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# Assessment of intake of nicotinic acid and nicotinamide 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: 27  
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# **Assessment of intake of nicotinic acid and nicotinamide in relation to tolerable upper intake levels**

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## **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 niacin in the Norwegian population. NFSA has also requested that VKM conduct scenario calculations to illustrate the consequences of establishing separate maximum limits for nicotinic acid (1, 4, 8 or 10 mg/day) and nicotinamide (100, 500, 700 or 900 mg/day) in food supplements, by assessing these scenarios against existing tolerable upper intake levels (ULs). The current maximum limit for niacin added to food supplements is 32 mg/day, including nicotinic acid, nicotinamide and inositol hexanicotinate.

The term niacin (vitamin B<sub>3</sub>) comprises the two main water-soluble forms nicotinic acid and nicotinamide (niacinamide). The human body can get niacin from the diet or synthesise it from the essential amino acid tryptophan. Dietary intakes are expressed as milligram niacin equivalents (NEs), which correspond to 1 mg of pure niacin or 60 mg of tryptophan.

In the body, niacin primarily functions as a component of the coenzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) which are present in all cells. These coenzymes play essential roles for the functioning of a wide range of enzymes involved in the metabolism of carbohydrates, amino acids and fat. In addition to its function in coenzymes, niacin is involved in DNA repair and gene stability. Niacin has a half-life of 20-40 minutes in the human body.

Late symptoms of severe niacin deficiency (pellagra) include fatigue, headache, apathy, depression, memory loss, dementia, pigmented skin rash after sun exposure, bright red tongue, vomiting, diarrhoea, and constipation.

Flushing (burning and itching of the face, arms and chest) and stomach irritation are the main side effects of moderately high supplemental intake of nicotinic acid (>35 mg/day). Long-term use of high doses ( $\geq 3000$  mg/day) of nicotinic acid as a cholesterol-lowering drug can also be toxic to the liver. Nicotinamide, however, does not have these effects. In general, the risk of nicotinamide toxicity appears to be quite low.

VKM proposes to adopt the ULs of nicotinic acid and nicotinamide set by the Scientific Committee for Food Safety (SCF) in 2002, which are based on one human dose-response study (nicotinic acid) and several human dose-response studies (nicotinamide), respectively. Hence, the UL for supplemental nicotinic acid is suggested to 10 mg/day for adults and the UL for supplemental nicotinamide to 900 mg/day for adults. The ULs for children and adolescents have been derived on the basis of their body weights.

The ULs set for nicotinic acid and nicotinamide concern only intake from supplements since intake of nicotinic acid and nicotinamide from regular foods is considered to be without risk of negative health effects. Therefore, VKM has not conducted or evaluated scenarios with

intake from both diet and the separated new maximum limits for nicotinic acid and nicotinamide in food supplements suggested by NFSA.

Dietary calculations, however, have been performed for niacin intakes (includes both nicotinic acid and nicotinamide) in various percentiles (P5, P25, mean, P50, P75 and P95) in children (2-, 4- and 9-year-olds), adolescents (13-year-olds) and adults as background information.

Mean and median intakes of niacin from the diet alone are above or at the recommended intakes for all age groups.

Because UL for supplemental nicotinic acid is 10 mg/day for adults, none of the suggested maximum limits in food supplements (1, 4, 8, or 10 mg/day) will lead to exceedance of this UL in adults. In 13-year-olds and 9-year-olds, supplements with 8 mg nicotinic acid per day will lead to exceedance of UL, and in 4-year-olds and 2-year-olds supplementation of 4 mg nicotinic acid per day will lead to exceedance of the UL for nicotinic acid.

Because UL for supplemental nicotinamide is 900 mg/day for adults, none of the suggested maximum limits in food supplements (100, 500, 700 or 900 mg/day) will lead to exceedance of UL in adults. In 13-year-olds, supplements with 700 mg nicotinamide per day will lead to exceedance of UL. In 9-year-olds, 4-year-olds and 2-year-olds, supplementation of 500 mg nicotinamide per day will lead to exceedance of the UL for nicotinic acid.

**Key words:** VKM, risk assessment, Norwegian Scientific Committee for Food Safety, niacin, nicotinamide, nicotinic acid, food supplement, upper level, exposure.

# Sammendrag på norsk

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet vurdert inntaket av niacin i den norske befolkningen. Mattilsynet har også bedt VKM om å gjøre scenarioberegninger for å illustrere konsekvensene av å etablere separate maksimumsgrensene i kosttilskudd for nikotinsyre (på 1, 4, 8 eller 10 mg/dag) og nikotinamid (på 100, 500, 700 eller 900 mg /dag), og vurdere disse scenariene mot eksisterende tolerable øvre inntaksnivåer (UL). Dagens maksimumsgrense i kosttilskudd er kun satt for niacin, og er 32 mg/dag og inkluderer nikotinsyre, nikotinamid og inositolheksanikotinat (inositolheksaniacinat).

Niacin (vitamin B<sub>3</sub>) er vannløselig og finnes i to hovedformer; nikotinsyre og nikotinamid (niacinamid). Vi kan få i oss niacin fra kosten eller ved å syntetisere det fra den essensielle aminosyren tryptofan. Inntak av niacin fra kosten uttrykkes som niacinekvivalenter (NE), og 1 NE tilsvarer 1 mg niacin eller 60 mg tryptofan.

I kroppen inngår niacin i koenzymene NAD (nikotinamid dinukleotid) og NADP (nikotinamid dinukleotid fosfat), som finnes i alle celler og spiller avgjørende roller for funksjonen til en rekke enzymer som er involvert i metabolismen av karbohydrat, aminosyrer og fett. I tillegg til å fungere som koenzym, er niacin også involvert i reparasjon av DNA og bevaring av genetisk stabilitet. Niacin har en halveringstid på 20-40 minutter i kroppen.

Alvorlig niacin-mangel (pellagra) gir symptomer som tretthet, hodepine, apati, depresjon, hukommelsestap, demens, økt hudpigmentering etter eksponering for sollys, lys rød tunge, oppkast, diaré og forstoppelse.

Et moderat høyt inntak av nikotinsyre (>35 mg/dag) fra kosttilskudd kan gi bivirkninger som rødming (brennende kløe i ansikt, på armer og bryst), og irritabel mage. Inntak av veldig høye doser nikotinsyre (≥3000 mg/dag) over lang tid, f.eks. ved bruk av kolesterolsenkende medikamenter, kan i verste fall medføre leversvikt. Inntak av nikotinamid, har ikke vist slike effekter. Generelt har nikotinamid vist lav toksisitet.

