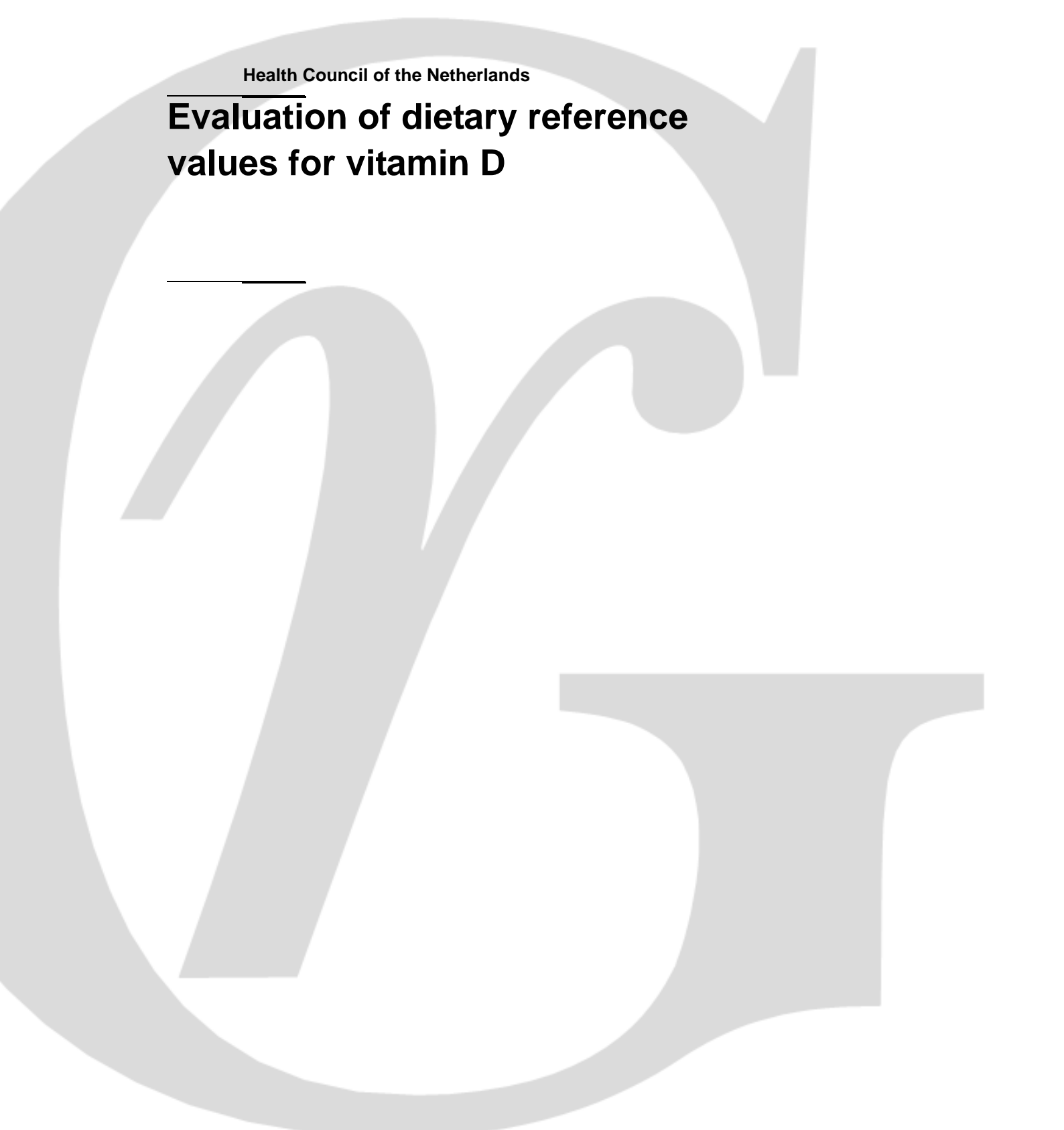


Health Council of the Netherlands

Evaluation of dietary reference values for vitamin D



Gezondheidsraad

Health Council of the Netherlands



To the Minister of Health, Welfare & Sport

Subject : presentation of advisory report *Evaluation of dietary reference values for vitamin D*

Your reference : -

Our reference : U-7310/RW/db/877-D

Enclosure(s) : 1

Date : September 26, 2012

Dear Minister,

I hereby submit the advisory report *Evaluation of Dietary reference values for vitamin D*. Defining dietary reference values is a continuing activity of the Health Council of the Netherlands. This new advisory report also maps the consequences of the new dietary reference values for the recommendations on supplementation published in 2008.

In order to advise you, a Committee of Experts examined the research into the health effects of vitamin D. The findings were reviewed by two permanent advisory and consultative bodies within the Health Council of the Netherlands, namely the Standing Committee on Medicine and the Standing Committee on Nutrition, along with four members of the Standing Committee on Health and the Environment. Additionally, 15 professional and consumer organisations provided commentary on the report on request of the Committee, which was specifically interested in comments regarding content. These comments were considered in drafting the final advisory report.

The Committee wishes to emphasise that the production of vitamin D in the skin, given sufficient exposure to sunlight, remains the most important source of vitamin D in the Netherlands, certainly among light-skinned people. Less vitamin D is produced in case of insufficient exposure to sunlight or darker skin. This lower production may not be compensated fully by a healthy diet according to the Guidelines for a Healthy Diet. Supplementation may therefore be required.

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Subject : presentation of advisory report *Evaluation of dietary reference values for vitamin D*
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The most significant change from previous advisory reports is that the Committee only derived dietary reference values that apply in the event of insufficient exposure to sunlight. The distinction according to exposure to sunlight and skin colour is included in the recommendations on supplementation. The Committee wishes to emphasise the importance of conscientious sunbathing, as outlined by the Dutch Cancer Society.

In deriving the dietary reference values, the Committee gave health effects such as rickets and breaking bones a central role. In deriving supplementation recommendations, the Committee distinguishes between recommendations with convincing evidence for health gains and recommendations based on less strong evidence.

Vitamin D is not only associated with rickets and bone fractures, but also countless other conditions. The Committee feels the evidence for these other health effects is currently too weak to serve as a basis for deriving dietary reference values and supplementation recommendations. A number of large-scale intervention trials are currently investigating these effects. The results may lead to re-evaluation of dietary reference values in the future.

I fully support the Committee's conclusions.

Yours sincerely,
(signed)
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Vice President

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Evaluation of dietary reference values for vitamin D

to:

the Minister of Health, Welfare and Sport

No. 2012/15E, The Hague, September 26, 2012

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, 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.

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



The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.



INAHTA

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with health technology assessment.

This report can be downloaded from www.healthcouncil.nl.

Preferred citation:

Health Council of the Netherlands. Evaluation of dietary reference values for vitamin D. The Hague: Health Council of the Netherlands, 2012; publication no. 2012/15E.

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ISBN: 978-90-5549-933-5

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Executive summary

Dietary reference values indicate the ideal amount of a given substance for daily intake in order to stay healthy. The Health Council of the Netherlands regularly checks whether the existing dietary reference values are still valid or whether they need to be adjusted. The Council bases these checks on the most recent scientific insights. This advisory report deals with vitamin D. The first step that the Council takes is to establish a dietary reference value, following which the Council evaluates which groups are at increased risk of deficiency. The Council makes recommendations on supplementation for these groups: who should take extra vitamin D? The advisory report has been drawn up by a committee of experts.

Effects and sources of vitamin D

Vitamin D is important for strong bones. Vitamin D deficiency causes rickets in children, while a serious vitamin D deficiency in adults results in osteomalacia. People suffering from these disorders have weak and painful bones, and a vitamin D deficiency can also cause muscular weakness and muscle cramps.

Vitamin D occurs naturally in a limited number of foods such as oily fish, liver, meat, eggs and dairy products. Furthermore, it has been added to

margarine, low-fat margarine and cooking fats and oils for many decades, and it may now be added to other products as well. In addition, people living in the Netherlands can synthesise vitamin D between March and November due to exposure to sunlight. It is useful to know that vitamin D is especially synthesised at the time of day when your shadow is shorter than your physical height. People with an increased risk of vitamin D deficiency can counteract this by supplementation.

What are dietary reference values?

Dietary reference values apply to healthy people in different age groups, including pregnant and lactating women. Although these values and recommendations on supplementation are intended to prevent vitamin D deficiency, they are not intended to treat this deficiency. The values do not take account of diseases which might result in an abnormal vitamin D requirement, such as kidney diseases or impaired fat absorption. Patients suffering from such diseases will be advised by their attending physician.

The dietary reference value relates to the total vitamin D requirement. Part of this requirement is fulfilled by the human body synthesising vitamin D when exposed to sunlight, but the remainder has to be obtained from food and supplementation (if applicable). On average, fair-skinned people* who are regularly exposed to sunlight obtain approximately two-thirds of their vitamin D requirement from this exposure, and one-third from their diet during the entire year.

Generally speaking, there is also an 'tolerable upper level' for the intake of nutrients. If this level is exceeded, this may result in undesirable effects. The Dutch government adheres to the European upper levels for vitamin D in this respect. These have been set by the European Food Safety Authority (EFSA) at a daily intake of 100 micrograms** for adults, 50 micrograms for children aged 10 or younger with the exception of children under 1 year of age, whose tolerable upper limit has been fixed at a daily intake of 25 micrograms.

* The Committee uses Fitzpatrick's classification: types I, II and III are classified as fair complexions and types IV, V and VI are classified as dark complexions.

** 1 microgram of vitamin D is equivalent to 40 international units.

Procedure for setting dietary reference values and drawing up recommendations on supplementation

Some scientists claim that vitamin D fulfils a protective function for many diseases, although the extent to which its beneficial effects have been scientifically proven varies considerably. With respect to the setting of dietary reference values, the Committee only examines those diseases concerning which evidence is convincing or probable that vitamin D plays a role. This mainly concerns bone health: the risk of rachitis and the risk of bone fractures. Reliable intervention research has proven that vitamin D can reduce these risks, and indications from this type of research have further demonstrated that it is probable that vitamin D can help protect elderly persons from falling. However, vitamin D's protective function for diseases such as cancer, diabetes, cardiovascular, infectious and autoimmune diseases has not been sufficiently demonstrated for this to be included in dietary reference values. Although there are admittedly indications showing an association between the vitamin D supply and a diminished risk of contracting these diseases, insufficient intervention research has been carried out into the effects of additional vitamin D on this risk. Large-scale intervention research is currently being carried out on this association. The outcome of this research may possibly give rise to a new evaluation of the dietary reference values for vitamin D in the future.

This means that the effects of vitamin D on bone health play a key role when setting these values. One indicator for bone health is the level of the major natural vitamin D metabolite in the serum, or the serum 25-hydroxyvitamin D level (serum 25OHD level), expressed in nanomoles (nmol) per litre*.

The Committee subsequently uses the dietary reference values as a basis to check whether there are any groups at increased risk of vitamin D deficiency, that would benefit from vitamin D supplementation**. The risk is related to age, sunlight exposure and complexion.

The Committee advises young children and elderly persons to take vitamin D supplements because it has been convincingly proven that this protects them against rachitis or bone fractures. For some other groups, the evidence is

* 1 nmol per litre 25OHD is equivalent to 0.40 nanograms per millilitre.

** The basic principle governing recommendations for supplementation is that there must be a sufficient intake of calcium, which means that this intake complies with the dietary reference value for calcium. Good bone health depends on a large number of different factors such as e.g. age, physical activity and calcium intake. These recommendations for supplementation are valid all year round.

probable that vitamin D supplements improve bone density or it is plausible that vitamin D helps maintain good health. In such cases, the Committee advises people to take vitamin D supplements to be on the safe side. The groups to which this applies can decide themselves whether or not they wish to take supplements. It is clear in any case that an extra 10 to 20 micrograms of vitamin D a day will not have any harmful effects.

When drawing up recommendations on supplementation, the Committee differentiates, wherever relevant, between persons who have been sufficiently exposed to sunlight and those who have not. Sufficient exposure to sunlight means a maximum exposure of 15 to 30 minutes* to the sun at its highest point (between 11:00 and 15:00 hours), with the head and hands exposed while performing everyday activities. Less time is required if more of the body is exposed, and only a few minutes are required when sunbathing in the bright summer sun. However, it is necessary to follow the Dutch Cancer Society's recommendations for the prevention of skin cancer. These recommendations state that anyone who spends regular amounts of time outdoors should protect their skin against the sun. The only people who benefit from 15 minutes' unprotected exposure to the midday sun with respect to vitamin D synthesis are those who do not normally spend a great deal of time outdoors. It is not advisable to allow children unprotected exposure to the midday sun, since their skin is delicate and there is a risk of skin cancer. Nor is exposure to the midday sun advisable for long periods of time, since this only results in small amounts of extra vitamin D being synthesised while causing additional damage such as e.g. skin ageing and skin cancer.

The extent to which people synthesise vitamin D by exposure to sunlight varies according to the skin type. People with dark skin are less sensitive to ultraviolet radiation and synthesise less vitamin D during everyday exposure to the sun than people with fair skin. Since a healthy diet does not contain sufficient vitamin D to compensate for the smaller amounts synthesised from sunlight, people who do not spend enough time outdoors or who have a dark skin should take vitamin D supplements.

* The 30-minute period is in line with the *Nederlandse Norm Gezond Bewegen* (the Dutch standard for healthy physical activity) for adults.

Dietary reference values and recommendations on supplementation for each group

Young children

Research has shown that supplementing young children's daily vitamin D intake by 7.5 to 10 micrograms reduces the risk of rachitis. These findings apply to children aged up to 1 year and young children with dark skin. The intervention research did not examine whether this would also apply to fair-skinned children aged between 1 and 4 who enjoy sufficient exposure to sunlight. However, hardly any cases of rachitis have been diagnosed in the Netherlands and other European countries since the introduction of recommendations for supplementation in these countries.

The further the serum 25OHD level drops below 30 nmol per litre, the greater the risk of rachitis. Since a daily vitamin D intake of 10 micrograms appears to be sufficient to guarantee that the serum 25OHD level remains above this figure with respect to this group, the Committee has set the daily requirement for children aged up to 4 at 10 micrograms. Incidentally, the Committee is assuming that these children have a sufficient calcium intake, since calcium is also necessary for healthy bones and teeth.

However, by no means all young children enjoy a diet containing sufficient vitamin D. Since the general recommendation is to make sure that young children are properly protected against the sun, the Committee takes the view that all children aged between 0 and 4 require an additional 10 micrograms of vitamin D daily.

Persons aged 70 and over

Research has resulted in convincing indications that elderly persons aged 70 and over require an additional daily vitamin D supplement of 10 to 20 micrograms in order to reduce the risk of bone fractures. It is also likely that this additional dose of vitamin D can reduce the risk of falling for fragile elderly persons. This intake level corresponds to a target value* of at least 50 nmol per litre for the serum 25OHD level. The Committee has set the daily requirement at 20 micrograms in order to ensure that (almost) the entire group of persons aged 70 and over

* The target value for the serum 25OHD level is the value above which (almost) everyone in the Netherlands has a sufficient supply.

achieves this target value. The importance of sufficient vitamin D intake for this age group should not be underestimated. The amounts of vitamin D that persons in this age group obtain from sunlight and from their diet vary considerably for each individual throughout the year. For example, fair-skinned persons aged 70 and over who are sufficiently exposed to sunlight might require a daily supplement of 10 micrograms. Nevertheless, the Committee advises all persons aged 70 and over to take a daily supplement of 20 micrograms of vitamin D in order to simplify matters.

Persons aged between 4 and 70, including lactating women

There are insufficient indications to demonstrate that all children, adolescents and adults aged between 4 and 70 require additional vitamin D for health reasons. Due to the lack of concrete health results, the Committee maintains a target value of at least 30 nmol per litre for the serum 25OHD level all year round for this age group. This is derived from the target value for young children, since a higher target value (as applicable for elderly persons) does not seem to be necessary for this group because there are no convincing indications that it would result in an improved state of health. On the basis of the target value of at least 30 nmol per litre, and the fact that there are insufficient convincing indications to show that all persons in this age group require additional vitamin D, the Committee has set the daily vitamin D requirement for children, adolescents and adults aged between 4 and 70 at 10 micrograms. Since breast milk contains very little vitamin D, the vitamin D requirement for lactating women seems to show hardly any increase.

Fair-skinned children, adolescents and adults who are sufficiently exposed to sunlight and who enjoy a healthy and varied diet (including low-fat margarine, margarine and cooking fats and oils) do not require additional vitamin D. It is estimated that they obtain approximately two-thirds of their vitamin D requirement from exposure to sunlight and one-third from their diet. However, there are certain subgroups within this age group who might well benefit from additional vitamin D.

- People who have little or no exposure to sunlight
Children, adolescents and adults who have hardly any daily exposure to the sun at its highest point, or who avoid exposure to sunlight or wear concealing clothes, may develop a vitamin D deficiency. It is also likely that additional vitamin D improves bone density in children and adolescents with a low serum 25OHD level. For this reason, the Committee advises this group to take an additional 10 micrograms of vitamin D daily.
-

- Dark-skinned people
It is probable that dark-skinned children, adolescents and adults also require an additional 10 micrograms of vitamin D daily. This is because dark-skinned people synthesise less vitamin D than fair-skinned people in the event of equal daily exposure to sunlight. The Committee recommends this just to be on the safe side, on the assumption that dark-skinned people's vitamin D requirements are the same as those of fair-skinned people; there is insufficient evidence available to allow a clear conclusion in this respect.
- Women aged between 50 and 70
We explained above why women aged between 50 and 70 who are dark-skinned or who spend insufficient time outdoors are advised to take additional vitamin D. It is not yet completely clear whether this also applies to other women in this age group. Insufficient research has been carried out on the effects of vitamin D and calcium supplements on women aged between 50 and 65-70 with respect to the risk of bone fractures. However, it is likely that additional vitamin D can help to combat loss of bone density in members of this group. For this reason, the Committee recommends an additional 10 micrograms of vitamin D daily, regardless of skin colour and the amount of time spent outdoors; this is also in order to be on the safe side.

Pregnant women

The recommendation to take additional vitamin D with respect to dark-skinned women or women who spend insufficient time outdoors similarly applies if these women are pregnant. It is still not quite clear whether other pregnant women would also benefit from additional vitamin D. Since pregnant women do not seem to have an increased need for vitamin D, the value for such women is the same as for other women in their age group, i.e. 10 micrograms daily. However, it is very important that pregnant women's vitamin D supply is sufficient, since a serious vitamin D deficiency not only has an adverse effect on the mother, but it may also have serious adverse effects on the newborn baby. For instance, cases are known of epileptic fits in newborn babies, and intervention research seems to indicate that additional vitamin D reduces the risk of babies with a low birth weight (< 2500 grams). In particular, pregnant women with dark skin or those who are not sufficiently exposed to sunlight are more at risk of developing a vitamin D deficiency. However, about 10% of fair-skinned pregnant women also suffer from a vitamin D deficiency. For this reason, the Committee takes the view that all pregnant women should be advised to take an additional 10 micrograms of vitamin D daily, just to be on the safe side. It is probably

important to start taking vitamin D supplements prior to pregnancy, since bone development in the foetus commences during the first three months of pregnancy.

Overview of dietary reference values and recommendations on supplementation for each group

Table Daily vitamin D requirements and the appropriate recommendations on supplementation (in micrograms per day).

Group	Criterion	Daily requirement ^a	Level of supplementation	
			Fair skin and sufficient exposure to sunlight ^b	Fair skin and insufficient exposure to sunlight, or dark skin
Age 0 to 4	Risk of rachitis and serum 25OHD level > 30 nmol/l	10	10	10
Age 4 to 50 (women) and age up to 70 (men)	Serum 25OHD level > 30 nmol/l and total supply	10 ^c	0	10
Age 50-70 (women)	Serum 25OHD level > 30 nmol/l and total supply	10	10 ^d	10 ^d
Age 70 and over	Risk of bone fractures and serum 25OHD level > 50 nmol/l	20 ^e	20 ^d	20
Pregnant women	Serum 25OHD level > 30 nmol/l	10	10	10

a Insufficient exposure to sunlight is defined as less than 15 to 30 minutes' daily exposure to the sun at its highest point (between 11:00 and 15:00 hours), with the head and hands exposed while performing everyday activities. Children and adults aged between 4 and 50 (women) and 70 (men) who spend sufficient time outdoors obtain - on average - approximately two-thirds of their vitamin D requirement from exposing their skin to sunlight and one-third from their diet during the entire year.

b When exposing the skin to sunlight, it is necessary to follow the Dutch Cancer Society's recommendations. These recommendations advise against allowing children unprotected exposure to the midday sun, since their skin is delicate and there is a risk of skin cancer.

c This is a daily increase from 5 to 10 micrograms of vitamin D for persons aged between 4 and 50 compared to the dietary reference values drawn up in 2000. The increase is due to new data on the relationship between vitamin D intake and the serum 25OHD level, and on the contribution made by sunlight to vitamin D intake, which has been published since 2000.

d This advisory report has been simplified in comparison with the previous report published in 2008 for reasons of communication.

e This is a daily increase from 15 to 20 micrograms of vitamin D compared to the dietary reference values drawn up in 2000. The increase is due to new data on the relationship between vitamin D intake and the serum 25OHD level, which has been published since 2000.

Introduction

1.1 A new assessment

In consultation with the Health Council of the Netherlands, the Ministry of Health, Welfare and Sport prioritised the evaluation of dietary reference values for vitamin D in 2011. This desire was addressed. The result can be found in this advisory report.

The Dutch dietary reference values for vitamin D were published in 2000.¹ The Health Council also issued an advisory report in 2008 on how citizens of the Netherlands can address their vitamin D requirement through the use of a vitamin D supplement. The re-evaluation of dietary reference values did not fall within the scope of this so-called supplementation advisory report. The report did conclude that the dietary reference values from 2000 may be too low for certain groups.²

In this advisory report, a Committee of Experts therefore defines new dietary reference values for vitamin D based on current scientific evidence, and examines the consequences of these new values for the previously issued advisory report on supplementation recommendations.

Committee membership is described in Annex A. The advisory report was reviewed by a number of permanent advisory and consultative bodies within the Health Council: the Standing Committee on Medicine and the Standing Committee on Nutrition. The advisory report was also submitted to four members of the Standing Committee on Health and the Environment, who were

previously members of the former Standing Committee on Radiation. Additionally, a number of organisations provided written commentary on the contents of the report on request (Annex B). Their comments and the Committee's responses are available on the Health Council website. As many organisations also provided unrequested feedback on the implementation of this report, the Committee briefly addresses these comments in Annex C.

Vitamin D

Vitamin D is only present in limited amounts in the diet. However, our skin can produce this substance in the Netherlands from March to November upon exposure to sunlight (ultraviolet radiation). Strictly speaking, vitamin D is not a vitamin, but we refer to it as such in this report as it is in common use. The amount of vitamin D formed in this manner is not only dependent on the time and degree of exposure to sunlight, but also on skin colour; in dark skin, under everyday conditions, the same exposure results in less vitamin D production than in light skin. Vitamin D plays a role in bone mineralisation. Serious deficiency leads to weak and painful bones in children and the elderly. Furthermore, severe vitamin D deficiency can lead to muscle weakness and muscle cramps. In order to determine vitamin D status, so-called serum 25OHD concentration is measured; this concentration is the result of both vitamin D intake from nutrition and supplements as well as vitamin D production due to exposure to ultraviolet radiation.²⁻⁴

1.2 Defining dietary reference values

Dietary reference values describe nutrient requirements and the tolerable upper level of intake. We first provide information about deriving dietary reference values in general. A more extensive description is included in Annex D. Section 1.3 addresses the specific methodology used for this advisory report.

