Assessment of copper 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: 19
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(Panel members in alphabetical order after chair of the panel)

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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), evaluated the intake of copper in the Norwegian population in relation to tolerable upper intake levels (ULs). VKM has also conducted scenario calculations to illustrate the consequences of amending maximum limits for copper to 1, 2, or 3, mg/day in food supplements. The existing maximum limit is 4 mg/day.

Copper is a micronutrient essential for energy utilisation, brain function (neurotransmitter regulation), soft tissue and bone (collagen synthesis), nutrient metabolism (especially iron) and antioxidant defence against free radicals. Foods account for 90% or more of copper intake in adults when the copper content in drinking water is low (< 0.1 mg/L). If the copper content is higher (> 1-2 mg/L), water may account for up to 50% of total intake (EFSA, 2015).

We reviewed four risk assessments undertaken by the Institute of Medicine (IOM), Scientific Committee on Food (SCF), Expert Committee on Vitamins and Minerals (EVM), and the Nordic Nutrition Recommendations (NNR). Liver damage was selected as a critical endpoint from which to derive a UL because it was judged to be the most reliable marker and consequence of a long-term chronic high copper intake. However, copper-related liver damage is observed almost exclusively in patients with genetic predispositions of copper accumulation.

VKM suggest to use the UL at 5 mg/day (NNR Project Group, 2012; SCF, 2003). This UL was derived from human studies. In the light of the evidence, SCF decided that an uncertainty factor (UF) of 2 was adequate to allow for potential variability within the normal population, whereas the Institute of Medicine (IOM) applied a UF of 1. VKM find the higher UF suitable because human data is limited, the uncertainty of the copper content of drinking water and the potential severe and irreversible adverse effects.

According to the scenario calculations, adults and 13-year-olds with high copper intakes from regular foods (95th percentile) will exceed the ULs with supplemental copper at doses of 3 mg/day or higher. 9-year-old children will exceed the UL with use of 2 mg supplemental copper per day. For younger children the ULs will be exceeded in more than 5% without adding supplemental copper.

In our calculations, copper from drinking water is not included. Copper concentrations in annual samples from waterworks are in general below 0.1 mg/L (Nordheim et al., 2016).

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food Safety, copper, food supplement, upper level, exposure.
Sammendrag på norsk

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet vurdert inntaket av kobber i den norske befolkningen opp mot fastsatte tolerable øvre inntaksnivåer (UL). VKM har også gjort scenarioberegninger for å illustrere konsekvenser av å endre maksimumsgrensen for kobber til 1, 2, eller 3 mg/dag i kosttilskudd. Den eksisterende maksimumsgrensen er 4 mg/dag.

Kobber er essensiell for kroppens energiomsetning, hjernefunksjon (regulering av nevrottransmittere), bindevev og beinvev (kollagensyntesen), omsetning av andre næringsstoffer, særlig jern, og kroppens antioksidantfunksjon mot frie radikaler. Mer enn 90 prosent av kobberinntaket hos voksne kommer fra maten der hvor kobbermengden i drikkevannet er lav (< 0,1 mg/L). Ved høye kobberkonsentrasjoner i drikkevannet, kan vann bidra med opptil 50 prosent av det totale kobberinntaket (EFSA, 2015).

Institute of Medicine (USA), Scientific Committee on Food (EU), Expert Group on Vitamins and Minerals (Storbritannia) og Nordic Nutrition Recommendations (NNR) har fastsatt øvre tolerable inntaksnivå (UL) for kobber for voksne. Det kritiske helseutfallet for øvre tolerable inntaksnivå for selen har vært leverskade, fordi leverskade er vurdert å være den mest pålitelige markøren for og en viktig konsekvens av et langvarig, kronisk høyt kobberinntak. Kobberrelatert leverskade er imidlertid i all hovedsak kun funnet hos pasienter som er genetisk predisponert for opphopning av kobber.