VKM foreslår at de øvre tolerable inntaksnivåene for nikotinsyre og nikotinamid som EUs tidligere vitenskapskomité for mat (Scientific Committee for Food) fastsatte i 2002, benyttes for den norske befolkningen. Disse inntaksnivåene er basert på humanstudier hvor det er gjort dose-responsforsøk, hvorav én studie er gjort på nikotinsyre og flere på nikotinamid. På bakgrunn av disse studiene foreslår VKM at det øvre tolerable inntaksnivå for tilskudd av nikotinsyre er 10 mg/dag og for nikotinamid 900 mg/dag. Tolerable øvre inntaksnivå for barn og unge ble ekstrapolert basert på kroppsvekt.

Ettersom inntak av nikotinsyre og nikotinamid fra kosten anses å være uten risiko for negative helseeffekter, gjelder disse tolerable øvre inntaksnivåene kun for inntak av nikotinsyre og nikotinamid fra tilskudd. VKM har derfor ikke gjort scenarioberegninger som inkluderer inntak av nikotinsyre og nikotinamid fra mat.



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

Gjennomsnittet og medianen av inntak av niacin fra kosten (uten kosttilskudd) overstiger eller samsvarer med anbefalt inntak i alle aldersgrupper.

Ettersom tolerabelt øvre inntaksnivå for nikotinsyre i tilskuddsform for voksne er 10 mg/dag, vil ingen av de foreslåtte maksimumsgrensene i kosttilskudd (1, 4, 8 eller 10 mg/dag) føre til overskridelser at øvre inntaksnivået hos voksne. For 9- og 13-åringer vil kosttilskudd med 8 mg nikotinsyre/dag, og for 4- og 2-åringer vil kosttilskudd med 4 mg nikotinsyre/dag føre til overskridelse av det øvre inntaksnivået.

Ettersom tolerable øvre inntaksnivå for nikotinamid i tilskuddsform for voksne er 900 mg/dag, vil ingen av de foreslåtte maksimumsgrensene i kosttilskudd (100, 500, 700 eller 900 mg/dag) føre til overskridelser at det øvre inntaksnivået hos voksne. For 13-åringer vil kosttilskudd med 700 mg nikotinamid/dag, og for 2-, 4- og 9-åringer vil kosttilskudd med 500 mg nikotinamid/dag føre til overskridelse av det øvre inntaksnivået.

# Abbreviations and/or glossary

## Abbreviations

|       |   |
|-------|---|
| AI    | – adequate intake   |
| AR    | – average requirement   |
| bw    | – body weight   |
| CI    | – confidence interval   |
| DNA   | – deoxyribonucleic acid   |
| 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                               |
| IOM   | – Institute of Medicine, USA  |
| IU    | – international unit  |
| LOAEL | – lowest observed adverse effect level  |
| NAD   | – nicotinamide adenine dinucleotide   |
| NADH  | – reduced nicotinamide adenine dinucleotide   |
| NADP  | – nicotinamide adenine dinucleotide phosphate   |
| NADPH | – reduced nicotinamide adenine dinucleotide phosphate   |
| NE    | – niacin equivalent   |
| NFSA  | – Norwegian Food Safety Authority [ <i>Norw.</i> : Mattilsynet]                                       |
| NNR   | – Nordic Nutrition Recommendations  |
| NOAEL | – no observed adverse effect level  |
| MJ    | – mega joule  |
| PRI   | – population reference intakes  |
| RDA   | – recommended dietary allowances  |
| RI    | – recommended intake  |
| SCF   | – Scientific Committee for Food   |
| SUL   | – safe upper intake level   |
| UF    | – uncertainty factor  |
| UL    | – tolerable upper intake level  |
| VKM   | – Norwegian Scientific Committee for Food Safety [ <i>Norw.</i> : 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 term for visualising the low, medium and high occurrences of a measurement by splitting the whole distribution into one hundred equal parts. A 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 (or score) below which 95 percent of the observations are found.

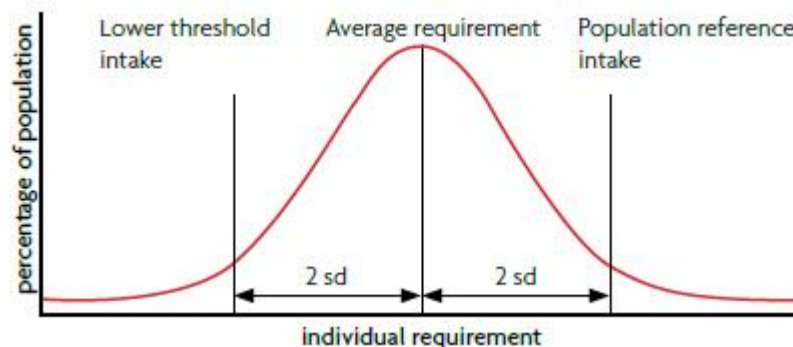
### ***EFSA - Dietary Reference Values (DRVs) (EFSA, 2010)***

**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 specific criterion for adequacy for the nutrient, in half of the healthy 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 than 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.

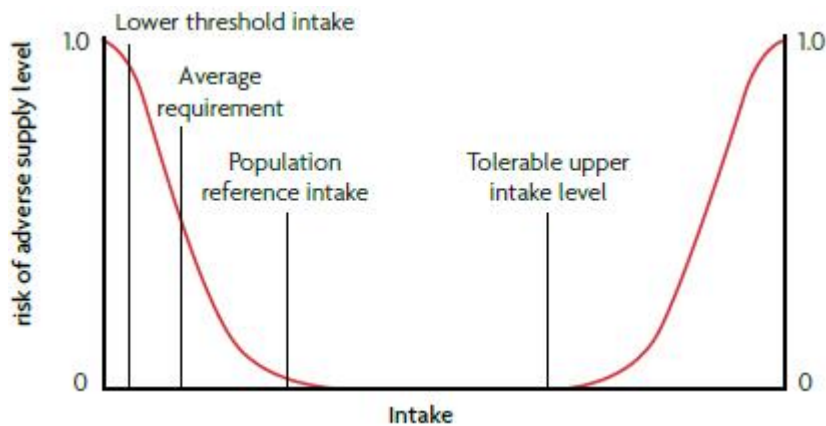
**Population Reference Intake (PRI)** is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals.



