Risk assessment of magnesium in food supplements

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety
Risk assessment of magnesium in food supplements

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Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety. Per Ole Iversen (chair), Livar Frøyland, Margaretha Haugen, Kristin Holvik, Martinus Løvik, Tor A Strand and Grethe S Tell.

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

Acknowledgment

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has appointed a working group consisting of VKM members to answer the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou. The members of the working group Margaretha Haugen, Inger Therese L Lillegaard and Tor A Strand are acknowledged for their valuable work on this opinion.

Competence of VKM experts

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

Summary ................................................................................................................................. 6
Sammendrag på norsk ........................................................................................................... 8
Abbreviations and glossary ............................................................................................ 10
Abbreviations ..................................................................................................................... 10
Glossary ............................................................................................................................... 10
Background as provided by the Norwegian Food Safety Authority ......................... 11
Terms of reference as provided by the Norwegian Food Safety Authority ........... 13
Assessment ......................................................................................................................... 14

1 Introduction .................................................................................................................... 14

2 Hazard identification and characterisation ................................................................ 15
  2.1 Chemistry, absorption and metabolism ...................................................................... 15
    2.1.1 Chemistry ........................................................................................................... 15
    2.1.2 Metabolism ....................................................................................................... 15
    2.1.3 Absorption ....................................................................................................... 15
    2.1.4 Occurrence ....................................................................................................... 16
    2.1.5 Interaction with calcium and zinc ..................................................................... 16

  2.2 Previous reports on safe upper level for magnesium ............................................. 16
    2.2.1 Dietary reference intakes for Calcium, Phosphorous, Magnesium Vitamin D and
         Fluoride. Institute of Medicine (USA), 1997 ......................................................... 16
    2.2.2 Opinion of the Scientific Committee on Food on the tolerable upper intake level
         of magnesium. Scientific Committee on Food (EU), 2001..................................... 17
    2.2.3 Expert Group on Vitamins and Minerals (UK), 2003 ....................................... 19
    2.2.4 A safe strategy for addition of vitamins and minerals to foods. (Denmark, 2005) 20
    2.2.5 Summary of previous reports on magnesium.................................................. 20

  2.3 Recommended intakes of magnesium ..................................................................... 22

  2.4 Literature searches .................................................................................................... 22
    2.4.1 Publication selection ......................................................................................... 23

  2.5 Human studies investigating supplementary magnesium and adverse health effects .. 24
    2.5.1 Randomised controlled trials .......................................................................... 24
    2.5.2 Other studies .................................................................................................... 29
      2.5.2.1 Systematic reviews and meta-analyses ........................................................ 29
      2.5.2.2 Other studies – not RCTs or systematic reviews ....................................... 29
2.5.3 Summary human studies investigating supplementary magnesium and adverse health effects ................................................................. 30

3 Magnesium intake ................................................................................. 31
3.1 General description of food consumption surveys........................................ 31
3.2 Estimated intakes in various age groups .................................................. 32
   In adults (n=1787) .............................................................................. 32
   In 13-year-olds (n=1005) ................................................................. 32
   In 9-year-olds (n=810) .................................................................. 33
   In 4-year-olds (n=391) .................................................................. 33
   In 2-year-olds (n=1674) ................................................................. 33
3.3 Estimated intake from water ................................................................. 34
3.4 Intakes below the recommendations for magnesium ................................. 34

4 Risk characterisation ........................................................................... 35
4.1 Establishment of a safe upper level or tentative safe upper level for magnesium in food supplements .............................................. 35
4.2 Evaluation of high magnesium intakes .................................................. 36
4.3 Evaluation of low magnesium intakes .................................................. 36
4.4 Special groups .................................................................................. 36

5 Uncertainties ....................................................................................... 38

6 Conclusions with answers to the terms of reference ................................. 39

7 Data gaps ............................................................................................ 40

8 References .......................................................................................... 42

Appendix 1 ............................................................................................ 45
Search strategy for human studies ........................................................ 45
Search strategy for animal studies ........................................................ 45

Appendix 2 ............................................................................................ 46
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 risk associated with magnesium in food supplements. VKM is requested to evaluate upper tolerable intake levels for magnesium and high and low intakes in the Norwegian population. Pending establishment of common maximum limits in the EU, the NFSA is evaluating the national maximum limits for vitamins and minerals in food supplements. This risk assessment is the scientific basis for NFSA's evaluation of national limits for magnesium.

Directive 2002/46/EC on food supplements was implemented in Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU. Until common limits are established in the EU, the national limits apply.

The present report is a risk assessment of magnesium in food supplements. It is based on published articles retrieved from literature searches and previous risk assessments of magnesium.