VKM foreslår å bruke et øvre tolerable inntaksnivå på 5 mg/dag (NNR Project Group, 2012; SCF, 2003). Basert på det samlede evidensgrunnlaget mente SCF at en usikkerhetsfaktor på 2 ville ivareta potensiell variasjon i normalbefolkningen og være dekkende, mens Institute of Medicine brukte en usikkerhetsfaktor på 1. VKM mener at den høyeste usikkerhetsfaktoren er best egnet, fordi antall relevante humane studier er begrenset, fordi inntak av kobber fra drikkevann er uavklart på individnivå og fordi de potensielle negative helseeffektene er alvorlige og permanente.

I henhold til VKMs scenarioberegninger vil daglig inntak av kosttilskudd som inneholder 3 mg kobber eller mer, føre til at øvre tolerable inntaksnivå overskrides hos voksne og hos 13-åringer som har et høyt kobberinntak fra vanlig mat (95-percentilen). 9-åringer vil overskride øvre tolerable inntaksnivå ved bruk av kosttilskudd som inneholder 2 mg kobber per dag. Over 5 prosent av de yngre barna overskriver øvre tolerable inntaksnivå uten kosttilskudd med kobber.

Kobber fra drikkevannet er ikke inkludert i disse beregningene. Årlige analyser av kobber fra vannverk viser lave konsentrasjoner under 0,1 mg/L (Nordheim et al., 2016).
Abbreviations and/or glossary

Abbreviations

AI – adequate intake
bw – body weight
DRI – dietary reference intake
DRV – dietary reference value
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
GI – gastrointestinal
ICC – Indian childhood cirrhosis
ICT – idiopathic copper toxicosis
IOM – Institute of Medicine, USA
LOAEL – lowest observed adverse effect level
NFSA – Norwegian Food Safety Authority [Norw.: Mattilsynet]
NRR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
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 [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 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 (DRV) (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 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.

![Population Reference Intake](image)

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.

\[ \text{AR}_{\text{NNR}} = \text{EAR}_{\text{IOM}} = \text{AR}_{\text{EFSA}} \]

**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\(_{AR}\).

\[ \text{RI}_{\text{NNR}} = \text{RDA}_{\text{IOM}} = \text{PRI}_{\text{EFSA}} \]

**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.

\[ \text{UL}_{\text{NNR}} = \text{UL}_{\text{IOM}} = \text{UL}_{\text{EFSA}} \]
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 copper

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

<table>
<thead>
<tr>
<th></th>
<th>Minimum amount per recommended daily dose</th>
<th>Maximum amount per recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper, mg</td>
<td>0.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Permitted copper substances which may be used in the manufacture of food supplements are listed in “Forskrift om kosttilskudd 2012”, [http://www.lovdata.no/cgi-wift/ldies?doc=/sf/sf/sf-20040520-0755.html](http://www.lovdata.no/cgi-wift/ldies?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 copper 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 copper to 1, 2 or 3, mg/day in food supplements, and to evaluate these scenarios against already established tolerable upper intake levels.
Assessment copper

1 Introduction

Copper is an antioxidant and important for metabolism and cell growth, it is vital to several bodily processes, and a deficiency can result in anaemia, irregular bone development, and affect the formation of white blood cells and cardiac function. It is a central component of many enzymes, including those involved in neurotransmitter synthesis, in energy metabolism and in collagen and elastin cross-linking.

Copper is found in a wide variety of mineral salts and organic compounds as well as in the metallic form. The main dietary sources of copper are nuts, organ meats, seafood, legumes, and vegetables. Besides food, drinking water can be another major source of copper, although the mineral content in drinking water is very variable. Factors such as natural mineral content, pH, and plumbing system determine copper concentration in water (US National Research Council, 2000). High concentrations of copper have been described in many countries including in Europe, and there is a substantial variability between the observed levels also within the same sources when the concentrations have been measured multiple times. In the European Union (EU), the maximum permitted concentration of copper in water intended for human consumption is 2 mg/L (EFSA, 2015).