**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 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.

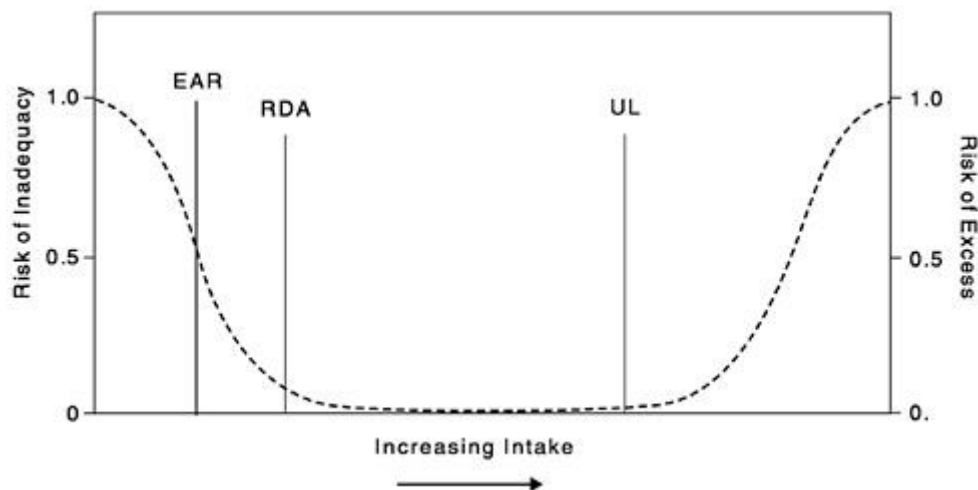
### ***IOM - Dietary Reference Intakes (DRIs) (IOM, 2000)***

**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.

***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.

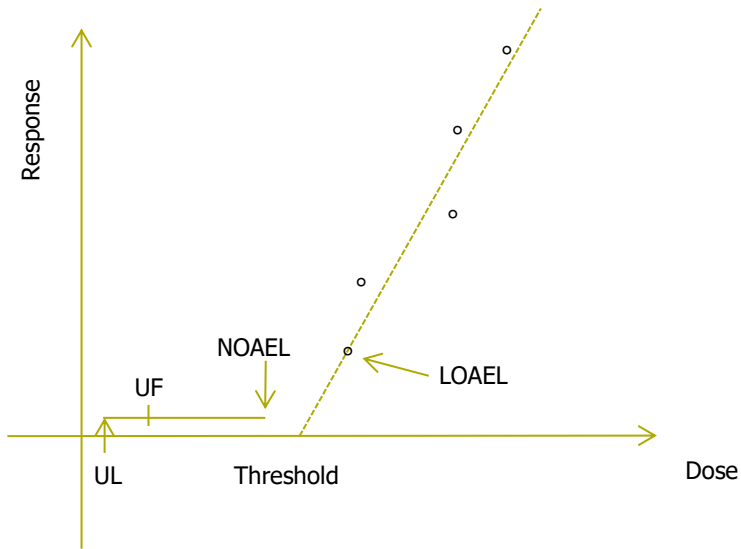
$$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$$

**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 niacin**

The Norwegian Food Safety Authority will evaluate the national maximum limits for niacin 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 niacin in the food supplement regulation (December 2016).

|                                      | <b>Minimum amount per recommended daily dose</b> | <b>Maximum amount per recommended daily dose</b> |
|--------------------------------------|--|--|
| <b>Niacin, mg niacin equivalents</b> | 4  | 32   |

Permitted niacin substances which may be used in the manufacture of food supplements are listed in "Forskrift om kosttilskudd 2012", <http://www.lovddata.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 niacin from the diet, including fortified products, in all age groups in the population above 1 year (mean intakes, median, P5, P95). Separate calculations are requested for nicotinamide and nicotinic acid.

VKM is also requested to conduct scenario calculations to illustrate the consequences of establishing separate maximum limits for nicotinic acid (1, 4, 8 or 10 mg/day) and nicotinamide (100, 500, 700 or 900 mg/day) in food supplements, and to evaluate these scenarios against existing tolerable upper intake levels (ULs).

# Assessment niacin, nicotinamide and nicotinic acid

## 1 Introduction

The term niacin comprises the two main water-soluble forms nicotinic acid (nicotinate, 3-pyridinecarboxylic acid, pyridine-beta-carboxylic acid, and niacin; molecular weight 123) and nicotinamide (3-pyridinecarboxamide, nicotinic acid amide and niacinamide; molecular weight 122).

In food, niacin is mainly present as bound forms that require hydrolysis to release the free nicotinic acid or nicotinamide prior to absorption. Nicotinic acid is mainly bound to macromolecules in plants, while nicotinamide is usually a component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) in animal tissue. Niacin may also be synthesised from the essential amino acid, tryptophan. Despite a low efficiency of this process, tryptophan, obtained both from food and from tissue protein breakdown, is considered important to the overall niacin content in the body.

Niacin-rich foods include liver, meat, and fish, mainly as NADH, NADPH (coenzymes in their reduced states), nicotinate, and nicotinamide. The outer (aleurone) layer of grains (but not the endospermium) is relatively niacin-rich, though much of this may be in the form of complexes with carbohydrates (niacytins) or peptides (niacinogens) (Kohlmeier, 2015). These niacin-containing macromolecules have low bioavailability (Carter and Carpenter, 1982). Niacin can be released from niacytin complexes, such as maize (corn) and millet, by treatment with alkali (van den Berg, 1997).

Dietary intake is expressed as milligram niacin equivalents (NEs), which correspond to 1 mg of pure niacin or 60 mg of tryptophan (the alternate precursor of NAD and NADP). The Nordic Nutrition Recommendations (NNR, 2012) has reported that the diet in the Nordic countries provides 33-43 NE/MJ.

Nicotinic acid and nicotinamide are absorbed in the small intestine by carrier-mediated facilitated diffusion. Both are transported in the plasma in free solution, but nicotinamide is the major form of niacin present in blood (Kirkland, 2014). Further, nicotinic acid and nicotinamide are taken up by most tissues by passive diffusion, except some tissues (e.g. erythrocytes, kidney, brain) which require a carrier (Gropper et al., 2009; Henderson, 1983). Nicotinamide and nicotinic acid are retained in tissues by being converted mostly to NAD and NADP in their reduced states (NADH/NADPH). These coenzymes are the most central electron carriers of cells, playing essential roles as co-substrates of more than 200 enzymes involved in the metabolism of carbohydrates, fatty acids, and amino acids. The NAD-dependent reactions are involved in intracellular respiration, whereas most of the NADP-

dependent reactions serve biosynthetic (e.g., fatty acids, sterols) functions (Combs, 2000). McCreanor and Bender (1986) have shown that even extremely high intake of nicotinamide or nicotinate will not result in greatly increased NAD production, despite the capacity for promoting NAD synthesis via the tryptophan/quinolate pathway. Regulation mechanisms of NAD production, however, is not well understood.

Long-term inadequate intake of niacin and tryptophan is associated with risk of developing pellagra. Symptoms of pellagra include fatigue, headache, apathy, depression, memory loss, dementia, pigmented skin rash after sun exposure, bright red tongue, vomiting, diarrhea, and constipation (Kohlmeier, 2015).