An individual's nutrient requirement is the minimum amount needed to prevent signs of deficiency, and the amount for which the risk of developing chronic diseases - insofar as affected by the nutrient in question - is minimal. For vitamin D, this relates to the level of vitamin D supply, which is determined by both intake and production in the skin. As the reference values in case of insufficient sunlight apply in this advisory report, the report refers to the required

level of intake. Insufficient exposure to sunlight is understood to mean less than 15 to 30 minutes spent outdoors during everyday activities while the sun is close to its zenith (between 11:00 and 15:00 hours) with bare head and hands.

If the requirements for a specific nutrient are distributed normally within a population, an intake equal to the 'estimated average requirement' means the needs of half of the population are met, while those of the other half are not.

Determining the 'recommended dietary allowance' is only possible if sufficient data are available to determine the estimated average requirement. If the estimated average requirement is distributed normally and we also know the range within which the differences between individuals may fall (between-person variation), the recommended dietary allowance is defined as the estimated average requirements plus twice the standard deviation of said requirement. This level of intake is sufficient for practically all people in that population (Figure 1).

In practice, between-person variation in requirements is almost never known. In such cases, a variation coefficient of 10 to 20% is often used. Depending on the choice, the recommended dietary allowance is between 1.2 and 1.4 times the estimated average requirement.

Should the estimated average requirement, and therefore the recommended dietary allowance not be determinable, an adequate intake is determined; adequate intake also covers the requirements of almost the entire population. Adequate intake will often be higher than the recommended dietary allowance would be if it could have been determined.⁵ Dutch dietary reference values for vitamin D published in 2000 describe adequate intake.¹

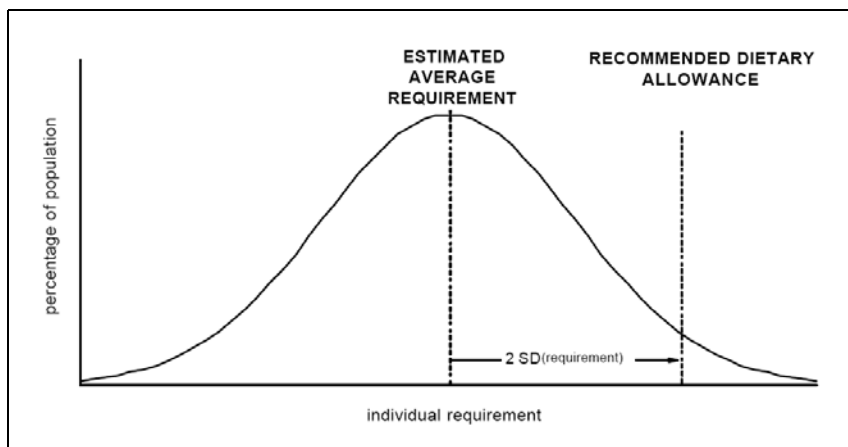


Figure 1 Estimated average requirement and recommended dietary allowance if the requirement is distributed normally.

Finally, dietary reference values encompass a ‘tolerable upper level of intake’: the highest levels of intake at which no harmful effects are seen or may be expected according to currently available data. The desirable level of intake is, however, the recommended dietary allowance or adequate intake, and not the tolerable upper level on intake.⁵

Dietary reference values may be considered a screening instrument. Even if average intake is lower than the estimated average requirement, recommended dietary allowance or adequate intake, this does not necessarily entail a problem. Data on nutritional status and health effects are required to determine this.⁶ The indicator for nutritional status for vitamin D is serum 25OHD concentration.^{1,7} The dietary reference values are designed to prevent vitamin D deficiency. The dietary reference values are not designed for the treatment of a vitamin D deficiency. Furthermore, they apply to apparently healthy individuals. Organ function may decline with age, for example kidney function. As research into the health effects of vitamin D has also been conducted in vulnerable elderly patients, the Committee assumes the dietary reference values also apply to elderly people with decreased kidney function. For certain patient groups, such as kidney patients and patients with fat malabsorption disorders, vitamin D requirements may differ. This is also true for patients using certain medicines. Examples include certain medicines against epileptic fits (carbamazepine, oxcarbazepine, phenytoin and phenobarbital), immunosuppressants (corticosteroids) or diuretics (thiazides) (Annex E).^{7,8}

1.3 Methodology of this advisory report

1.3.1 Relationship with previous advisory reports

Three previous advisory reports play a key role in the determination of Dutch dietary reference values for vitamin D: the Dutch dietary reference values advisory report from 2000, the Dutch supplementation advisory report from 2008 and the US Dietary Reference Intakes advisory report from 2010.^{1,2,7}

All three advisory reports used serum 25OHD concentration as a measure for bone health. All three define bone health as the risk of rickets, bone density and the risk of fractures. The Dutch supplementation advisory report also covers the risk of falling.

Serum 25OHD concentration was used to derive dietary reference values or supplementation recommendations in these previous advisory reports. The differences between the advisory reports are outlined below.

In determining a target value for serum 25OHD concentration, the degree to which the level of evidence for various relationships between serum 25OHD concentrations and bone health is considered differs. Section 3.4 addresses this in greater detail.^{1,2,7}

The ways in which the previous dietary reference values and Dutch supplementation recommendations for vitamin D were derived also differ somewhat. The dietary reference value advisory report uses one target value for serum 25OHD concentration, while the supplementation advisory report uses two target values, depending on age. In deriving the previous supplementation recommendations, greater value was assigned to the presence or absence of health effects than while deriving dietary reference values.^{1,2}

Two different target values for serum 25OHD concentration were used as measures for estimated average requirement and recommended dietary allowance in the determination of the US dietary reference values for vitamin D in 2010. Estimates were subsequently made of the average intake required to achieve the target value, for which the upper level of the estimates was used.⁷ The Committee objects to the method used, as the terms 'estimated average requirement' and 'recommended dietary allowance' were applied to serum 25OHD concentration rather than to vitamin D intake.

Dietary reference values for vitamin D have also been determined in other countries, such as in Scandinavia in 2004, in Australia and New Zealand in 2005* and in Belgium in 2009 (Annex F).¹³⁻¹⁵ Because the process for deriving these dietary reference values is largely comparable to the process for the Dutch reference values in 2000, these reports will not be examined in this advisory report. The new dietary reference values for vitamin D published in 2012 in German-speaking countries became available too late to be included in this advisory report.¹⁶

Furthermore, guidelines have been drawn up for the evaluation, treatment and prevention of vitamin D deficiencies in clinical practice by the US Endocrine Society. For people without a vitamin D deficiency – defined in the guidelines in question as a serum 25OHD concentration above 50 nmol per litre** – the reference values determined in the US Dietary Reference Intakes advisory report of 2010 apply.

* The Australian advisory report on dietary reference values also included dietary reference values published in the USA and Canada⁹, the United Kingdom¹⁰, and German-speaking countries¹¹ and by organisations such as the World Health Organisation of the United Nations¹², for example.

** 1 nmol per litre 25OHD is equivalent to 0.40 nanograms per millilitre.

For persons with a vitamin D deficiency, higher recommended dietary allowances and tolerable upper levels of intake have been derived. As the latter reference values are often based on weaker evidence than the US dietary reference values, the guidelines indicate they should be considered suggestions for the treatment of patients.^{8,17} This is why these guidelines have not been included in drafting this advisory report.

1.3.2 *Selecting an indicator for new reference values*

The Committee follows the same methodology outlined in the supplementation advisory report of 2008 for selecting an indicator and determining a reference value for serum 25OHD concentration. The methodology, which distinguishes between convincing, probable and insufficient evidence for health effects, is described in Annex G. This relates specifically to the assessment of the effects of vitamin D intake on disease risk and relationships between vitamin D intake or serum 25OHD concentration and these outcomes.²

Furthermore, the Committee primarily makes use of systematic review articles, where appropriate supplemented by more recent data from randomised, placebo-controlled trials. The systematic review by Chung et al about vitamin D and health is an important source in this regard.¹⁸ As this review summarises literature until April 2009, the Committee searched for additional literature published after this date. Annex H contains information about the PubMed search strategies used.

1.3.3 *Determining which factors affect requirements*

After determining the indicator for the dietary reference values, the factors that may affect the requirement are determined. The key question is whether the Committee must take account of the potential effects in determining dietary reference values and/or supplementation recommendations. Here too, the Committee followed the systematic approach used in the supplementation advisory report from 2008.²

1.3.4 *Deriving new reference values*

After the selection of indicators for dietary reference values, the Committee derives the dietary reference values based on the relationships between intake and bone health in terms of risk of rickets and risk of bone fractures, and between

intake and serum 25OHD concentration in case of insufficient exposure to sunlight.

1.3.5 *Consequences for daily practice*

For the determination of vitamin D dietary reference values, insufficient exposure to sunlight was assumed, meaning that vitamin D production in the skin would be too low to meet vitamin D requirements in combination with vitamin D intake from habitual diet. In practice, people will be exposed to varying amounts of sunlight. The Committee addresses exposure to sunlight in this advisory report, as well as the role of habitual diet, fortified foods and supplements designed to fulfil vitamin D requirements. High-risk groups are also addressed. To this end, the Committee evaluates the supplementation recommendations for high-risk groups from 2008 and specifies evidence levels further; it specifically indicates which supplementation recommendations are in agreement with dietary reference values with regard to convincing or probable evidence for health effects, and which have lesser evidence supporting them. This includes effects on bone density as well as case reports.

1.3.6 *No evaluation of tolerable upper levels of intake*

The Dutch government adheres to European tolerable upper levels of intake in its legislation, and therefore has no need for separate, Dutch tolerable upper levels of intake. The European Food Safety Authority EFSA defined new tolerable upper levels of intake for vitamin D in mid-2012.¹⁹

1.4 **Structure of the advisory report**

Chapter 2 provides general information about vitamin D. Chapter 3 is dedicated to the indicators for vitamin D supply that form the basis for new dietary reference values. In Chapter 4, the Committee discusses the factors that affect requirement. The dietary reference values are subsequently defined in Chapter 5. Chapter 6 addresses consequences for daily practice, addressing groups with a higher risk of vitamin D deficiency, and potential measures. Finally, Chapter 7 contains a complete overview of the new dietary reference values and supplementation recommendations.

Vitamin D

This Chapter describes the physiological role of vitamin D and the consequences of deficiency and overdose. Various sources of vitamin D are also discussed, along with estimates of vitamin D production under the influence of sunlight and habitual intake in the Netherlands. Finally, dietary reference values for vitamin D are addressed.

2.1 Types of vitamin D and physiological roles

Vitamin D is a collective name for steroids of which most have the same biological activity as the fat-soluble vitamin D₃ (cholecalciferol). Vitamin D is not really a vitamin, but rather a pro-hormone. Vitamin D is not only obtained through food, but is also produced in the skin under the influence of ultraviolet light from sunlight or a tanning bed. However, the term 'vitamin D' is in widespread use. The term is also used in this advisory report.

A key function of vitamin D is that it stimulates the absorption of calcium and phosphorous from food, thereby improving bone mineralisation. However, absorption of calcium is not entirely dependent on vitamin D. Two processes are distinguished in the intestines: a vitamin D dependent process and a vitamin D independent process. If calcium intake is high, absorption via the latter process is high in absolute terms, and vitamin D requirements are low. This vitamin D requirement is therefore inversely related to calcium intake.

Furthermore, vitamin D plays a role in other processes in the body, such as cell growth and development and muscle and immune system function.^{1,2,7,20}

Vitamin D is therefore a collective name covering a number of varieties. They are described as follows in this advisory report:

- Vitamin D₂, ergocalciferol, is a form produced under the influence of ultraviolet radiation in foods, such as certain mushrooms and moulds. Humans do not produce this form.
- Vitamin D₃, cholecalciferol, is found in foods of animal origin and is also produced in the skin. The latter occurs as follows: 7-dehydrocholesterol is converted to previtamin D₃, or precholecalciferol, under the influence of ultraviolet light, and subsequently converted into vitamin D₃ via isomerisation under the influence of heat.^{1,2,7,20} A meta-analysis concluded that vitamin D₃ at high doses is more effective than vitamin D₂ at increasing the serum 25OHD concentration. A similar difference was visible at lower doses, but was not significant.²¹ Whether both forms differ in toxicity is unclear. Based on animal studies, vitamin D₂ appears to be less toxic than vitamin D₃.²²
- 25-hydroxyvitamin D (25OHD), calcidiol, is the minimally active to inactive metabolite of vitamin D produced in the liver from vitamin D₂ or D₃. 25OHD is a good indicator of vitamin D status. The half-life is estimated at 10 to 40 days.²³ Because serum and plasma 25OHD concentrations do not differ, this advisory report only refers to serum 25OHD concentration, even when the 25OHD concentration was measured in plasma.
- 1,25-dihydroxyvitamin D (1,25(OH)₂D), calcitriol, is the active metabolite of vitamin D produced in the kidneys and other tissues. The 1,25(OH)₂D produced in the kidneys circulates in the blood and stimulates absorption of calcium in the intestines, ensuring sufficient calcium is present for bone mineralisation. The 1,25(OH)₂D produced in other tissues appears to be important for the development and growth of cells and immune function.^{1,2,7,20} 1,25(OH)₂D is not a suitable indicator for vitamin D status, as it has a half-life of only a few hours, formation is not directly regulated by vitamin D intake and serum levels of 1,25(OH)₂D may be normal or even elevated in even severe cases of vitamin D deficiency.⁷

2.2 Consequences of deficiency and overdose

A vitamin D deficiency develops due to insufficient exposure to ultraviolet radiation combined with too low intake. Severe vitamin D deficiency leads to rickets in children, and osteomalacia in adults. In these conditions, the bone is

weak and painful, as the newly formed bone matrix (osteoid) is not mineralised. Lack of vitamin D can also lead to loss of bone mass and osteoporosis via secondary hyperparathyroidism (an over-active parathyroid gland). This occurs mostly in the elderly. Furthermore, severe vitamin D deficiency can lead to muscle weakness and muscle cramps.^{1,2}

An excess of vitamin D cannot develop through exposure to ultraviolet radiation, but it is possible following too high intake. Long-term exposure to ultraviolet radiation does not lead to vitamin D intoxication, as both the previtamin D₃ and vitamin D₃ will then be converted into inactive sterols.

Very high vitamin D intake, on the other hand, can lead to toxic effects. An overdose initially results in high calcium levels in the urine, which is associated with an increased risk of kidney stones. At a later stage, high calcium levels develop in the blood (serum calcium concentration > 2.60 mmol/l). As soon as the kidneys are unable to excrete sufficient amounts of this excess calcium, symptoms of overdose develop, such as anorexia, weakness, fatigue, disorientation, vomiting and constipation. In the longer term, excess calcium storage may occur in soft tissues, particularly the kidneys (nephrocalcinosis) and urinary tract, vascular walls, muscles and ligaments.^{2,22} The highest level of intake at which these effects were not seen is 250 micrograms per day*.⁷

It remains unclear whether there are deleterious effects other than those related to high calcium content in the blood. A very high annual dose of vitamin D of 7,500 micrograms administered intramuscularly or 12,500 micrograms administered orally, resulted in an elevated risk of falling and bone fractures in two intervention studies.^{24,25} These findings lead the Committee to conclude that a very high annual dose of vitamin D is not effective in preventing falling or bone fractures, and may have undesirable effects.

2.3 Sources of vitamin D

Vitamin D may be obtained in two ways, via the skin under the influence of sunlight, and through diet. In general, the most important source of vitamin D is the production of vitamin D in the skin under the influence of ultraviolet radiation, particularly wavelengths between 290 and 320 nanometres, from sunlight or tanning beds. Under the influence of this radiation, 7-dehydro-cholesterol is converted into previtamin D₃, which subsequently spontaneously isomerises into vitamin D₃.

* 1 microgram of vitamin D is equivalent to 40 international units.

Sunlight exposure is a very important source of vitamin D in the Netherlands from March to November. An easy way to remember this is that vitamin D production in the skin under the influence of sunlight occurs primarily when a person's shadow is shorter than the person's actual height.³ In previous Dutch advisory reports, 'sufficient sunlight exposure' or 'sufficient time outdoors' was defined as spending 15 minutes outdoors per day with head and hands uncovered.^{1,2} From November to March, sunlight in the Netherlands (situated on the 52nd parallel) contains insufficient ultraviolet radiation with the correct wavelength for any significant amount of vitamin D production.^{2,3,26}

Nutrients that contain natural vitamin D are primarily of animal origin. For example, fatty fish is rich in vitamin D. Eggs, liver, meat and milk products contain limited amounts. In the Netherlands, vitamin D is also added to margarine, low-fat margarine and products used in baking and frying. Additionally, since 2007, an exemption has been in place for the addition of a maximum of 4.5 micrograms of vitamin D per 100 kcal.^{2,27}

2.4 Factors that affect vitamin D production in the skin

Vitamin D production in the skin has been associated with age, skin colour, use of sunscreen and sun avoidance. For a given exposure to sunlight, older skin produces less vitamin D than young skin.²⁸ Because the skin has excess capacity with respect to vitamin D production, the negative effect of older skin appears to be much smaller than previously assumed. For example, in elderly nursing home inhabitants, supplementation with 10 micrograms of vitamin D per day was as effective in increasing serum 25OHD concentration as radiation with artificial ultraviolet B light.²⁹

We do know there are ethnic differences, and that people with a darker skin colour require longer exposure to achieve equivalent vitamin D production compared with people with lighter skin. The Fitzpatrick classification is commonly used for skin color.³⁰ In this advisory report, the Committee uses the term 'light skin' for skin type I through III, and 'dark skin' for skin types IV through VI (Table 1).

After the winter, during which the skin has not been exposed to bright sunlight for a long time, the difference in vitamin D production between an individual with light and one with dark skin will be less significant than after the summer, when the darker skin is more tanned.^{4,7} In cloudier weather (UV index 4 to 5), longer or more frequent exposures may be needed.^{31,32} However, exposure to a lot of ultraviolet radiation is also associated with an elevated risk of all forms of skin cancer, some of which are very dangerous (melanomas), and immune

Table 1 Characterisation of skin sensitivity to ultraviolet radiation (UV).^{3,30}

Skin type	Skin/eye/hair colour	UV sensitivity	Skin reaction to UV exposure	Minimal erythema radiation dose (MED ^a)(Jxm ⁻²)	SCF ^b
Type I	White, pale skin, freckles, blue eyes, blonde or red hair	Very sensitive	Non-tanning and burns very quickly	200	0.8
Type II	White, pale skin, freckles, blue or green eyes, blonde or red hair	Very sensitive	Tans with difficulty, usually burns easily	250	1.0
Type III	White with darker skin, Asian with light skin	Sensitive	Burns moderately, tans gradually	300	1.2
Type IV	Southern European, Asian	Moderately sensitive	Always tans, rarely burns	450	1.8
Type V	Middle-Eastern, Latin, Negroid with light skin, Indian	Minimally sensitive	Tans very easily, burns very rarely, dark skin colour	600	2.4
Type VI	Negroid with dark skin colour	Not sensitive	Never burns, very dark skin colour	1,000	4.0

^a MED: effective radiation dose that leads to minimal redness in unaccustomed skin (taken from³⁷).

^b SCF: correction factor for skin sensitivity – the exposure time should be multiplied by this factor in order to obtain the same vitamin D production as in an individual with skin type II under the same exposure conditions.

suppression, and can contribute to aging of the skin and eye conditions such as cataract.³³

Experimental research and research in patients who need to carefully protect themselves against exposure to sunlight show that continued, strict use of sunscreen products can reduce the production of vitamin D in the skin.^{34,35} However, normal use of sunscreen products does not appear to affect vitamin D status, and does not appear to lead to a vitamin D deficiency.^{7,34-36} This is likely due to limited use, related exclusively to long-term exposure to sunlight, as well as issues such as using insufficient amounts of sunscreen, not applying it often enough or applying it incorrectly.^{7,35,36} However, people who do not expose themselves to a great deal of sunlight do run a risk of developing a vitamin D deficiency.²

2.5 Estimated vitamin D production in the skin

Vitamin D production in the skin under the influence of sunlight exposure can only be estimated roughly. In addition to a better physiological understanding of vitamin D production and metabolism, more precise determination would require data on how and the conditions under which the skin is exposed (orientation, protection by clothing or sunscreen products), the degree of habituation of the

skin and skin colour. Furthermore, atmospheric and local conditions during exposure, including the sun's altitude, the degree of visibility of sun and sky and atmospheric conditions (cloud cover, ozone layer thickness, aerosols) all play a role.

Hardly any data are available on personal exposure to UV radiation in the Netherlands. Measurements date back to the 1980s, and systematic research is lacking. The report by the Signalling Committee Cancer of the Dutch Cancer Society, entitled *The relation between cancer, sun exposure and vitamin D*, estimates exposure based on international research and National Institute for Public Health and the Environment (RIVM) data on ultraviolet radiation in Bilthoven.³

Based on these data, it was roughly estimated that sunlight exposure in the Netherlands leads to the production of, on average, 6 to 7 micrograms per day. This average daily production will be significantly higher during the summer and disappears almost entirely during the winter. This is illustrated in Figure 2, which shows the annual change in calculated vitamin D production in the skin for a daily exposure time calculated based on the behaviour specified in Table 2.

In turn, this Table displays the estimated exposure time required at high sun altitude (between 11:00 and 15:00 hours) to realise the annual average daily production of 6 to 7 micrograms of vitamin D for people with different skin types and for various activities and types of dress.³

However, significant between-person variation is possible for the estimates in Table 2. The analyses conducted by the RIVM for the Dutch Cancer Society report showed that the estimated skin production was 10 to 30% lower than an estimate of skin production among blood donors based on seasonal variations in serum 25OHD levels. It may well be that larger amounts of skin are exposed during the summer than the assumed 10% of overall skin surface, or that exposure times are longer, or that vitamin D production in the skin is more efficient than previously assumed. A combination of these explanations is also possible.³

British research from 2010 and 2011 shows results similar to the estimates in Table 2. Regular, brief exposure to sunlight of a limited amount of unprotected skin during lunch has been shown to result in serum 25OHD concentrations over 50 nmol per litre in people with light skin colour, and in an average concentration of 25 nmol per litre in people with skin type V.^{31,38-40} The brief exposure described in the observational study was an average of 9 minutes spent outdoors on weekdays during lunchtime in the summer, and 18 minutes during the weekend, while in the experimental research, people were exposed to doses of

ultraviolet radiation equivalent to normal midday sunshine in the summer three times per week for about 15 minutes.^{39,40}

The estimates in Table 2 apply under Dutch circumstances. Because the estimates in Table 2 and Figure 2 are based on very indirect calculations and simple models, they should be interpreted with necessary caution.

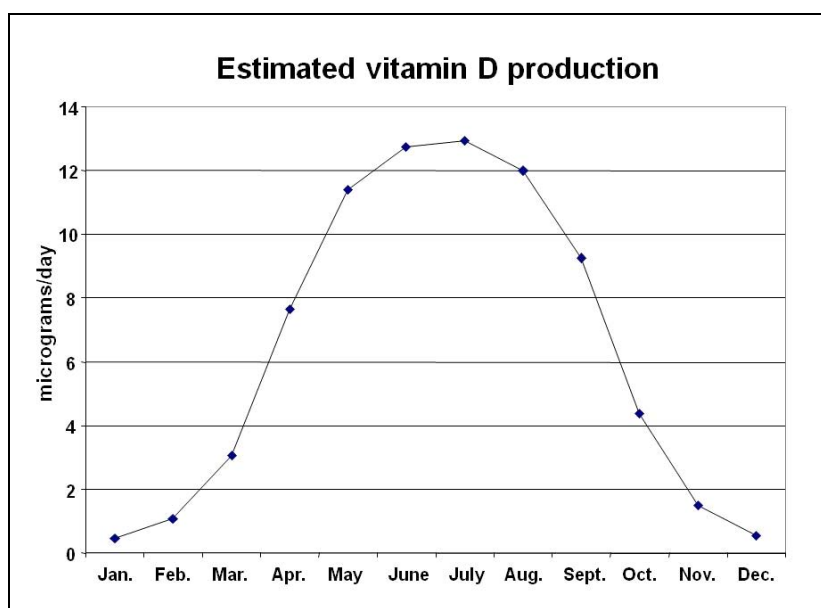


Figure 2 Estimated vitamin D production in the skin in relation to the season, for an annual average daily production of 6 to 7 micrograms. This production applies to every exposure situation in Table 2 in the Netherlands. Calculations by Dr H. Slaper (RIVM) based on data from:³.