Foods account for 90% or more of copper intake in adults when the copper content in drinking water is low (< 0.1 mg/L). If the copper content is higher (> 1-2 mg/L), water may account for up to 50% of total intake. In infants, contribution of water to daily copper intake may be higher because they consume proportionally more water than adults (de Romana et al., 2011). In Norway, the average copper content of drinking water in a survey of trace metals in 566 Norwegian waterworks serving 64% of the population was 56 µg/L (range 1-1500 µg/L) (Dahl et al., 2015; Hongve et al., 1994), and copper concentrations in annual samples from waterworks are in general below 0.1 mg/L (Nordheim et al., 2016). However, the copper content of tap water reaching the consumer may be considerably higher (up to 3 mg/L) if the water has stood in copper pipes (Andersen, 2016).

Various dietary components affect the absorption of copper. For example, absorption is higher from a diet high in animal protein compared with plant protein. Milk proteins have both positive or negative effect on copper status, with whey protein having a negative effect on copper absorption. Zinc and copper interact, and high concentrations of one element may inhibit the absorption of the other.

Copper is mainly absorbed in the duodenum bound to specific proteins as divalent copper. Both passive diffusion and carrier mediated transfer occur. Infants are apparently unable to absorb copper to the same extent as adults, and are often found to be in negative copper
balance. Deficiency is rare and, because of the ubiquitous presence of copper in foods, almost never due to insufficient copper in the diet.

Homeostasis of copper is maintained largely by the rate of excretion. The major route of copper excretion is via the bile, which is directly correlated with absorbed dose.

Copper homeostasis is generally well regulated and the symptoms generated from excess copper intake can be caused indirectly by the mechanisms that regulate copper. These symptoms include mood disorders, fatigue, irritability and other vague psychological symptoms. Chronic excess copper can result in liver and kidney damage as well as zinc deficiency. Acute toxicity causes gastrointestinal (GI) symptoms and may eventually lead to GI bleeding.

1.1 Requirements and recommendations

Table 2.1-1: Norwegian recommendations for intake of copper according to age (Helsedirektoratet, 2014).

<table>
<thead>
<tr>
<th>Age, both sexes</th>
<th>mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 mo.</td>
<td>0.3</td>
</tr>
<tr>
<td>1-2 years</td>
<td>0.3</td>
</tr>
<tr>
<td>2-5 years</td>
<td>0.4</td>
</tr>
<tr>
<td>6-9 years</td>
<td>0.5</td>
</tr>
<tr>
<td>10-13 years</td>
<td>0.7</td>
</tr>
<tr>
<td>14- &gt;75 years</td>
<td>0.9</td>
</tr>
<tr>
<td>Pregnant</td>
<td>1.0</td>
</tr>
<tr>
<td>Lactating</td>
<td>1.3</td>
</tr>
</tbody>
</table>

The Norwegian recommendations are based on the NNR (2012) recommendations.

Table 2.1-2: EFSA's Adequate Intakes (AIs) for copper, both sexes (EFSA, 2015).

<table>
<thead>
<tr>
<th>Age, both sexes</th>
<th>mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>7-11 mo.</td>
<td>0.4</td>
</tr>
<tr>
<td>1-3 years</td>
<td>0.7</td>
</tr>
<tr>
<td>3-10 years</td>
<td>1.0</td>
</tr>
<tr>
<td>10-18 years</td>
<td>1.3</td>
</tr>
<tr>
<td>14- &gt;75 years</td>
<td>1.6</td>
</tr>
<tr>
<td>Pregnant</td>
<td>-</td>
</tr>
<tr>
<td>Lactating</td>
<td>-</td>
</tr>
</tbody>
</table>
2 Tolerable upper intake levels

**Institute of Medicine (IOM, 2001), USA**

Liver damage was selected as the critical endpoint used to establish an UL. The no observed adverse effect level (NOAEL) of 10 mg/day was considered to be valid for the general population. Therefore, an uncertainty factor (UF) of 1.0 was selected. A larger UF was considered unnecessary in view of the large international database in humans indicating no adverse effects from daily consumption of 10 to 12 mg/day of copper in foods and the rarity of observed liver damage from copper exposures in human populations with normal copper homeostasis.

