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Norwegian Scientific Committee for Food Safety

VKM Report 2017: 3

Assessment of vitamin B_6 intake in relation to tolerable upper intake levels

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2017: 3
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07.03.2017

ISBN: 978-82-8259-260-4
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Cover photo: iStock photo

Suggested citation: VKM (2017). Assessment of vitamin B_6 intake in relation to tolerable upper intake levels. Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety. VKM Report 2017: 3, ISBN: 978-82-8259-260-4, Oslo, Norway. Available online: www.vkm.no

Assessment of vitamin B_6 intake in relation to tolerable upper intake levels

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Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM). Per Ole Iversen (chair), Livar Frøyland, Margaretha Haugen, Sigrun Henjum, Kristin Holvik, Martinus Løvik, Bjørn Steen Skålhegg, Tonje Holte Stea and Tor A. Strand.

(Panel members in alphabetical order after chair of the panel)

Acknowledgment

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou. Margaretha Haugen and Inger Therese L. Lillegaard are acknowledged for their valuable work on this opinion.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the intake of vitamin B_6 (pyridoxine) in the Norwegian population in relation to tolerable upper intake levels (ULs). The existing maximum limit for vitamin B_6 in food supplements is 4.2 mg/day. VKM has also conducted scenario calculations to illustrate the consequences of amending the maximum limitto 2, 6, 8, 10, 20 or 25 mg/day.

Vitamin B_6 is water soluble and comprises six compounds with vitamin B_6 activity; pyridoxine (PN, an alcohol), pyridoxal (PL, an aldehyde) and pyridoxamine (PM, the amine) and their corresponding phosphates; pyridoxine 5′-phosphate (PNP), pyridoxal 5′ -phosphate (PLP) and pyridoaxamin 5′ –phosphate (PMP). These six forms of vitamin B_6 are all present in food in addition to the glycosylated form, pyridoxine-5′-β-δ-glucoside (PNG), in some plants. In food supplements the most common vitamin B_6 form is pyridoxine hydrochloride.

Eighty to ninety percent of vitamin B_6 in the body is found in muscles and estimated body stores in adults amount to about 170 mg with a half-life of 25-33 days. Vitamin B_6 deficiency is mostly seen in combination with deficiency of other B vitamins. Symptoms of vitamin B_6 deficiency are anaemia and neurological abnormalities (EFSA, 2016).

Intakes of vitamin B_6 from the diet alone have not been reported to cause adverse effects. Sensory neuropathy has been reported to be the most sensitive adverse health effect of vitamin B_6 supplementation. VKM proposes to adopt the tolerable upper intake level (UL) set by the Scientific Committee for Food (SCF) in 2000 at 25 mg/day for vitamin B_6, which was based on a lowest observed adverse effect level (LOAEL) of 100 mg/day found in one randomised controlled trial. VKM recognises that there are no well-designed dose-response studies of long-term use available. However, for adults, no adverse effects have been reported at doses with vitamin B_6 up to 25 mg/day.

Dietary calculations have been performed for mean intakes and in various percentiles (P5, P25, P50, P75 and P95) in children (2-, 4- and 9-year-olds), adolescents (13-year-olds) and in adults.

To illustrate the consequences of amending the maximum limit for vitamin B_6 in food supplements to 2, 6, 8, 10, 20 or 25 mg/day in the different age groups, VKM has used the scenarios with P95 from food and added the alternative amounts of supplements. VKM has compared these scenarios with the tolerable upper intake levels set by the Scientific Committee for Food in 2000 for adults, adolescents and children. In these scenarios, the 2- and 4-year-old children will exceed the tolerable upper intake level with use of 6 mg/day or higher vitamin B_6 in supplements. The 9-year-old children will exceed the tolerable upper intake level with supplemental use of 10 mg/day. The 13-year-old adolescents will exceed the tolerable upper intake level with 20 mg/day of vitamin B_6 in supplements. Adults will

exceed the tolerable upper intake level with use of 25 mg/day of vitamin B_6/pyridoxine in supplements.

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food Safety, vitamin B_6, pyridoxine, food supplement, upper level, exposure.

Sammendrag på norsk

Vitenskapskomiteen for mattrygghet har vurdert inntak av vitamin B_6 (pyridoksin) i den norske befolkningen i relasjon til øvre tolerable inntaksnivåer (UL). Den eksisterende maksimumsgrensen for vitamin B_6 i kosttilskudd er 4,2 mg/dag. VKM har også gjort scenarioberegninger for å illustrere konsekvensene av å endre denne maksimumsgrensen til 2, 6, 8, 10, 20 eller 25 mg/dag.

Vitamin B_6 er vannløselig, og det finnes seks ulike forbindelser med vitamin B_6-aktivitet; pyridoksin (PN, en alkohol), pyridoksal (PL, et aldehyd) og pyridoksamin (PM, et amin) og fosfater av disse: pyridoksin 5'-fosfat (PNP), pyridoksal 5 'fosfat (PLP) og pyridoaksamin 5' fosfat (PMP). Alle disse seks formene av vitamin B_6 finnes i maten. I tillegg finnes en glykosylert form, pyridoksin-5'-β-δ-glukosid (PNG), i noen planter. Pyridoksin hydroklorid er den vanligste forbindelsen i kosttilskudd.

80 til 90 prosent av vitamin B_6 i kroppen finnes i muskler. Kroppens B_6-lager er beregnet til å være rundt 170 mg hos voksne, med en halveringstid på 25-33 dager. Vitamin B_6-mangel forekommer som regel i kombinasjon med mangel på andre B-vitaminer. Kliniske symptomer på vitamin B_6-mangel er anemi og nevrologiske utslag eller sykdommer (2).

Det er ikke rapportert om negative helseeffekter fra inntak av vitamin B_6 fra mat og drikke alene. Sensorisk nevropati er rapportert å være det mest følsomme utfallet av kosttilskudd med vitamin B_6. VKM foreslår å bruke det øvre tolerable inntaksnivået som er fastsatt av Scientific Committee for Food (SCF, 2000) på 25 mg/dag. Dette øvre tolerable inntaksnivået er basert på den laveste observerte dosen som har gitt negativ helseeffekt (LOAEL), i en randomisert kontrollert studie. VKM erkjenner at studien ikke er godt egnet som dose-respons studie, og ikke representerer langvarig bruk. Imidlertid har det ikke blitt rapportert om noen negative helseeffekter hos voksne mennesker ved et inntak av vitamin B_6 på opptil 25 mg/dag.