Magnesium is an essential alkaline mineral and occurs as free cation Mg$^{2+}$ in aqueous solution, or as the mineral part of a large variety of compounds such as chlorides, carbonates and hydroxides. Dietary sources of magnesium include green leafy vegetables, legumes, whole grain cereals, dark chocolate, nuts, fish and seafood, banana and coffee. NFSA has especially requested VKM to consider water as a source of magnesium. A few waterworks reported magnesium concentrations at 10 mg/L. Consumption of water from these waterworks may contribute up to 10% of recommended magnesium intake. However, most waterworks reported negligible magnesium concentrations.

Magnesium has multiple functions in the body; it is a required cofactor for more than 300 enzyme systems in the body; for energy-dependent membrane transport, for gene regulation, and for sustained electrical potential in excitable cells. Magnesium also plays a major role in bone and mineral homeostasis.

No tolerable upper intake level (UL) has been established for magnesium intake from food sources for the reason that no adverse effects have been recognised in healthy populations.

Magnesium salts in food supplements may cause osmotic diarrhoea which is the most frequently reported adverse effect. However, these effects are considered relatively mild.

Previous reports have arrived on UL or guidance levels (GLs) for supplemental magnesium ranging from 250 mg/day in the EU (Scientific Committee for Food (SCF, 2001)) through 350 mg/day in the USA (Institute of Medicine (IOM, 1997)) and up to 400 mg per day in the UK (Expert group on Vitamins and Minerals (EVM, 2003)).
The UL from SCF (2001) is below the recommended daily dietary intakes for adults. Since the critical endpoint (gastrointestinal symptoms) is mild, rapidly reversible and no NOAEL could be identified, VKM finds it appropriate to base the UL for magnesium salts in food supplements on the LOAEL from IOM (1997). For the same reason, an uncertainty factor of 1 may be applicable for establishing a UL for magnesium salts in food supplements. VKM therefore proposes an amendment of the ULs suggested by SCF (2001) for magnesium in supplements.

The IOM (1997) suggestion of a UL at 350 mg supplementary magnesium per day for adults was based on a LOAEL for mild diarrhea. VKM found no results to support an alteration of this UL.

VKM therefore suggests a UL of 350 mg magnesium in food supplements per day in adults which is in accordance with the UL suggested by (IOM, 1997). This UL will also cover the recommended intakes for the adult population.

VKM suggests that the ULs for children equal the recommended intakes for each age group:

<table>
<thead>
<tr>
<th>Age group</th>
<th>ULs (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-3 years</td>
<td>85</td>
</tr>
<tr>
<td>Children 3-10 years</td>
<td>120-200</td>
</tr>
<tr>
<td>Children (10-&lt;14 years)</td>
<td>280</td>
</tr>
<tr>
<td>Adolescents (14-&lt;18 years)</td>
<td>280</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>350</td>
</tr>
</tbody>
</table>

According to the habitual dietary intakes of magnesium estimated from nationwide dietary surveys in Norway, about 25% of adults have intakes of magnesium below the recommendations from food and supplements. Almost the same percentage was below the recommended intakes among 9-year-old children, while approximately 70% of 13-year-olds had an intake of magnesium below the recommendations. It should be noted that the intakes have been estimated with use of different dietary survey methods for the different age categories and a comparison of estimates across age groups can be misleading and has a high degree of uncertainty.

Concentration of magnesium in water is low and about 60% of the waterworks reporting to the Norwegian Waterworks Registry had a magnesium concentration below 2 mg/L, indicating water as a negligible source of magnesium for the majority of the population.

**Key words:** VKM, risk assessment, Norwegian Scientific Committee for Food Safety, magnesium, food supplement, upper level.
På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko forbundet med magnesium i kosttilskudd. VKM har fått i oppdrag å vurdere øvre tolerabelt inntaksnivå for magnesium, og høyt og lavt inntak i den norske befolkningen. I påvente av felles maksimumsgrenser i EU, vurderer Mattilsynet nasjonale maksimumsgrenser for vitaminer og mineraler i kosttilskudd. Denne risikovurderingen er det vitenskapelige grunnlaget for Mattilsynets vurdering av nasjonale grenser for magnesium.

Direktiv 2002/46/EF om kosttilskudd ble implementert i norsk lov i 2004 i forskrift 20 mai 2004 nr 755 om kosttilskudd. Felles maksimums- og minimumsgrenser for vitaminer og mineraler i kosttilskudd skal fastsettes i EU, men inntil disse grensene er etablert i EU, er det de nasjonale grensene gjelder.

Denne rapporten er en risikovurdering av magnesium i kosttilskudd. Den er basert på publiserte artikler hentet fra litteratursøk og tidligere risikovurderinger av magnesium.