It was recommended that the UL for pregnant and lactating females should be the same as that for the nonpregnant and nonlactating females. The report also acknowledged the fact that there was limited data from children and that “the only source for infants should be food and formula”. The ULs for children was extrapolated based on their standardised body weight.

It was also discussed that certain subgroups may be at increased risk of adverse effects from excess intake: Individuals with Wilson’s disease, idiopathic copper toxicosis (ICT), and Indian childhood cirrhosis (ICC) were considered to be subgroups at increased risk of adverse effects from excess intake.

**Table 2.2-1** Tolerable upper intake levels for copper in different age groups adjusted by body weight suggested by the IOM (2001).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>UL mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>1</td>
</tr>
<tr>
<td>4-8</td>
<td>3</td>
</tr>
<tr>
<td>9-13</td>
<td>5</td>
</tr>
<tr>
<td>14-18</td>
<td>8</td>
</tr>
<tr>
<td>19 and older</td>
<td>10</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>10</td>
</tr>
<tr>
<td>Lactation</td>
<td>10</td>
</tr>
</tbody>
</table>

**Scientific Committee for Food (SCF, 2003), EU**

SCF also selected liver damage as critical endpoint from which to derive a UL because it was judged to be the most reliable indicator of a long-term chronic ingestion of copper.

A NOAEL of 10 mg/day was based on the absence of any adverse effects on liver function in a study of Pratt et al (1985). In a study by Turnlund (1991) homeostatic data indicated that a 10-fold increase in dietary copper resulted in the absorption of only twice as much copper and that indices of copper status, as a result of the body’s regulation of copper, are resistant...
to change except under extreme dietary conditions. For example, Turnlund (1991) showed that when dietary intakes increased from 0.8 mg/day to 7.5 mg/day (for 24 days), putative indices of status, including plasma copper, erythrocyte superoxide dismutase, caeruloplasmin and urinary copper excretion were not significantly altered. In the light of this evidence, the Committee decided that a UF of 2 is adequate to allow for potential variability within the normal population. A UL of 5 mg/day was accordingly derived. This UL was not considered to be applicable during pregnancy or lactation because of inadequate data relating to this critical life stage.

In children, liver damage appeared to be restricted to those with a predisposition for enhanced copper toxicity, and UL values for children were derived from extrapolating adult UL values based on relative body weight. The SCF noted that the additional copper intakes from drinking water may be appreciable and may need to be taken into account.

SCF did not want to use any data from animal studies to establish the ULs for copper.

**Table 2.2-2  Tolerable upper intake levels for copper in different age groups by the SCF (2003).**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>UL mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>1</td>
</tr>
<tr>
<td>4-6</td>
<td>2</td>
</tr>
<tr>
<td>7-10</td>
<td>3</td>
</tr>
<tr>
<td>11-14</td>
<td>4</td>
</tr>
<tr>
<td>15-17</td>
<td>4</td>
</tr>
<tr>
<td>Adults</td>
<td>5</td>
</tr>
</tbody>
</table>

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

EVM based their UL mainly on results from human studies such as Pratt et al., 1985; Turnlund et al., 1989; Olivares et al., 1998 and Pizarro et al., 1999 as well as one study in rats (Hébert et al., 1993) all cited in EVM (2003).

The following justification was given for the establishment of the UL in the EVM (2003) report: “Acute copper toxicity in humans is rare due to the emetic properties and unpleasant taste of the compounds. There are relatively few data on lower level or chronic oral copper exposure in man. Copper is kept under tight homeostatic control to prevent the accumulation of excess amounts. Where dietary copper is high, absorption is reduced and, in particular, biliary excretion increased. Other mechanisms, which sequester excess copper within the cell, may also occur. Copper toxicity occurs when such defences are overwhelmed. Thus, in man, liver toxicity has only been seen in genetically determined conditions such as Wilson’s disease and in Indian Childhood Cirrhosis where hepatic copper accumulation occurs. There is no evidence for copper carcinogenicity in the general population, although an elevated incidence of hepatoma has been suggested in untreated Wilson’s disease patients or subjects recovering from ICC. In the general human population, the key adverse effects usually associated with excess copper intake are gastrointestinal, resulting from consumption of
copper in water or beverages. There are some animal data for copper, although few from adequate chronic studies.”