VKM har gjort inntaksberegninger av vitamin B_6 for ulike persentiler for inntak (P5, P25, P50, P75 og P95), samt gjennomsnittlig inntak hos barn (2-, 4- og 9-åringer), ungdom (13-åringer) og hos voksne menn og kvinner.

For å illustrere konsekvensene av å endre maksimumsgrensene i kosttilskudd til 2, 6, 8, 10, 20 eller 25 mg/dag for ulike aldersgrupper, har VKM tatt utgangspunkt P95-inntaket fra mat og lagt de foreslåtte mengdene fra kosttilskudd. Disse beregningene er vurdert opp mot det øvre tolerable inntaksnivået fastsatt av Scientific Committee for Food (2000) for voksne, ungdom og barn. I henhold til disse scenariene, vil vitamin B_6-inntaket hos to- og fireåringer overskride øvre tolerabelt inntaksnivå 5 mg/dag dersom tilskudd inneholder 6 mg vitamin B_6 eller mer. Niåringer vil overskride øvre tolerabelt inntaksnivå med kosttilskudd på 10 mg vitamin B_6 per dag. Trettenåringer vil overskride øvre tolerabelt inntaksnivå med tilskudd på 20 mg/dag. Voksne vil overskride øvre tolerabelt inntaksnivå med kosttilskudd på 25 mg vitamin B_6 per dag.

Abbreviations and/or glossary

Abbreviations

AI – adequate intake
AR – average requirement
bw – body weight
DRI – dietary reference intake
DRV – dietary reference value
EAR – estimated average requirement (IOM).
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
GABA – gamma-aminobutyric acid
IOM – Institute of Medicine, USA
LOAEL – lowest observed adverse effect level
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
PL – pyridoxal
PLP – pyridoxal 5'-phosphate
PM – pyridoxamine
PMP – pyridoxamine 5'-phosphate
PN – pyridoxine
PNP – pyridoxine 5'-phosphate
PRI – population reference intakes
RDA – recommended dietary allowances
RI – recommended intake
SCF – Scientific Committee for Food
SD – standard deviation
SUL – safe upper intake level
UF – uncertainty factor
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee for Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet]

Glossary

P5, P25, P50, P75 or P95-exposure is the calculated exposure at the 5, 25, 50, 75 or 95-percentile.

Percentile is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value below which 95 percent of the observations are found.

EFSA - Dietary Reference Values (DRVs) (EFSA, 2010)

Average Requirement (AR) is the level of intake of a defined group of individuals estimated to satisfy the physiological requirement of metabolic demand, as defined by a the specific criterion for adequacy for the nutrient, in half of the heathy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate.

If an AR cannot be determined then an Adequate Intake is used.

Adequate Intake (AI) is defined as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of a nutrient intake, by a group (or groups) of apparently healthy people, and therefore assumed to be adequate. The practical implication of an AI is similar to that of a population reference intake, i.e. to describe the level of intake that is considered adequate for health reasons. The terminological distinction relates to the different ways in which these values are derived and to the resultant difference in the "firmness" of the value.

Population Reference Intake (PRI) is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals. PRI is defined as the AR + 2 x SD where SD is the standard deviation of the AR.

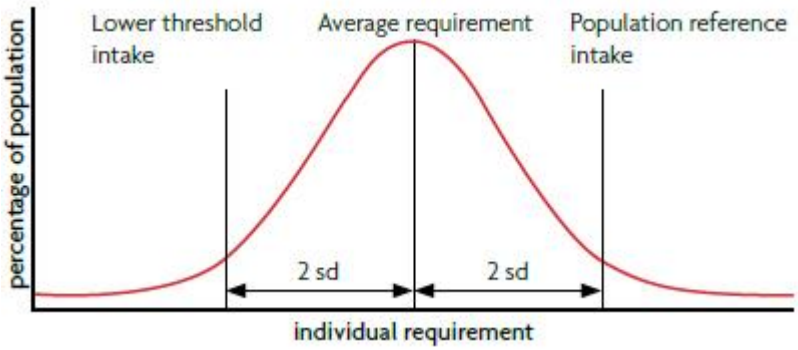

Figure 1: Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

Lower Threshold Intake (LTI) is the lowest estimate of requirement from the normal distribution curve, and is generally calculated on the basis of the AR minus twice its standard deviation (SD). This will meet the requirement of only 2.5% of the individuals in the population.

Tolerable Upper intake Level (UL) is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

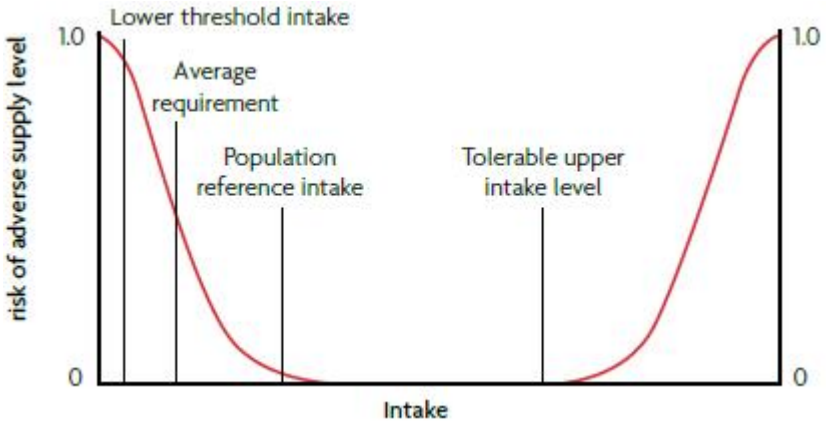

Figure 2: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake using EFSA terminology.

IOM - Dietary Reference Intakes (DRIs)(IOM, 2000)

Estimated Average Requirement (EAR) is a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a life stage and gender group.

Recommended Dietary Allowances (RDA) is the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. RDA = EAR + 2 SD_{EAR} or if insufficient data to calculate SD a factor of 1.2 is used to calculate RDA; RDA = 1.2*EAR

Adequate Intake (AI) is the recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined

Tolerable Upper Intake Level (UL) is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population.

