products and lower fat cheeses are restored to the level of full-fat milk and full-fat cheese. The intake of vitamin A increases by 65 micrograms RAE per day (approximately 7 percent) if low-fat and skimmed milk and milk products are restored and by 3 micrograms RAE per day (approximately 0.3 percent) if lower fat cheeses are restored. It has not been reported whether this restoration would result in a larger number of people with an excessive intake of retinol. The Committee deems this unlikely due to the skewed distribution of the retinol intake. The excessive retinol intake is caused by frequent use of liver and liver products. This means that the average intake will increase as a result of restoration, but this restoration will not have a large effect on the tail of the intake distribution.

6.3 Fortification of oil with retinol

In contrast to restoration, fortification involves the addition of micronutrients to a level that is higher than the natural level in the food product or its raw materials. The RIVM has calculated the effect on the intake if all oils except oil for deep-fat frying are fortified with 800 micrograms RAE retinol per 100 millilitres. This is the current level of retinol in margarine, low-fat margarine and products for baking and frying. The reason for calculating this scenario is that the use of these products by people of a non-western background is lower than by people of Dutch origin, whilst the opposite is the case for oil.[51,61]

The fortification of oil with retinol would result in a small increase in the median intake, which varies with age from 5 to 26 micrograms RAE retinol per day. As a result of the small increase and the skewed distribution of the retinol

intake, the number of people with excessive retinol intake would remain virtually the same.[59]

6.4 Foreign advice for policy

For this advisory report, the Committee also looked at policy advice in other European countries. The Committee is only aware of advice from Great Britain and Sweden. Both concern measures to prevent excessive retinol intake.

The British Scientific Advisory Committee report Review of Dietary Advice on Vitamin A offers options to lower the incidence of excessive retinol intake in Great Britain. In Great Britain, the guidance level for adults is 1,500 micrograms RAE retinol per day, which is approximately half the tolerable upper level of intake in other countries.[42] Intake data show that 9 percent of adult men under 65 years and 4 percent of adult women have an intake that exceeds the guidance level. This is also the case in approximately 10 percent of people aged 65 years and older. The conclusion by the British committee is that excessive retinol intake is primarily associated with the consumption of liver, because liver accounts for 70 percent of the total retinol intake by people with an intake that exceeds 1,500 micrograms RAE retinol per day. Nutritional supplements also play an important role in excessive intake. Nutritional supplements account for 16 to 17 percent of the total retinol intake by people under the age of 65 years with an excessive intake.

The British committee concludes that scientific data published since the guidance level was set do not sufficiently demonstrate the relationship between an intake of retinol that exceeds 1,500 micrograms RAE retinol and the bone density or the risk of bone fractures. Therefore the British committee sees no reason to decrease the intake of foods and supplements that contain retinol by the entire population. This committee does advise that people who eat liver at least once a week should, as a precaution, not eat any more liver and should not start using any supplements that contain retinol (including those that contain fish liver oil). Certain population groups with an increased risk of osteoporosis – such as postmenopausal women and the elderly – also should not consume more than 1,500 micrograms of RAE retinol per day. This can be achieved by limiting the intake of liver and supplements that contain retinol. The advice is also given to check whether the retinol level in supplements and in feed for livestock and poultry can be reduced.

The advice is less far-reaching in Sweden and also focuses on the type of retinol. It concludes that primarily pregnant women and possibly also all women of childbearing age should be advised not to consume more than 3 milligrams of

RAE retinol per day. The advice also states that only oil-based retinol should be added to food products and supplements and that retinol in water-soluble form or in emulsions should not be used. This is because the latter are absorbed more quickly, resulting in a stronger effect.[41]

6.5 Conclusion

In the Netherlands, it is currently not permitted to fortify products with retinol – other than the addition of retinol to margarine, low-fat margarine and products for baking and frying – because children, men over the age of 18 years and postmenopausal women would run the risk of exceeding the tolerable upper level of intake. This is already the case for children in the current situation.

The restoration of milk, milk products and cheese and the fortification of oil with retinol will result in small increases in the intake of this substance, with both the number of people with an excessive intake and the extent to which the tolerable upper level of intake is exceeded remaining virtually unchanged.

A British advice for the policy on vitamin A suggests that people who eat liver once a week should be advised not to eat any more liver and not to use supplements with retinol. In addition, people with an increased risk of osteoporosis are advised to limit the use of liver and supplements. By contrast, the Swedish advice focuses only on limiting the intake of retinol by pregnant women. It also advises the use of oil-soluble retinol for addition to food products and supplements.

Chapter 7

Conclusions and recommendations

The request for an advisory report concerned four questions. Firstly, the question about new scientific developments that require a re-evaluation of the Dutch policy, secondly the question about the intake and nutritional status of the Dutch population for vitamin A. The third question asked to provide a guideline to ensure (continued) adequate supply of vitamin A if the supply was found to be suboptimal and the fourth question asked what the best method would be of achieving this. The four questions are answered in order below. Additional research is required before some of the recommendations can be made. This is discussed as a fifth point.