A NOAEL of 16 mg/kg bw/day was identified in a sub-chronic toxicity study in rats. Higher doses resulted in damage to the stomach, kidney and liver. It was argued that “If uncertainty factors of 10 for inter-species variation and 10 for intra-individual variation (total 100) are applied, a Safe Upper Level of 0.16 mg/kg bw day for total intake of copper is derived. This is equivalent to 10 mg/day in a 60 kg adult. This is consistent with the data from small scale human studies which suggest that up to 10 mg/day supplemental copper may be without adverse effect. EVM estimated that the worst-case maximum daily copper exposure from food and water in the UK diet is 9 mg/day, suggesting that there is a margin of 1 mg/day for supplementation or other additional intake.

“The exposure estimate suggests that individuals in the UK could theoretically consume in excess of 6 mg/day copper from water alone if it was assumed that 2 L/day water was consumed containing copper at the statutory limit of 3 mg/L. This was also the dose associated with gastrointestinal effects in the Pizarro study. However, in practice copper levels in UK drinking water are much lower, so this level of exposure is unlikely to occur. There is no evidence that copper intakes in water in the UK present any risk to health.”

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

The NNR Project Group (2012) supported the UL set for adults by the SCF (2003) at 5 mg/day.

**2.1.1 Summary tolerable upper intake levels**

Two different ULs at 5 and 10 mg per day have been established for intake of copper from both foods, drinks and supplements in adults. These ULs set by IOM, SCF, EVM and NNR are mainly based on the same human studies. Liver damage was selected as critical endpoint from which to derive a UL because it was judged to be the most reliable indicator of a long-term chronic high copper intake. However, liver damage is observed almost exclusively in patients with genetic predispositions of copper accumulation.

An overview is given in Table 2.2.1-1.
### Table 2.2.1-1 Overview of upper levels in adults set by various authorities.

<table>
<thead>
<tr>
<th></th>
<th>UL mg/day</th>
<th>Critical endpoint</th>
<th>Based on</th>
<th>NOAEL</th>
<th>LOAEL</th>
<th>UF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IOM, 2001</strong></td>
<td>10</td>
<td>Liver damage</td>
<td>Human clinical studies</td>
<td>10 mg/day</td>
<td>30 mg/day for 2 years</td>
<td>1</td>
</tr>
<tr>
<td><strong>SCF, 2003</strong></td>
<td>5</td>
<td>Liver damage</td>
<td>Human clinical studies</td>
<td>10 mg/day</td>
<td>30 mg/day for 2 years</td>
<td>2</td>
</tr>
<tr>
<td><strong>EVM, 2003</strong></td>
<td>10*</td>
<td>Damage to internal organs.</td>
<td>Rat study supported by human clinical studies</td>
<td>16 mg/kg bw/day</td>
<td>10 mg/day</td>
<td>10x10 (rats)</td>
</tr>
<tr>
<td><strong>NNR, 2012</strong></td>
<td>5</td>
<td>SCF, 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Safe Upper Level

IOM, SCF, and EVM based their ULs on the same human studies and from the same NOAEL of 10 mg/day. VKM suggest to use the lowest UL at 5 mg/day (NNR Project Group, 2012; SCF, 2003). This UL was derived from human studies. In the light of the evidence, SCF decided that a UF of 2 was adequate to allow for potential variability within the normal population, whereas IOM applied a UF of 1. VKM find the higher UF suitable because human data is limited, the uncertainty of the copper content of drinking water and the potential severe and irreversible adverse effects.
3 Intakes and scenarios copper

3.1 Short description of the Norwegian dietary surveys

The estimated intakes of copper presented in this opinion are based on data from the dietary surveys in young children (2-year-olds), children and adolescents (4-, 9- and 13-year-olds) and adults (aged 18 to 70 years). The dietary 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 three different surveys and thus direct comparisons between the age groups may be misleading.