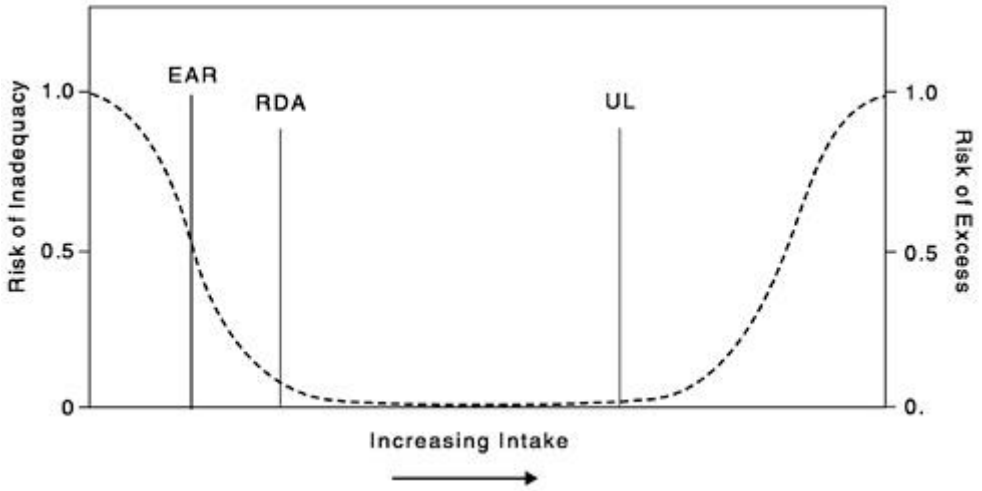

Figure 3: Dietary reference intakes using IOM terminology.

NNR -Recommended Intake (NNR Project Group, 2012)

Average Requirement (AR) is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual i.e. the level of a nutrient that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement.

$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$

Recommended Intake (RI) is defined as the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. $RI = AR + 2SD_{AR.}$

$RI_{NNR} = RDA_{IOM} = PRI_{EFSA}$

Upper Intake Level (UL) is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans.

$UL_{NNR} = UL_{IOM} = UL_{EFSA}$

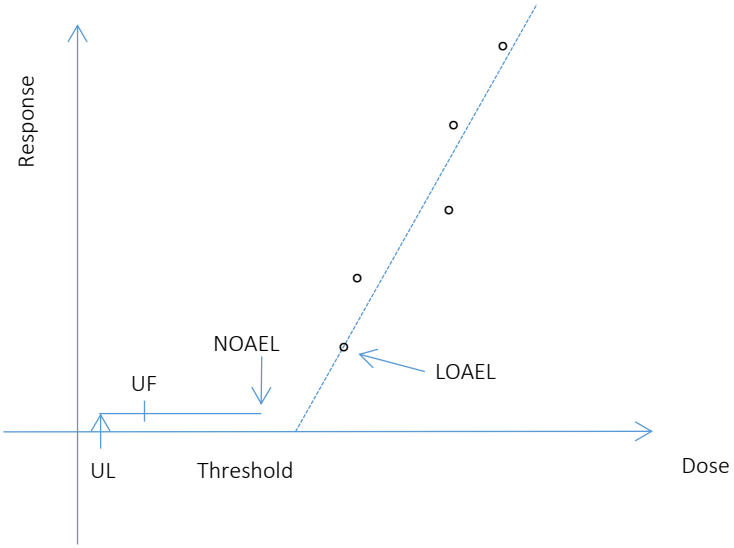

Figure 4: Derivation of Upper Intake Level (UL).

UF: Uncertainty factor

Expert group on vitamins and minerals (EVM), UK (EVM, 2003)

Safe Upper Intake Level (SUL): EVM used SUL instead of UL and defined SUL as the determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provided a framework within which the consumer could make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative.

Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented in Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Pursuant to Directive 2002/46/EC, common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU.

National maximum limits for vitamins and minerals were established in the former vitamin and mineral supplements regulation from 1986 and were continued in the 2004 regulation.

The European Commission started establishing common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

Maximum limits for levels of vitamins and minerals in food supplements shall be set on the basis of the following criteria, pursuant to article 5 in Directive 2002/46/EC:

- Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups
- Intake of vitamins and minerals from other dietary sources

When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Pending establishment of common maximums limits in the EU, the Norwegian Food Safety Authority is evaluating the national maximum limits for vitamins and minerals in food supplements.

Assessment of vitamin B_6

The Norwegian Food Safety Authority will evaluate the national maximum limits for B_6 in the food supplement regulation. The minimum and maximum limits for the content of vitamins and minerals in food supplements are listed in Annex 1 to the food supplement regulation:

Background Table: Minimum and maximum limits for vitamin B_6 in the food supplement regulation (May 2016).

	Minimum amount per recommended daily dose	**Maximum amount per recommended daily dose**
Vitamin B_6 (mg)	0.5	4.2

Permitted vitamin B_6 substances which may be used in the manufacture of food supplements are listed in "Forskrift om kosttilskudd 2012", http://www.lovdata.no/cgi-wift/ldles?doc=/sf/sf/sf-20040520-0755.html.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA, Mattilsynet) requests the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of vitamin B_6 from the diet, including fortified products, in all age groups in the population above 1 year (mean intakes, median, P5, P95).

VKM is also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for vitamin B_6 to 2, 6, 8, 10, 20 or 25 mg/day in food supplements, and to evaluate these scenarios against already established tolerable upper intake levels.

Assessment vitamin B_6

1 Introduction

Vitamin B_6 is water soluble and comprises six compounds with vitamin B_6 activity; pyridoxine (PN, an alcohol), pyridoxal (PL, an aldehyde) and pyridoxamine (PM, the amine) and their corresponding phosphates; pyridoxine 5'-phosphate (PNP), pyridoxal 5' -phosphate (PLP) and pyridoaxamin 5' –phosphate (PMP). These six forms of vitamin B_6 are all present in food in addition to the glycosylated form, pyridoxine-5'-β-δ-glucoside (PNG), in some plants. In food supplements the most common vitamin B_6 form is pyridoxine hydrochloride.

Absorption of the non-phosphorylated forms of vitamin B_6 takes place in the jejunum, mostly through passive diffusion, and it is calculated that about 95% of dietary B_6 is absorbed (EFSA, 2016). Pyridoxine hydrochloride in food supplements is absorbed to a similar extent (IOM, 1998). PNG may be hydrolysed in the gut lumen but can also be absorbed intact. The bioavailability of PNG is evaluated to be 50-60% of PN and the bioavailability of vitamin B_6 from a mixed diet is therefore estimated to 75% (EFSA, 2016; Gregory et al., 1991; Tarr et al., 1981). PN and PM are first oxidised to PL, and then rapidly phosphorylated to PLP, mainly in the liver. PLP is the main circulating form of vitamin B_6 (70-90%) and is considered the most relevant direct measure of vitamin B_6 status (Lui et al., 1985). An adequate tissue store and enzyme functionality of PLP have been suggested to be reached at a plasma concentration of 20-30 nmol/L, with below 10 nmol/L indicating vitamin B_6 deficiency (IOM, 1998; NNR Project Group, 2012). A new metabolomics analysis indicated perturbation of the metabolism of several amino acids with a plasma level < 30 nmol/L and as a consequence EFSA has used this level as an indication of vitamin B_6 deficiency (EFSA, 2016; Gregory et al., 2013). Eighty to ninety percent of vitamin B_6 in the body is found in muscles and estimated body stores amount to about 170 mg with a half-life of 25-33 days. Vitamin B_6 deficiency is mostly seen in combination with deficiency of other B vitamins. The most typical clinical symptoms of vitamin B_6 deficiency are anaemia and neurological abnormalities (EFSA, 2016).