Flushing (burning and itching of the face, arms, and chest) and stomach irritation are the main side effects of moderately high supplemental intake of nicotinic acid (more than 35 mg/day). Long-term use of high doses ( $\geq 3000$  mg/day) of nicotinic acid as cholesterol-lowering drug, can also be too toxic to the liver (Kohlmeier, 2015). High intake of nicotinic acid may also interfere with the effects of sulfinpyrazone (Anturane) (Kohlmeier, 2015). Nicotinamide, however, does not have these adverse effects and nicotinamide toxicity in general appears to be quite low.

There are no studies suggesting any adverse effects from consumption of nicotinamide and nicotinic acid naturally occurring in foods.

# 2 Recommendations and tolerable upper intake levels

## 2.1 Recommendations

The primary method used to estimate the requirement for niacin relates intake to the urinary excretion of niacin metabolites. The requirement is expressed in niacin equivalents, allowing for some conversion of the amino acid tryptophan to niacin.

The NNR of 2012 concluded that in absence of new scientific data, the recommended intake of niacin given in NNR 2004 remained unchanged. The Norwegian recommended intakes for niacin for the different age groups, based on NNR (2012), are presented in Table 2.1-1 (Helsedirektoratet, 2014; NNR Project Group, 2012).

**Table 2.1-1** Recommended intakes (RI) for niacin in Norway, both sexes.

| Age, both sexes | NE  |       |
|-----------------|-----|-------|
|                 | Men | Women |
| 1-2 years       | 7   | 7     |
| 2-5 years       | 9   | 9     |
| 6-9 years       | 12  | 12    |
| 10-13 years     | 15  | 14    |
| 14-17 years     | 19  | 16    |
| 18-30 years     | 19  | 15    |
| 31-60 years     | 18  | 14    |
| 61-74 years     | 16  | 13    |
| >75 years       | 15  | 13    |
| Pregnant        |     | 17    |
| Lactating       |     | 20    |

In 2014, the European Food Safety Authority (EFSA) concluded that no new scientific data have become available to change the Population Reference Intake (PRI) for niacin set by SCF in 1993. Therefore, EFSA endorses the PRI at 1.6 mg NE/MJ for all population groups (EFSA, 2014).

## 2.2 Tolerable upper intake levels

### Institute of Medicine (IOM, 1998), USA

IOM (1998) stated that there was no evidence of adverse effects from the consumption of naturally occurring niacin in foods. Therefore, the identification of a tolerable upper intake level (UL) was limited to evidence concerning intake of niacin as a supplement, food fortificant, or pharmacological agent.

IOM reported that flushing, nonspecific gastrointestinal effects, hepatotoxicity, glucose intolerance and ocular effects had been identified in previous studies after niacin treatment. Flushing that results in patients deciding to change the pattern of niacin intake (i.e., reduce the amount taken at a time or withdraw from treatment) was selected as the most appropriate endpoint on which to base a UL. The report from IOM described that flushing was the adverse effect first observed after excess niacin intake and has been generally observed at lower doses than other adverse effects. In addition, the report underlined that "although nicotinamide appears not to be associated with flushing effects, a UL for nicotinic acid that is based on flushing is considered protective against potential adverse effects of nicotinamide". According to IOM, the data on hepatotoxicity was considered less relevant to the general population because they involved large doses taken for long periods of time for the treatment of a medical condition.

The data sets that were used to identify the lowest-observed-adverse-effect level (LOAEL) for niacin included anecdotal reports and clinical trials involving oral intake of niacin by healthy individuals. Studies involving parenteral administration were not considered in the dose-response assessment. Furthermore, studies involving immediate-release forms of niacin were considered more relevant to niacin intake by the general population than were studies involving sustained-release forms.

The IOM-report stated that the data were not adequate to identify a no-observed-adverse-effect level (NOAEL) for flushing. On the other hand, flushing reactions which resulted in a patient either changing the form or amount of niacin used or withdrawing from treatment were considered relevant for identification of a LOAEL.

IOM used a study by Sebrell and Butler (1938) to set a LOAEL of 50 mg nicotinic acid per day and deriving a UL because it provided the lowest effect level. In that study, four out of six persons experienced a flushing sensation after oral intake of 50 mg/day of nicotinic acid given with meals for 92 days. In one of the four subjects who experienced flushing effects, the daily dose of 50 mg was given as 25 mg in the morning and evening. Although this study also reported a flushing reaction in one of six subjects taking 30 mg of nicotinic acid daily on day 32 of intake, this reaction was not bothersome enough to change the dosing pattern.

In addition, IOM described that a study by Spies et al. (1938) provided supportive evidence for a LOAEL of 50 mg/day. In this study, five of 100 individuals (5%) experienced flushing

after a single oral dose of 50 mg of nicotinic acid, 50 individuals (50%) experienced flushing after 100 mg, and all individuals experienced flushing after 500 mg.

A case report was also mentioned, which showed that 14 of 69 persons (20%) experienced onset of rash, itching, and a sensation of warmth about 30 minutes after consuming one or more pumpernickel bagels to which niacin had been inadvertently added from an improperly labelled container (CDC, 1983 cited in IOM, 1998). The bagels were found to contain an average of 190 mg of nicotinic acid.

Due to the transient nature of the flushing effect, a small uncertainty factor (UF) of 1.5 was selected. IOM stated that a smaller UF was not appropriate because it is applied to a LOAEL rather than a NOAEL.

Thus, a LOAEL of 50 mg/day was divided by a UF of 1.5 to obtain the UL for adults of 35 mg/day, a rounded estimate.

The IOM report did not identify any data suggesting that other life stage groups have increased susceptibility to flushing effects from excess niacin intake. Therefore, the UL of 35 mg/day was also considered to apply for pregnant and lactating adult women. For children aged 1 year and older and adolescents up to age 18 years, the UL identified for adults (of 35 mg/day) was adjusted on the basis of relative body weights. The UL was judged not determinable for infants because of a lack of data on adverse effects in this age group and concern about the infant's ability to handle excess amounts. In order to prevent a high intake of niacin, IOM (1998) recommended that the only source of intake for infants should be from food.

**Table 2.2-1** Tolerable upper intake levels for niacin in different age groups adjusted by body weight suggested by the IOM (1998).

| <b>Age (years)</b> | <b>UL mg/day</b> |
|--------------------|------------------|
| 1-3                | 10               |
| 4-8                | 15               |
| 9-13               | 20               |
| 14-18              | 30               |
| 19 and older       | 35               |
| Pregnancy          | 35               |
| Lactation          | 35               |

### **Scientific Committee for Food (SCF, 2002), EU**

According to SCF (2002), the only reports of adverse effects associated with the ingestion of niacin with food have occurred following the addition of free nicotinic acid to food prior to consumption. Thus, the report from SCF (2002) has underlined that all of the available data on hazard identification and characterisation relate to studies following the administration of either nicotinic acid or nicotinamide. The SCF developed separate ULs for nicotinic acid and nicotinamide due to the difference in adverse effect profiles.