A description of the 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 web based 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 copper in the Norwegian population

Intakes of copper in the various age groups and in users of copper supplements are presented in tables in Appendix 1. The tables in Appendix 1 also include estimates for P25 and P75. Copper from drinking water is not included in the dietary calculations for any age groups.
Adults

The mean intake of copper from the diet alone is 1.3 mg/day (median 1.2 mg/day) in adults (n=1787). The P5 intake is 0.6 mg/day and the P95 intake is 2.2 mg/day.

In Norkost 3, 221 participants (12%) reported use of copper-containing supplements. Their mean total intake of copper including that from food supplements is 2.5 mg/day (median 2.1 mg/day), P5 intake is 1.2 mg/day and P95 intake is 4.8 mg/day.

Mean intake of copper from supplements alone in adults reporting use of copper-containing supplements is 1.2 mg/day (median 1.0 mg/day), P5 intake is 0.3 mg/day and P95 intake is 2.6 mg/day.

13-year-olds (n=687)

The mean intake of copper from the diet alone is 0.9 mg/day (median 0.9 mg/day) in 13-year-olds. The P5 intake is 0.5 mg/day and the P95 intake is 1.5 mg/day.

In Ungkost 2016, 21 13-year-olds (3%) reported use of copper-containing supplements. Their mean total intake of copper including that from food supplements is 1.1 mg/day (median 1.2 mg/day).

Mean intake of copper from supplements alone in 13-year-olds reporting use of copper-containing supplements is 0.3 mg/day (median 0.3 mg/day).

In 9-year-olds (n=636)

The mean intake of copper from the diet alone is 0.9 mg/day (median 0.8 mg/day) in 9-year-olds. The P5 intake is 0.5 mg/day and the P95 intake is 1.4 mg/day.

In Ungkost 2016, 12 9-year-olds (2%) reported use of copper-containing supplements. Their mean total intake of copper including that from food supplements is 1.2 mg/day (median 1.2 mg/day).

Mean intake of copper from supplements alone in 9-year-olds reporting use of copper-containing supplements is 0.3 mg/day (median 0.3 mg/day).

In 4-year-olds (n=399)

The mean intake of copper from the diet alone is 0.8 mg/day (median 0.7 mg/day) in 4-year-olds. The P5 intake is 0.4 mg/day and the P95 intake is 1.2 mg/day.

In Ungkost 2016, 10 4-year-olds (3%) reported use of copper-containing supplements. Their mean total intake of copper including that from food supplements is 0.3 mg/day (median 0.2 mg/day).
Mean intake of copper from supplements alone in 4-year-olds reporting use of copper-containing supplements is 0.8 mg/day (median 0.8 mg/day).

**In 2-year-olds (1674)**

The mean intake of copper from the diet alone is 0.7 mg/day (median 0.7 mg/day) in 2-year-olds. The P5 intake is 0.4 mg/day and the P95 intake is 1.2 mg/day.

In Småbarnskost 2007, 66 2-year-olds (4%) reported use of copper-containing supplements. Their mean total intake of copper including that from food supplements is 1.2 mg/day (median 1.2 mg/day). The P5 intake is 0.7 mg/day and the P95 intake is 1.7 mg/day.

Mean intake of copper from supplements alone in 2-year-olds reporting use of copper-containing supplements is 0.4 mg/day (median 0.5 mg/day) P5 intake is 0.1 mg/day and P95 intake is 1.0 mg/day.

**3.3 Scenario calculations for copper**

For scenario calculations VKM used the intake groups below P5 and above P95 from food alone to calculate copper intake and added the suggested supplementation levels from NFSA (1, 2, 3 or 4 mg copper per day), see Tables 3.3-1 and 3.3-2.