Table 2 Estimated daily unprotected exposure time (minutes) for skin production of 6 to 7 micrograms per day (annual average) in relation to skin type (I through VI), exposed skin area (fraction of surface area) and behaviour in the Netherlands. Calculations by Dr H. Slaper (RIVM) based on data from:³.

Exposure conditions ^a	Skin type					
	I	II	III	IV	V	VI
Everyday lunch activities (walking, cycling)	Minutes					
Clothed: hands, head, neck (10%)	26	32	38	58	77	128
Summer clothing: hands, head, neck, arms or legs (15%)	17	21	25	39	51	85
Swimwear, not sunbathing (50%)	5	6	8	12	15	26
In full sunlight:						
Clothed (10%)	13	16	19	29	38	64
Summer clothing (15%)	8	10	13	19	26	43
Swimwear, sunbathing (50%)	3	3	4	6	8	13

^a Exposure around highest sun altitude (11:00-15:00 hours), average conditions.

2.6 Estimated intake from diet and supplements

2.6.1 Intake from habitual diet and fortified foods

Average vitamin D intake from diet and fortified foods is below 5 micrograms per day. In the food consumption survey 2007-2010, median vitamin D intake from foods in age groups between 7 and 70 years varied from 2.3 to 4.1 micrograms per day for men, and from 2.3 to 3.2 micrograms per day for women.⁴¹ In children ages 2 to 6, average intake of vitamin D in 2005/2006 was about 2.2 micrograms per day.⁴² Fats accounted for 36% of vitamin D intake in age groups between 7 and 70 years, meat and meat products accounted for 20%, fish and shellfish for 8%, and eggs and egg products for 5%, just like dairy products.⁴¹ The food consumption survey among young adults conducted in 2003 showed that young men who use margarine and low-fat margarine consumed 1.7 micrograms more of vitamin D compared with men who did not use these products; in women, the difference was 0.7 micrograms per day.⁴³

The data above are based on research conducted in people with a Dutch ethnic background. Vitamin D intake of adults and adolescents with Turkish or Moroccan backgrounds is about 1 microgram per day lower.⁴⁴

Under current legislation, any food may be fortified with vitamin D. In practice, vitamin D intake from these foods to date has proved to be very limited, with the exception of nursing infants and young children eating baby food (see 2.6.3).^{41,45,46} Furthermore, there is no guarantee that high-risk groups use these products. Therefore, the effects of this voluntary fortification on vitamin D supply for the Dutch population are very uncertain.

2.6.2 Intake from supplements

Currently, the use of vitamin D supplements is uncommon in most high-risk groups (Table 3).^{41,42,45,46} Of young children up to the age of 1.5 years, more than half receive vitamin D supplements. Because most bottle-fed toddlers who do not receive vitamin D supplements receive follow-on formula with extra vitamin D, their vitamin D supply is still adequate.^{45,46} According to the food consumption survey among children ages 2 to 6 years from 2005/2006, about 60% of two- and three-year-olds use a supplement with vitamin D; among four- to six-year-olds, the figure is 25%.⁴²

The food consumption survey 2007-2010 showed that the use of supplements with vitamin D was over 30% in the winter, and over 20% the rest of the year.

Among children and adolescents, the percentage of people using vitamin D supplements all year round varies between 12 and 23%, for adults this figure varies from 14 to 32%.^{41,47} In individuals with a non-Western background, use of supplements with vitamin D varies from 6 to 21%.⁴⁸

Table 3 Percentage of supplement users per age group.^{42,45-48}

Population group	% of users of supplement containing Vitamin D	Users in the winter	Users during the rest of the year	Extra vitamin D intake from supplements (micrograms per day)
9 months	16			
12 months	48			
18 months	88			
2-3 years	59			2.7
4-6 years	25			0.6
7-8 years	23 ^a	41	24	0.5
9-13 years				
Boys	19 ^a	32	21	0.5
Girls	17 ^a	33	17	0.2
14-18 years				
Boys	12 ^a	18	13	0.2
Girls	15 ^a	24	16	0.2
19-30 years				
Men	14 ^a	23	14	0.3
Women	25 ^a	39	27	0.6
31-50 years				
Men	20 ^a	28	21	0.5
Women	32 ^a	44	34	0.8
51-69 years				
Men	18 ^a	27	19	0.5
Women	26 ^a	37	28	1.0
Adults ages 18-65 years				
Dutch	25			
Turkish	6			
Moroccan	10			
Surinamese	21			
South-Asian				
Surinamese-Creole	16			
Sub-Saharan African	26			
Other ethnic	20			

^a This is the percentage of people who use extra vitamin D all year round.

2.6.3 *Children receiving both infant nutrition and supplements*

The recommendation in the Health Council advisory report from 2008 stating that only children receiving less than half a litre of infant nutrition require additional vitamin D from a supplement, was not taken on board by the minister.² In the US advisory report, adequate intake in breastfed infants assumes the early introduction of a supplement. For infants receiving infant nutrition exclusively, a gradual increase to 800-1000 ml is assumed, equivalent to an intake of about 10 micrograms of vitamin D. Therefore, there is no recommendation for supplementing bottle-fed children in the USA.⁷

During a round of consultations conducted by the Netherlands Nutrition Centre among professionals, the pragmatic decision was made to recommend supplementation of 10 micrograms of vitamin D for all children ages 0 to 4, regardless of diet. The reason for this was that the number of children receiving vitamin D supplements after their first birthday drops significantly after the age of 1, which corresponds to the switch from follow-on formula to regular milk. If parents are used to giving vitamin D from the first week after birth, it was thought it was more likely to become daily routine than if supplementation had to be restarted after stopping the use of follow-on formula.⁴⁹

The National Institute for Public Health and the Environment (RIVM) calculated the intake for children receiving a supplement with vitamin D, follow-on formula, and other vitamin D-fortified foods. The calculations showed that both the percentage of children (a maximum of 7%) and the degree to which European tolerable upper levels of intake were exceeded (with less than 4 micrograms per day) were limited.⁵⁰ The Committee concludes that there are no safety concerns associated with recommending giving young children a vitamin D supplement regardless of the type of infant nutrition used.

The RIVM also performed calculations for a scenario in which formula was fortified with vitamin D up to the legally permitted maximum. In this situation, both the percentage of individuals who exceed European tolerable upper levels of intake as well as the degree to which they would be exceeded increases. The calculations the Committee was privy to were based on the European tolerable upper levels of intake from 2006. Because the new European tolerable upper levels of intake from 2012 for children up to the age of one are equally high and because this scenario is currently unusual, this situation should be re-evaluated in future as required.^{19,50}

2.7 Dietary reference values for vitamin D

Table 4 lists the Dutch dietary reference values for vitamin D from 2000, the Dutch supplementation recommendations from 2008 and the American dietary reference values from 2010. The dietary reference values for children up to the age of 1 year are the same, for other age groups the US reference values are higher than the Dutch values from 2000.^{1,2,7}

Table 4 Dutch dietary reference values from 2000, recommended levels of supplementation from 2008 and the new US dietary reference values from 2010 per population group (micrograms per day).^{1,2,7}

	Dutch dietary reference values ^a	Dutch supplementation recommendations	US dietary reference values
	Without sunlight exposure and/or dark skin colour and/or women who wear a veil		Without sunlight exposure
0-1 year	10	10	AI ^b 10
1-3 years	10	10	EAR ^c 10, RDA ^d 15
4-50 years	5	10	EAR 10, RDA 15
51-70 years			
men	10	10	EAR 10, RDA 15
women	10	20	EAR 10, RDA 15
71 years +	15	20	EAR 10, RDA 20
Pregnant and lactating women	10	10	EAR 10, RDA 15
Osteoporosis patients, inhabitants of care and nursing homes	not determined	20	not determined
	With sufficient sunlight exposure and light skin colour		
0-1 year	5	10	not determined
1-3 years	5	10	
4-50 years	2.5	0	
51-60 years			
men	5	0	
women	5	10	
61-70 years			
men	7.5	0	
women	7.5	10	
71 years +	12.5	10	
Pregnant and lactating women	7.5	10	
Osteoporosis patients, inhabitants of care and nursing homes	not determined	20	

^a The Dutch dietary reference values are adequate intakes.

^b AI adequate intake.

^c EAR estimated average requirement.

^d RDA recommended dietary allowance.

Table 5 Tolerable upper levels of intake (micrograms per day).^{1,2,7,9,14,19,22}

	United States 1997/ Health Council 2001	Australia and New Zealand 2005	EFSA ^a 2006/ Health Council 2008	United States 2010	EFSA 2012
Up to 6 months	25	25	25	25	25
6 months - 1 year	25	25	25	38	25
1-3 years	50	80	25	63	50
4-8 years	50	80	25	75	50
9-10 years	50	80	25	100	50
From 11 years	50	80	50	100	100

^a European Food Safety Authority.

The tolerable upper level of intake is the highest level of intake at which no harmful effects occur.⁵ Tolerable upper levels of intake for vitamin D have been defined in various countries based on the lowest level of intake at which no effects of overdose have been observed (NOAEL, no observed adverse effect level).^{7,9,14,19,22} However, significant differences exist between these tolerable upper levels of intake, while more recent upper levels are also higher than older ones (Table 5).^{7,9,14,22,19}

This is because determination of tolerable upper levels for vitamin D is surrounded by significant uncertainty. Data are only available for very high levels of intake that cause classic toxicity, while little is known about long-term intake at a lower (but still too high) level.⁷

2.8 Conclusion

Vitamin D may be obtained in two ways, via the skin under the influence of sunlight exposure, and through diet. In practice, exposure to sunlight provides an estimated average of 7 micrograms of vitamin D per day over the course of the year; this amount is lower for people with a dark skin. A healthy diet including margarine, low-fat margarine and frying and baking fats provides an estimated 3 micrograms per day. Current use of vitamin D containing supplements is limited.

Indicators for requirement

The goal of this Chapter is to select one or more indicators that may serve as a starting point for deriving the new Dutch dietary reference values for vitamin D. Health effects play a central role in this regard.

3.1 Evaluation of indicators

The Committee uses the findings of the supplementation advisory report from 2008 as the starting point for indicator selection, and subsequently tests these against up-to-date evidence. Two types of indicators will be discussed. First, the relationship between vitamin D and bone health, in relation to or independently of calcium. In this Chapter, bone health is understood to mean the risk of rickets, bone density and the risk of falling and breaking a bone.² Second, the relationship between vitamin D and certain other conditions will be discussed.

3.1.1 *Vitamin D and bone health*

The Committee examines and re-evaluates the conclusions of the supplementation advisory report below, where possible based on new scientific findings.

3.1.2 Vitamin D supplementation and rickets

In 2008, the Health Council of the Netherlands noted that rickets among infants and young children has practically disappeared in the Netherlands and other European countries following introduction of vitamin D supplementation.^{2,51} The Health Council did not test the level of evidence of these findings at the time.

A systematic review by Cranney et al from 2007 states it is uncertain whether a specific 25OHD serum concentration exists that is related to the risk of rickets. This uncertainty is related to the fact that many of the studies included in the review were conducted in developing nations, where calcium intake is low. When calcium intake is low, rickets can already develop at higher 25OHD serum concentrations.⁵² If calcium intake is adequate, it appears likely that the risk of rickets increases the further serum 25OHD concentration drops below 30 nmol per litre, particularly if it drops below 20 nmol per litre.^{7,53}

The importance of vitamin D for the prevention of rickets was already identified in the 1920s.⁷ However, a systematic review of studies conducted over the past 50 years into the effects of additional vitamin D on the risk of rickets resulted in only four studies of good quality, with no cases of rickets occurring during the study period in two. The other two intervention studies in children up to the age of 3 years did show that supplementation with vitamin D decreases the risk of rickets. In one study, supplementation with 10 micrograms of vitamin D per day decreased the risk of rickets by 96% (RR=0.04, 95% confidence interval 0-0.71) in Turkish children up to the age of 3 years. In the other, supplementation with 7.5 micrograms of vitamin D and 378 milligrams of calcium per day reduced the risk of rickets by 24% (RR=0.76, 95% confidence interval 0.61-0.95) in Chinese children up to the age of 2.5 years. Compliance in the latter study was low, however.⁵⁴ Despite the limited availability of high-quality intervention studies, the Committee is of the opinion that, based on the overall available evidence, it has been convincingly demonstrated that vitamin D supplementation can reduce the risk of rickets.

Conclusion: It has been convincingly demonstrated that vitamin D supplementation reduces the risk of rickets. (B1⁵⁴)*

* See Annex G for the meaning of the quality coding for the research. The method for evaluating study quality means that only randomised, controlled intervention studies can provide convincing evidence, while prospective cohort studies can provide probable evidence.

Vitamin D supplementation, calcium and bone density

In 2008, the conclusion was that it was probably that high serum 25OHD concentration in children and adolescents correlates with high bone density.² The serum 25OHD concentration at which the relationship levels off varied from 30 to over 80 nmol per litre in the studies included.⁵²

Post-mortem data have also become available on the relationship between serum 25OHD concentration and histological indicators of osteomalacia in middle-aged individuals.⁵⁵ However, there is ongoing debate regarding the target value used for histological indicators in the study in question, which appear to be at the low end of the scale.^{7,56} The Committee is of the opinion that the study in question cannot lead to hard conclusions regarding target values for serum 25OHD concentration.

Despite the likely link between serum 25OHD concentration and bone density, the conclusion of the supplementation advisory report from 2008 was that there was insufficient evidence that supplementation with vitamin D alone improves bone density in children, adolescents and adults.² This is confirmed by a recent study in infants, two studies in girls and one study into very high doses of vitamin D in overweight young adults. Vitamin D supplementation was only associated with improved bone density in one study, namely in prepubescent girls.⁵⁷⁻⁶⁰

According to a systematic review from 2011, it is also unlikely that bone density in children with serum 25OHD concentrations above 35 nmol per litre will improve due to use of a vitamin D supplement. It is likely that children with lower serum 25OHD concentrations will benefit from supplementation with vitamin D. In one of the interventions described in the systematic review article, the daily dose was 50 micrograms per day, all other studies used doses varying from 3 to 10 micrograms per day.⁶¹

The supplementation advisory report from 2008 also concluded there is insufficient evidence that supplementation with 5 to 10 micrograms of vitamin D per day combined with calcium increases bone density in children and adolescents.² The same applies to adults.⁷ A more recent study, however, found that in 9- to 13-year-old girls, supplementation with vitamin D and calcium does improve bone density.⁶² The Committee is not aware of any other recent research on this subject.

Conclusion: It is probable that vitamin D supplementation may improve bone density in children with a serum 25OHD concentration below 35 nmol per litre. (AI⁶¹) There is insufficient evidence that vitamin D supplementation, alone or in combination with calcium, improves bone density in adolescents and adults. (A2^{57-59,62}, B2⁶⁰)

Vitamin D supplementation, calcium and bone density in elderly women and men

In 2008, the conclusion was that it is likely a high serum 25OHD concentration in postmenopausal women is related to high bone density.² As is the case in younger people, serum 25OHD concentration in this group varies, with the relationship levelling off somewhere between 30 and over 80 nmol per litre according to various studies.⁵²

Despite the likely relationship, there is insufficient evidence that vitamin D supplementation alone decreases the reduction in bone density in postmenopausal women and older men.^{2,63} A more recent study in postmenopausal women also failed to show reduced bone loss when a combination of 1,000 milligrams of calcium and 25 micrograms of vitamin D was used per day, compared with calcium alone.⁶⁴ A possible exception is the group of postmenopausal women with calcium intake at recommended levels. In 2008, the conclusion was that it was probable supplementation with vitamin D reduces bone density loss in this group.^{2,65,66} The Committee is not aware of new research on this subject.^{18,67}

Additionally, the supplementation advisory report from 2008 concluded it was probable that supplementation with vitamin D in combination with calcium reduces the decrease in bone density in elderly people with light skin colour, particularly in postmenopausal women. Most studies on which this conclusion was based were conducted with doses varying from 5 to 20 micrograms of vitamin D per day, and at least 500 milligrams of calcium per day.²

More recent studies are available on postmenopausal women now, which also indicate decreased bone density loss in women receiving vitamin D supplementation combined with calcium. The Women's Health Initiative study showed that daily supplementation with 10 micrograms of vitamin D in combination with 1,000 milligrams of calcium resulted in a small but significant preventive effect on decrease in bone density.⁶⁸ A three-year study in postmenopausal women found an improvement in bone density following supplementation with 20 micrograms of vitamin D per day in combination with calcium compared to women not receiving treatment.⁶⁹

Furthermore, a study among postmenopausal women with decreased bone mass found that additional vitamin D* in combination with 1,200 milligrams of calcium per day from fortified dairy products countered the reduction in bone density in the winter compared with a control group that did not receive additional products.⁷⁰

The question remains to what degree a change in bone mass is related to the risk of breaking a bone. A recent systematic review did not find any indications that bone loss is associated with a lower risk of bone fracture in people who use 500 to 1,600 milligrams of calcium per day, either alone or in combination with 10 to 20 micrograms of vitamin D.⁷¹

What has been demonstrated convincingly is that supplementation with vitamin D and calcium can reduce the risk of breaking a bone in individuals from the age of 65 to 70 years.² Therefore, the authors assume that the effect of supplementation with vitamin D and calcium on the risk of fractures occurs via a mechanism other than bone density.⁷¹

As regards postmenopausal women between the ages of 50 and 65 to 70 years of age, there is another explanation for the fact that vitamin D and calcium supplementation counters a decrease in bone density but no studies have examined the effect on the risk of breaking a bone. After all, in this population the absolute risk of breaking a bone is significantly lower than in older women (Table 6).⁷² This means larger studies would be required in women between the ages of 50 and 70 years than among older women in order to demonstrate a comparable effect on the risk of bone fractures.

Conclusion: It is probable that vitamin D supplementation in combination with calcium reduces the decrease in bone density among postmenopausal women and older men; (A1^{52,73}, A2⁶⁸, B2^{69,70}) vitamin D alone does not appear to be effective (A1⁶³, A2⁶⁴) unless habitual calcium intake is high. (A2⁶⁵, B2⁶⁶)

Vitamin D supplementation, calcium and bone fractures in elderly women and men

The supplementation advisory report of 2008 concluded that it was convincingly demonstrated that supplementation with 5 to 20 micrograms of vitamin D per day combined with calcium** reduces the risk of bone fracture by 13% (95%

* Dosage was 7.5 micrograms of vitamin D per day in the first year, and 22.5 micrograms per day in the subsequent year and a half.

** Supplemental calcium intake in most studies was 1,000 milligrams.²

Table 6 Incidence of hip fractures, absolute and per 1,000 persons in men and women in 2007.⁷²

Age	Absolute incidence		Incidence per 1,000	
	Men	Women	Men	Women
0-1	3	2	0.03	0.02
1-4	19	12	0.05	0.03
5-9	12	6	0.02	0.01
10-14	31	18	0.06	0.04
15-19	47	8	0.09	0.02
20-24	26	7	0.05	0.01
25-29	31	10	0.06	0.02
30-34	33	13	0.06	0.02
35-39	84	16	0.13	0.03
40-44	113	46	0.17	0.07
45-49	129	73	0.21	0.12
50-54	214	203	0.37	0.36
55-59	271	294	0.49	0.54
60-64	278	419	0.58	0.88
65-69	349	591	0.99	1.62
70-74	472	1,042	1.73	3.32
75-79	693	1,957	3.40	7.08
80-84	1,064	2,977	8.55	13.77
85+	1,276	5,102	17.26	26.34
Total	5,145	12,796	0.64	1.55
Total 65+	3,854	11,669	3.76	8.54

confidence interval 0.77-0.97) in individuals from the age of 70 years with light skin, particularly in postmenopausal women. The effect is most clearly seen in elderly individuals living in care or nursing homes. In most studies, the dose of vitamin D was 10 to 20 micrograms per day.² Limited available research showed that the effects of supplementation with vitamin D and calcium in elderly men were comparable to those in elderly women.^{2,52} More recent studies show no clear differences between men and women.⁷⁴

Since April 2009, a number of (systematic) reviews have been published on the effect of supplementation with vitamin D, either alone or in combination with calcium, on the risk of bone fracture in the elderly from the age of 65 years, including the Dutch Institute for Healthcare Improvement CBO guideline on osteoporosis and fracture prevention. No intervention studies in younger age groups are available. However, these review articles draw different conclusions regarding the required doses of vitamin D, the potentially required combination with calcium and the differences between elderly who are and elderly who are not living in care or nursing homes.^{63,74-81} The differences are related to the

studies included, the type of data (patient level or study level) and whether corrections were performed for compliance.

What the review articles do demonstrate convincingly is that supplementation with vitamin D in combination with calcium reduces the risk of bone fracture in elderly women, and possibly also in men. The relative risks found varied from 0.70 to 0.93.^{63,74-81} According to the most recent systematic review article, doses of 20 micrograms of vitamin D per day appeared to be more effective than lower doses. The degree to which calcium affects these findings remains uncertain; all doses of 20 micrograms were given in combination with calcium, while this was not always the case for lower doses.⁸¹ Because the studies were conducted among both independently and non-independently living elderly, it may be assumed that participants in some studies did and participants in other studies did not have sunlight exposure.^{63,74-81}

Conclusion: There is convincing evidence that supplementation with vitamin D and calcium reduces the risk of bone fractures in individuals from the age of 65 to 70 years, particularly in women; vitamin D alone does not appear to be effective. (A1^{63,75-79,82}, B2⁷⁵)

Vitamin D supplementation, calcium and the risk of falling in the elderly

The supplementation advisory report from 2008 concluded that it is probable an intake of 10 to 20 micrograms of vitamin D per day in combination with calcium reduces the risk of falling by 15% (95% confidence interval 0.76-0.96). The dose of vitamin D in individual studies varied from 10 to 20 micrograms per day. Most research was conducted among postmenopausal women with light skin.²

Over the past years, debate has raged in medical journals regarding whether or not convincing evidence exists that vitamin D, either alone or in combination with calcium, reduces the risk of falling, and at what target serum 25OHD concentration this effect would occur. The main points of discussion were which studies are of sufficient quality to be included in a meta-analysis, uncertainties surrounding determination of serum 25OHD concentration (see also Section 3.2) and the way in which data were analysed in the review articles.^{83,84}

Bischoff-Ferrari is of the opinion that 15 to 20 micrograms of vitamin D per day may reduce the risk of falling, but that lower doses are ineffective.⁸³ Gallagher and Rosen conclude, however, that there is no significant relationship between vitamin D intake and the risk of falling.⁸⁴

Four other review articles concluded that vitamin D, alone or in combination with calcium, can reduce the risk of falling by about 15%, with the effect being strongest in individuals with a vitamin D deficiency and elderly individuals not living independently, and if vitamin D is administered together with calcium.⁸⁵⁻⁸⁸ Two of these reviews only found an effect of supplementation with vitamin D, either alone or in combination with calcium, on the number of falls, but not on the number of individuals falling.^{88,86}

Insofar as data are available, the review articles stated there are no indications that higher doses of vitamin D are more effective than lower doses. Due to the heterogeneity of included studies and the possibility of publication bias, the quality of evidence was moderate.⁸⁵⁻⁸⁸

The reduction in the risk of falling due to supplementation with vitamin D and calcium in elderly people with low serum 25OHD concentrations or those in nursing homes or hospitals is in part supported by the possible effects of vitamin D supplementation on physical functioning, muscle strength and balance. One review concluded, based on three intervention trials, that supplementation with 20 to 25 micrograms of vitamin D per day may improve balance and performance on the Timed Up and Go Test. In the sensitivity analysis, in which the weakest study was excluded, the effect on balance was no longer significant. It was also concluded that vitamin D supplementation can improve leg muscle but not hand grip strength.⁸⁹ Another review, however, found no effect of vitamin D supplementation on either leg muscle or hand grip strength. Only in elderly individuals with a serum 25OHD concentration below 25 nmol per litre, but not in those with a higher serum 25OHD concentration, positive effects on hip muscle strength were found.⁹⁰

Conclusion: It is probable that supplementation with vitamin D, particularly combined with calcium, reduces the risk of falling in persons from the age of 70 years with a low 25OHD concentration or who do not live independently. (A1^{7,83,85-88}) There is insufficient evidence that vitamin D can improve balance and muscle strength in persons from the age of 70. (B1^{89,90})

3.1.3 *Supplementation with vitamin D, other conditions and premature death*

Vitamin D supplementation and auto-immune disease

The supplementation advisory report from 2008 concluded there was insufficient evidence that a high serum 25OHD concentration is related to a lower risk of auto-immune diseases, such as multiple sclerosis and type I diabetes.² Recent

observational research leads to a different conclusion. Both retrospective and prospective observational studies appear to show a relationship between high serum 25OHD levels and a low risk of auto-immune diseases. This association was not confirmed in intervention studies into the effects of supplementation with vitamin D. The intervention studies are of limited use, as they are of small scale, the results from different studies are inconsistent, and dose-response data are lacking.^{7,91,92} More recent intervention studies found that vitamin D may have a positive effect on multiple sclerosis, but the methodology was lacking in one study, and no clinical outcome measure was determined in the other. As a result, no definitive conclusion may be drawn at this time.^{93,94} In short, evidence for the role of vitamin D in lowering the risk of auto-immune disease is inconsistent.