The metabolically active coenzyme forms of vitamin B_6 are PLP and PMP. They function as coenzymes for a number of enzymes, mainly in the amino acid metabolism involving transamination, deamination, decarboxylation and desulfurisation, while others are related to one-carbon metabolism, lipid metabolism and the phosphorolytic cleavage of glycogen (in liver and muscle) to glucose 1-phosphate. Vitamin B_6 is also involved in the biosynthesis of the heme component of haemoglobin and of neurotransmitters, including serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA). Excess pyridoxine is metabolised to the inactive form 4-pyridoxic acid which is excreted in the urine.

Important sources of vitamin B_6 are meat, milk and other dairy products, beans, nuts, fish, potatoes, fruits and vegetables. In the Norwegian Food Composition Table vitamin B_6 is expressed as pyridoxine in the form of pyridoxine hydrochloride. To convert to pure

pyridoxine a factor of 0.823 is applied. In animal products vitamin B_6 is mostly found as PLP, whereas in plant products vitamin B_6 is most commonly in the form of PN, PNP and as PNG.

2 Recommendations and tolerable upper intake levels for vitamin B_6

2.1 Recommendations

Different methods have been used to establish dietary reference values for vitamin B_6; like urinary excretion of 4-pyridoxic acid, excretion of xanthurenic acid, and measurements of homocysteine concentration. Xanthurenic acid is a tryptophan metabolite, which normally is very low and requires PLP dependent enzymes, and homocysteine is dependent on vitamin B_6 and folate to be converted to methionine. Protein intake has also been used as a reference to requirements because B_6 is closely related to the amino acid metabolism (EFSA, 2016). No available method gives an exact picture of vitamin B_6 status, but plasma PLP concentration has been shown to correlate positively with both vitamin B_6 intake and PLP store in tissue and is accepted as a standard measurement of vitamin B_6 status (EFSA, 2016).

IOM (1998) used RCTs and review articles including tryptophan metabolites, homocysteine concentration and protein intake to derive at an EAR of vitamin B_6 for men. IOM sat an EAR at 1.1 mg/day and a RDA at 1.3 mg/day for men 19-50 years. For women IOM used five depletion/repletion studies and one effect study with different protein intake levels. A value of 20 nmol/L of PLP was used as the major indicator of adequacy and EAR and RDA were derived at the same magnitude as for men. For men and women 51-70 years a higher dose of vitamin B_6 is required to maintain plasma PLP concentration above 20 nmol/L. EAR for men 51-70 years was set at 1.4 mg/day and at 1.3 mg/day for women in the same age range. RDA was set to 1.7 mg/day and 1.5 mg/day for men and women 51-70 years respectively. The EAR and RDA for children and adolescents were extrapolated from adult values with standard methods. $EAR_{child} = EAR_{adult} *(weight_{child}/weight_{adult})^{0.75} *(1 + \text{growth factor})$.

The Nordic Nutritional Recommendations of 2012 (NNR) maintain the same recommendations as derived in 2004 (NNR Project Group, 2012). These recommendations are based on protein intake and an AR at 0.013 mg vitamin B_6/g protein was set for both men and women. The value is based on results from 7 depletion-repletion studies that reached a plasma PLP concentration above 20 nmol/L. RI was set at 0.015 mg vitamin B_6/g protein. The basic requirements are increased during pregnancy and lactation.

The Norwegian recommended intakes for vitamin B_6 for the different age groups are given in Table 2.1-1. The Norwegian recommendations are adopted from the Nordic Nutrition Recommendations (2012).

Table 2.1-1 Recommended intakes for vitamin B6 in Norway, both sexes.

Age, both sexes	Vitamin B_6, mg/day	
	Men	Women
1-2 years	0.4	0.4
2-5 years	0.7	0.7
6-9 years	1.0	1.0
10-13 years	1.2	1.1
14-17 years	1.6	1.3
18-30 years	1.5	1.2
31-60 years	1.5	1.2
61-74 years	1.5	1.3
≥ 75 years	1.5	1.3
Pregnant	-	1.4
Lactating	-	1.5

In an extensive opinion summarising current knowledge about vitamin B_6 requirements, EFSA published dietary reference values for vitamin B_6 in April 2016 (EFSA, 2016). The EFSA panel referred to plasma PLP > 30 nmol/L as indication of adequate vitamin B_6 status (Gregory et al., 2013). Furthermore, it is stated that the relationship between protein intake in the range observed in Europe is of no relevance for vitamin B_6 requirement. Based on the same studies as IOM in 1998 but with one additional study from 2001, EFSA derived an AR of 1.2 mg /day for women 20-30 years and 1.3 mg/day for women > 60 years. It was concluded that AR could be set to 1.3 mg/day for all women and PRI to 1.6 mg/day. The vitamin B_6 AR for men was extrapolated from the AR for women with use of allometric scaling ($AR_{men} = AR_{women} * (weight_{men}/weight_{women})^{0.75}$) arriving at an AR of 1.5 mg/day and PRI of 1.7 mg/day. The same allometric scaling as for adults was applied to derive an AR for children and adolescents, including a factor for growth similar to IOM. The PRI was derived by use of a coefficient of variance (CV) of 10% in the absence of information on variability. In pregnancy an additional 0.2 mg/day is required based on a general gestational weight gain, and during lactation 0.1 mg/day for loss through breastfeeding.

2.2 Tolerable upper intake levels

Both deficient and excessive intakes of vitamin B_6 can lead to neurological disturbances in humans. Neuropathy of the extremities was first described in women with a daily intake of 2 to 6 g of pyridoxine in attempts to alleviate premenstrual symptoms (Schaumburg et al., 1983). The pyridoxine neuropathy was shown to regress slowly and incompletely (Albin and Albers, 1990; Santoro et al., 1991). Other adverse effects reported have been dermatological lesions, photosensitivity and impaired memorisation, however, evidence for causal association with these endpoints are lacking. Sensory neuropathy with pain and numbness of the extremities has therefore been selected as the critical endpoint.