**Table 3.3-1**  Calculated total copper intakes for various age groups in scenarios with 1, 2, 3 or 4 mg as supplements added to the P5 of intake from food alone (mg/day).

<table>
<thead>
<tr>
<th>Age group</th>
<th>P5 from food</th>
<th>Including 1 mg from suppl</th>
<th>Including 2 mg from suppl</th>
<th>Including 3 mg from suppl</th>
<th>Including 4 mg from suppl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>0.6</td>
<td>1.6</td>
<td>2.6</td>
<td>3.6</td>
<td>4.6</td>
</tr>
<tr>
<td>13 years</td>
<td>0.5</td>
<td>1.5</td>
<td>2.5</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td>9 years</td>
<td>0.5</td>
<td>1.5</td>
<td>2.5</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td>4 years</td>
<td>0.4</td>
<td>1.4</td>
<td>2.4</td>
<td>3.4</td>
<td>4.4</td>
</tr>
<tr>
<td>2 years</td>
<td>0.4</td>
<td>1.4</td>
<td>2.4</td>
<td>3.4</td>
<td>4.4</td>
</tr>
</tbody>
</table>

**Table 3.3-2**  Calculated total copper intakes for various age groups in scenarios with 1, 2, 3 or 4 mg as supplements added to the P95 of intake from food alone (mg/day).

<table>
<thead>
<tr>
<th>Age group</th>
<th>P95 from food</th>
<th>Including 1 mg from suppl</th>
<th>Including 2 mg from suppl</th>
<th>Including 3 mg from suppl</th>
<th>Including 4 mg from suppl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>2.2</td>
<td>3.2</td>
<td>4.4</td>
<td>5.2</td>
<td>6.2</td>
</tr>
<tr>
<td>13 years</td>
<td>1.5</td>
<td>2.2</td>
<td>3.4</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>9 years</td>
<td>1.4</td>
<td>2.4</td>
<td>3.4</td>
<td>4.4</td>
<td>5.4</td>
</tr>
<tr>
<td>4 years</td>
<td>1.2</td>
<td>2.2</td>
<td>3.2</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>2 years</td>
<td>1.2</td>
<td>2.2</td>
<td>3.2</td>
<td>4.2</td>
<td>5.2</td>
</tr>
</tbody>
</table>
4 Assessment of the intakes of copper

4.1 Evaluation of copper intakes, including scenarios with supplementation

VKM suggest to use the ULs for copper from SCF (2003) at 5 mg/day for adults, and the body weight adjusted ULs for children.

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

**Table 4.1-1**  Norwegian recommended intakes (RI), ULs from SCF (2003), and 5th and 95th percentiles of copper intake from food alone in various age groups (mg/day).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>RI, mg/day</th>
<th>Age (years)</th>
<th>P5 mg/day</th>
<th>P95 mg/day</th>
<th>Age (years)</th>
<th>UL mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>0.3</td>
<td>2</td>
<td>0.4</td>
<td>1.2</td>
<td>1-3</td>
<td>1</td>
</tr>
<tr>
<td>2-5</td>
<td>0.4</td>
<td>4</td>
<td>0.4</td>
<td>1.2</td>
<td>4-6</td>
<td>2</td>
</tr>
<tr>
<td>6-9</td>
<td>0.5</td>
<td>9</td>
<td>0.5</td>
<td>1.4</td>
<td>7-10</td>
<td>3</td>
</tr>
<tr>
<td>10-13</td>
<td>0.7</td>
<td>13</td>
<td>0.5</td>
<td>1.5</td>
<td>11-14</td>
<td>4</td>
</tr>
<tr>
<td>14- &gt;75</td>
<td>0.9</td>
<td>Adults</td>
<td>0.6</td>
<td>2.2</td>
<td>Adults</td>
<td>5</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactation</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The RI was lower and UL higher than the P5-P95 range for almost all age groups. Thus according to these figures the copper intakes are seemingly adequate and risk of toxicity low. It should be noted, however, that the intake from drinking water is not included in these numbers.
5 Uncertainties

For the determinations of the ULs for copper, SCF, IOM and EVM arrived on different conclusions because different UFs were used. This discrepancy indicates uncertainty regarding establishment of these ULs both for adults, and even more for children and adolescents. Long-term clinical studies are requested by all these scientific bodies to ascertain ULs of scientific value.