#### ***Nicotinic acid***

According to SCF, the adverse effects associated with excessive intakes of nicotinic acid included flushing, gastrointestinal effects such as dyspepsia, diarrhoea and constipation, hepatotoxicity, glucose intolerance in addition to some other rare effects (e.g. blurred vision, macular oedema and increased plasma homocysteine concentrations). Further, SCF has described that the limiting adverse effect at lower doses is flushing, whereas the most severe and potentially life-threatening adverse effects, such as hepatotoxicity, occur principally at much higher doses of nicotinic acid (higher than 500 mg/day). Although flushing might be considered a minor health effect, it was used as the basis for setting the UL for nicotinic acid due to concerns about the risk of transient hypotensive episodes, especially in the elderly.

In line with IOM (1998), the report from SCF refers to the studies conducted by Sebrell and Butler (1938) and Spies et al. (1938) for derivation of a tolerable upper intake level of nicotinic acid. As previously mentioned, Spies et al. (1938) reported only 5% incidence of flushing after a single oral dose of 50 mg nicotinic acid and a 50% incidence at 100 mg. The uncontrolled study by Sebrell and Butler (1938), in which groups of six subjects were given 10, 30 or 50 mg nicotinic acid daily for 92 days, reported flushing intermittently in 0, 2 and 4 individuals, respectively.

Although SCF (2002) underlined that flushing would be unlikely to occur repeatedly in subjects given less than 50 mg/day, the study by Sebrell and Butler (1938) which showed

occasional flushing at 30 mg nicotinic acid per day (LOAEL) was used to establish a UL. An uncertainty factor of 3 was used to allow for the fact that a slight effect was reported, and that the study was performed in a small number of subjects, but taken into account the steep dose-response relationship. Thus, the UL for nicotinic acid was established at 10 mg/day.

According to SCF, this UL is 300-fold below the dose frequently used clinically for the treatment of hypercholesterolaemia (3 g/day) and which is associated with a high incidence of serious adverse reactions.

Finally, SCF (2002) states that the UL of 10 mg/day for free nicotinic acid is not applicable during pregnancy or lactation because of inadequate data relating to this critical life stage. The upper levels for intake by children and adolescents was derived on the basis of their body weights.

**Table 2.2-2** Tolerable upper intake levels for nicotinic acid in different age groups adjusted for body weight suggested by the SCF (2002).

| Age (years) | UL mg/day |
|-------------|-----------|
| 1-3         | 2         |
| 4-6         | 3         |
| 7-10        | 4         |
| 11-14       | 6         |
| 15-17       | 8         |
| Adults      | 10*       |

\* Not applicable during pregnancy and lactation.

### ***Nicotinamide***

The report from SCF (2002) stated that nicotinamide does not produce the flushing response that has been used as the basis for the UL for nicotinic acid and that gastrointestinal effects following high-dose treatment with nicotinamide are rare. Only one reported case of hepatotoxicity in a patient receiving high-dose nicotinamide was identified. SCF underlined, however, that no significant adverse effects have been reported in trials investigating possible benefits of nicotinamide in patients with or at risk of diabetes, which have used doses up to the equivalent of 3 g per day, for periods up to 3 years (Mendola et al, 1989; Chase et al, 1990; Vague et al, 1987; IMDIAB III trial; DENIS trial all cited in SCF, 2002).

Based on these latter mentioned studies, a NOAEL for nicotinamide was set to 25 mg/kg bw/day. SCF argued that this value represented the lowest reported dose in a number of trials of high quality, many of which used sensitive markers of hepatic function and glucose homeostasis, and included a range of age groups, with some subjects treated with up to 50 mg/kg bw/day.

An uncertainty factor of 2 was used to allow for the fact that adults may eliminate nicotinamide more slowly than the study groups, many of which were children, and that data



for children would not reflect the full extent of inter-subject variability that could occur in an older population.

Thus, the UL for nicotinamide was established at 12.5 mg/kg bw/day or approximately 900 mg/day for adults.

According to the SCF report, the UL of 900 mg/day for nicotinamide is not applicable during pregnancy or lactation because of inadequate data relating to this critical life stage. The ULs for children and adolescents were derived on the basis of their body weights.

**Table 2.2-3** Tolerable upper intake levels for nicotinamide in different age groups adjusted for body weights suggested by the SCF (2002).

| Age (years) | UL mg/day |
|-------------|-----------|
| 1-3         | 150       |
| 4-6         | 220       |
| 7-10        | 350       |
| 11-14       | 500       |
| 15-17       | 700       |
| Adults      | 900*      |

\* Not applicable during pregnancy and lactation.

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

Although the report from EVM (2003) concluded that there were insufficient data from human or animal studies to establish a Safe Upper Level, the report present guidance levels for nicotinic acid and nicotinamide, respectively.

#### ***Nicotinic acid***

In line with IOM and SCF, EVM has also acknowledged adverse effects from the use of large doses of nicotinic acid in the treatment of hypercholesterolemia, including flushing, skin itching, nausea, vomiting and gastrointestinal disturbance. At higher intakes of nicotinic acid over long period of time, liver dysfunction has been reported. According to EVM, other adverse effects which has been identified includes hyperglycaemia and adverse ophthalmological effects such as blurred vision and cystoid macular oedema.

For risk assessment of nicotinic acid, EVM has, in line with the previously mentioned reports, referred to the studies conducted by Spies et al. (1938) and Sebrell and Butler (1938). In addition, EVM has referred to case reports and controlled clinical trials, in which doses of approximately 3000 mg/day nicotinic acid have apparently caused hepatotoxic effects (the Coronary Drug Project, 1975; Knopp et al., 1985; Fraunfelder et al., 1995, all cited in EVM, 2003). The randomised double-blind Coronary Drug Project was especially emphasised, in which one third or more of 1119 patients who received 3000 mg nicotinic acid/day for up to 5 years were reported to have elevated levels of liver enzymes. Elevations in serum uric acid levels and an increased incidence of gout were also reported.

In line with other reports, the two studies by Spies et al. (1938) and Sebrell and Butler (1938), were used as the basis for setting the upper level for nicotinic acid. Thus, 50 mg nicotinic acid per day was set as a LOAEL and an uncertainty factor of 3 was applied to extrapolate to a NOAEL, which resulted in a guidance level for supplementation only of 17 mg/day (50/3). EVM emphasised that this guidance level was given for supplements only, as free nicotinic acid levels in food are low and adverse effects appear to be related to acute, bolus intakes of nicotinic acid, rather than more sustained exposure as would occur with ingestion of nicotinic acid via food.

EVM has also emphasised that their guidance level was based on intakes of conventional formulations of nicotinic acid and, therefore, would not be applicable to sustained release preparations which is thought to be more hepatotoxic. Nicotinic acid contained in food supplements, however, is not in the sustained release form.