Magnesium er et essensielt alkalisk mineral og forekommer som frie Mg$^{2+}$ kationer i vandig løsning, eller som mineral i flere ulike forbindelser som klorider, karbonater og hydroksider. Kilder til magnesium i kosten er grønne bladgrønnsaker, belgfrukter, helkorncereal, mørk sjokolade, nøtter, fisk og sjomat, banan og kaffe. Mattilsynet har særskilt bedt VKM vurdere vann som magnesiumkulde. Noen få vannverk anga en magnesiumkonsentrasjon opp mot 10 mg/L. Inntak av vann fra slike vannverk vil kunne bidra med opp mot 10 % av anbefalt magnesium inntak. Imidlertid er magnesiumkonsentrasjonene i de fleste vannverkene ubetydelige.

Det er ikke fastsatt et tolerabelt øvre inntaksnivå (UL) for magnesium fra kosten ettersom det ikke er rapportert om negative helseeffekter fra magnesium i vanlig kost hos den friske populasjonen. Magnesium har mange funksjoner i kroppen; det er en nødvendig kofaktor for over 300 enzymatikere i kroppen; bl.a. for aktiv membrantransport, for genregulering, og for å opprettholde elektrisk potensiale over cellemembraner. Magnesium spiller også en viktig rolle i bein og mineral homeostasen.

Magnesiumsalter i kosttilskudd kan forårsake osmotisk diaré som er den hyppigst rapporterte negative effekten. De negative helseeffektene anses imidlertid for å være av mild karakter.

I tidligere rapporter er det etablert UL eller såkalt Guidance Level (GL) for magnesium i kosttilskudd som spenner fra 250 mg/dag i EU (Scientific Committee for Food (SCF, 2001)) via 350 mg/dag i USA (Institute of Medicine (IOM, 1997)) opp til 400 mg per dag i Storbritannia (Expert group on Vitamins and Minerals (EVM, 2003)).

UL fra SCF (2001) er lavere enn anbefalt daglig inntak fra kosten for voksne. Ettersom det kritiske endepunktet (gastrointestinale effekter/symptomer) er mildt og raskt reversibelt, og VKM ikke kan identifisere en NOAEL (no observed adverse effect level), finner VKM det
hensiktsmessig å basere UL for magnesium i kosttilskudd på en LOAEL (lowest observed adverse effect level). VKM mener også at en usikkerhetsfaktor på 1 vil være egnet for fastsettelse av UL for magnesium i kosttilskudd, fordi de negative helseeffektene observert ved LOAEL er av en mild og reversibel art. VKM foreslår derfor en endring av UL foreslått i SCF (2001) for magnesium i kosttilskudd.

I 1997 foreslo IOM en UL for voksne på 350 mg magnesium per dag i kosttilskudd, basert på en LOAEL for mild diaré. VKM har ikke funnet noen data som indikerer at det er behov for en endring av IOM (1997) UL.

VKM foreslår derfor en UL på 350 mg magnesium i kosttilskudd per dag for voksne, i overensstemmelse med IOM (1997). Dette øvre inntaksnivået vil også dekke det anbefalte inntaket for magnesium i den voksne befolkningen.

VKM foreslår at de øvre inntaksnivåene for barn settes på samme nivå som anbefalt inntak for de ulike aldersgruppene:

<table>
<thead>
<tr>
<th>Aldersgruppe</th>
<th>UL (mg/dag)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barn 1-3 år</td>
<td>85</td>
</tr>
<tr>
<td>Barn 3-10 år</td>
<td>120-200</td>
</tr>
<tr>
<td>Barn (10-&lt;14 år)</td>
<td>280</td>
</tr>
<tr>
<td>Ungdom (14-&lt;18 år)</td>
<td>280</td>
</tr>
<tr>
<td>Voksne (≥18 år)</td>
<td>350</td>
</tr>
</tbody>
</table>

Ifølge inntaksberegnings basert på landsomfattende kostholdsundersøkelser i Norge, vil om lag 25 % av voksne ha et inntak av magnesium under anbefalingene. Omlag samme andelen av 9-åringene har et inntak under anbefalingene. Så mange som ca 70 % av 13-åringer hadde et magnesiuminntak under anbefalingene. Det må imidlertid bemerkes at inntaket for de ulike aldersgruppene er beregnet på grunnlag av ulike kostholdsundersøkelsesmetoder, og en sammenligning av inntaksberegninger på tvers av aldersgruppene kan være misvisende og har en høy grad av usikkerhet.