An inverse relationship between duration of intake and dose is recognised and high doses can be tolerated for short periods without adverse effects, giving studies of short duration

limited value for the purpose of risk assessment. No adverse effects have been associated with high intakes of vitamin B_6 from food sources.

Institute of Medicine (IOM, 1998), USA

IOM used long-term studies and case reports with administration of less than 1 g/day of pyridoxine hydrochloride to evaluate a UL for adults, because neurotoxicity due to higher intakes was known. No long-term human dose-response study was found and studies with single doses were used. A NOAEL of 200 mg/day of vitamin B_6 was derived from two clinical studies; in one study 70 patients with diabetic neuropathy and carpal tunnel syndrome were treated with 100 – 150 mg/day of PN for up to 5 years (Bernstein and Lobitz, 1988 cited in IOM), and in a second study 24 patients with carpal tunnel syndrome were treated with 100 to 300 mg pyridoxine (mean 200 mg/day) for 4 months (Del Tredici, 1985 cited in IOM). An uncertainty factor (UF) of 2 was used and UL was set at 100 mg/day for adults. ULs for children were derived based on body weight using allometric scaling: $UL_{child} = UL_{adult} * (weight_{child}/weight_{adult})^{0.75}$.

Table 2.2-1 Tolerable upper intake levels (UL) for vitamin B_6 for different age groups proposed by the Institute of Medicine (1998).

Age (years)	UL mg/day
1-3	30
4-8	40
9-13	60
14-18	80
Adults	100

Scientific Committee for Food (SCF, 2000), EU

Based on the same human studies as IOM, SCF however, did not set a NOAEL for vitamin B_6 but rather concluded that an intake of 100 mg/day could not be excluded as a possible effect level for sensory neuropathy development. SCF based this conclusion on a study performed by Dalton and Dalton (1987) which had been disregarded by the IOM due to too many weaknesses (Dalton and Dalton, 1987). This study referred to 172 women attending a private practice specialising in premenstrual syndrome. In a cross-sectional sample of 172 women who attended a private clinic for premenstrual syndrome, all women had serum PLP levels above 100 nmol/L, and mean PN intakes were 117 mg/day. Sixty percent of the women reported neurological symptoms. PN intake did not differ between those with symptoms and those without symptoms, but those with symptoms had been using vitamin B_6 supplements for a longer period of time (mean 2.9 vs. 1.6 years). Based on the study of Dalton and Dalton (1987) and case reports, SCF suggested 100 mg/day as a LOAEL. A composite UF comprising a factor of 2 to allow for long-term intake and another factor 2 for deficiencies in the database was applied, arriving at a UL of 25 mg/day for vitamin B_6 for adults. It was also remarked that at an intake of 25 mg/day of vitamin B_6, no adverse effects had been reported in a large number of published studies, also after long term use. No reports of adverse effects in infants born to mothers with high intakes of pyridoxine or to

breastfed infants had been reported, and 25 mg/day was considered to apply also to pregnant and lactating women. UL for children were based on ULs for adults adjusted to body weights. In 2012, NNR adopted the UL set by SCF.

Table 2.2-2 Tolerable upper intake levels UL for vitamin B_6 for different age groups proposed by the SCF (2000).

Age (years)	UL mg/day
1-3	5
4-6	7
7-10	10
11-14	20
Adults	25

Expert Group on Vitamins and Minerals, (EVM, 2003), UK

In 2003, EVM proposed a safe upper level (SUL) for vitamin B_6 at 10 mg/day. EVM disregarded all available human studies as insufficient and of poor scientific value and as inadequate for risk assessment. Instead EVM derived at a SUL based on one animal study by Phillips et al. 1978 (Phillips et al., 1978). In this subacute oral toxicity study, female beagles (dogs) received 0, 50 or 200 mg/pyridoxine hydrochloride/kg bw per day for 100-112 days (five dogs in each treatment group). No sign of toxicity was seen in the 50 mg/kg bw per day group, but loss of myelin was seen in the dorsal nerve roots. Dogs in the 200 mg/kg bw per day group showed signs of ataxia and loss of balance after 45 days.

LOAEL was set at 50 mg/kg bw per day and SUL was derived by dividing with a UF of 300 (3 for uncertainty between LOAEL and NOAEL, 10 for inter-species variation and 10 for inter-individual variation) = 50/300 =0.17 mg/kg bw/day (equivalent to 10 mg/day for a 60 kg adult).

2.2.1 Summary and discussion tolerable upper intake level

Table 2.2.1-1 summarises available upper intake levels for vitamin B_6.

Table 2.2.1-1: Upper intake levels for vitamin B_6 from IOM, SCF, EVM and NNR.

	UL/SUL mg/day	Based on	NOAEL mg/day	LOAEL	UF
IOM, 1998	100	2 human studies	200	-	2
SCF, 2000	25	1 human study		100	4
EVM, 2003	10	1 animal study		50 mg/kg bw	300
NNR, 2012	25	Acceptance of SCF´s UL		100	4

Intakes of vitamin B_6 from food sources have not been reported to cause adverse effects. The hazard identification revealed sensory neuropathy as the most sensitive adverse health

effect of vitamin B_6 supplementation. IOM used two RCTs in adult patients treated with pyridoxine for premenstrual symptoms and carpal tunnel syndrome to set a NOAEL. SCF referred to the same studies as IOM but included in addition one long-term study to set a LOAEL. EVM used a dose-response study in dogs from 1978 to set a LOAEL. In general it is stated that human data are preferable to animal studies to set ULs and animal studies should only be used when data from human studies are insufficient (EFSA, 2010). For vitamin B_6 no dose-response study in humans was identified, but several single-dose clinical studies and case reports were identified.

VKM proposes to adopt the UL set by SCF at 25 mg/day for adults for vitamin B_6, which was based on a LOAEL found in one RCT (Dalton and Dalton, 1987). VKM recognises that there are no well-designed dose-response studies in humans, still uncertainties of long-term use, and a notion that no adverse effects have been reported with use at this intake level.

3 Intakes and scenarios vitamin B_6

3.1 Short description of the Norwegian dietary surveys

The estimated intakes of vitamin B_6 presented in this opinion are based on data from the national food consumption surveys for young children (2-year-olds), children and adolescents (4-, 9- and 13-year-olds) and adults (aged 18 to 70 years). The national food consumption surveys were conducted by the Department of Nutrition, University of Oslo in collaboration with the Directorate of Health, the Norwegian Food Safety Authority and the Norwegian Institute of Public Health. Different methodologies were used in the tree different surveys and thus direct comparisons between the age groups may be misleading.

A description of the food consumption surveys and the different methodologies used is given below.