### ***Nicotinamide***

In line with other reports, EVM (2003) emphasised that few data were available on the safety of nicotinamide, but the occurrence of nicotinamide toxicity appeared to be quite low.

According to EVM, studies have shown that doses up to 3000 mg/day for periods up to 3 years seem to be well tolerated, but most of these trials have studied only one dose level and included only a small number of participants (Vague et al., 1987; Mendola et al., 1989; Chase et al., 1990; Pozzilli et al., 1995; Lampeter et al., 1998 all cited in EVM, 2003). Two of these studies were used as a basis for establishing guidance level of nicotinamide; a study conducted by Pozzilli et al. (1995) and Lampeter et al. (1998). Results from these studies showed that doses of 25 and 42 mg/kg bw/day did not affect biochemical parameters such as liver and kidney function tests in small groups of Type 1 diabetics (or those at high risk of developing the condition).

Due to methodological limitations of these studies and to account for inter-individual variability because of the nature of the study population, EVM used an uncertainty factor of 3.

Thus, a guidance value, for supplementation of nicotinamide only, was established at 8.3 mg/kg bw/day (25/3), or approximately 500 mg supplemental nicotinamide per day for 60 kg adults.

Due to lack of data on the safety of nicotinamide in pregnancy, EVM has emphasised that these guidance values do not apply to pregnant women.

### **Nordic Nutrition Recommendations (NNR, 2012)**

NNR (2012) has described that there were no studies indicating adverse effects of consumption of naturally occurring niacin in foods. In line with other reports, NNR emphasize that intakes of nicotinic acid, but not nicotinamide, as a supplement or fortificant in the

range of 30 mg/day to 1000 mg/day can result in mild symptoms such as flushing. Higher intakes have been reported to induce liver damage.

NNR (2012) supported the ULs set by SCF in 2002.

## 2.2.1 Summary of tolerable upper intake levels

Table 2.2.1-1 summarises available tolerable upper intake levels or guidance levels for nicotinic acid and nicotinamide in adults.

**Table 2.2.1-1** Overview of ULs or guidance levels in adults set by various authorities.

|              | UL/SUL<br>mg/day                 | Substance      | Critical<br>endpoint                              | Based on   | NOAEL<br>mg/kg<br>bw/day | LOAEL<br>mg/day | UF  |
|--------------|----------------------------------|----------------|---|--|--------------------------|-----------------|-----|
| IOM,<br>1998 | 35                               | Nicotinic acid | Flushing  | Key study: Sebrell and Butler (1938)<br>Supportive: Spies et al. (1938) and case reports   | -                        | 50              | 1.5 |
| SCF,<br>2002 | 10                               | Nicotinic acid | Flushing  | Key study: Sebrell and Butler (1938)   | -                        | 30              | 3   |
|              | 900<br>(12.5<br>mg/kg<br>bw/day) | Nicotinamide   | Hepatic<br>function and<br>glucose<br>homeostasis | Several trials on the possible benefits of nicotinamide in patients with or at risk of diabetes, which have used doses up to the equivalent of 3 g per day, for periods up to 3 years. | 25                       | -               | 2   |
| EVM,<br>2003 | 17*<br>(0.28<br>mg/kg<br>bw/day) | Nicotinic acid | Flushing  | Key study: Sebrell and Butler (1938)<br>Supportive: Spies et al. (1938) and case reports   | -                        | 50              | 3   |
|              | 500*<br>(8.3<br>mg/kg<br>bw/day) | Nicotinamide   | Hepatic<br>function and<br>glucose<br>homeostasis | Key studies: Pozzilli et al. (1995) and Lampeter et al. (1998)   | 25                       | -               | 3   |
| NNR,<br>2012 | 10                               | Nicotinic acid |   | SCF, 2002  |                          |                 |     |
|              | 900                              | Nicotinamide   |   | SCF, 2002  |                          |                 |     |

\*Guidance levels, not sufficient data to establish SUL

Intake of niacin (either as nicotinic acid or as nicotinamide) from food sources has not been reported to cause adverse effects. The hazard identification revealed flushing as the most sensitive adverse health effect of nicotinic acid from supplements. Furthermore, gastrointestinal effects such as dyspepsia, diarrhoea and constipation, hepatotoxicity,

glucose intolerance in addition to some other rare effects (e.g. blurred vision, macular oedema and increased plasma homocysteine concentrations) has been reported.

Nicotinamide, however, does not have these effects. In general, nicotinamide toxicity seems to be quite low; only one reported case of hepatotoxicity in a patient receiving high-dose nicotinamide was identified and no significant adverse effects were reported in trials on the possible benefits of nicotinamide in patients with or at risk of diabetes, which have used doses up to the equivalent of 3 g per day, for periods up to 3 years (Mendola et al, 1989; Chase et al, 1990; Vague et al, 1987; IMDIAB III trial; DENIS trial all cited in EVM, 2003).

VKM proposes to adopt the tolerable upper intake levels of nicotinic acid and nicotinamide set by the SCF in 2002, which are based on one human dose-response study (nicotinic acid) and several human dose-response studies (nicotinamide), respectively. Hence, the UL for supplemental nicotinic acid is suggested to 10 mg/day for adults and the UL for supplemental nicotinamide to 900 mg/day for adults. The ULs for intake by children and adolescents have been derived on the basis of their body weights.

Although SCF (2002), IOM (1998) and EVM (2003) have used the same dose-response study (Sebrell and Butler, 1938) as the main basis for setting the UL for supplemental nicotinic acid, they have not reached the same conclusions. In line with SCF, VKM has acknowledged that 2 out of 6 individuals reported flushing symptoms at daily doses of 30 mg nicotinic acid for 92 days in the study by Sebrell and Butler (1938), and that this is considered a LOAEL. Although flushing has been considered a minor health effect, it was used as the basis for setting the UL for nicotinic acid due to concerns about possible transient hypotensive episodes, especially in the elderly. VKM also support the use of an uncertainty factor of 3 due to the limited number of studies which have included only a small number of participants. IOM (1998) did not establish separate UL for nicotinamide. EVM (2003) and SCF (2002) have based their upper levels for nicotinamide on the same NOAEL, but SCF applied a lower uncertainty factor (2) than EVM (3). VKM supports the UL for nicotinamide from SCF (2002) as in general, the risk of nicotinamide toxicity appears to be quite low.

The tolerable upper intake levels set for nicotinic acid and nicotinamide concern only intake from supplements and fortification. There are no studies suggesting any adverse effects from consumption of nicotinamide and nicotinic acid naturally occurring in foods.

Therefore, VKM has not conducted or evaluated scenarios with intake from both diet and the separated new maximum limits for nicotinic acid and nicotinamide in food supplements suggested by NFSA.