7.1 New developments

The response to the question whether there have been any new developments in the past few years is affirmative. The most important developments are related to the risk of lung cancer.

Supplements with a high dose of beta-carotene can increase the risk of lung cancer

There is conclusive evidence from intervention studies that the use of supplements containing at least 20 milligrams of beta-carotene per day (10

milligrams RAE per day or more) increases the risk of lung cancer in individuals who smoke or have been systematically exposed to asbestos.

The evidence for other health effects is far less convincing, or there are indications that there is no effect

There are suggestions from observational studies that a high retinol intake is associated with a lower bone density and a higher risk of bone fractures. There are also indications from this observational research that there is a relationship between the intake of food products that are rich in carotenoids and a lower risk of cancer of the mouth, the epiglottis, the throat and the oesophagus. However, as was the case for the risk of lung cancer, intervention studies with beta-carotene supplements did not confirm these findings.

There are also suggestions that a high dose of retinol or beta-carotene can increase the risk of death, with the effect being most pronounced in smokers and people who were exposed to asbestos on an occupational basis. There are no other indications that beta-carotene affects the risk of prostate cancer or that retinol or beta-carotene affects the risk of cardiovascular diseases and age-related macular degeneration.

7.2 Intake of vitamin A

Both an intake of retinol that is too high and an intake of vitamin A that is too low appears to occur, but it is not clear whether this is really a problem

Intake data show that nearly 10 percent of young children may have an intake of retinol that is too high, with the extent of excess at a maximum of 600 micrograms RAE retinol. The excessive intake is primarily associated with a high intake of liver, liver products and supplements containing retinol. In contrast, 20 to 30 percent of the Dutch population may have an intake of vitamin A that is too low. It is not clear whether the excessively low or excessively high intake cause health problems.

7.3 Ensuring an adequate supply

Small increases in the intake of vitamin A can be achieved with fortification or substitution, with the number of people with an excessively high intake remaining virtually unchanged

The restoration of milk, milk products and cheese and the fortification of oil with retinol to the level of margarine, low-fat margarine and products for baking and frying result in small increases in the intake of this substance, whilst the exceeding of the tolerable upper level of intake of intake remains virtually unchanged. The latter is explained by the skewed distribution of the intake. The excessive intake is the result of frequent use of liver and liver products, which contain far more retinol than restored or fortified products.

7.4 Recommendations to achieve an adequate supply

Consume a varied diet

A varied diet provides sufficient vitamin A, without people risking an excessive intake. The Committee takes the view that the advice to avoid liver, liver products and supplements containing retinol during pregnancy should be maintained, in order to reduce the risk of congenital defects in the child.

Discourage smokers from using supplements with high doses of beta-carotene

The advice to smokers and those exposed to asbestos on an occupational basis – apart from the advice to stop smoking – is to avoid supplements with high doses of beta-carotene (20 milligrams per day or more; 10 milligrams of RAE per day or more).

Ensure that vitamin A is expressed as retinol activity equivalents on labels

The Committee deems it desirable to express the level of vitamin A in food products and supplements on the label as retinol activity equivalents instead of retinol equivalents. Agreements need to be reached at a European level to achieve this.

7.5 Recommendations for additional research

Investigate whether low vitamin A intake is really a problem

In order to determine whether the low intake of vitamin A poses a real problem, the Committee recommends that a study be performed using stable isotopes to determine the vitamin A status in people who do not consume margarine, low-fat margarine or products for baking and frying.

Investigate whether the high intake of retinol by young children is really a problem

In order to determine whether a high intake of retinol in children up to the age of 4 years is actually harmful, the Committee recommends that a study be performed on the relationship between the intake of retinol and the activity of the liver enzymes alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) in the blood – indicators of liver function. In addition, stable isotopes can be used to measure the vitamin A status and the extent of vitamin A accumulation in the liver. This method is significantly more expensive and more burdensome for the participants than the determination of liver enzyme activity.

Investigate the relationship between the intake of retinol and the risk of osteoporosis

The Committee takes the view that further research is required on the relationship between a high intake of retinol and a lower bone density and a higher risk of bone fractures.

Evaluate the dietary reference values for vitamin A

The Committee recommends that the dietary reference values for vitamin A and the tolerable upper levels of intake for retinol be evaluated. The Committee has pre-empted this in the current advisory report by using standards that are based on the dietary reference values set by the American Institute of Medicine, in which the Dutch growth curves have been incorporated. The Committee also used the tolerable upper levels of intake as set by the EU Scientific Committee on Food.