Adults: "Norkost 3" is based on two 24-hour recalls by telephone at least one month apart. Food amounts were presented in household measures or estimated from photographs (Totland et al., 2012). The study was conducted in 2010/2011, and 1787 adults (925 women and 862 men) aged 18-70 participated.

9- and 13-year-old children/adolescents: "Ungkost 3" is based on a 4-day food intake registration with a web-based food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 2016). The study was conducted in 2015 and 636 9-year-old children and 687 13-year-old adolescents participated.

4-year-old children: "Ungkost 3" is based on a 4-day food intake registration with a webbased food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 2017). The study was conducted in 2016, and 399 4-year-olds participated.

2-year-old children: "Småbarnskost 2007" is based on a semi-quantitative food frequency questionnaire. In addition to predefined household units, food amounts were also estimated from photographs. The study was conducted in 2007, and a total of 1674 2-year-olds participated (Kristiansen et al., 2009).

3.2 Dietary intakes of vitamin B_6 in the Norwegian population

Intakes of vitamin B_6 in the various age groups and in groups of users of vitamin B_6 supplements are presented in tables in Appendix 1. The tables in Appendix 1 also include calculations for P25 and P75.

Adults (n=1787)

The mean intake of vitamin B_6 from the diet alone is 1.7 mg/day (median 1.6 mg/day) in adults (n=1787). Intake of B_6 in P5 is 0.8 mg/day and in P95 is 3.0 mg/day.

In Norkost 3, 416 participants (23%) reported use of supplements containing vitamin B_6. Their mean total intake of vitamin B_6 including that from food supplements is 3.6 mg/day (median 2.9 mg/day), P5 intake is 1.7 mg/day and P95 intake is 7.4 mg/day.

Mean intake of vitamin B_6 from supplements alone in adults reporting use of supplements containing vitamin B_6 is 2.0 mg/day (median 1.2 mg/day), P5 intake is 0.4 mg/day and P95 intake is 5.3 mg/day.

13-year-olds (n=687)

The mean intake of vitamin B_6 from the diet alone is 1.2 mg/day (median 1.1 mg/day) in 13-year-olds. The P5 intake is 0.5 mg/day and the P95 intake is 2.1 mg/day.

In Ungkost 3 (13-year-olds), 158 participants (23%) reported use of supplements containing vitamin B_6. Their mean total intake of vitamin B_6 including that from food supplements is 2.1 mg/day (median 2.0 mg/day), P5 intake is 1.1 mg/day and P95 intake is 3.1 mg/day.

Mean intake of vitamin B_6 from supplements alone in 13-year-olds reporting use of supplements containing vitamin B_6 is 0.9 mg/day (median 0.9 mg/day), P5 intake is 0.3 mg/day and P95 is 1.7 mg/day

9-year-olds (n=636)

The mean intake of vitamin B_6 from the diet alone is 1.1 mg/day (median 1.0 mg/day) in 9-year-olds. The P5 intake is 0.5 mg/day and the P95 intake is 1.7 mg/day.

In Ungkost 3 (9-year-olds), 209 participants (33%) reported use of supplements containing vitamin B_6. Their mean total intake of vitamin B_6 including that from food supplements is 1.7 mg/day (median 1.6 mg/day), P5 intake is 1.0 mg/day and P95 intake is 2.5 mg/day.

Mean intake of vitamin B_6 from supplements alone in 9-year-olds reporting use of supplements containing vitamin B_6 is 0.7 mg/day (median 0.6 mg/day), P5 intake is 0.2 mg/day and P95 is 1.2 mg/day.

4-year-olds (n=399)

The mean intake of vitamin B_6 from the diet alone is 0.9 mg/day (median 0.9 mg/day) in 4-year-olds. The P5 intake is 0.5 mg/day and the P95 intake is 1.4 mg/day.

In Ungkost 3 (4-year-olds), 168 participants (42%) reported use of supplements containing vitamin B_6. Their mean total intake of vitamin B_6 including that from food supplements is 1.6 mg/day (median 1.6 mg/day), P5 intake is 1.0 mg/day and P95 intake is 2.3 mg/day.

Mean intake of vitamin B_6 from supplements alone in 4-year-olds reporting use of supplements containing vitamin B_6 is 0.9 mg/day (median 0.9 mg/day), P5 intake is 0.5 mg/day and P95 is 1.4 mg/day.

2-year-olds (n=1674)

The mean intake of vitamin B_6 from the diet alone is 0.9 mg/day (median 0.9 mg/day) in 2-year-olds. The P5 intake is 0.5 mg/day and the P95 intake is 1.4 mg/day.

In Småbarnskost 2007, 554 participants (33%) reported use of supplements containing vitamin B_6. Their mean total intake of vitamin B_6 including that from food supplements is 1.5 mg/day (median 1.4 mg/day), P5 intake is 0.8 mg/day and P95 intake is 2.3 mg/day.

Mean intake of vitamin B_6 from supplements alone in 2-year-olds reporting use of supplements containing vitamin B_6 is 0.6 mg/day (median 0.6 mg/day). P95 intake of B_6 from supplements is 1.2 mg/day.

3.3 Scenario calculations for vitamin B_6

For scenario calculations VKM used the intake groups below P5 and above P95 from food alone to calculate vitamin B_6 intake and added the suggested supplementation levels from NFSA (2, 6, 8, 10, 20 or 25 mg B_6 per day), see Tables 3.3-1 and 3.3-2.

Table 3.3-1 Calculated total B_6 intakes for various age groups in scenarios with 2, 6, 8, 10, 20 or 25 mg as supplements added to the P5 of intake from food alone (mg/day).

Age group	P5 from food	Including 2 mg from suppl	Including 6 mg from suppl	Including 8 mg from suppl	Including 10 mg from suppl	Including 20 mg from suppl	Including 25 mg from suppl
Adults	0.8	2.8	6.8	8.8	10.8	20.8	25.8
13 years	0.5	2.5	6.5	8.5	10.5	20.5	25.5
9 years	0.5	2.5	6.5	8.5	10.5	20.5	25.5
4 years	0.5	2.5	6.5	8.5	10.5	20.5	25.5
2 years	0.5	2.5	6.5	8.5	10.5	20.5	25.5

Table 3.3-2 Calculated total B_6 intakes for various age groups in scenarios with 2, 6, 8, 10, 20 or 25 mg as supplements added to the P95 of intake from food alone (mg/day).