Conclusion: Based on observational studies, it is probable a relationship exists between a high serum 25OHD concentration and a lower risk of auto-immune disease. Whether vitamin D supplementation reduces this risk has not been demonstrated sufficiently. (B1^{7,91,92}, A2⁹⁴, B2⁹³)

Vitamin D supplementation and infections

The supplementation advisory report from 2008 concluded there is insufficient evidence that high serum 25OHD concentrations are associated with a lower risk of tuberculosis.² Recent observational research leads to a different conclusion, and studied other infectious diseases in addition to tuberculosis, such as upper respiratory tract infections and flu in various age groups. Both retrospective and prospective observational studies appear to show a relationship between high serum 25OHD levels and a lower risk of infectious diseases. However, this relationship could not be confirmed in intervention studies into the effects of supplementation with vitamin D. The intervention studies are of limited usefulness, as they are of small scale, and outcome measures are often poorly defined.^{7,95} A more recent post-hoc analysis did find that patients with chronic obstructive pulmonary disease with serum 25OHD concentrations below 25 nmol per litre may benefit from higher doses of vitamin D.⁹⁶ A small-scale intervention study in Tanzania appears to indicate a protective effect of additional vitamin D exists for the risk of influenza A.⁹⁷ Another study, in which former participants of intervention studies with vitamin D were asked whether they had influenza during the course of the study, found no effect on the risk of influenza.⁹⁸ Intervention research in Afghanistan found no effect of a high dose of vitamin D on development of pneumonia, while another study in the same

country did find a small risk of recurrence.^{99,100} Another intervention study showed no distinct added value of a high dose of vitamin D in the treatment of tuberculosis.¹⁰¹ In short, evidence for the role of vitamin D in reducing the risk of infectious diseases is insufficient.

Conclusion: Based on observational studies, it is probable a relationship exists between a high serum 25OHD concentration and a lower risk of infections. Whether vitamin D supplementation reduces this risk has not been demonstrated sufficiently. (BI^{7,95}, B2⁹⁶⁻¹⁰⁰)

Vitamin D supplementation and neuropsychological function

Vitamin D has been associated with neuropsychological function, including autism, cognitive function and depression. However, there is insufficient evidence supporting a role for vitamin D in these conditions. While some studies show a protective association, results are far from consistent. Furthermore, most studies are case-control studies, in which it is unclear whether potential confounding variables have been corrected for sufficiently and a large risk of information bias exists. Information bias occurs if data relating to, for example, vitamin D intake in the past differ in terms of completeness and quality between the cases and the controls. Additionally, there is a lack of high-quality intervention studies.^{7,102}

Conclusion: There is insufficient evidence from observational studies that serum 25OHD concentration is associated with neuropsychological function and that vitamin D supplementation improves said function.(BI^{7,102})*

Vitamin D supplementation and cancer

The supplementation advisory report from 2008 concluded it is probable a very high serum 25OHD concentration (>75 nmol per litre) is associated with a lower risk of internal forms of cancer developing, such as colon cancer.² Whether a change in vitamin D supply can play an actual role in prevention or treatment has not been examined in sufficient detail.² More recent reviews specify this conclusion.^{63,103-107} The review by Chung et al published in 2011 concluded a high serum 25OHD concentration is associated with a lower risk of colorectal

* The supplementation advisory report published in 2008 did not examine the effects of vitamin D on neuropsychological function.

cancer, but is unrelated to prostate or breast cancer. Furthermore, the article describes that one of the two available intervention studies found a risk-lowering effect of vitamin D supplementation on any form of cancer. This study was smaller and of lower quality than the other study that found no effect, however.⁶³

Conclusion: Based on observational studies, it is probable a relationship exists between a high serum 25OHD concentration and a lower risk of colorectal cancer. There is insufficient evidence that vitamin D supplementation reduces the risk of cancer. (B1^{63,103-107})

Vitamin D supplementation, high blood pressure and cardiovascular disease

The supplementation advisory report from 2008 concluded it is probable a relationship exists between a high serum 25OHD concentration and low blood pressure.² Most of the more recent reviews fail to find a consistent association, however. There are also insufficient indications that vitamin D supplementation has an effect on blood pressure.^{18,108-110}

With regard to cardiovascular disease, the conclusion in 2008 was that there is insufficient evidence that high serum 25OHD levels are associated with lower risk. More recent reviews do show signs of such a relationship. Whether vitamin D supplementation can actually lower the risk of cardiovascular disease has not been examined in sufficient detail.^{18,108-112}

Conclusion: It has been insufficiently demonstrated in observational studies that high serum 25OHD concentrations are associated with a lower risk of high blood pressure and that vitamin D supplementation reduces the risk of high blood pressure. (A1^{18,108-110}) Based on observational research, it is probable that high serum 25OHD concentrations are associated with a lower risk of cardiovascular disease. Whether vitamin D supplementation reduces this risk has not been demonstrated sufficiently. (B1^{18,108-112})

Vitamin D supplementation and type 2 diabetes mellitus

The supplementation advisory report from 2008 concluded there is insufficient evidence that serum 25OHD concentrations are associated with the risk of type 2 diabetes mellitus.² Recent cohort studies showed that both high intake and high serum 25OHD concentrations are associated with a lower risk of type 2 diabetes mellitus. In post-hoc analyses of intervention studies, however, no clear effect of

vitamin D supplementation on glycaemic outcome measures in diabetes patients was visible. Whether individuals with insulin resistance but without diabetes may benefit from vitamin D supplementation also remains unclear; results are contradictory. In summary, it is insufficiently clear what role vitamin D plays in the development and progression of type 2 diabetes.^{18,113,114} A more recent meta-analysis, however, found a minimal improvement in fasting glucose and insulin resistance in diabetes patients and people with reduced glucose tolerance. These findings are not sufficiently strong to support recommending giving these groups additional vitamin D.¹¹⁵

Conclusion: Based on observational research, it is probable that high serum 25OHD concentrations are associated with a lower risk of type 2 diabetes mellitus. Whether vitamin D supplementation reduces the risk of type 2 diabetes mellitus has been insufficiently demonstrated. (B)^{18,113-115}

Vitamin D supplementation and premature death of postmenopausal women

The supplementation advisory report from 2008 concluded there is insufficient evidence that the use of 10 to 20 micrograms of vitamin D per day is associated with the risk of premature death.²

A recent systematic review of cohort studies in men and women found a U-shaped association between serum 25OHD concentration and the risk of premature death. The studies analysed were heterogeneous, however, with differences regarding methodology, tests for serum 25OHD concentration, and the presence of potential confounding variables and how these were corrected for.¹¹⁶

A systematic review of four intervention studies on the effect of vitamin D found a relative risk of 0.97 for the effect of vitamin D supplementation (95% confidence interval 0.92-1.02). The included studies were originally designed to evaluate the effect of vitamin D supplementation on breaking a bone.^{7,18} A systematic review encompassing 50 intervention studies found a similar effect of supplementation with vitamin D, either alone or combined with calcium, on the risk of premature death in postmenopausal women (RR 0.97; 95% confidence interval 0.94-1.00). In most studies, women were 70 years or older. In this systematic review,¹¹⁷ three¹¹⁸⁻¹²⁰ of the four studies¹²¹ included in the systematic review article mentioned in the previous paragraph⁶³ were included. If the type of vitamin D used is examined, only supplementation with vitamin D₃, either alone or in combination with calcium, is associated with a lower risk of

premature death (RR 0.94; 95% confidence interval 0.91-0.98). Most studies included women in care or nursing homes.¹¹⁷

A systematic review for which both individual and study-level data were examined found that, on an individual level, risk was only reduced if vitamin D was supplemented combined with calcium (HR 0.91; 95% confidence interval 0.84-0.98), and not for supplementation with vitamin D alone. Analyses at the study level showed similar results.¹²² Based on these data, the Committee concludes that additional vitamin D, alone or in combination with calcium, has no negative effects on the risk of premature death. With regard to a protective effect, findings are insufficiently consistent.

Conclusion: It has been insufficiently demonstrated that vitamin D supplementation reduces the risk of premature death in postmenopausal women. (B)^{118,117,122}

Future intervention studies should provide clarification

As described above, prospective cohort studies found a relationship between low serum 25OHD concentrations and the risk of colorectal cancer, cardiovascular disease, type 2 diabetes mellitus, infections and auto-immune diseases. In order to obtain greater certainty regarding the role of vitamin D in these conditions, the results of current intervention studies into the effects of vitamin D supplementation on, for example, cancer, cardiovascular disease and diabetes, which will become available in a few years, will have to be awaited.^{114,123}

Examples of such trials from the clinicaltrials.gov registry are: NCT01169259, the Vitamin D and Omega-3 Trial VITAL, with cancer and cardiovascular disease as outcome measures; NCT00736632, Vitamin D, Insulin Resistance, and Cardiovascular Disease, with insulin resistance and cardiovascular disease as outcome measures; NCT01052051, Clinical Trial of Vitamin D₃ to Reduce Cancer Risk in Postmenopausal Women, with cancer as outcome measure; and NCT01490502, Vitamin D Supplementation in Multiple Sclerosis, with multiple sclerosis relapse as outcome measure.

The Committee currently believes evidence is insufficiently strong to be used as a foundation for defining dietary reference values and supplementation recommendations. The Committee also refers to previous situations in which findings from observational studies were not confirmed in intervention studies (folic acid and cardiovascular disease) or in which intervention studies even showed opposite, undesirable effects (beta-carotene and lung cancer) compared to observational studies.¹²⁴⁻¹²⁶

3.2 Selection of indicators and target values per age group

The key issue in selecting indicators for defining dietary reference values is evidence for health effects of vitamin D. The evaluation of potential indicators shows there is convincing evidence that supplementation with vitamin D can reduce the risk of rickets in children. Additionally, it has been convincingly demonstrated that supplementation with vitamin D combined with calcium can reduce the risk of bone fractures in the elderly, and it is likely it may reduce the risk of falling, particularly in postmenopausal women and elderly patients with lower serum 25OHD concentrations or who do not live independently. Levels for vitamin D supplementation for various endpoints in the elderly are comparable. Therefore, the Committee selected the direct effect of vitamin D intake on bone health as the basis for defining the dietary reference values for vitamin D. The Committee does not use intermediary measures such as calcium absorption or bone density to define dietary reference values, as the significance of these outcome measures for bone health is less well established than that of the outcome measures risk of rickets, bone fractures and falling.

Bone health does not only refer to bone composition at a young age, but also to ensuring good bone composition later in life. This means maximum bone density should be achieved during adolescence (peak bone mass), and subsequent bone loss should be minimised.^{1,7}

In addition to the direct effect of vitamin D intake on bone health, the Committee selected serum 25OHD concentration as a risk factor for bone health. The target value for serum 25OHD concentration is derived from levels of supplementation that reduce the risk of rickets in young children and of fractures in elderly people from the age of 65 to 70.

This method of defining reference values was selected as the evidence for the level of effective dosage with vitamin D for bone health is significantly stronger than the evidence for a target serum 25OHD concentration at which a protective effect on bone health is seen. In these studies, vitamin D dosage was clearly defined, although the degree of compliance varied significantly. Serum 25OHD concentration, on the other hand, was often only determined in a selection of participants, while also using analysis methods with poor accuracy and comparability.¹²⁷ After all, serum 25OHD concentration measurements are not very precise, so that comparing outcomes of studies is difficult. Determination of serum 25OHD concentration is generally associated with a variation coefficient of 15 to 20%.^{7,128} It is also often unclear during which season serum 25OHD concentration measurements were performed. In large trials, such as the

Longitudinal Aging Study Amsterdam (LASA), determinations of serum 25OHD concentrations are available from every season, and seasonal effects are corrected for.¹²⁹ Finally, insufficient research has been conducted examining the question of whether there are differences in predictive values for disease between serum 25OHD concentration at the end of summer and the end of winter.¹³⁰

Most protective effects relate to vitamin D supplementation in combination with calcium. However, many of the studies examining the risk of falling and fractures were performed in populations with low calcium intake.^{2,52} There are indications that if calcium intake meets dietary reference values, vitamin D supplemented without additional calcium also counters bone loss in older women.^{2,65,66} Based on these data, the Committee assumes that given adequate calcium intake, vitamin D supplementation also has a protective effect on the risk of bone fracture without additional calcium.

3.2.1 *For young children up to 4 years old*

For young children, the relationship between vitamin D intake and the risk of rickets plays a central role. Furthermore, the Committee proposes a target value for serum 25OHD concentration of at least 30 nmol per litre. Above this target value, the risk of rickets given adequate calcium intake is minimal.^{1,2,7,53,54}

3.2.2 *For persons from 70 years of age*

For persons from 70 years of age, the effect of supplementation with vitamin D and calcium on the risk of breaking a bone plays a central role. Additionally, the Committee proposes a target value for serum 25OHD concentration of at least 50 nmol per litre for elderly people from the age of 70. This target value is based on the effects of supplementation with vitamin D and calcium on the risk of breaking a bone.^{2,7}

3.2.3 *For women ages 4 to 50 years and men ages 4 to 70 years*

Hard evidence for the effect of vitamin D supplementation on bone health and therefore the desired target value for serum 25OHD concentrations is lacking for this age group.^{2,7,127} One review based on intervention studies does conclude that it is probable vitamin D supplementation may improve bone density in children and adolescents with low serum 25OHD concentrations.⁶¹ Whether this improvement also leads to a lower risk of bone fractures in the longer term has not been studied, however. Based on intermediate measures of bone health, such

as bone density and calcium absorption, the target value for serum 25OHD concentrations in 4- to 70-year-olds may rise above 30 nmol per litre.⁷ Because the meaning of these intermediate measures for bone health is insufficiently clear, the Committee did not consider these findings in determining dietary reference values. The Committee assumes a target value of at least 30 nmol per litre in this age group. This is derived from the target value for young children, which is based on the risk of rickets. The effects of pregnancy and breastfeeding are addressed in the following Chapter.

3.2.4 *For women ages 50 to 70 years*

For women between the ages of 50 and 65 to 70 years, it is probable supplementation with vitamin D and calcium can counteract the decrease in bone density. However, insufficient research has been conducted into the effects of supplementation on the risk of breaking a bone in these women. Most research on the subject is limited to people over the age of 65 years. This makes determining a reference value for serum 25OHD concentration for this group of women difficult. Based on bone density data, the target level should be 50 nmol per litre.² Because it remains unclear what the health benefits of higher bone density would be for these women, the Committee assumes a target value of at least 30 nmol per litre in determining the dietary reference values. In the supplementation recommendations, the Committee does note that women between the ages of 50 and 70 years may use a supplement with vitamin D just to be sure (see also Chapter 7, supplementation recommendations for high-risk groups).

3.3 **Comparison with other advisory reports**

The indicators and target levels used by the Committee are largely consistent with previous Dutch dietary reference values and supplementation recommendations. The starting point in 2008 was that supplementation with vitamin D had to result in health gains.² In this advisory report, the Committee also places health effects centre stage in defining dietary reference values. Unlike the supplementation advisory report, this report adheres to a lower target value for serum 25OHD concentration of at least 30 nmol per litre for women between the ages of 50 and 70 years, because it is insufficiently clear whether supplementation with vitamin D and calcium in this group can actually reduce the risk of bone fractures in this group.

In the US Dietary Reference Intakes advisory report published in 2010, an integrated approach to bone health was used. Correlations that are convincing (the risk of bone fractures), probable (bone density) and insufficiently supported (osteomalacia) are all considered. If these outcomes are taken together, the US advisory report states there is a great degree of overlap between age groups in serum 25OHD concentrations at which the risk of undesirable bone-related effects are increased or above which they no longer decrease. This overlap, the report argues, leaves room for defining a serum 25OHD concentration that corresponds to the estimated average requirement and recommended dietary allowance, with 40 nmol per litre corresponding to the estimated average requirement and 50 nmol per litre to the recommended dietary allowance.⁷ As indicated in the introduction, the Committee does not support this methodology. It believes the concepts of 'estimated average requirement' and 'recommended dietary allowance' should only refer to intake, not to a biochemical marker.

Based on data from research into, among other things, the relationship between serum 25OHD concentration and the risk of cancer and cardiovascular diseases, some researchers have called for a target value for serum 25OHD above 75 or 100 nmol per litre, with corresponding intake of 25 micrograms per day for children and 50 micrograms per day for adults, in combination with exposure to sunlight.^{131,132} These target values are generally based on observational studies in which risk is reduced as serum 25OHD concentration rises. However, the health effects of these doses have not been examined in intervention research to a meaningful degree. The long-term effects of such intakes have also barely been studied.^{2,17}

This advisory report adheres to the target value of at least 30 nmol per litre for individuals up to the age of 70, and of at least 50 nmol per litre for persons aged 70 and older as individual minimums that should be maintained all year round.

3.4 Conclusion

The Committee has selected bone health as the key indicator for defining dietary reference values for vitamin D. Too little vitamin D can reduce bone health. In young children, this translates into the risk of rickets, and in the elderly over the age of 70 into the risk of bone fractures. The risk of falling is an additional indicator in the elderly. The required dose for the prevention of this endpoint is equivalent to the dose required to prevent fractures. Additionally, the Committee uses serum 25OHD concentration as an indicator for bone health.

For young children up to the age of 4 years, the Committee sets the target value for serum 25OHD concentration at a minimum of 30 nmol per litre, as the risk of rickets is minimal at this level, provided calcium intake is adequate. Committee proposes a target value for serum 25OHD concentration of at least 50 nmol per litre for persons from the age 70 years. This target value is based on the effects of supplementation with vitamin D and calcium on the risk of breaking a bone.

Hard data on the effect of vitamin D on bone health and the corresponding target value for serum 25OHD concentration are lacking for other groups. Therefore, the Committee elects to derive the target value for serum 25OHD concentration from the target for young children, which is based on the risk of rickets. The Committee proposes a target value for serum 25OHD concentration of at least 30 nmol per litre for people ages 4 to 70 years.

Influences on requirements

The starting point for determining dietary reference values for vitamin D is that insufficient exposure to sunlight takes place. In practice, exposure to sunlight can contribute to vitamin D supply in the Netherlands. The effect of this depends on skin colour. These aspects are discussed in Chapter 6. This Chapter addresses other factors that affect vitamin D requirements: pregnancy, breastfeeding, ethnicity, overweight and obesity, and calcium intake.^{1,2,7} The Committee evaluates whether these potential influences should be considered when defining the new Dutch dietary reference values for vitamin D.

4.1 Pregnancy

Pregnancy does not appear to increase vitamin D requirements.⁷ Observational research does suggest a relationship exists between low serum 25OHD concentrations during early pregnancy and a number of complications during pregnancy and foetal skeletal development, as well as during growth and maturation of the immune system. The lack of intervention studies, heterogeneity between study populations and small samples with insufficient attention for possible confounding factors in observational studies make it difficult to draw hard conclusions surrounding the significance of additional vitamin D during pregnancy.¹³³⁻¹³⁷ The effect of the increase in blood volume and fat tissue during pregnancy on serum 25OHD concentration is also unclear. Three intervention studies do point in the direction of a protective effect of supplementation with 20

to 30 micrograms of vitamin D per day on the risk of having a low birth weight baby (<2500 grams) (RR 0.48, 95% confidence interval 0.23-1.01).¹³⁶

Additionally, it is known that severe vitamin D deficiency in pregnant women can lead to health complaints such as muscle pain, fatigue and, in extremely serious cases, convulsions in the newborn.¹³⁸

The Dutch dietary reference values advisory report from 2000 defined higher reference values for pregnant women than for other women of the same age, while stating that what little is known does not indicate greater requirements. It is considered probable that the pregnant woman requires vitamin D supplementation in order to absorb sufficient amounts of calcium from diet to meet the requirements of both herself and the foetus. Because the interests of both mother and child are at stake, the decision was made to define higher reference values for safety's sake.¹ The supplementation advisory report from 2008 did not address the question of whether pregnancy increases vitamin D requirements.²

The US Dietary Reference Intakes advisory report concluded that the vitamin D requirements for pregnant women are not elevated compared to those of other women.⁷ The main reasons for this are (1) that there is insufficient evidence that serum 25OHD concentration during pregnancy is associated with maternal bone density and (2) that in case of a vitamin D deficiency or certain congenital defects* no influence of the mother's serum 25OHD concentration is seen on the child's bone density.

However, the US advisory report also reported on two studies that did find an effect. In one, lower bone density in newborns was found at serum 25OHD concentrations in the pregnant woman below 40 nmol per litre. In the other, a serum 25OHD concentration below 50 nmol per litre was associated with reduced bone density in offspring at the age of nine years. Therefore, the US Dietary Reference Intakes advisory report used a target value for serum 25OHD concentration, and therefore a dietary reference value, identical (50 nmol per litre) to that for women who are not pregnant.⁷ If these findings are viewed in conjunction with those from other studies, they are insufficiently convincing to form the basis for higher reference values for pregnant women.¹³³⁻¹³⁷

Conclusion: Vitamin D requirements of pregnant women are the same as for other women.

* Absence of vitamin D receptor or 1-alpha-hydroxylase.

4.2 Breastfeeding

Breastfeeding hardly appears to affect vitamin D requirement of the mother. Breast milk only contains about 0.4 to 0.6 micrograms of vitamin D per litre.¹

Despite this, the Dutch advisory report from 2000 set higher dietary reference values for breastfeeding women than for other women of the same age just in case, while concluding that little is known about vitamin D requirements during lactation, and that what little is known does not indicate increased requirements. The supplementation advisory report from 2008 did not address the question of whether breastfeeding increases vitamin D requirements.²

The US Dietary Reference Intakes advisory report concluded that vitamin D requirements for breastfeeding women are not elevated compared to requirements of women who are not breastfeeding.⁷ The reason given was that human milk - at usual levels of vitamin D intake by the mother - only contains minimal amounts of vitamin D, unless breastfeeding women are using 100 or more micrograms of vitamin D per day.⁷

The story is different for the infants being breastfed: in order to prevent a vitamin D deficiency, it is important that they receive a supplement containing vitamin D.²

Conclusion: Vitamin D requirements in breastfeeding women are barely elevated.