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A Request for advice

B The Committee

C Assessment of methodological quality and level of evidence

D Dietary reference values and tolerable upper levels of intake for vitamin A from 1989

E Definitions

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 bread making) 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 bread making 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 bread making 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 micronutrients 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 of 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 chairperson 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 inaugural 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.*[20] 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.[62] 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.[63]

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 vitamin A 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.[62,63]

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.[20,62]

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**

Dietary reference values and tolerable upper levels of intake for vitamin A from 1989

Table D.1 Dietary reference values for vitamin A (retinol and carotenoids) and the tolerable upper level of intake for retinol in micrograms RE per day.[22]

	Minimum requirement	Adequate intake		Tolerable upper level of intake	
0 – 5 months			450[a]		1,100
6 – 11 months			400		1,700
1 – 3 years			400		2,800
4 – 6 years			500		4,100
7 – 9 years			700		5,700
10 to 12 years		Boys	1,000		7,600
		Girls	800		7,900
13 to 18 years				13-15	10,800
		Boys	1,000		
		Girls	800		
				16-18	
				Men	13,500
				Women	11,800
19 to 49 years	600			19-21	
		Men	1,000	Men	14,400
		Women	800	Women	12,000
				22-49	
				Men	15,000
				Women	13,000
From 50 years	600			50-64	
		Men	1,000	Men	15,000
		Women	800	Women	13,000
				≥ 65	
				Men	14,000
				Women	13,000
Pregnant women			1,000		3,150
Lactating women			1,250		13,000

[a] Based on supply from breast milk. Corresponds to 80 retinol equivalents per kg body weight per day.

Annex **E**

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.[64]

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.[64]

Diet

Unless specified otherwise, diet refers to food products 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.[16]

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 requirement 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.[65] The intake of vitamin A has a skewed distribution. This has not been taken into consideration in this example.

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.[64]

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.[16]

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.[16]

Supplementation

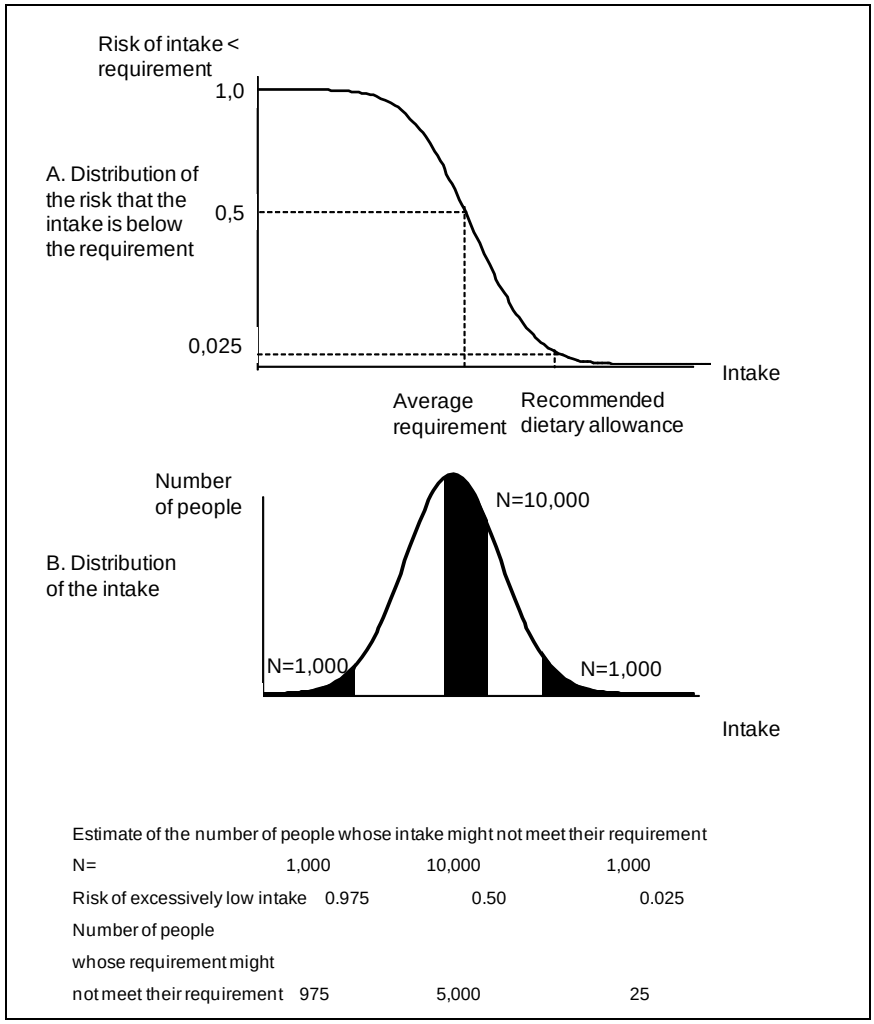
Using a supplement containing micronutrients as an addition to diet.

Threshold method

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

Tolerable upper level of intake

Highest level of intake at which no harmful effects are observed or are to be expected.[64]



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).