Age group	P95 from food	Including 2 mg from suppl	Including 6 mg from suppl	Including 8 mg from suppl	Including 10 mg from suppl	Including 20 mg from suppl	Including 25 mg from suppl
Adults	3.0	5.0	9.0	11	13	23	29
13 years	2.1	4.1	8.1	10.1	12.1	22.1	27.1

Age group	P95 from food	Including 2 mg from suppl	Including 6 mg from suppl	Including 8 mg from suppl	Including 10 mg from suppl	Including 20 mg from suppl	Including 25 mg from suppl
9 years	1.7	3.7	7.7	9.7	11.7	21.7	26.7
4 years	1.4	3.4	7.4	9.4	11.4	21.4	26.4
2 years	1.4	3.4	7.4	9.4	11.4	21.4	26.4

4 Assessment of the intakes of vitamin B_6

4.1 Evaluation of intakes of vitamin B_6, including scenarios with supplementation

Dietary calculations have been performed for intake in P5, P25, mean, P50, P75 and P95 in children (2-, 4- and 9-year-olds), adolescents (13-year-olds) and in adult men and women. The dietary calculations have been performed among vitamin B_6 supplement users as well as without use of supplements.

Mean and median intakes of vitamin B_6 from diet are within the recommended intakes for all age and sex groups, except for 9- and 13-year-old girls where mean and median intakes were below RI. Only the 2-year-old children reach the recommended intake in P5 and 4-year-old children in P25. For 9- and 13-year-old girls recommended intake is reached in P75 from diet alone.

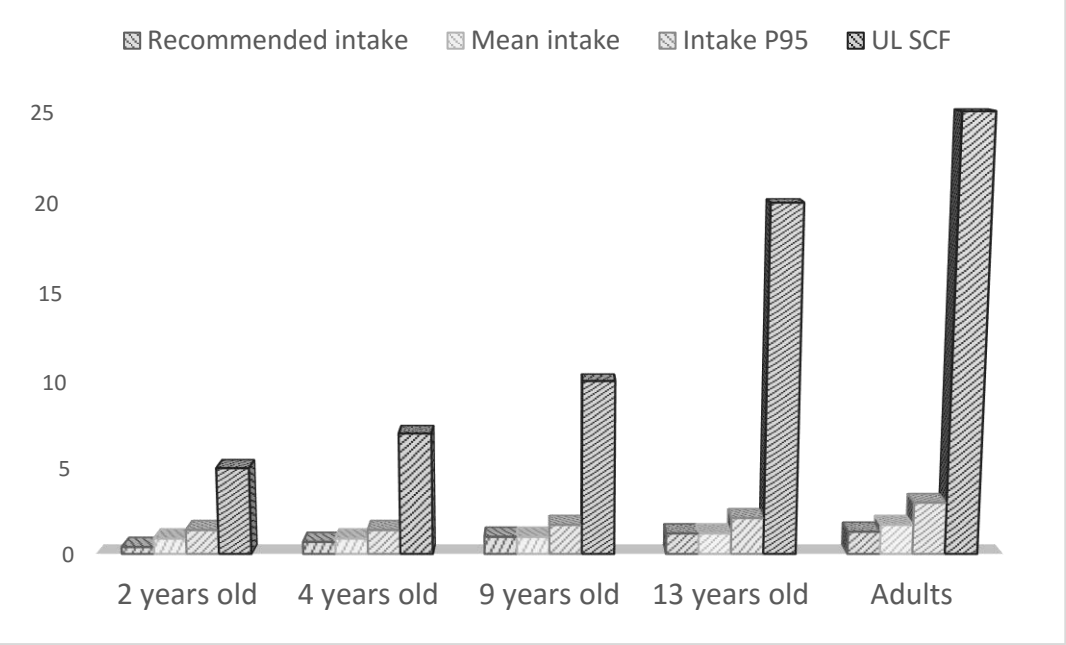

Figure 4.1-1: Recommended intake, mean intake, intake at P95 and suggested UL for vitamin B_6 in mg/day.

To illustrate the consequences of vitamin B_6 supplementation at high dietary intakes, the example doses 2, 6, 8, 10, 20 and 25 mg/day were added to the 95-percentile of vitamin B_6 intake from diet alone for each age group. As illustrated in the scenarios (Table 3.3-2), 2- and 4-year-old children with a dietary intake from food at P95 will exceed UL if

supplemented with a dose of 6 mg vitamin B_6 per day or higher. Nine-year-old children with a dietary intake from food at P95 will exceed UL if supplemented with 10 mg vitamin B_6 per day or higher, and 13-year-old adolescents with a dietary intake from food at P95 will exceed UL if supplemented with 20 mg vitamin B_6 per day or higher. Adults with a dietary intake from food at P95 will exceed UL if supplemented with 25 mg vitamin B_6 per day.

5 Uncertainties

It should be noted that the intakes have been calculated based on various dietary surveys for the different age categories and a comparison of calculations across age groups can be misleading. The calculated intakes in the higher and lower percentiles are always associated with a higher degree of uncertainty than mean or median intakes.

The percentile estimates of dietary intake are prone to random error due to the limited number of participants in the dietary surveys. The largest degree of uncertainty is present in the estimated percentiles for 4-year-olds with a sample size of n=399, corresponding to about 20 observations below the 5-percentile and above the 95-percentile, respectively.

Another issue is the validity of the estimated exposure data. Low participation rates in the national dietary surveys give rise to systematic errors and limit the representativeness of the participants compared with the background population in Norway. The participation rates among adults, 13-, 9-, 4- and 2-year-olds in the dietary surveys were 37%, 53%, 55%, 20%, and 56%, respectively. In general, those participating had a considerably higher education level than the background population, and they are expected to represent a health-conscious subgroup of the population. Some population subgroups are not covered, e.g. ethnic minorities.

For the determinations of the ULs for vitamin B_6, EFSA, IOM and EVM have not reached the same conclusions, indicating uncertainty regarding establishment of these ULs both for adults, and even more for children and adolescents. Long-term RCTs are requested by all these scientific bodies to ascertain ULs.

6 Answers to the terms of reference

The Norwegian Food Safety Authority (NFSA, Mattilsynet) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of vitamin B_6 from the diet, including fortified products, in all age groups in the population above 1 year in relation to tolerable upper intake levels (ULs).

VKM was also requested to conduct scenario estimations to illustrate the consequences of amending the existing maximum limit for vitamin B_6 (to 2, 6, 8, 10, 20 or 25 mg/day, as examples) in food supplements. The existing maximum limit for vitamin B_6 in food supplements is 4.2 mg/day.

Dietary intake calculations of vitamin B_6 have been performed for intake in the P5, P25, mean, P50, P75 and P95 in 2-, 4- and 9-year-old children, 13-year-old adolescents and among adult men and women. The dietary calculations have been performed among vitamin B_6 supplement users as well as without use of supplements.