4.3 Ethnic background

Most research into vitamin D, serum 25OHD concentration and health has been conducted in Caucasians with skin types I-III. Whether these data also apply to individuals with darker skin, types IV-VI, has only been examined to a limited degree. Available research data do indicate that serum 25OHD concentrations of Dutch citizens of Turkish, Moroccan, Indian or Sub-Saharan African descent do not differ significantly from those of people in their countries of origin.¹³⁹

Other research suggests that the effects of low serum 25OHD concentrations on the risk of bone fracture and bone density may not be the same for all ethnic groups. Among participants in the Women's Health Initiative study, a relatively lower serum 25OHD concentration (less than or equal to 44 nmol per litre) in women with light skin was associated with a higher risk of bone fractures, while the opposite was true for women of African or Asian descent.^{140*} In the National Health and Nutrition Examination Survey, a relationship between serum 25OHD

concentration and bone density was found in adults with a light skin colour, but not in adults of African descent.¹⁴¹

In general terms, people of African descent have a lower serum 25OHD concentration than people with light skin, but also have a lower risk of bone fractures.^{7,142} There are various factors that play a role in this regard. For example, bone mass is greater in people of African descent than in people with light skin. Bone mass does appear to decrease more swiftly after menopause in women of African descent than in women with light skin.¹⁴³ Other potentially protective factors are the higher incidence of obesity, lower bone turnover, the micro-architecture of the bone, bone geometry, efficient calcium metabolism, body composition, falling patterns and hereditary factors. However, elderly people of African descent still have a significant absolute risk of breaking a bone.^{7,144,145} A short hip axis has been indicated as a protective factor specific to Asian women.¹⁴⁶

The Committee is of the opinion that the above data indicate that women of African or Asian descent may have less serious symptoms due to low serum 25OHD concentrations than women of Western descent.

Previous Dutch and US advisory reports defined the same reference values for people with light and people with dark skin, as it is insufficiently clear whether the effects of low serum 25OHD concentrations on the risk of bone fracture differ between individuals with different ethnic backgrounds.^{2,7} This is true not only for people of African or Asian descent, but also for people with Mediterranean or Arab backgrounds, for example. However, the production of vitamin D in the skin given equivalent everyday exposure to sunlight is lower in dark skin than in light skin. This lower production may not be compensated fully by healthy diet according to the Guidelines for a Healthy Diet. In Chapter 7, the Committee addresses supplementation recommendations for people with darker skin.²⁻⁴

Conclusion: Vitamin D and calcium requirements may be different for people of African and possibly also of Asian descent than for people with light skin, based on the risk of bone fractures. However, too little solid research data is available to define separate dietary reference values for individuals of African descent. Therefore, the Committee has not defined a separate value for people with different ethnic backgrounds based on the risk of bone fractures. The effects of sunlight are addressed in Chapter 7.

* How these findings relate to tolerable upper levels of intake falls outside the scope of this advisory report.

4.4 Overweight

There is an inverse relationship between the amount of body fat and serum 25OHD concentrations.^{2,7} A possible explanation is that overweight and obese people may spend less time outdoors or use fewer supplements with vitamin D.¹⁴⁷ Another explanation for the inverse relationship may be excessive storage or dilution of vitamin D in intracellular fluid or fat tissue, resulting in lower serum 25OHD concentrations than in people with a desirable weight.¹⁴⁸⁻¹⁵⁰ Some studies have found that given equivalent additional vitamin D intake or equivalent sunlight exposure, the rise in serum 25OHD concentration is smaller for overweight or obese people than for people with normal body weight, although these findings are not entirely consistent.¹⁵⁰⁻¹⁵³

Overweight or obese people have a higher risk of falling than people with low body weight, but their risk of bone fractures is lower due to their higher bone densities and the buffering action of the fat surrounding the hip, for example.^{2,154} Weight loss via a calorie-limited diet results in lower bone density, while serum 25OHD concentration rises.¹⁵⁵

In the previous US Dietary Reference Intakes advisory report and the Dutch supplementation advisory report, overweight and obese people were not considered as a separate high-risk group.^{2,7}

Conclusion: Overweight or obese people often have lower serum 25OHD concentrations. Because it is unclear whether this is associated with an elevated risk of health complaints in this population, the Committee has not defined separate dietary reference values for this group.

4.5 Calcium intake

The effects of vitamin D and calcium are strongly related to each other in the body. If calcium intake is low, vitamin D requirements appear to rise.¹ Many studies have been conducted into the health effects of vitamin D and calcium together. However, this makes it difficult to distinguish the health effects of each nutrient individually.⁷

Previous dietary reference values and supplementation advisory reports for vitamin D assumed adequate calcium intake, defined as 1.0 grams of calcium per

day for the age group 19 to 50 years of age*.^{1,2,7} The Committee has insufficient data to define dietary reference values for vitamin D that apply in case of low calcium intake.

Food consumption data indicate that for most people aged 7 to 69 years, average calcium intake lies above adequate intake. In a few groups of people, average calcium intake lies below adequate intake. This is the case among adolescents (850 milligrams for girls and 1,000 milligrams per day for boys), and among women up to the age of 30 years (900 milligrams per day) and from the age of 50 years (1,000 milligrams per day).⁴¹ Compared to intake among people with a Dutch background, average calcium intake among Turkish and Moroccan women and their eight-year-old children (about 600 milligrams per day) was significantly lower.^{156,157} This is also true for young adult men (about 870 milligrams per day) and women (about 500 milligrams per day) of Turkish, Moroccan or Surinam descent.^{44,158} This may also apply to others of non-Western descent, as lactose intolerance is common in these groups.¹⁵⁹ Among nursing home residents, median calcium intake is 750 milligrams per day.¹⁶⁰

Dutch reference values are based on achieving maximum peak bone mass around the age of 30 years and minimising bone mass decrease with age. Given the relatively minor difference between average calcium intake by persons with a Dutch background and adequate intake, the Committee does not expect any negative effects due to current intake. Whether this is true for people of non-Dutch descent remains in question. Research has shown that the risk of bone fracture in people at risk for osteoporosis does not increase until daily calcium intake is 400 milligrams or less.^{7,75,161,162}

Conclusion: Dietary reference values for vitamin D assume adequate calcium intake. Persons of Turkish, Moroccan or Surinamese descent have lower calcium intakes. Whether this results in a higher risk of bone fractures is unknown.

* Adequate calcium intake has been defined as 0.21 grams per day for breastfed infants up to the age of 6 months and 0.32 grams per day for bottle-fed infants up to 6 months, 0.45 grams per day for children ages 6 to 12 months, 0.5 grams per day for children ages 1 through 3 years, 0.7 grams per day for children ages 4 through 8 years, 1.2 grams per day for boys ages 9 to 18 years and 1.1 grams per day for girls ages 9 to 18 years, 1.1 grams per day for the age group 51 to 70 years, 1.2 grams per day for the ages 71 years and up, and 1.0 grams per day for women who are pregnant or breastfeeding.

4.6 Conclusion

Dietary reference values for pregnant or breastfeeding women are as high as for other women. There are no signs that pregnancy or breastfeeding greatly influence vitamin D requirements.

No separate dietary reference values are required on the basis of skin colour, based on using bone health as an indicator. It remains unclear whether people of African and possibly also of Asian descent have different vitamin D requirements than people with light skin. What is clear is that in people with dark skin, healthy diet is not sufficient to compensate for the lower contribution sunlight makes to their vitamin D supply. Supplementation is therefore required.

The Committee has not defined any separate dietary reference values for overweight or obese people, as it is unclear whether the lower vitamin D status in these individuals is in fact associated with additional negative health effects.

Finally, the Committee assumes that dietary reference values for vitamin D apply given adequate calcium intake. The Committee notes that certain populations of non-Western descent have low calcium intake. However, available data is too sparse to allow dietary reference values to be defined that apply specifically in case of low calcium intake.

Defining dietary reference values

This Chapter addresses the definition of dietary reference values of vitamin D, taking into account insufficient exposure to sunlight. The dietary reference values are defined according to one of the ‘classical’ methods (Annex D). Different groups are distinguished in this regard. First, children up to the age of 1 year and children ages 1 to 4 years are discussed. Subsequently, the Committee discusses a number of estimated requirements for persons ages 4 to 70 years and people over the age of 70. It then defines dietary reference values, rounding off daily amounts in units of 10 micrograms to prevent the semblance of accuracy. Finally, the defined reference values are compared to past Dutch and US dietary reference values.

5.1 Dietary reference values for young children

5.1.1 *Adequate intake in children up to the age of 1 year*

A symptom of severe vitamin D deficiency in children is rickets. The risk of rickets increases, given sufficient calcium intake, the further serum 25OHD concentration drops below 30 nmol per litre.⁷ In the Netherlands and other European countries, rickets has all but disappeared thanks to the introduction of supplementation with 10 micrograms of vitamin D per day in infants and young children.²

In Chapter 3, data from two intervention studies were used to determine that supplementation with 7.5 to 10 micrograms of vitamin D reduces the risk of rickets.⁵⁴ Furthermore, very limited research into the relationship between vitamin D intake and serum 25OHD concentrations in this group indicates that this level of intake safeguards serum 25OHD concentrations higher than 30 nmol per litre in a large proportion of infants.^{1,7} Intake falling within this margin therefore appears to meet the requirements of children up to the age of 1 year.⁷ Given their swift growth rates, the Committee has set adequate intake at 10 micrograms per day.

5.1.2 *Adequate intake in children ages 1 to 4 years*

As is the case for children under the age of 1 year, it is probable that 10 milligrams of vitamin D per day will minimise the risk of rickets and safeguard serum 25OHD concentrations above 30 nmol per litre in children ages 1 to 4 years.^{1,7,54} There are no clear indications in this group that a target level of at least 50 nmol per litre would provide health benefits compared to a target level of at least 30 nmol per litre. Based on the above, taking into account the high growth rates in this age group, the Committee defined an adequate intake of 10 micrograms per day for this group.

5.2 **Estimated requirement from the age of 4 years**

This section describes four different methods for estimating vitamin D requirement: to prevent bone fractures, and on the basis of on the relationship between vitamin D intake and serum 25OHD concentrations, based on either study averages, individual data or dose-response data.

5.2.1 *Estimate based on the risk of bone fractures*

There is convincing evidence that 10 to 20 micrograms of vitamin D per day, combined with calcium, reduces the risk of bone fractures in people from the age of 70 years. This level of intake may also be a starting point for deriving dietary reference values for this age group.

5.2.2 *Estimate based on averages*

The US Dietary Reference Intakes advisory report from 2010 describes the relationship between vitamin D intake and serum 25OHD concentration in case

of insufficient exposure to sunlight for children, adolescents and young, middle-aged and elderly men and women.⁷ However, a new analysis has since become available of research into the relationship between vitamin D intake and serum 25OHD concentrations in case of insufficient exposure to sunlight.¹⁶³ Both analyses are based on average vitamin D intake and average serum 25OHD concentration per study or treatment within the study, negating between-person variation. The estimates look at the effect of total vitamin D intake on serum 25OHD concentration compared to a drop from a summertime level. The degree to which release of vitamin D produced and stored in the body during summer affects the relationship between vitamin D intake and serum 25OHD concentration is unknown. The US Dietary Reference Intakes advisory report assumes that the influence of the body's stored supply is minimal.⁷ The Committee believes this influence cannot be ignored, but cannot quantify it.

In a new analysis, Cashman et al made use of, among other things, other studies than those examined for the original US advisory report, in part because they used different inclusion criteria. For example, study duration had to be at least 6 weeks instead of 4 to 5 weeks, studies investigating the combination of vitamin D and calcium were included as well, and a single more recent study was included.^{7,163}

Cashman et al described the relationship between vitamin D intake and serum 25OHD concentration using both a logarithmic model, like the US Dietary Reference Intakes advisory report used, and a linear model. For intakes between 5 and 15 micrograms per day, estimates from the logarithmic and linear models do not deviate significantly (Figure 3, Table 7).¹⁶³

The study by Cashman et al did not include enough 25OHD concentrations around 30 nmol per litre to provide a solid estimate of intakes required to remain above 30 nmol per litre. Based on the logarithmic model, 1 microgram per day should be enough to achieve the target value, but the Committee does not feel this estimate is reliable. No estimate can be defined using the linear model, as no formula is given for estimation of the lower limit of the 95% confidence interval.

Sufficient data are present to estimate the intake required to achieve a serum 25OHD concentration target value of at least 50 nmol per litre. According to the logarithmic model, 50% of people using 6 micrograms per day receive enough, and among those with intake of 10 micrograms per day, the figure is 97.5%. According to the linear model, 50% of people using 10 micrograms per day have a serum 25OHD concentration above 50 nmol per litre. For people using 12 micrograms per day, the figure is 97.5%.¹⁶³

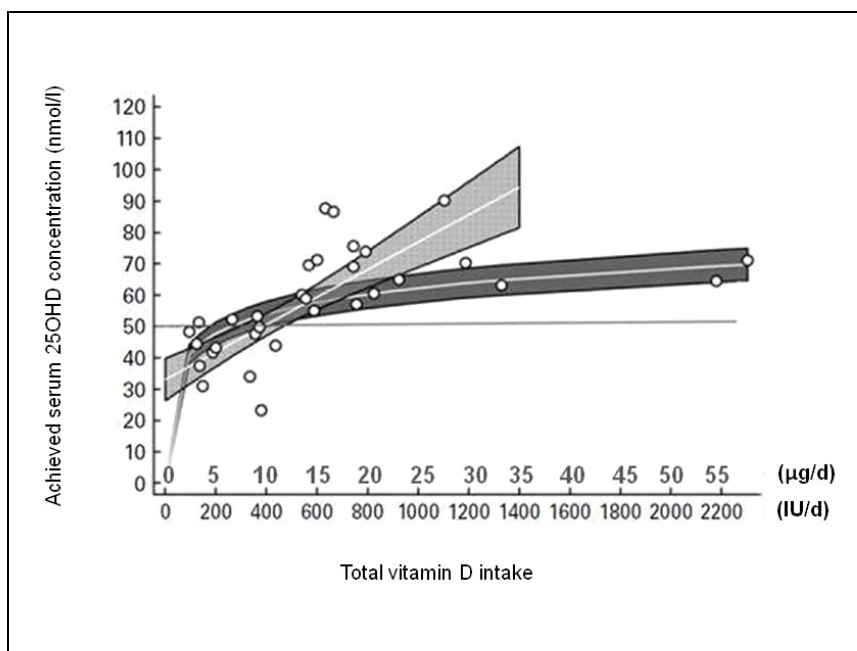


Figure 3 Achieved serum 25OHD concentration as a function of total vitamin D intake in Northern Europe (>49.5 degrees of latitude north) and Antarctica (78 degrees of latitude south) during the winter, when effective sunlight exposure for vitamin D production in the skin is minimal.¹⁶³ Data from various age groups were analysed jointly, as there were no significant differences in the relationship between vitamin D intake and serum 25OHD concentration between groups.⁷ Average responses (white lines) and the 95% confidence interval based on a linear meta-regression model following natural log transformation (dark grey, curvilinear model) and without log transformation (light grey, linear model) of total vitamin D intake. The highest total intake was 35 micrograms (1400 International Units). The figure was reprinted with permission from Cambridge University Press from: Cashman et al. A systematic review and meta-regression analysis of the vitamin D intake – serum 25-hydroxyvitamin D relationship to inform European recommendations. *British Journal of Nutrition* 2011; 106(11): 1638-1648.¹⁶³

Table 7 Classical derivation of individual levels of intake at which 50% and 97.5% of the population achieve serum 25OHD concentrations above 30 and 50 nmol per litre.¹⁶³

Regression model		P97.5
Serum 25OHD concentration > 30 nmol/l		
Logarithmic regression model Cashman 2011		0.9 µg/day
Linear regression model Cashman 2011		Not reported
Serum 25OHD concentration > 50 nmol/l		
	P50	P97.5
Logarithmic regression model Cashman 2011	6 µg/day	10 µg/day
Linear regression model Cashman 2011	10 µg/day	12 µg/day

5.2.3 Estimate based on individual data

In a series of studies conducted by Cashman et al, individual data were used to determine the level of vitamin D intake that is required in order to achieve a certain serum 25OHD concentration.¹⁶⁴⁻¹⁶⁶ These studies examined the effect of various levels of supplementation on serum 25OHD concentrations in adolescent girls, young adults and the elderly during autumn and winter. Habitual vitamin D intake was also determined. The baseline values for serum 25OHD concentration at the beginning of the study varied from 50 to 70 nmol per litre, equivalent to average Dutch serum 25OHD concentrations.¹⁶⁷ As for the estimates based on average data described in 5.2.2, the estimates based on individual data examine the effect of total vitamin D intake on serum 25OHD concentration after a drop from summertime levels. Because these studies only determined serum 25OHD concentrations at the end of the winter (after 22 weeks of intervention), the effects of vitamin D supplies built up during the summer is likely smaller than for the estimates based on average data, where the minimum intervention duration was 6 weeks.

These data were used to estimate the required vitamin D intake at which half of the population and almost everyone achieves serum 25OHD levels above 25, 37.5 and 50 nmol per litre were estimated (Table 8).

Table 8 Estimated vitamin D requirement to achieve serum 25OHD concentrations above 25, 37.5 and 50 nmol per litre in half (P50) or 97.5% (P97.5) of adolescent girls and adults below and above 65 years of age.¹⁶⁴⁻¹⁶⁶

	P50	P97.5
Serum 25OHD concentration > 25 nmol/l		
Adolescent girls	0.2 (0-1.7)	8.3 (7.3-9.4)
Adults ages 20-40 years	- ^a	8.7 (6.5-11.1)
Adults from the age of 64 years	- ^a	8.6 (6.4-10.4)
Serum 25OHD concentration > 37.5 nmol/l		
Adolescent girls	5.3 (4.4-6.1)	13.5 (12.2-14.8)
Adults ages 20-40 years	2.3 (0.0-4.2)	19.9 (17.2-23.5)
Adults from the age of 64 years	- ^a	17.2 (15.4-19.4)
Serum 25OHD concentration > 50 nmol/l		
Adolescent girls	10.4 (9.7-11.1)	18.6 (16.7-20.5)
Adults ages 20-40 years	10.2 (8.9-11.4)	28.0 (24.2-32.8)
Adults from the age of 64 years	7.1 (5.2-8.5)	24.7 (21.9-27.7)

^a No estimate possible.

For a reference value of at least 25 and 37.5 nmol per litre, it was only possible to estimate the level of intake likely to be required to achieve serum 25OHD concentrations of over 30 nmol per litre in almost the entire population. Based on interpolation, the Committee estimates that this target value is achieved at vitamin D intakes between 11 and 15 micrograms per day.

The data do allow derivation of the intake at which half and almost the entire population would achieve the target level for serum 25OHD concentration of at least 50 nmol per litre. In this scenario, intake at which half of the population achieves the target value is estimated at 10 micrograms per day. Intake at which 97.5% of the population achieves the target value is 20 to 25 micrograms, according to this model.¹⁶⁴⁻¹⁶⁶

It should be noted that estimated levels of intake at which almost everyone achieves target values included the full range of variation found in the measurements; not only between-person variation, but also within-person variation, which includes, among other things, variation due to the measurement method. This means adequate intake and recommended dietary allowances derived from individual data will likely be a little high.¹⁶⁸ Additionally, the question arises of whether the values are representative, for example, for children, adolescents, adults with dark skin and pregnant women.¹⁶⁸

5.2.4 *Estimate based on dose-response relationship*

Requirements may also be derived based on the dose-response relationship between additional vitamin D intake and serum 25OHD concentration.

The increase in serum 25OHD concentration is relatively larger at vitamin D doses up to 25 micrograms per day, for starting levels of serum 25OHD concentrations below 40 nmol per litre, and when supplementation continues for at least three months.^{7,18,52,169-171} There are no clear age-related differences in the degree to which serum 25OHD concentrations rise following additional vitamin D intake.^{7,164-166,172}

Only a limited number of studies have accounted for the fact the relationship between vitamin D intake and serum 25OHD concentration is not linear; the rise in serum 25OHD concentration per microgram of vitamin D appears to become smaller as the level of intake and serum 25OHD concentration rise.⁷ Gallagher et al examined this non-linear dose-response relationship at levels of supplementation varying between 10 and 120 milligrams of vitamin D per day in postmenopausal women aged 57 to 90 years in Nebraska with an average serum 25OHD concentration of 38 nmol per litre. They concluded that estimated average requirement to achieve a serum 25OHD concentration target value of at least 50

nmol per litre was 10 micrograms per day, and the recommended dietary allowance 15 micrograms per day.¹⁵⁰

Additionally, Autier et al described the non-linear relationship between change in serum 25OHD concentration in relation to baseline serum 25OHD concentration and level of supplementation in a systematic review. They estimated that for a baseline serum 25OHD level of 10 nmol per litre, 10 micrograms of additional vitamin D per day will increase serum 25OHD concentrations with 30 nmol per litre on average (95% confidence interval 3 to 58 nmol per litre). At a baseline level of 50 nmol per litre, the average increase at this dose is 18 nmol per litre (95% confidence interval -30 to +68 nmol per litre). The confidence intervals for these point estimates are wide, indicating the high degree of uncertainty surrounding the estimates.¹⁷¹

The Committee believes these data are insufficiently usable for defining dietary reference values. Estimates from the study by Autier et al did not take account of habitual vitamin D intake, and the dose-response relationship was not examined separately for insufficient exposure to sunlight.¹⁷¹ The Committee has a preference for data on the relationship between total vitamin D intake and serum 25OHD concentrations during insufficient exposure to sunlight for defining dietary reference values.

5.3 Dietary reference values for persons from the age of 4 years

For persons aged 4 to 70 years, the Committee defined adequate intake. Estimated average requirement and therefore recommended dietary allowance cannot be determined with precision in this group. Estimated average requirement and therefore a recommended dietary allowance can be derived for the elderly.

5.3.1 Adequate intake for persons aged 4 to 70 years

Evidence for a protective effect of additional vitamin D on bone health is limited for people aged 4 to 70 years. For example, one review article based on intervention studies concluded that it is probable that vitamin D supplementation may improve bone density in children with a serum 25OHD concentration below 35 nmol per litre. One of the studies included in the review used a daily dose of 50 micrograms of vitamin D, all other treatments varied between 3 and 10 micrograms per day.⁶¹ Furthermore, it is probable that supplementation with vitamin D and calcium limits the reduction of bone density in postmenopausal women. Most studies on which this conclusion is based were conducted with a

maximum of 20 micrograms of vitamin D per day, and a minimum of 500 milligrams of calcium per day.^{52,68-70,73} What this improvement in bone density entails for the risk of bone fractures is unclear due to a lack of research.² Therefore, the Committee does not use the above-mentioned effects on bone density in determining dietary reference values, but uses serum 25OHD concentration as an indicator for bone health. The target value is derived from the target value for young children (rickets). The Committee sees no pressing reason to increase the target level for serum 25OHD concentration for women aged 50 to 70 years. However, In Chapter 7, the Committee does recommend women between the ages of 50 and 70 years take a vitamin D supplement just in case.

The estimate for dietary reference values can also be based on the target level for serum 25OHD concentration, which is derived from that for young children for this age group and is defined as at least 30 nmol per litre. Adequate intake may also be derived from the level of intake at which almost the entire population has a serum 25OHD concentration above this target value*. As described above, the estimated adequate intake based on individual data is 11 to 15 micrograms per day for individuals ages 4 to 70 years**. This estimate is derived from the average required intake to safeguard a serum 25OHD concentration of 25 and 37.5 nmol per litre. It is therefore not a precise estimate of the level of intake that will safeguard serum 25OHD concentrations above 30 nmol per litre among 97.5% of the population (Table 8).¹⁶³⁻¹⁶⁶

In defining dietary reference values for persons ages 4 to 70 years, the Committee also considered there is insufficient evidence that all people in this age category with light skin require vitamin D supplementation given sufficient exposure to sunlight. Therefore, the Committee also considered the average vitamin D supply in the Netherlands in its definition.² This includes not only intake of vitamin D, but also vitamin D produced in the skin under the influence of sunlight.