# 3 Assessment of dietary intakes of niacin

## 3.1 Short description of the Norwegian dietary surveys

The estimated intakes of niacin presented in this opinion are based on data from the national food consumption surveys in young children (2-year-olds), children and adolescents (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 and the Norwegian Food Safety Authority. Different methodologies were used in the three 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 2003" 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., 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 2003" 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 niacin in the Norwegian population

Intake of niacin in the various age groups and in groups of users of niacin supplements are presented in tables in Appendix 1. Separate values for nicotinic acid and nicotinamide is not

available in the Norwegian Food Database. The tables in Appendix 1 also include estimates for P25 and P75.

## **Adults**

The mean intake of niacin from the diet alone is 22.2 mg/day (median 20.5 mg/day) in adults (n=1787). The P5 intake is 9.3 mg/day and the P95 intake is 41.4 mg/day.

In Norkost 3, 394 participants (22%) reported use of niacin-containing supplements. Their mean total intake of niacin including that from food supplements is 34.3 mg/day (median 30.8 mg/day), P5 intake is 17.7 mg/day and P95 intake is 60.1 mg/day.

Mean intake of niacin from supplements alone in adults reporting use of niacin-containing supplements is 13.5 mg/day (median 9.0 mg/day), P5 intake is 4.0 mg/day and P95 intake is 32.8 mg/day.

## **In 13-year-olds (n=687)**

The mean intake of niacin from the diet alone is 15.3 mg/day (median 14.2 mg/day) in 13-year-olds. The P5 intake is 7.2 mg/day and the P95 intake is 27.6 mg/day.

In Ungkost 3, 156 13-year-olds (23%) reported use of niacin-containing supplements. Their mean total intake of niacin including that from food supplements is 26.0 mg/day (median 25.0 mg/day), P5 intake is 12.8 mg/day and P95 intake is 41.2 mg/day.

Mean intake of niacin from supplements alone in 13-year-olds reporting use of niacin-containing supplements is 16.4 mg/day (median 15.8 mg/day), P5 intake is 7.4 mg/day and P95 intake is 30.9 mg/day.

## **In 9-year-olds (n=636)**

The mean intake of niacin from the diet alone is 12.9 mg/day (median 11.9 mg/day) in 9-year-olds. The P5 intake is 6.6 mg/day and the P95 intake is 22.3 mg/day.

In Ungkost 3, 209 9-year-olds (33%) reported use of niacin-containing supplements. Their mean total intake of niacin including that from food supplements is 19.5 mg/day (median 19.3 mg/day), P5 intake is 11.5 mg/day and P95 intake is 28.1 mg/day.

Mean intake of niacin from supplements alone in 9-year-olds reporting use of niacin-containing supplements is 7.1 mg/day (median 6.0 mg/day), P5 intake is 2.0 mg/day and P95 intake is 12.0 mg/day.

### **In 4-year-olds (n=399)**

The mean intake of niacin from the diet alone is 9.8 mg/day (median 9.4 mg/day) in 4-year-olds. The P5 intake is 5.3 mg/day and the P95 intake is 15.0 mg/day.

In Ungkost 3, 166 4-year-olds (39%) reported use of niacin-containing supplements. Their mean total intake of niacin including that from food supplements is 16.7 mg/day (median 16.4 mg/day), P5 intake is 10.2 mg/day and P95 intake is 25.1 mg/day.

Mean intake of niacin from supplements alone in 4-year-olds reporting use of niacin-containing supplements is 9.5 mg/day (median 9.1 mg/day), P5 intake is 4.8 mg/day and P95 intake is 14.9 mg/day.

### **In 2-year-olds (n=1674)**

The mean intake of niacin from the diet alone is 9.1 mg/day (median 8.7 mg/day) in 2-year-olds. The P5 intake is 4.9 mg/day and the P95 intake is 14.8 mg/day.

In Småbarnskost 2007, 554 2-year-olds (33%) reported use of niacin-containing supplements. Their mean total intake of niacin including that from food supplements is 21.4 mg/day (median 20.6 mg/day). The P5 intake is 5 mg/day and the P95 intake is 24 mg/day.

Mean intake of niacin from supplements alone in 2-year-olds reporting use of niacin-containing supplements is 9.0 mg/day (median 8.6 mg/day). P5 intake is 4.9 mg/day and P95 intake is 14.7 mg/day.

## **3.3 Assessment of the intakes of niacin**

Intake of niacin from foods has only been evaluated in relation to recommended intakes as the ULs only apply for food supplements and fortification agents. Dietary calculations for niacin have been performed for intake in P5, P25, mean, P50, P75 and P95 in children (2- and 9-year-olds), adolescents (13-year-olds) and in adults. Niacin intake from fortified products is not included in the calculations, but are however, evaluated to be low.

Mean and median intakes of niacin from the diet alone (which includes both nicotinic acid and nicotinamide) are above or at the recommended intakes for all age groups.

As described earlier, present maximum limits in food supplements is given for niacin only, and includes nicotinic acid, nicotinamide and inositol hexanicotinate. If we assume that all niacin in food supplements is present as nicotinic acid, all age groups have intakes from supplements alone above the ULs (mean, median and P95). Even in P5 the intakes in 2- and 9-year-olds are above the ULs.

## 4 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.

Thus, the percentile estimates of dietary intake are prone to random error due to the limited number of participants in the dietary surveys. The degree of uncertainty is largest 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 that low participation limits the representativeness of the participants compared with the general background population in Norway. The participation among 13-, 9- and 4-year-olds in the dietary surveys were 53%, 55% and only 20%, respectively, while they were 37% in adults and 56% in 2-year-olds. In general, participants had considerably higher education level than the background population, and 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 nicotinic acid and nicotinamide, IOM, SCF 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.

The terms of reference have been to assess the intake in Norway in relation to already established tolerable upper intake levels which were established between 2000 and 2012. No literature search has been conducted for this VKM assessment and relevant recent evidence may accordingly not have been included.



## 5 Answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the intake of niacin from the diet, 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 calculations to illustrate the consequences of establishing separate maximum limits for nicotinic acid (1, 4, 8 or 10 mg/day) and nicotinamide (100, 500, 700 or 900 mg/day) in food supplements, and to evaluate these scenarios against existing tolerable upper intake levels (ULs). The previous maximum limit for niacin was 32 mg/day, including nicotinic acid, nicotinamide and inositol hexanicotinate.

Dietary calculations have been performed for niacin intake in the P5, P25, mean, P50, P75 and P95 in children (2- and 9-year-olds), adolescents (13-year-olds) and among adults. Mean and median intakes of niacin from diet alone are above or at the recommended intakes for all age groups.