The terms of reference has been to assess the intake in Norway in relation to already established tolerable upper intake levels which were established between 2001 and 2012. No literature search has been conducted for this VKM assessment and relevant recent evidence to support amendments to existing ULs may accordingly not have been included.

Copper exposure from drinking water has not been used in the calculations. Generally, drinking water content of copper measured at the waterworks level is low (<0.1 mg/L) and below regulatory limits. However, tap water standing in copper pipes may have considerably higher copper content, up to 3 mg/L.

The intake of copper for 2-year-olds from the study Småbarnskost 2007, was originally calculated in the database (AE07) which do not contain values for all foods. However, for the food codes used in the frequency questionnaire in Småbarnskost 2007 the coverage for copper values were satisfactory, and the designated database AE07 was used.

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 limit 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.
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 copper from the diet, including fortified products, in all age groups in the population above 1 year.

VKM was also requested to conduct scenario calculations to illustrate the consequences of amending maximum limits for copper to 1, 2 or 3 mg/day in food supplements. The existing maximum limit is 4 mg/day, and is therefore included in the conclusion.

VKM suggest to use the ULs established by SCF in 2003 at 5 mg/day for adults and ranging from 1 to 4 mg/day for children and adolescents. Dietary calculations have been performed for intake in the P5, P25, mean, P50, P75 and P95 in children 2-, 4- and 9-year-olds, 13-year-old adolescents and among adults.

In adults and adolescents additional 3 mg/day and in 9-year-old children 2 mg/day supplemental copper will lead to exceedance of the ULs established by SCF. For younger children the ULs will be exceeded in more than 5% without adding supplemental copper.

The calculations do not include copper from drinking water. Water content of copper measured at the waterworks level is low (<0.1 mg/L). Tap water standing in copper pipes may have considerably higher copper content, up to 3 mg/L.

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

**Table 6-1 An overview of the conclusions for copper according to doses in supplements.**

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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Doses in supplements</th>
<th>1 mg/day</th>
<th>2 mg/day</th>
<th>3 mg/day</th>
<th>4 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7 Data gaps

More age groups should be included in dietary surveys in addition to subgroups like different ethnical groups. Data from well conducted randomised trials with proper registration of adverse events is lacking.
8 References


Appendix I

Summary tables of copper intake for all age groups

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

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

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=1787)</th>
<th>13 years (n=687)</th>
<th>9 years (n=636)</th>
<th>4 years (n=399)</th>
<th>2 years (n=1674)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper from diet alone, mean</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Copper from diet alone, median</td>
<td>1.2</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Copper from diet alone, P5</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Copper from diet alone, P25</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Copper from diet alone, P75</td>
<td>1.5</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Copper from diet alone, P95</td>
<td>2.2</td>
<td>1.5</td>
<td>1.4</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=221)</th>
<th>13 years (n=21)</th>
<th>9 years (n=12)</th>
<th>4 years (n=10)</th>
<th>2 years (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total copper from diet and supplements, mean</td>
<td>2.5</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Total copper from diet and supplements, median</td>
<td>2.1</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Total copper from diet and supplements, P5</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
</tr>
<tr>
<td>Total copper from diet and supplements, P25</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>Total copper from diet and supplements, P75</td>
<td>2.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>Total copper from diet and supplements, P95</td>
<td>4.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
</tr>
<tr>
<td>Copper from supplements alone, mean</td>
<td>1.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Copper from supplements alone, median</td>
<td>1.0</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Copper from supplements alone, P5</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
</tr>
<tr>
<td>Copper from supplements alone, P25</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
</tr>
<tr>
<td>Copper from supplements alone, P75</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>Copper from supplements alone, P95</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
</tr>
</tbody>
</table>