To illustrate the consequences of supplementation with 2, 6, 8, 10, 20 or 25 mg/day in the different age groups, VKM has used the scenarios with P95 from food and added the suggested amounts of supplements. VKM has compared these scenarios with SCF's UL for adults and body weight adjusted ULs for children for exceedance. In these scenarios, the 2-, and 4-year-old children will exceed UL with use of 6 mg/day of vitamin B_6 in supplements. The 9-year-old children will exceed UL with supplemental use of 10 mg/day. The 13-year-old adolescents will exceed UL with 20 mg/day of vitamin B_6 in supplements. Adults will exceed UL with use of 25 mg/day of vitamin B_6 in supplements.

An overview of the conclusions is presented in Table 6-1.

Table 6-1 An overview of the conclusions for vitamin B_6.
Green: No exceedance of the UL.
Red: Exceedance of the UL.

Doses in supplements / Age group	2 mg/day	6 mg/day	8 mg/day	10 mg/day	20 mg/day	25 mg/day
Adults						
13 years						
9 years						
4 years						
2 years						

7 Data gaps

Long-term RCTs with vitamin B_6 that also thoroughly address adverse health effects are missing.

More age groups should be included in dietary surveys in addition to subgroups like different ethnical groups.

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Appendix I

Summary tables of the intake of vitamin B_6 for all age groups

Intakes of vitamin B_6 in the various age groups are presented in the tables below. The tables summarise intakes from the diet alone, B_6 containing supplements alone (users only) and total intakes from both diet and supplements (Tables 1-6). Intakes are also given for both genders.

Table 1 Vitamin B_6 intakes from diet alone in various age groups (mg/day).

	Adults (n=1787)	13 years (n=687)	9 years (n= 636)	4 years (n=399)	2 years (n=1674)
B6 from diet alone, mean	1.7	1.2	1.0	0.9	0.9
B6 from diet alone, median	1.6	1.1	1.0	0.9	0.9
B6 from diet alone, P5	0.8	0.5	0.5	0.5	0.5
B6 from diet alone, P25	1.2	0.8	0.8	0.8	0.7
B6 from diet alone, P75	2.1	1.4	1.2	1.1	1.0
B6 from diet alone, P95	3.0	2.1	1.7	1.4	1.4

Table 2 Vitamin B_6 supplement users intake of total B_6 from diet and supplements, and from supplements alone (users only), in various age groups (mg/day).

	Adults (n=416)	13 years (n=158)	9 years (n=209)	4 years (n=168)	2 years (n=554)
Total B6 from diet and supplements, mean	3.6	2.1	1.7	1.6	1.5
Total B6 from diet and supplements, median	2.9	2.0	1.6	1.6	1.4
Total B6 from diet and supplements, P5	1.7	1.1	1.0	1.0	0.8
Total B6 from diet and supplements, P25	2.3	1.7	1.4	1.3	1.1
Total B6 from diet and supplements, P75	3.8	2.5	2.0	1.9	1.7
Total B6 from diet and supplements, P95	7.4	3.1	2.5	2.3	2.3
B6 from supplements alone, mean	2.0	0.9	0.7	0.9	0.9
B6 from supplements alone, median	1.2	0.9	0.6	0.9	0.9
B6 from supplements alone, P5	0.4	0.3	0.2	0.5	0.5
B6 from supplements alone, P25	1.0	0.4	0.5	0.7	0.7
B6 from supplements alone, P75	2.0	1.2	0.8	1.1	1.0
B6 from supplements alone, P95	5.3	1.7	1.2	1.4	1.4

Table 3 Vitamin B_6 intakes from diet alone in various age groups, women/girls (mg/day).

	Women (n=925)	Girls 13 years (n= 355)	Girls 9 years (n= 341)
B6 from diet alone, mean	1.5	1.1	1.0
B6 from diet alone, median	1.4	1.0	0.9
B6 from diet alone, P5	0.7	0.5	0.5
B6 from diet alone, P25	1.1	0.7	0.8
B6 from diet alone, P75	1.8	1.3	1.2
B6 from diet alone, P95	2.5	1.9	1.6

Table 4 Vitamin B_6 supplement users intake of total B_6 from diet and supplements, and from supplements alone, in various age groups, women/girls (mg/day).

	Women (n=262)	Girls 13 years (n= 82)	Girls 9 years (n=125)
Total B6 from diet and supplements, mean	3.6	1.9	1.6
Total B6 from diet and supplements, median	2.8	1.9	1.6
Total B6 from diet and supplements, P5	1.6	0.9	0.8
Total B6 from diet and supplements, P25	2.1	1.6	1.3
Total B6 from diet and supplements, P75	3.7	2.2	2.0
Total B6 from diet and supplements, P95	7.3	3.1	2.6
B6 from supplements alone, mean	2.1	0.8	0.7
B6 from supplements alone, median	1.2	0.8	0.6
B6 from supplements alone, P5	0.40	0.3	0.2
B6 from supplements alone, P25	1.0	0.4	0.5
B6 from supplements alone, P75	2.0	1.1	0.9
B6 from supplements alone, P95	5.7	2.0	1.2

Table 5 Vitamin B_6 intakes from diet alone in various age groups, men/boys (mg/day).

	Men (n=862)	Boys 13 years (n= 332)	Boys 9 years (n= 295)
B6 from diet alone, mean	1.9	1.3	1.1
B6 from diet alone, median	1.8	1.2	1.0
B6 from diet alone, P5	0.92	0.6	0.6
B6 from diet alone, P25	1.4	0.9	0.8
B6 from diet alone, P75	2.3	1.5	1.3
B6 from diet alone, P95	3.3	2.2	1.8

Table 6 Vitamin B_6 supplement users intake of total B_6 from diet and supplements, and from supplements alone, in various age groups, men/boys (mg/day).

	Men (n=154)	Boys 13 years (n= 76)	Boys 9 years (n=84)
Total B6 from diet and supplements, mean	3.7	2.2	1.7
Total B6 from diet and supplements, median	3.1	2.2	1.7
Total B6 from diet and supplements, P5	1.9	1.2	1.1
Total B6 from diet and supplements, P25	2.4	1.8	1.5
Total B6 from diet and supplements, P75	4.2	2.6	2.0
Total B6 from diet and supplements, P95	7.4	3.1	2.4
B6 from supplements alone, mean	1.8	0.9	0.7
B6 from supplements alone, median	1.2	0.9	0.7
B6 from supplements alone, P5	0.50	0.3	0.2
B6 from supplements alone, P25	1.0	0.6	0.5
B6 from supplements alone, P75	2.0	1.4	0.7
B6 from supplements alone, P95	5.1	1.4	1.2