Median intake of vitamin D is about 3 micrograms per day.⁴¹ This intake is based on intake among people of Dutch descent. Vitamin D intake of (young) adults of Turkish or Moroccan descent is about 1 microgram per day lower.⁴⁴ Vitamin D production in the skin can only be estimated very roughly and varies significantly between individuals. Based on rough estimates of vitamin D production under the influence of ultraviolet radiation and the comparison with seasonal variations in serum 25OHD concentrations in blood donors, it has been

* There are insufficient data to estimate average requirements.

** The study by Cashman¹⁶³ using averages did not include enough 25OHD concentrations around 30 nmol per litre to provide a solid estimate of intakes required to remain above 30 nmol per litre.

Table 9 Contribution of habitual diet and exposure to sunlight to vitamin D supply. The contribution of exposure to sunlight is an overall estimate.^{3,41,44}

Skin type	Diet	Sunlight	Total supply
I-III	3 µg/day	7 µg/day	10 µg/day
IV-VI	2 µg/day	Less than 7 µg/day	Less than 10 µg/day

estimated that vitamin D production in the skin due to the effects of sunlight in the Netherlands is about 7 micrograms per day, on average, over the course of the entire year.³ Recent British observational and intervention studies into the effects of exposure to sunlight and ultraviolet radiation on serum 25OHD concentrations point in the same direction.^{31,38-40} This results in a total estimated supply of about 10 micrograms per day (Table 9).

Based on the target value for serum 25OHD concentration of at least 30 nmol per litre, adequate intake amounts to 11 to 15 micrograms per day. As there are no signs that everyone in this group requires vitamin D supplementation, the Committee has rounded off adequate intake for persons aged 4 to 70 years to 10 micrograms per day.

Because vitamin D requirements for pregnant or breastfeeding women do not appear to be elevated, adequate intake also applies to pregnant or breastfeeding women.⁷

5.3.2 *Dietary reference values for persons from the age of 70 years*

The basis for defining dietary reference values for persons from the age of 70 years lies in convincing evidence that supplementation with 10 to 20 micrograms of vitamin D in combination with calcium* may reduce the risk of bone fractures^{2,7,18,52} At this level of intake, a target value for serum 25OHD concentration of at least 50 nmol per litre may be achieved.

The estimated average requirement may be derived from the level of vitamin D intake at which 50% of the population achieves a serum 25OHD concentration above 50 nmol per litre. The estimate for the average requirement of elderly people from the age of 70 at this target value lies around 6 to 10 micrograms per day based on study averages, and at 10 micrograms per day based on individual data.

The recommended dietary allowance may be derived in a number of ways. First, assuming a normal distribution of requirements, the recommended dietary allowance is equal to the estimated average requirement plus twice the standard

* In most studies, the amount of calcium given was about 1,000 milligrams per day.

deviation. As between-person variation in vitamin D requirements is unknown, a variance coefficient of 20 to 40% is generally used.⁵ For an estimated average requirement of 10 micrograms per day, this results in an estimated recommended dietary allowance of 12 to 14 micrograms per day.

Another method for estimating the recommended dietary allowance is based on the level of intake at which 97.5% of the population achieves a serum 25OHD concentration above 50 nmol per litre. This method results in a wider spread of recommended dietary allowances: from 10 to 12 micrograms per day based on average study data to 20 to 25 micrograms per day based on individual data (Tables 7 and 8).¹⁶⁴⁻¹⁶⁶

There are two different reasons why the estimate for the recommended dietary allowance based on average data is lower than for the estimate based on individual data. As already indicated in Section 5.2.3, the effect of the vitamin D supply built up during the summer is likely to be greater for the average data than for the individual data, as the required intervention duration was shorter for the average data. Secondly, the estimate based on average data is on the low side, as between-person variation has not been accounted for fully, while the estimate based on individual data is on the high side, because it includes not only between-person but also within-person variation (including variation relating to the testing method).

There is one more consideration. Like the authors of the US Dietary Reference Intakes advisory report, the Committee assumes that age-related physiological changes increase the variation in vitamin D requirements in this group compared to younger age groups.⁷ Based on the above considerations, the Committee has set the recommended dietary allowance at 20 micrograms per day.

5.3.3 Conclusion

For children, adolescents and adults ages 4 to 70 years, adequate intake is set at 10 micrograms per day; for persons from the age of 70 years, an estimated average requirement of 10 and a recommended dietary allowance of 20 micrograms per day apply.

5.4 Vitamin D₂ or D₃?

That vitamin D₃ appears to be more effective in increasing serum 25OHD concentrations than vitamin D₂ was already mentioned in Chapter 2, with the difference being most striking at higher doses. The Dutch supplementation

advisory report from 2008 further described that non-endogenous vitamin D₂ is also not equivalent to endogenous vitamin D₃ for other reasons. For example, vitamin D₂ metabolites have lower binding capacity to the vitamin D binding protein. Additionally, due to a lack of research, it is unclear whether vitamin D₂ protects against fractures. The conclusion was, therefore, that vitamin D₃ is preferred for inclusion in supplements and foods because vitamin D₃ is more effective than vitamin D₂.^{2,173} The Committee agrees with this conclusion.

5.5 Comparison with previous advisory reports

How do these new reference values compare to those in previous advisory reports? When formulating Dutch dietary reference values for vitamin D in 2000 separate values were derived for people with light skin colour and sufficient exposure to sunlight, for people with dark skin colour, and for people with insufficient exposure to sunlight. The dietary reference values for vitamin D in this new advisory report are valid for insufficient exposure to sunlight, and are therefore similar to the reference values that used to apply for dark skin or insufficient exposure to sunlight (Table 4).¹ Adequate intake for persons aged 4 to 50 years has been increased from 5 to 10 micrograms per day, and for persons from the age of 70 years it has been increased from 15 to 20 micrograms per day. This is due to new data that have become available since 2000 regarding the relationship between vitamin D intake and serum 25OHD concentration and – for 4- to 70-year-olds – about the contribution of sunlight to vitamin D supply.

The new dietary reference values for children up to the age of 1 year and persons from the age of 70 years are consistent with the US dietary reference values from 2010. For other age groups, the Committee has defined adequate intakes lower than the US recommended dietary allowances.⁷

5.6 Conclusion

For children up to the age of 1 year and from 1 to 4 years old, adequate vitamin D intake has been set at 10 micrograms per day. The prevention of rickets plays a central role in this regard.

For people over the age of 70 years, an estimated average requirement of 10 micrograms and a recommended dietary allowance of 20 micrograms of vitamin D per day has been established. At this level of intake, prevention of bone fractures plays a central role.

For children from the age of 4, adolescents and adults up to the age of 70 years, including breastfeeding or pregnant women, adequate intake has been

determined to be 10 micrograms per day. Hard evidence on the effects of additional vitamin D on bone health is lacking in this group. The reference value determined is therefore based on serum 25OHD concentration and on the fact that there is insufficient evidence that all people in this age group require vitamin D supplementation. As vitamin D may be obtained not only through diet, but also via influence of sunlight on the skin, Chapter 6 examines the impact of these dietary reference values for daily practice.

As previously concluded, evidence for effects of vitamin D on other conditions, such as cancer, cardiovascular disease, diabetes, infectious diseases and auto-immune diseases has not been sufficiently established to be considered when defining dietary reference values. However, large-scale studies will be conducted in the coming years. Once the results become available, re-evaluation of dietary reference values for vitamin D may become necessary.

High-risk groups and measures

This Chapter examines groups with an increased risk of vitamin D deficiency. Additionally, potential measures for combating vitamin D deficiency will be outlined.

6.1 High-risk groups

Groups may be at risk for vitamin D deficiency and related health complaints for a variety of reasons. These may be related to individual, lifestyle and environmental factors, with insufficient exposure to sunlight playing a key role.¹⁷⁴

Examples of individual factors are, for vitamin D, age and skin colour; examples of lifestyle factors include the amount of time spent outdoors, sun-avoiding behaviour and wearing a veil; and an environmental factor is the degree of latitude of a country. The factors related to an increased risk differ between high-risk groups. In young children, vitamin D supply through sunlight exposure and habitual diet may be low, with breastfed infants who do not receive a vitamin D supplement at particularly high risk. The same holds true for children receiving a macrobiotic diet, resulting in both low calcium and low vitamin D supplies.^{7,175}

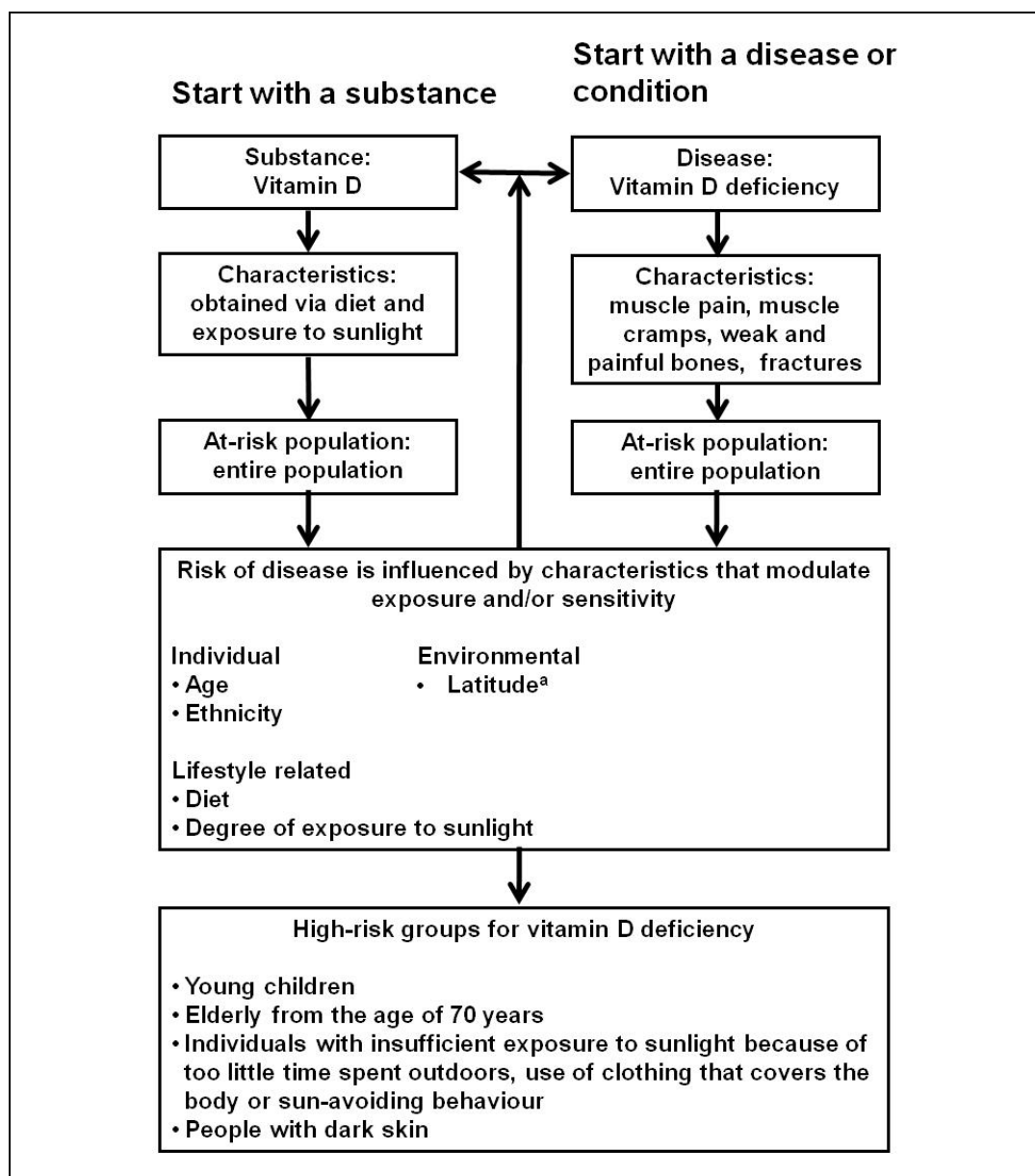


Figure 4 Assessment framework for the identification of high-risk groups for vitamin D deficiency.¹⁷⁴

^a Within the Netherlands, the variation in latitude is so minimal that the risk of deficiency is the same for people in the South and the North of the Netherlands.

In children, adolescents and adults with dark skin or insufficient exposure to sunlight, low vitamin D production in the skin is the limiting factor. This is confirmed by the smaller seasonal fluctuations in serum 25OHD concentration as the skin is darker. For the sake of comparison: seasonal fluctuation can be up to 40 to 60% in people with light skin.^{3,40}

The SUNSET study found that people with a Dutch background showed clear seasonal fluctuations in serum 25OHD concentrations, while this was less apparent in people with a Creole Surinamese background, and absent in people of Hindu Surinamese descent.¹⁷⁶

In the elderly from the age of 70 years, the risk of deficiency is higher, as their vitamin D requirements are higher than those in younger age groups. Furthermore, a lack of exposure to sunlight also plays a role for part of this group (Figure 4).

New* Dutch data on serum 25OHD concentrations confirm some of the findings above (Table 10).^{167,176-180} Information on adolescents is lacking. Research conducted in the United Kingdom did show that on average over the course of the year, about 20% of children between the ages of 9 and 18 have serum 25OHD concentrations below 30 nmol per litre. In children between 4 and 8 years old, this percentage is slightly lower.¹⁸¹ Another study found that 15% of European adolescents have a serum 25OHD concentration below 27.5 nmol per litre.¹⁸²

For several of the high-risk groups described above, health complaints have been described that are due to a low vitamin D supply. A pilot study found that about half of veiled women with a serum 25OHD concentration below 20 nmol per litre complains of muscle aches, muscle weakness or fatigue.¹⁸³

However, data on symptoms and conditions due to a severe vitamin D deficiency are largely limited to case reports. For example, case reports from the Netherlands have been published of seizures in newborns and rickets in children with non-Western backgrounds.^{138,184-186} There are also reports of serious muscle weakness in the locomotor system and osteomalacia in veiled and/or dark-skinned girls and women as a result of a severe vitamin D deficiency.^{184,187,188}

* In the advisory report *Towards an adequate intake of vitamin D*, Table 7.3 lists previous data for, among others, children and adults with different ethnic backgrounds.²

Table 10 Occurrence of vitamin D deficiency in the Dutch population.

Population group	Low serum 25OHD concentration	Period	% low serum 25OHD concentration
Newborns ¹⁷⁷	< 25 nmol/l	Year-round	5
Children 4-8 years ¹⁷⁸	< 30 nmol/l	Year-round	1
Men 18+ NL de Maat ¹⁶⁷	< 30 nmol/l	Year-round	10
		Summer	8
		Autumn	8
		Winter	16
Women 18+ NL de Maat ¹⁶⁷	< 30 nmol/l	Year-round	8
		Summer	3
		Autumn	6
		Winter	14
Pregnant women from Amsterdam ¹⁸⁰	< 30 nmol/l	Year-round	23
		Dutch background	8
		Surinamese background	58
		Turkish background	78
		Moroccan background	74
		Other non-Western background	35
		Other Western background	17
Pregnant women from Delft ¹⁸⁹	< 25 nmol/l	Year-round	18
Men up to 50 years ¹⁷⁶	< 30 nmol/l	Year-round	8
		Dutch background	41
		Creole Surinamese background	39
Women up to 50 years ¹⁷⁶	< 30 nmol/l	Year-round	5
		Dutch background	38
		Creole Surinamese background	41
Women from 50 years ¹⁷⁶	< 50 nmol/l	Year-round	41
		Dutch background	85
		Creole Surinamese background	78
Non-Western immigrants ¹⁷⁹	< 25 nmol/l	Year-round	55

6.2 Measures

6.2.1 Supplementation

The supplementation advisory report from 2008 describes a number of high-risk groups that obtain insufficient vitamin D from exposure to sunlight, which cannot be compensated fully by healthy diet in accordance with the Guidelines

for a Healthy Diet, using low-fat margarine, margarine and frying and baking products. Supplementation is therefore required (Table 4).² Chapter 7 expounds these supplementation recommendations further, distinguishing between supplementation recommendations with convincing or probable evidence for health benefits, and supplementation recommendations for which less strong evidence is available.

6.2.2 *Exposure to sunlight: weighing the importance of vitamin D against the risk of skin cancer*

A complicating factor when it comes to formulating recommendations for exposure to sunlight is that this exposure is good for vitamin D production, but is also associated with a risk of skin cancer. Exposing the skin to ultraviolet radiation may, after all, result in sunburn, which is the most important cause of the development of skin cancer, particularly of highly malignant melanomas. But even regular exposure to a lower dose of sunlight (or ultraviolet radiation from tanning beds) results in DNA damage that increases the risk of skin cancer in the long term, particularly of squamous cell carcinomas.

Avoiding sunburn is the key principle in responsible sunbathing. For vitamin D production in the skin, exposure of larger areas of skin for a short period of time when the sun is at high altitude (between 11:00 and 15:00 hours) is better than longer exposure of a small area of skin. Vitamin D production in the skin due to longer exposure to ultraviolet radiation is subject to saturation, so production becomes less and less efficient, while the risk of damage to the skin increases.³ For skin type III, saturation time is roughly equivalent to the minimum time to sunburn.³² Given equal exposure to sunlight, people with darker skin do have a lower risk of skin cancer than people with light skin. However, people with dark skin still run a greater risk as exposure time increases.³

In order to limit the long-term risks of cancer and in order to produce vitamin D under optimal conditions in the skin, the report on the relationship between cancer, sunlight and vitamin D by the Dutch Cancer Society lists brief exposure while the sun is at high altitude with a maximum exposed area of skin as the best option. In swimwear, a few minutes of unprotected exposure to summer sun near its zenith are enough for vitamin D production, while exposure of head, hands and forearms alone during a lunchtime stroll may require fifteen to thirty minutes.³ This time is in line with the guideline for healthy physical activity for adults from the age of 18 years, amounting to half an hour of moderately intense exercise at least 5 days per week (preferably 7 days per week).¹⁹⁰ In its current

awareness raising materials, the Dutch Cancer Society states that everyone who regularly spends time outdoors should protect themselves from the sun. Only people who normally spend no or hardly any time outdoors benefit from fifteen minutes of unprotected exposure to sunlight at lunchtime.¹⁹¹ The Society recommends against exposing children to midday sun unprotected due to the sensitivity of their skin and the risk of skin cancer.¹⁹²

In short, vitamin D production in the Dutch situation requires spending a short amount of time in midday sun from March to November. As described in previous Health Council advisory reports on vitamin D, at least the head and hands should be exposed. Longer exposure time only provides a small amount of additional vitamin D, but does do more damage to the skin. It is important to follow the recommendations of the Dutch Cancer Society for preventing skin cancer during exposure to sunlight.¹⁹³

6.3 Conclusion

The key high-risk groups for vitamin D deficiency are young children, children, adolescents and adults with dark skin or insufficient exposure to sunlight, and the elderly from the age of 70 years. These groups need additional vitamin D from supplements, as a healthy diet alone contains insufficient vitamin D to compensate for the lower contribution of sunlight exposure to vitamin D supply.

Vitamin D can also be obtained from exposure to midday sun. In swimwear, a few minutes of unprotected exposure to the summer sun near its zenith are enough for vitamin D production, while exposure of head and hands alone during a lunchtime stroll and other everyday activities may require fifteen to thirty minutes. Longer exposure time only provides a small amount of additional vitamin D, but does do more damage to the skin.

It is important to follow the recommendations of the Dutch Cancer Society for preventing skin cancer during exposure to sunlight. In its current awareness raising materials, the Dutch Cancer Society states that everyone who regularly spends time outdoors should protect themselves from the sun. Only people who normally spend no or hardly any time outdoors benefit from fifteen minutes of unprotected exposure to sunlight during lunchtime. For children, due to their sensitive skin and the risk of skin cancer, measures to protect them from the sun are of primary importance.

Conclusions

Dietary reference values for vitamin D

Table 11 lists the dietary reference values for vitamin D, with a description of the methods used to determine them. These reference values are valid for insufficient exposure to sunlight, and apply to everyone, regardless of skin colour. Furthermore, they are applicable for calcium intake in accordance with dietary reference values.*

Health effects were of central importance in determining dietary reference values. For children up to the age of 4, this is the prevention of rickets. For people from the age of 70 years, this is the prevention of bone fractures and falling. For children from the age of 4 years, adolescents and adults up to the age of 70 years, and for breastfeeding or pregnant women, hard data on the effect of vitamin D supplementation on bone health are lacking.** In these groups, derived reference values are based on serum 25OHD concentration and total vitamin D supply, with target values for serum 25OHD concentrations being derived from those for young children (rickets). When using intermediate measures of bone health such as bone density and calcium absorption, the target value for serum

* In populations of non-Western origin, low calcium intake is common. However, available data is too sparse to allow dietary reference values for vitamin D to be defined that apply specifically in case of low calcium intake.

** Effects of vitamin D on bone density are only considered in the determination of supplementation recommendations, as it is insufficiently clear what this measures means in terms of bone health.

Table 11 Dietary reference values^a for vitamin D in micrograms per day. These values apply in case of insufficient exposure to sunlight.

Group	Criterion	Adequate intake	Estimated average requirement	Recommended dietary allowance
0 to 1 year	Risk of rickets and serum 25OHD concentration > 30 nmol/l	10		
1 to 4 years	Risk of rickets and serum 25OHD concentration > 30 nmol/l	10		
4 to 50 years (women) and 4 to 70 years (men)	Serum 25OHD concentration > 30 nmol/l and total supply	10		
50 to 70 years, women	Serum 25OHD concentration > 30 nmol/l and total supply			
From 70 years	Risk of fractures and serum 25OHD concentration > 50 nmol/l		10	20
Pregnant women	Serum 25OHD concentration > 30 nmol/l	10		
Breastfeeding women	Serum 25OHD concentration > 30 nmol/l	10		

^a Dietary reference values encompass total vitamin D supply from diet and sunlight. Sufficient exposure to sunlight results in about two thirds of the required vitamin D being produced in the skin, and one third coming from diet.

25OHD concentration among 4- to 70-year-olds might be higher than 30 nmol per litre. As the significance of these measures for health is insufficiently clear, the Committee decided not to consider them in defining dietary reference values.

Prospective cohort studies showed a relationship between low serum 25OHD concentrations and a higher risk of colorectal cancer, cardiovascular disease, type 2 diabetes mellitus, infectious and auto-immune diseases. The Committee currently believes this evidence is insufficiently strong to be used as a foundation for defining dietary reference values and supplementation recommendations. However, large-scale studies will be conducted in the coming years. Once the results become available, re-evaluation of dietary reference values for vitamin D may become necessary.

The protective effects of vitamin D on bone health have primarily been found in combination with calcium. There are indications that if calcium intake meets dietary reference values, vitamin D supplementation also prevents bone loss in older women without additional calcium. Based on this finding, the Committee assumes that at adequate levels of calcium intake, additional vitamin D also has protective effects on fracture risk without additional calcium.

Compared to the dietary reference values advisory report from 2000, adequate intake for persons ages 4 to 70 years has been increased from 5 to 10 micrograms per day. For people from the age of 70 years, an estimated average requirement of 10 micrograms and a recommended dietary allowance of 20 micrograms of vitamin D per day have been established. These increases are

related to the availability of more data on the relationship between vitamin D intake and serum 25OHD concentrations, and - for 4- to 70-year-olds - about vitamin D production in the Netherlands under the influence of sunlight.

Supplementation recommendations for high-risk groups

Vitamin D can also be obtained through exposure to sunlight from March to November in the Netherlands. Exposure to sunlight contributes to about two thirds of vitamin D supply throughout the year for people with light skin, while diet accounts for one third. In case of insufficient exposure to sunlight, healthy diet in accordance with the Guidelines for a Healthy Diet alone contains too little vitamin D to meet requirements. This means that certain groups will require vitamin D supplementation. Table 12 lists supplementation recommendations for various groups, which apply all year round. These are meant to supplement a good and varied diet that includes low-fat margarine, margarine and frying and baking products. Supplementation with vitamin D₃ is preferred, as it is more effective than vitamin D₂.