The ULs set for the two main forms of niacin; nicotinic acid and nicotinamide concern only intakes from supplements, since intake of niacin from regular foods is considered to be without risk of negative health effects. Therefore, VKM has not conducted or evaluated scenarios with intake from both diet and the separated new maximum limits for nicotinic acid and nicotinamide in food supplements suggested by NFSA. As a result, the tolerable upper intake levels for nicotinic acid and nicotinamide for the various age groups equals the amounts that can be tolerated in food supplements and in fortified products. Niacin intake from fortified products is not included in the calculations, but are however, evaluated to be low.

VKM proposes to adopt the UL for supplemental nicotinic acid and nicotinamide set by the Scientific Committee for Food Safety (SCF) in 2002, which are suggested to 10 mg/day and 900 mg/day, respectively, for adults. The ULs for intake by children and adolescents have been derived on the basis of their body weights.

Because tolerable upper intake level for supplemental nicotinic acid is 10 mg/day for adults, none of the suggested maximum limits in food supplements (1, 4, 8, or 10 mg/day) will lead to exceedance of this tolerable upper intake level in adults. In 13-year-olds and 9-year-olds, supplements with 8 mg nicotinic acid per day, and in 4-year-olds and 2-year-olds, supplementation of 4 mg nicotinic acid per day will lead to exceedance of the tolerable upper intake level of nicotinic acid. An overview of the conclusions is presented in Table 5-1.

**Table 5-1** An overview of the conclusions for nicotinic acid according to doses in supplements.

| <b>Doses in supplements</b> | <b>1 mg/day</b> | <b>4 mg/day</b> | <b>8 mg/day</b> | <b>10 mg/day</b> |
|-----------------------------|-----------------|-----------------|-----------------|------------------|
| <b>Age group</b>            |                 |                 |                 |                  |
| <b>Adults</b>               | Green           | Green           | Green           | Green            |
| <b>13 years</b>             | Green           | Green           | Red             | Red              |
| <b>9 years</b>              | Green           | Green           | Red             | Red              |
| <b>4 years</b>              | Green           | Red             | Red             | Red              |
| <b>2 years</b>              | Green           | Red             | Red             | Red              |

Green: No exceedance of the UL  
 Red: Exceedance of the UL

Further, because tolerable upper intake level for supplemental nicotinamide is 900 mg/day for adults, none of the suggested maximum limits in food supplements (100, 500, 700 or 900 mg/day) will lead to exceedance of this tolerable upper intake level in adults. In 13-year-olds, supplements with 700 mg nicotinamide per day, and in 9-year-olds, 4-year-olds and 2-year-olds, supplementation of 500 mg nicotinamide per day will lead to exceedance of the tolerable upper intake level of nicotinic acid. An overview of the conclusions is presented in Table 5-2.

**Table 5-2** An overview of the conclusions for nicotinamide according to doses in supplements.

| <b>Doses in supplements</b> | <b>100 mg/day</b> | <b>500 mg/day</b> | <b>700 mg/day</b> | <b>900 mg/day</b> |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| <b>Age group</b>            |                   |                   |                   |                   |
| <b>Adults</b>               | Green             | Green             | Green             | Green             |
| <b>13 years</b>             | Green             | Green             | Red               | Red               |
| <b>9 years</b>              | Green             | Red               | Red               | Red               |
| <b>4 years</b>              | Green             | Red               | Red               | Red               |
| <b>2 years</b>              | Green             | Red               | Red               | Red               |

Green: No exceedance of the UL  
 Red: Exceedance of the UL

## 6 Data gaps

There is a lack of long-term well-designed studies with a high number of participants that specifically examine possible adverse health effects of nicotinic acid and nicotinamide, respectively.

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 niacin intake for all age groups

Intakes of niacin in the various age groups are presented in the tables below. The tables summarise intakes from the diet alone, niacin-containing supplements alone (users only) and total intakes from both diet and supplements (Tables 1 and 2).

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

|                                       | Adults<br>(n=1787) | 13 years<br>(n= 687) | 9 years<br>(n=636) | 4 years<br>(n=399) | 2 years<br>(n=1674) |
|---------------------------------------|--------------------|----------------------|--------------------|--------------------|---------------------|
| <b>Niacin from diet alone, mean</b>   | 22.2               | 15.3                 | 12.9               | 9.8                | 9.1                 |
| <b>Niacin from diet alone, median</b> | 20.5               | 14.2                 | 11.9               | 9.4                | 8.7                 |
| <b>Niacin from diet alone, P5</b>     | 9.3                | 7.2                  | 6.6                | 5.3                | 4.9                 |
| <b>Niacin from diet alone, P25</b>    | 15.0               | 10.4                 | 9.6                | 7.6                | 7.0                 |
| <b>Niacin from diet alone, P75</b>    | 26.7               | 18.6                 | 15.1               | 11.6               | 10.8                |
| <b>Niacin from diet alone, P95</b>    | 41.4               | 27.6                 | 22.3               | 15.0               | 14.8                |

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

|   | Adults<br>(n=394) | 13 years<br>(n=156) | 9 years<br>(n=209) | 4 years<br>(n=166) | 2 years<br>(n=554) |
|---|-------------------|---------------------|--------------------|--------------------|--------------------|
| <b>Total niacin from diet and supplements, mean</b>   | 34.3              | 26.0                | 19.5               | 16.7               | 14.8               |
| <b>Total niacin from diet and supplements, median</b> | 30.9              | 25.0                | 19.3               | 16.4               | 14.3               |
| <b>Total niacin from diet and supplements, P5</b>     | 17.7              | 12.8                | 11.5               | 10.2               | 7.7                |
| <b>Total niacin from diet and supplements, P25</b>    | 24.2              | 20.4                | 16.0               | 13.7               | 11.3               |
| <b>Total niacin from diet and supplements, P75</b>    | 39.5              | 31.0                | 22.9               | 19.3               | 17.9               |
| <b>Total niacin from diet and supplements, P95</b>    | 60.1              | 41.2                | 28.1               | 25.1               | 23.8               |
| <b>Niacin from supplements alone, mean</b>            | 22.8              | 9.6                 | 12.3               | 7.2                | 9.0                |
| <b>Niacin from supplements alone, median</b>          | 19.8              | 9.0                 | 11.5               | 8.0                | 8.6                |
| <b>Niacin from supplements alone, P5</b>              | 9.1               | 3.0                 | 6.6                | 2.0                | 4.9                |
| <b>Niacin from supplements alone, P25</b>             | 15.1              | 4.0                 | 9.4                | 5.0                | 6.8                |
| <b>Niacin from supplements alone, P75</b>             | 24.7              | 12.0                | 14.5               | 9.0                | 10.8               |
| <b>Niacin from supplements alone, P95</b>             | 36.8              | 17.5                | 21.7               | 12.0               | 14.7               |