Table 12 Overview of vitamin D supplementation recommendations per population group (micrograms per day). Evidence for supplementation recommendations given to make sure is less strong than evidence for other supplementation recommendations.

Age	Light skin ^a with sufficient sunlight exposure ^b	Light skin with insufficient exposure to sunlight or dark skin ^c
Children 0 to 1 year ^d	10	10
Children 1 to 4 years	10 to make sure ^e	10
Women 4 to 50 years ^f and men 4 to 70 years	0	10
Women ages 50 to 70 years	10 to make sure ^g	10
Adults from the age of 70 years ^h	20	20
Pregnant women	10 to make sure ⁱ	10

^a Skin type I through III according to the Fitzpatrick classification.

^b Sufficient exposure to sunlight is defined as 15 to 30 minutes spent outdoors daily in midday sun (between 11:00 and 15:00 hours) with head and hands bare, without burning. The 30 minutes are in line with the Dutch Guideline for Healthy Physical Activity for adults.

^c Skin type IV through VI according to the Fitzpatrick classification. To make sure: for older children, adolescents, adults and elderly people with dark skin, the Committee provides a supplementation recommendation to make sure, for which it assumes the requirements of these individuals are as high as those of people of the same age with light skin.

^d Regardless of the amount and type of infant nutrition. For prevention of rickets.

^e To make sure. This effect was studied in Chinese and Turkish intervention studies. Because it is recommended skin be protected well against sunlight at this age, this recommendation to make sure also applies to children with light skin who spend enough time outdoors.

^f This recommendation also applies to breastfeeding women.

^g To make sure: based on the effect of vitamin D supplementation on bone density in intervention studies.

^h Based on the effect of vitamin D supplementation on the risk of bone fractures in intervention studies.

ⁱ To make sure: to prevent deficiencies in the mother and deleterious effects of serious shortages in the newborn, such as epileptic seizures and possibly also low birth weight (<2,500 grams).

The effects on bone health hold a central position in defining dietary reference values and supplementation recommendations. The Committee wishes to emphasise that good bone health is determined by a large variety of factors, such as age, physical activity and calcium intake. The Committee assumes adequate calcium intake for the supplementation recommendations.* What is new, is the distinction between supplementation recommendations based on probable or convincing evidence for health effects and recommendations based on less strongly supported findings, such as probable effects on bone density and other plausible indications that vitamin D may support health.

Children up to 4 years: 10 micrograms per day

It has been demonstrated convincingly that supplementation with 10 micrograms of vitamin D per day prevents rickets. This conclusion is based on intervention research into the effect of vitamin D on the prevention of rickets performed in Turkish and Chinese children. The Committee feels this finding is applicable to children up to the age of 1 year and young children with dark skin or who do not spend enough time outdoors. The question is whether these findings also apply to children aged 1 to 4 years with light skin and sufficient exposure to sunlight. Since the introduction of supplementation recommendations in the Netherlands and other European countries, rickets has become almost nonexistent. As it is recommended children be protected well against the sun due to the risk of cancer, the Committee is of the opinion use of a vitamin D supplement is a good idea to ensure adequate supply. The supplementation recommendation applies regardless of the type of infant nutrition the children receive.

Older children, adolescents and adults with insufficient exposure to sunlight or dark skin colour: 10 micrograms per day

- In case of insufficient exposure to sunlight, older children, adolescents and adults require a supplement of 10 micrograms of additional vitamin D per day for good bone health. It is probable that vitamin D supplementation can improve bone density in children and adolescents with a vitamin D deficiency. A healthy diet contains insufficient amounts of vitamin D to compensate for the lower vitamin D supply from sunlight.
- Given the lack of research examining vitamin D requirements of older children, adolescents and adults with dark skin, the Committee has assumed

* Adequate refers to intake at the level of dietary reference values.

the requirements in this group are the same as for individuals with light skin. Because production of vitamin D given the same exposure to sunlight under everyday conditions is lower for dark skin than for light skin, the Committee recommends supplementation with 10 micrograms of vitamin D per day to be sure.

Women ages 50 to 70 years: 10 micrograms per day

As indicated above, women aged 50 to 70 years with insufficient exposure to sunlight or dark skin would do well to use extra vitamin D. Whether this recommendation applies to all women in this age group is uncertain. Insufficient research is available into the effects of supplementation with vitamin D and calcium on the risk of fracture in this group. It is probable that this supplementation can counter bone loss. Therefore, the Committee takes the view that all women aged 50 to 70 years would do well to use a supplement of 10 micrograms of vitamin D per day to be sure.

Elderly from 70 years: 20 micrograms per day

It has been demonstrated convincingly that supplementation with vitamin D and calcium can reduce the risk of bone fractures. Additionally, it is probable that supplementation with vitamin D can reduce the risk of falling in vulnerable elderly individuals. Adequate vitamin D intake for this age group is therefore very important. The amount of vitamin D that people over the age of 70 obtain from diet and sunlight will vary significantly from person to person and throughout the year. It cannot be ruled out that people over the age of 70 with light skin who are exposed to sufficient sunlight would only require 10 micrograms of supplementation. To keep things simple, the Committee recommends all people over the age of 70 use a supplement of 20 micrograms of vitamin D per day.

Pregnant women: 10 micrograms per day

As indicated above, pregnant women with insufficient exposure to sunlight or dark skin would do well to use extra vitamin D. 60 to 75% of pregnant women with dark skin and women who wear clothing that covers large parts of their body have a vitamin D deficiency. Whether this supplementation recommendation should apply to all pregnant women is uncertain. A vitamin D deficiency has also been found in 10% of pregnant women with a Western

background. As pregnancy does not appear to increase requirements, these deficiencies are due to insufficient vitamin D supplies in the past. These pregnant women require vitamin D supplementation, not only for their own health, but potentially also for the health of their unborn children. There are case reports of epileptic fits in newborns, and intervention studies point towards a protective effect of vitamin D supplementation on the risk of having a child with a low birth weight (<2500 grams). There are insufficient avenues for reaching these women in a targeted manner. Therefore, the Committee is of the opinion that all pregnant women should be advised to use a supplement containing 10 micrograms of vitamin D per day, just in case. Starting supplementation before pregnancy appears to be important, as the child's bone development begins during the first trimester of the pregnancy, although bone mineralisation does not take place until the last six weeks.

The new supplementation recommendations are largely the same as those from 2008. Compared to the 2008 supplementation advisory report, there are three changes. Women between 50 and 70 years old are advised supplementation with 10 micrograms of vitamin D per day, regardless of skin colour or time spent outdoors, and the supplementation recommendation for people from the age of 70 is 20 micrograms of vitamin D per day. The Committee has elected to simplify the previous supplementation recommendations in order to facilitate implementation and communication. Furthermore, breastfeeding is no longer a reason to use a vitamin D supplement. Breast milk contains very little vitamin D, so the requirement of breastfeeding women is hardly elevated.*

Recommendations for exposure to sunlight and responsible sunbathing

In terms of dietary reference values, sufficient exposure to sunlight means that, under conditions in the Netherlands, fifteen to thirty minutes per day from March to November are spent outdoors in midday sun** (between 11:00 and 15:00 hours) with, for instance, head and hands bare during everyday activities. This amount of time is in line with the Dutch Guideline for Healthy Physical Activity. Longer exposure to midday sun is recommended against, as it only results in

* Breastfeeding women with dark skin or insufficient exposure to sunlight do require 10 micrograms of additional vitamin D per day.

** Vitamin D is primarily produced at times when a person's shadow is shorter than his or her height.

minimal additional vitamin D, but does cause additional damage in the form of skin aging and skin cancer, for example.

It is important to follow the recommendations of the Dutch Cancer Society for the prevention of skin cancer. In its current awareness raising materials, the Dutch Cancer Society states that everyone who regularly spends time outdoors should protect themselves from the sun. Only people who normally spend no or hardly any time outdoors benefit from fifteen minutes of unprotected exposure to sunlight at lunchtime. For children, due to their sensitive skin and the risk of skin cancer, measures to protect them from the sun are of primary importance.

No new tolerable upper levels of intake

The tolerable upper levels of intake have not been re-examined, as new tolerable upper levels were defined at the European level in mid-2012. The new European tolerable upper levels have been set at 25 micrograms per day for children up to the age of 1 year, 50 micrograms per day for children aged 1 through 10 years, and 100 micrograms per day for persons over the age of 11 years. The recommended supplementation levels are significantly lower than these tolerable upper levels of intake.

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- A The Committee
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Annexes

A

The Committee

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- Professor C. van Weel, *Chairman*
Professor of Family Medicine, Radboud University Nijmegen Medical Centre
 - Dr. H. van den Berg
Nutrition expert, Netherlands Nutrition Centre, The Hague
 - Dr. F.R. de Gruijl
Associate professor of Biophysics, Leiden University Medical Center
 - Professor H.S.A. Heymans
Professor of Paediatrics, Academic Medical Center, University of Amsterdam
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 - Professor M. Visser
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 - Professor R. Bouillon, *advisor*
Emeritus Professor of Endocrinology, Catholic University Leuven
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- Dr .P.J. Elders, *advisor*
GP, VU University Medical Center Amsterdam
- Professor P.T.A.M. Lips, *advisor*
Professor of Endocrinology, VU University Medical Center Amsterdam
- E.N. Blok, *observer*
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- Dr. R.M. Weggemans, *Scientific secretary*
Health Council of the Netherlands, 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.

B

Organisations that provided written commentary

In May 2012, 15 organisations provided content-level commentary on the draft advisory report *Evaluation of Dietary Reference Values for Vitamin D* upon request of the Committee. Comments and the Committee's responses to them are [in Dutch] available on the website www.gr.nl

- Dutch Youth Health Care Physicians Association (AJN):
Dr. L. Smit, Secretary of the National AJN Board and Youth Health Care Physician 0-4 years
 - Consumentenbond:
H. Uitslag, Campaign Head for Nutrition, and
A. Houmes, Editor-Researcher for Nutrition
 - Royal Dutch Pharmacists Association, Medicines Information Centre:
A.P. Hielema, Coordinator for Informatorium Medicamentorum
 - Royal Dutch Organisation of Midwives:
Dr. J.B. de Boer, Policy Employee for Guideline Development
 - Dutch College of General Practitioners:
Dr. Tj. Wiersma, Senior Scientific Employee
 - Dutch Dietetic Association:
B. Wieman, Acting Policy Employee for Quality
 - Paediatric Association of the Netherlands:
Dr. K. Joosten, Chairman of the Dutch Association for Paediatrics' Nutrition Committee
-

- Netherlands Society for Clinical Chemistry and Laboratory Medicine:
Dr. J.P.M. Wielders, Clinical Chemist, and
Professor F. Muskiet, Professor of Pathophysiology and Clinical Chemistry
Analysis
- Dutch Geriatrics Society:
Dr. J. Bootsma, Clinical Geriatriest - Clinical Pharmacologist, and
Dr. E. van Melick, Clinical Geriatriest
- Netherlands Society of Obstetrics and Gynecology:
Dr. B.P.M.G. Havenith, Gynaecologist, and
Dr. H.R. Franke, Gynaecologist
- Pharos National Knowledge and Advisory Centre on Migrants, Refugees and
Health Care Issues:
Dr. M.E.T.C. van den Muijsenbergh, GP and Senior Researchers/Advisor
- Dr. F. Schreuder, GP, Delft, and
Dr. G.A.E. Nering Bögel, GP, Leiden
- National Foundation Child and Hospital:
H. Rippen, Director
- Verenso (Elderly Care Physicians):
Dr. V. Chel, Nursing Home Doctor and Geriatric Medicine Specialist
- Netherlands Nutrition Centre:
Dr. J. de Goede, Senior Nutritional Expert,
Dr. A.J.P.G. Smeets, Senior Nutritional Expert, and
Dr. A.M. Werkman, Senior Nutritional Expert

Written comments from the Commentary round on implementation

As indicated in Chapter 1, some of the consulted organisations commented on the implementation of the advisory report. The Health Council of the Netherlands' task is to advise the Minister and Parliament. The policy makers decide whether to adopt the advisory report. Should this be the case, they can implement the recommendations in the report themselves or have third parties, such as the Netherlands Nutrition Centre, do so.

The Netherlands Nutrition Centre, for example, implemented the vitamin D supplementation advisory report from 2008 upon request of the Minister of Health, Welfare and Sport. Within the context of this implementation, the Netherlands Nutrition Centre conducted a round of consultation among professionals. It became clear that, among other things, there was a lack of consistency between the recommendations of various care providers, resulting in a great deal of confusion among both care providers and consumers.^{2,49}

The Committee provides a point-by-point overview of the comments regarding implementation from the written round of commentary. These may be seen as a supplement to the Netherlands Nutrition Centre's report.⁴⁹ As these comments are unsolicited and only come from some of the consulted organisation, this description is not exhaustive.

The first point is the issue of who will implement the advisory report, will it be done by the government via awareness raising campaigns, by Municipal Health Services targeting the public or by medical and paramedical professionals?

The second point relates to the question of what is actually being communicated. The supplementation recommendations have changed since 2008. This can lead to confusion among consumers who are only now becoming accustomed to the previous recommendations. In order to prevent misunderstandings or people giving up, informing consumers of the reasons for the changes would be wise.

The third point relates to the barriers that must be considered during implementation. Examples include phased implementation of this advisory report, how supplementation should occur, how to optimise compliance and the financial consequences of (implementing) the advisory report.

Below are two specific examples. Migrants generally participate less in preventive health measures, such as taking dietary supplements, than other Dutch citizens. This is due to a lack of knowledge, limited financial means and in some cases culturally determined beliefs.¹⁹⁴ If the Health Council advisory report hopes to be effective for all groups, including this high-risk group, education for migrants should receive special attention. This is certainly true for pregnant immigrant women, given the high prevalence of vitamin D deficiency and associated risks for the newborn on the one hand,^{138,195,196} and poor supplementation compliance on the other¹⁸⁹.

The impression youth doctors have is that compliance for vitamin D use has improved significantly now that vitamin supplementation is also recommended for all children receiving formula. In order to maintain this effect, they feel it is necessary that infant nutrition manufacturers not increase the levels of vitamin D in nutrition for young children.

The Committee agrees with these points for attention.

D

Method for deriving dietary reference values (Health Council of the Netherlands Advisory Report 2003)

This text is based on Chapter 1 of the dietary reference values advisory report on vitamin B₆, folic acid and vitamin B₁₂ from 2003.⁵ It first outlines the history of dietary reference values in the Netherlands. Subsequently, the methods for deriving dietary reference values and their implementation are discussed. As deriving tolerable upper levels of intake falls outside the scope of the current advisory report, that area is not addressed in this Annex.

D.1 History

The first recommendations in the Netherlands for amounts of energy and nutrients to consume were published in 1949. They were drafted by the Committee on Nutrition and Agricultural Politics of the Ministry of Agriculture, Fisheries and Food Provision of the time. Until 1959, this Committee was responsible for recommendations, and published various revisions and addenda during that period.

In 1959, the Committee on Dietary Reference Values of the Nutrition Council took over the task. This Committee, in various forms, regularly tested the recommendations against current scientific insights and, where necessary, updated or supplemented them.

In 1995, the Nutrition Council organised an international workshop on dietary reference values. It had been noted that scientific research increasingly pointed towards an association between the intake of certain nutrients and the

development of chronic diseases, alongside other causes. Examples included calcium and vitamin D, nutrients that were at that time assumed to affect the development of osteoporosis and bone fractures. This development, among others, led to the conclusion that review of the dietary reference values in use was in order. When the Nutrition Council was dissolved in 1996, its mandate, including the review of dietary reference values, was taken over by the Health Council of the Netherlands.

In July of the year 2000, the Health Council defined dietary reference values for calcium, vitamin D, thiamine, riboflavin, niacin, pantothenic acid and biotin.¹ In 2001, dietary reference values for energy and for the energy providing nutrients proteins, fats and digestible carbohydrates were derived, and in 2003, dietary reference values were established for vitamin B₁₂, vitamin B₆ and folic acid.^{5,197}

D.2 Terminology and definitions

The term ‘dietary reference value’ is a collective name for the following reference values for energy and nutrients:

- estimated average requirement and recommended dietary allowance
- adequate intake

Figure 5 shows how dietary reference values are established. Both the recommended dietary allowance and adequate intake are quantifications of the level of intake that is considered desirable for health reasons. These measures are derived in different ways, however (see D.2.2 and D.2.3).

D.2.1 *Estimated average requirement*

If the requirements for a specific nutrient are distributed normally within a population, an intake equal to the estimated average intake means the needs of half of the population are met, while those of the other 50% are not (Figure 1). Determining the estimated average requirement is possible if research data describe a dose-effect relationship between intake and requirement for an intake close to this estimated average requirement. However, such data are often unavailable. If the requirements are not normally distributed, it would be more accurate to refer to median rather than average requirement.

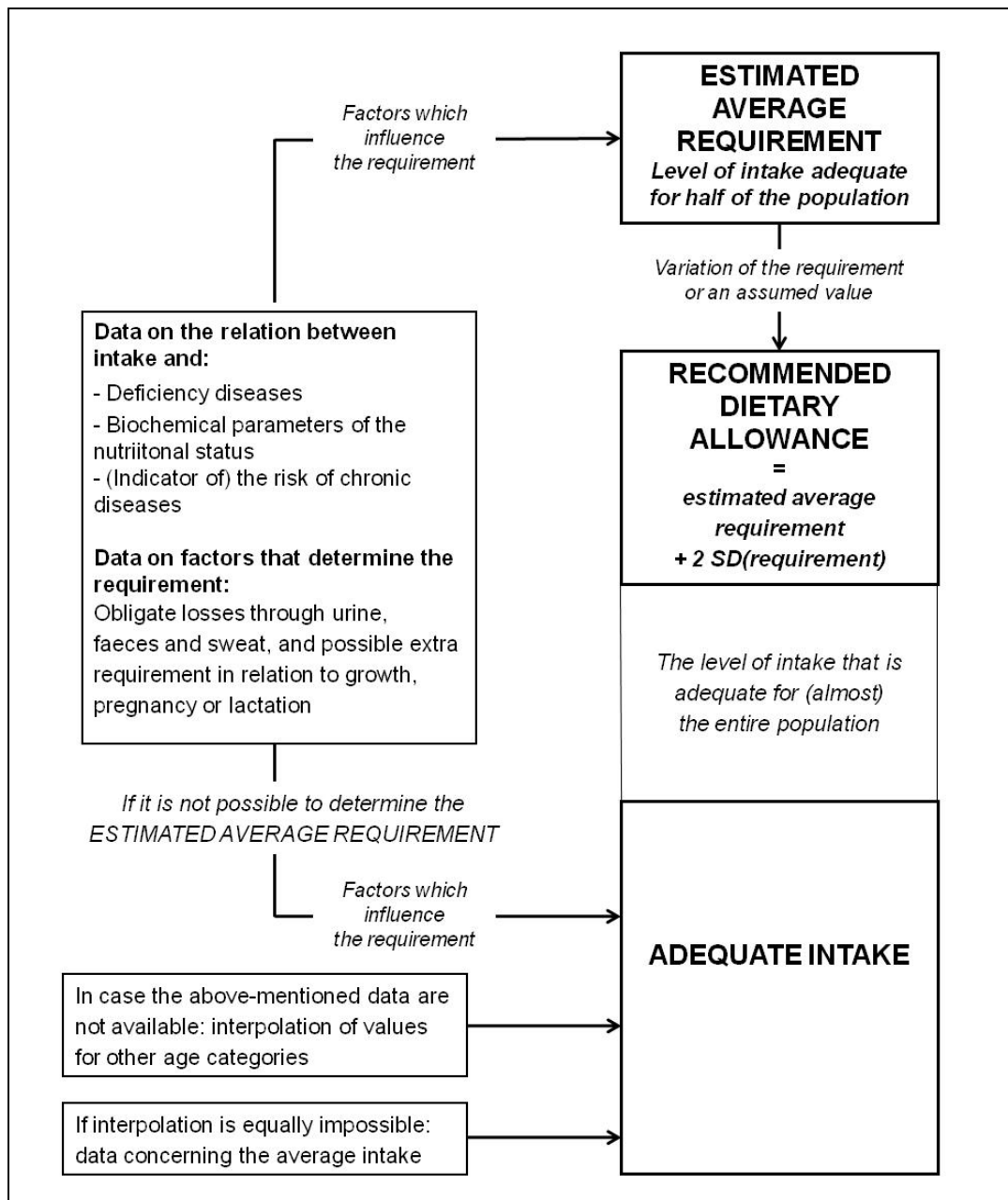


Figure 5 Schematic representation of the determination of dietary reference values (see D.2, D.3 and D.4).

D.2.2 Recommended dietary allowance

Determining the recommended dietary allowance is only possible if sufficient data are available to determine the estimated average requirement (Figures 1 and 5).

If between-person variation in requirements is known

If requirement is normally distributed (Figure 1) and between-person variation in requirement is known, the recommended dietary allowance is calculated as the estimated average requirement plus twice the standard deviation thereof. This covers the requirements of 97.5% of individuals within a population.

If between-person variation in requirements is unknown

Information on between-person variation in requirement is often unavailable, insufficient or inconsistent. In such cases, the variation coefficient is often based on a number of nutrients for which variation coefficients for requirement* have been estimated.

In general, for nutrients with an unknown variation in requirement, a variation coefficient between 10% and 20% is used. Depending on the choice, the recommended dietary allowance is set at 1.2 to 1.4 times the estimated average requirement.

D.2.3 Adequate intake

For many nutrients, insufficient research data are available to determine what level of intake is adequate for exactly 50% of a specific group; the estimated average requirement is therefore unknown in these cases. The recommended dietary allowance, which is derived from the estimated average requirement, can then also not be determined. In such cases, the lowest level of intake that appears sufficient for practically the entire population is estimated: the adequate intake. Adequate intake will generally be higher than the recommended dietary allowance would be (if it could have been determined).

The practical meaning of adequate intake is equivalent to that of the recommended dietary allowance: both describe the level of intake that is

* Variation coefficient = 100% x standard deviation/average.

considered desirable for health reasons. The terminological distinction relates to the difference in how each is determined (Figure 1) and the resulting robustness of the value (Figure 6).

D.2.4 Terminology and definitions based on US Dietary Reference Intakes advisory report

The terminology and definitions in this advisory report are consistent with those of the US Dietary Reference Intakes.^{7,9,198-201} There are a number of differences in terminology and definitions used throughout the world. The EURECCA project has created a clear overview of these differences.²⁰²

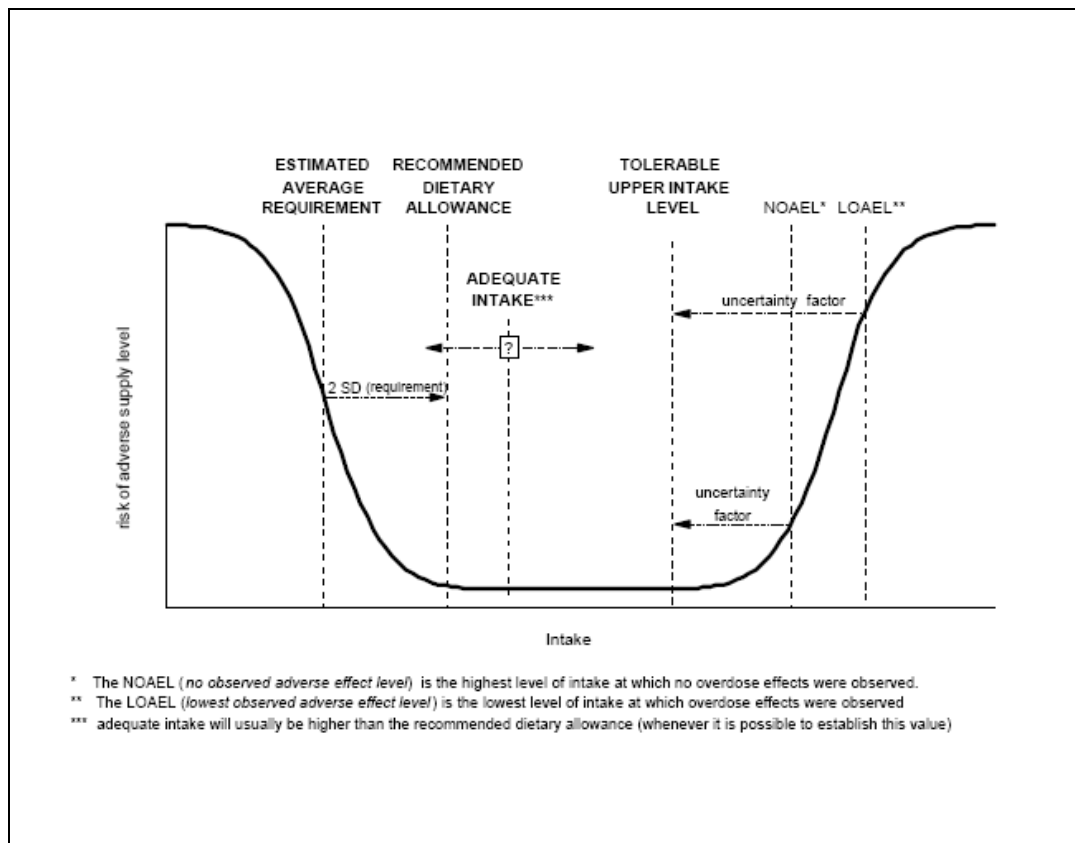


Figure 6 Schematic representation of the relationship between individual intake and the odds of it being at an undesirable level.

D.3 Determining estimated average requirement or adequate intake

There are a number of methods available for determining the estimated average requirement or adequate intake.

D.3.1 Risk of disease

Risk of deficiency diseases

It is not ethically acceptable to cause symptoms of deficiency in people. Therefore, data on the level of intake at which deficiency symptoms arise are scarce. As a result, dietary reference values are generally not based on this type of data. In practice, it is assumed that dietary reference values derived using the methods outlined below are amply sufficient to prevent deficiency symptoms.

Risk of chronic diseases

For some nutrients, there is convincing evidence that intake affects the chances of developing certain chronic diseases. Data on this may relate to the occurrence of the disease itself, but also to 'intermediate endpoints', which are very likely to influence the development of these diseases. Dietary reference values are defined in part based on such data.

In the evaluation of study results that indicate a possible causal relationship between intake of a nutrient and the development of chronic diseases, the type of study from which results were obtained (Table 13), the strength of the association found, the consistency of research results and the presence or absence of a dose-effect relationship are taken into account.

The results of intervention studies or prospective cohort studies are the most reliable (the first two types of study in Table 13), and primarily these results are used for the determination of dietary reference values focused on the prevention of chronic diseases. Results from research of the third and fourth categories are largely of supporting value. For some nutrients or populations, data are only available from the two latter types of study; in such cases, the dietary reference values are not based on the relationship with chronic diseases.

If dietary reference values are based on the risk of chronic diseases, adequate intake is generally determined rather than a recommended dietary allowance. After all, information from intervention research and prospective cohort studies

Table 13 Types of study, in order of decreasing strength of evidence.

Intervention studies in human subjects, with disease or death as the yardstick for results
Intervention studies in human subjects, with intermediate end points or risk factors as the yardstick for results; prospective cohort studies
Controlled studies of patients; migrant studies^a
Ecological studies^b; descriptions of individual patients, experimental animal research, in vitro research

- ^a In migrant studies, disease and death in the first and second generation of migrants are compared. The dietary practices of the first generation usually show marked similarities with those of their country of origin, while those of the second generation more closely resemble the dietary habits of the destination country.
- ^b Ecological analyses usually involve comparisons (also involving observation) between countries or regions. These are not based on observations of individuals but on population averages.

is generally insufficient for quantifying estimated average requirements. Information from intervention studies generally only describes several levels of intake; the results from prospective cohort studies generally do not report specific levels of intake, but so-called tertiles, quartiles or quintiles of intake.⁵ Median intake is often reported per category, an estimate that is generally not very reliable.^{203,204}

In determining dietary reference values, the effects of the nutrients on chronic diseases play a central role. Of course there are often also other factors that affect the development of the chronic disease.

D.3.2 Biochemical markers of nutritional status

For some biochemical parameters, reaching or failing to reach a certain threshold value indicates too low intake of a nutrient. In such cases, based on the relationship between intake of the nutrient and the biochemical marker, average requirement or adequate intake may be estimated. The average intake at which the biochemical marker reaches the threshold is the estimated average requirement.

If insufficient data are available to determine this level of intake, the level of intake above which the biochemical marker value is higher than the threshold for almost all people is determined. This level of intake is referred to as 'adequate intake'.

Biochemical markers of nutritional status may be divided into two main groups:

- 1 Concentration of the nutrient in question in various body compartments.
- 2 Functional parameters that are indicative of the nutrient's efficacy at a cellular level or in a physiological system. If (an active form of) the nutrient acts as a co-enzyme or co-substrate of an enzyme, the activity of said enzyme or the amount of holo-enzyme may represent a functional measure for nutritional status. Intermediate metabolic products may also serve as functional parameters for nutritional status.

For some nutrients, a variety of biochemical variables characterise nutritional status. Variable selection also affects the levels for dietary reference values. Expectations with regard to health gains play a guiding role in this choice.

D.3.3 Factorial method

The factorial method encompasses summarising the individual factors that determine requirement (Figure 7). This includes the amounts of the nutrient excreted via stools, urine and skin and, if applicable, the amounts required for growth, pregnancy or lactation. The additional requirement during growth and pregnancy is the amount of the nutrient found in the newly formed tissues, also referred to as 'retention'. The additional requirement during lactation is the amount of the nutrient that leaves the body via breast milk.

The apparent absorption percentage is the difference between intake and faecal excretion divided by intake. This is an underestimation of the actual absorbed fraction, as nutrients in faeces do not only come from diet, but also from digestive fluids and excreted intestinal wall cells. Isotope techniques have allowed actual absorption percentages to be determined. This type of data is preferred over estimates of apparent absorption, but is not always available.

D.3.4 Determining average intake

Age group up to 5 months

For infants up to 5 months, no research is generally available describing both intake and nutritional status. It is assumed that breast milk is optimal nutrition for this age group. Therefore, adequate intake is equal to average intake of infants who are breastfed exclusively*. An average consumption of 0.80 litres of breast

* Average intake via breast milk is insufficient for vitamins D and K, and supplementation of breastfed infants is recommended and generally accepted.

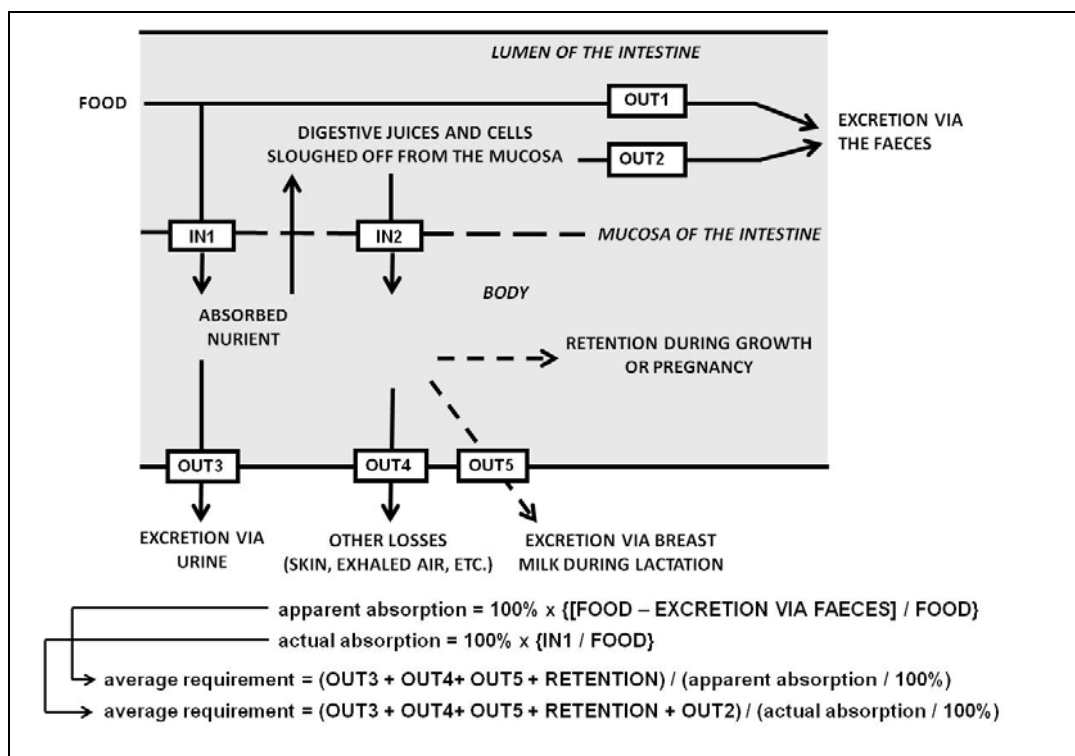


Figure 7 Estimating average requirement using the factorial method.

milk per day or 0.15 litres per kilogram per day, and the average concentration of nutrients in breast milk* are assumed in this regard.

For some nutrients, maternal intake affects the composition of breast milk. For such nutrients, concentrations achieved at habitual intake levels for lactating women in the Netherlands are used.

Wherever the term infant nutrition is used, it is used to mean complete infant nutrition, with a composition as described in the Commodities Act Regulation on Infant Nutrition. Adequate intake for infants receiving infant nutrition is sometimes higher than for breastfed infants, as bioavailability of certain nutrients in infant nutrition is lower than in breast milk.

* The composition of breast milk of mothers with a healthy nutritional status is assumed. The different composition of breast milk during the first days after delivery (colostrum) is not accounted for.

Adults

For some nutrients, the knowledge required to derive dietary reference values for adults using one of the previously described methods is lacking. If no symptoms of deficiency are reported for micronutrients in the Netherlands, adequate intake for adults is defined at the level of average intake.

D.3.5 Interpolation

For some nutrients, data on younger age groups are missing. In such cases – after having studied the procedure for determining reference values for B vitamins recently followed in the United States¹⁹⁹ – the following approach has been selected: adequate intake is defined via interpolation between adequate intake for infants up to the age of 5 months receiving only breast milk and the recommended dietary allowance or adequate intake for adults. The assumption is made that:

- Based on the median age in the age groups, requirement increases in a linear fashion with age for age groups through 18 years
- The requirement for the age group 14 through 18 years is the same as for 19- through 50-year-olds.

Adequate intake is then calculated as:

$$AI = AI_{0-5 \text{ months}} + (AF \times [\{AI \text{ or RDA} \}_{>14 \text{ years}} - AI_{0-5 \text{ months}}])$$

In this formula, 'AI' stands for adequate intake, and 'RDA' for recommended dietary allowance. 'AF' is the age factor, which has the following values: 0.00 for the age group up to and including 5 months; 0.03 for 6 through 11 months; 0.14 for 1 through 3 years; 0.38 for 4 through 8 years; 0.69 for 9 through 13 years; and 1.00 for 14 through 18 years.

D.4 Factors that affect requirement

D.4.1 Differences between groups

Differences in dietary reference values between countries can often be traced back to different interpretations of available knowledge or differences in starting points and definitions. However, it is also possible that requirements between countries actually do differ. Such differences may be related to diet, individual

characteristics, including ethnicity, and differences in lifestyle and environmental factors. The same factors can also lead to differences in requirement between subgroups within a country.

Population subgroups may also display different sensitivity to overdose of a nutrient. For example, iron absorption is increased in some people due to hereditary causes, so that harmful effects of overconsumption are already seen at relatively low levels of intake.

There are also population groups with normal nutritional requirements, but who - due to different dietary habits - relatively often have a low intake of certain nutrients. However, not the amount used, but the amount required is central in defining dietary reference values. Identification of the groups described above does not play a role in defining the reference values, but it is an area of application for the dietary reference values (see D.6.4).

The dietary reference values relate to the requirements and sensitivity of the majority of the Dutch population. When defining dietary reference values, an average Western diet, healthy lifestyle and most common demographic characteristics in our country are assumed. Where relevant, significantly higher requirements for specific groups are indicated.

D.4.2 Dietary factors

Dietary patterns may affect the requirements for nutrients via bioavailability of nutrients and the degree to which precursors* meet nutritional needs. Dietary reference values always refer to the amount of a nutrient in the diet; bioavailability and bioconversion have already been taken into account when determining the values.

Bioavailability

The dietary reference values are tailored to suit average bioavailability of nutrients in the Western diet. In nutritional science, bioavailability is defined as the fraction of intake available for normal physiological functions – for precursors, this is the conversion into the active form – or for storage.

Bioavailability is determined by: the structure and chemical form of the nutrient (for example Fe²⁺ versus Fe³⁺), the amount of the nutrient in the diet, the matrix containing the nutrient (for example carotenoids in a vegetable or

* Precursors are substances the body can use to make the nutrient; for example, β-carotene is a vitamin A precursor.

dissolved in a food oil), and the presence of substances that play a role in absorption. Nutritional status, genetic factors and intestinal infections may also affect nutrient bioavailability.

Bioconversion and efficacy of precursors

The requirements for certain nutrients may – partially – be met by the consumption of precursors, which the body converts into the nutrient in question. For example, the body converts certain carotenoids into vitamin A, and tryptophan into niacin. The degree to which the bioavailable precursor is converted into the active nutrient is called bioconversion. The processes of bioavailability and bioconversion taken together are termed 'efficacy'.

D.4.3 *Other factors*

In addition to nutritional factors, individual factors, lifestyle and environmental factors can have an effect on requirements. For example, skin colour and exposure to sunlight affect vitamin D requirements, body weight and physical activity dictate energy requirements, smoking habit determines vitamin C requirements and infectious burden the requirement for vitamin A. Risk factors for chronic disease, genetic factors and medication use can also affect requirement.

D.5 **Age groups and categories**

The dietary reference values are specified according to age and sex. Separate dietary reference values apply to pregnant or lactating women. This classification into groups is consistent with the US Dietary Reference Intakes.^{9,198-201}

The Dutch dietary reference values advisory report from 2003 describes reference values for height and weight for all age groups. Since then, new information about these reference values has become available, among other things via the Fifth National Growth Study performed by the Netherlands Organisation for Applied Scientific Research TNO, and the NL de Maat study, conducted by the National Institute for Public Health and the Environment. Future dietary reference values should be based on these new data.^{205,206}

D.6 Applications

D.6.1 Use of the dietary reference values

The dietary reference values are meant for healthy individuals and are focused primarily on disease prevention. They are used for:

- Programming food supply for healthy groups
- Drafting nutritional guidelines for healthy individuals
- Evaluating consumption figures for healthy groups
- Evaluating intake for people with a poor nutritional status
- Drafting the so-called Guidelines for a Healthy Diet.

Estimated average requirement, not the recommended dietary intake or adequate intake should be used to evaluate intake of nutrients for healthy groups. The rest of this section describes which type of dietary reference value is suitable for which application. See also Table 14.

D.6.2 Programming food supply for healthy groups

In order to programme the food supply for healthy groups, the recommended dietary allowances and adequate intakes should be used. This application is intended for institutions that provide meals, such as prisons, boarding schools and military barracks. If food contains the recommended dietary allowances and adequate intakes for various nutrients, it will fulfil the requirements for almost all individuals.

Table 14 Summary of applications and corresponding types of dietary reference intakes.

application	type of dietary reference intakes ^a	
	estimated average requirement and variation in requirement	recommended dietary allowance or adequate intake
dietary planning for groups of healthy individuals		+
drawing up dietary guidelines for healthy individuals		+ b
evaluating the consumption figures of groups of healthy individuals	+	
evaluating the intake of individuals whose poor nutritional status has been established using biochemical parameters	+ b	+ b
drawing up guidelines for a healthy diet		+

^a The upper level of intake is considered appropriate for all applications.

^b Here it is possible to take into account dietary factors, individual characteristics and lifestyle factors that affect requirement.

D.6.3 Drafting nutritional guidelines for healthy individuals

Recommended dietary allowances and adequate intakes are also used to draft nutritional guidelines for healthy individuals. When used at the individual level, the nutritional guidelines may – if applicable – be tailored to dietary and other factors that affect requirement (see D.4).

D.6.4 Evaluating consumption figures for healthy groups

If the average as well as the variation in both intake and requirement are known for a group, the percentage of individuals with insufficient intake can be estimated (see 1.5.3 in ²⁰⁷). Identifying individuals with insufficient supply using such data is not possible, however; this requires determination of individual nutritional status (see also D.6.5).

It is not possible to estimate the percentage of individuals with insufficient intake based on recommended dietary allowances or adequate intakes. However, if a recommended dietary allowance has been defined, estimates of average requirement and variation therein become available (see D.2.2). With these data, the percentage of individuals with insufficient intake can be estimated.

If adequate intake is derived, it means that the estimated average requirement is not known (see D.2.3.). For these nutrients, only an overall assessment of consumption figures is possible. An example of this is the situation in which average intake is equal to adequate intake. In this situation, half of the population has an intake lower than the adequate intake, but this level of intake will be insufficient for only – an unknown – part of this group.

D.6.5 Evaluating intake for people with a poor nutritional status

Sometimes, the level of a biochemical parameter indicates whether someone has a deficiency of a certain nutrient. By comparing his or her intake to the estimated average requirement and recommended dietary allowance (or adequate intake), it can be estimated whether or not this is caused by low intake. The further below the estimated average requirement, recommended dietary allowance or adequate intake actual intake is, the greater the chance it is insufficient (Figure 6).

Without individual information about parameters for nutritional status, dietary reference values do not provide enough information for assessing consumption figures for individuals. If a person's intake is lower than the recommended dietary allowance or adequate intake, there is a chance his or her

requirements are not being met (Figure 6). Status parameters are then required to determine whether or not intake is sufficient.

D.6.6 Drafting Guidelines for a Healthy Diet

In 2006, the Health Council of the Netherlands described changes to dietary patterns in the Netherlands that were desirable for the prevention of both deficiencies and chronic diseases; the so-called Guidelines for a Healthy Diet. In this advisory report, the desirable levels of intake were derived and compared with Dutch data on food consumption and nutritional status.

D.6.7 Applications for which the dietary reference values are not intended

Diet guidelines for ill or recovering people or people losing weight

Nutritional requirements can change due to disease, recovery from disease or while losing weight. The dietary reference values may therefore not apply in these situations. The dietary reference values for healthy individuals may, however, be used as a basis for drafting recommendations for groups of patients.

Nutritional value labelling of foods

In the Netherlands, the Commodities Act describes the reference values for nutritional value labelling of foods. These values are based on European labelling legislation, not on Dutch dietary reference values. The Commodities Act Decree of 20 April 1993 is currently in effect, based on a European guideline from 1990 (90/496/EEC).

Medication*Table 15 Medications and their effect on vitamin D metabolism.⁷*

Name of medication/category	25OHD	1,25OH ₂ D	24,25-dihydroxy-vitamin D
Aluminium	Unchanged	Increased/decreased	- ^a
Anti-epileptic medication with enzyme-inducing properties (carbamazepine, oxcarbazepine, phenytoin and phenobarbital)	Decreased	Unchanged	Decreased
Anti-tuberculosis	Decreased	Decreased	-
Bisphosphonates	Unchanged	Increase/decreased/unchanged	Increased
Cimetidine	Decreased	Unchanged	Unchanged
Corticosteroids	Decreased/unchanged	Decreased/unchanged	Unchanged
Ethanol	Increased	Decreased	-
Heparin	Unchanged	Decreased	Unchanged
Hypolipidemic substances	Decreased/unchanged	Unchanged	-
Immunosuppressants	Unchanged	Unchanged	-
Ketoconazole	Unchanged	Decreased	Decreased
Lithium	Unchanged	Unchanged	-
Rifabutin (anti-tuberculosis)	Decreased	Unchanged	-
Thiazides	Increased	Decreased	Increased

^a - no information available.

F

Dietary reference values in the Netherlands and other countries

Country	1 month	5 years	15 years	40 years	80 years	pregnant women	lactating women
This advisory report ^a	10	10	10	10	EAR ^b 10 RDA ^b 20	10	10
Germany, Switzerland, Austria 2012 ^{16 a,c}	10	20	20	20	20	20	20
US Dietary Reference Intakes 2010 ^{7 a}	10	EAR 10 RDA 15	EAR 10 RDA 15	EAR 10 RDA 15	EAR 10 RDA 20	EAR 10 RDA 15	EAR 10 RDA 15
Belgium 2009 ¹⁵	10	10	10-15	10-15	15	20	20
Australia and New Zealand 2005 ¹⁴	5	5	5	5	15	5	5
Scandinavia 2004 ¹³	10	7.5	7.5	7.5	10	10	10
Dutch dietary reference values 2000 ^{1 d}	5 (10)	2.5 (5)	2.5 (5)	2.5 (5)	12.5 (15)	7.5 (10)	7.5 (10)
Europe 1993 ²⁰⁸	-	0 - 10	0 -15	0 - 10	10	10	10
United Kingdom 1991 ^{10 d}	8.5	0 (10)	0 (10)	0 (10)	0 (10)	10	10

a In case of insufficient exposure to sunlight.

b EAR: estimated average requirement; RDA: recommended dietary allowance

c These data became available too late to be included in this advisory report.

d For habitual sunlight exposure; for insufficient sunlight exposure between parentheses.

Evaluation of methodological quality and level of evidence

The methodology used to draft the Guidelines for a Healthy Diet 2006 was used to evaluate the literature.²⁰⁹ This methodology was made more explicit in the advisory reports on micronutrients by including tables in which conclusions are classified by level of evidence, referring to the studies on which the classification was based.^{2,210-212}

The methodology is largely consistent with the system used for the development of evidence-based guidelines.²¹³ Furthermore, the methodology implemented in the current advisory report was intensified using the SIGN grading system, meaning that the highest level of evidence (A1) only encompasses systemic reviews of good quality (Tables 16 and 17).²¹⁴

The goal of the assessment system used was to evaluate the effects of vitamin D intake on disease risk and intermediate markers, as well as correlations between vitamin D intake or serum 25OHD concentration and these outcome measures.

Table 16 Grades of methodological quality used to classify individual studies into interventions with vitamin D or the relationship between vitamin D intake of serum 25OHD concentration and the risk of various conditions.^{213,214}

Niveau	Type onderzoek
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 17 Level of evidence of conclusions.^{209,213}

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: Insufficientt	Based on the Committee's opinion (grade D).

Search strategies

A literature search for new publications was performed in various databases. The most important search strategies in PubMed (from April 2009) were:

Vitamin D (general articles):

Vitamin D[MeSH Terms]

Limits: reviews

Vitamin D and bone health:

vitamin d[MeSH Terms] AND (rickets[MeSH Terms] OR osteomalacia[MeSH Terms] OR fracture[MeSH Terms] OR bone[MeSH/Terms] OR osteoporosis[MeSH Terms])

Limits: meta-analysis, randomized controlled trials, reviews

Vitamin D and other conditions:

vitamin d[MeSH Terms] AND (autoimmune[Title/Abstract] OR cancer[MeSH Terms] OR immune[Title/Abstract] OR cardiovascular diseases[MeSH Terms] OR diabetes[MeSH Terms] OR infection[MeSH Terms] OR infectious[MeSH Terms])

Limits: meta-analysis, randomized controlled trials, reviews

Factors that affect vitamin D requirements

Vitamin D[MeSH Terms] AND (sunlight[MeSH Terms] OR menopause[MeSH Terms] OR pregnancy[MeSH Terms] OR complexion[Title/Abstract] OR pigmentation[MeSH Terms] OR breast feeding[MeSH Terms])

Additionally, from August 2011 to 6 July 2012, new literature was collected continuously using PubMed and Google Scholar alerts using the search term 'vitamin D'.