Konsentrasjoner av magnesium i drikkevann er lav, og i rundt 60 % av vannverkene var konsentrasjonene av magnesium under 2 mg per liter, noe som indikerer at vann fra vannverk vil være en ubetydelig kilde til magnesium for flertallet av befolkningen.
Abbreviations and glossary

Abbreviations

AI – adequate intake
bw – body weight
CRP – C-reactive protein
DRV – dietary reference value
EFSA – European Food Safety Authority
EMBASE – Excerpta Medica dataBASE
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
IOM – Institute of medicine, USA
LOAEL – lowest observed adverse effect level
MEDLINE – Medical Literature Analysis and Retrieval System Online
NIDDM – non-insulin dependent diabetes mellitus
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
PMS – premenstrual syndrome
RCT – randomised controlled trial
RI – recommended intake
SCF – Scientific Committee on Food, EU
UF – uncertainty factor
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee For Food Safety

Glossary

Recommended Dietary Allowance (RDA): The average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a group. Used by Institute of Medicine (IOM), USA.

Adequate intake (AI): A value based on observed or experimentally determined approximation of nutrient intake by a group (or groups) of healthy people – used when an RDA cannot be determined. Used by IOM and European Food Safety Authority (EFSA).

Recommended intake (RI): Is used in the Nordic Nutrition Recommendations (NNR) and is based on different types of scientific evidence, and should, when consumed as part of a varied, well-balanced diet, assure optimal function and development and contribute to a reduced risk of major chronic diseases.
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. These maximum limits apply until common limits are established in the EU.

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

Assessment of magnesium

The Norwegian Food Safety Authority will evaluate the national maximum limit for magnesium in the food supplement regulation, which is currently 600 mg per daily dose. The minimum limit for magnesium is 75 mg per daily dose. Permitted magnesium substances, which may be used in the manufacture of food supplements, are listed in annex 2 in the food supplement regulation.

Relevant background documents

- Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Magnesium (26 September 2001)
Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority requests the Norwegian Scientific Committee for Food Safety (VKM) to assess the risk of magnesium in food supplements. The risk assessment should address the following aspects and questions:

- In 2001, the Scientific Committee on Food (SCF) set a tolerable upper intake level (UL) for magnesium of 250 mg/day for adults, including pregnant and lactating women, and children from 4 years on. The UL applies to readily dissociable magnesium salts. In the light of the latest scientific data on magnesium, should the UL be amended? Which UL should be used for establishing a maximum limit for children below 4 years?
- VKM is requested to estimate the intake of magnesium from the diet, in all age groups in the population above 1 year. VKM is also requested to estimate the intake of magnesium from drinking water.

VKM is also requested to assess the risk for a too low intake in some population groups, evaluated against the Norwegian recommendation for intake of magnesium.
Assessment

1 Introduction

Magnesium is an essential mineral which has multiple functions; it is a required cofactor for more than 300 enzyme systems in the body, e.g. for energy-dependent membrane transport, for gene regulation, and for sustained electrical potential in excitable cells.

Magnesium plays a major role in bone and mineral homeostasis and can directly affect bone cell functions as well as hydroxyapatite crystal formation and bone-growth. Low magnesium concentration in drinking water has been shown to be a risk factor for hip fractures in Norway (Dahl et al., 2013), although no association was found between dietary intake of magnesium and hip fractures in a recent meta-analysis (Farsinejad-Marj et al., 2016).

The Norwegian nutrition recommendations (Helsedirektoratet, 2014), based on the Nordic Nutrition Recommendations 2012 (NNR Project Group, 2012), advise a daily intake of 280 mg magnesium per day for women and 350 mg for men.

VKM emphasises that this risk assessment is addressing magnesium in food supplements and not in foods in general. Magnesium ingested as a naturally occurring substance in foods is not found to be of health concern.

Excessive magnesium intake (magnesium salts) has a well-known laxative effect and is also used as a pharmaceutical drug for that purpose. This pharmacological effect of desired laxative effect is not the scope of this report.
2 Hazard identification and characterisation

2.1 Chemistry, absorption and metabolism

The paragraphs in this chapter (2.1) are mostly obtained directly from the following sources: 1) Nordic Nutrition Recommendations 2012 (NNR Project Group, 2012) and 2) EFSA, Scientific Opinion on Dietary Reference Values for magnesium (EFSA, 2015).

2.1.1 Chemistry

Magnesium belongs to group II of the third period in the Periodic System of Elements. Calcium and zinc belong to the same group II. Magnesium has the molecular weight 24.312 g/mol with atomic number 12 and valency 2.

2.1.2 Metabolism

Magnesium is a required cofactor for over 300 enzyme systems and is required for both anaerobic and aerobic energy generation and for glycolysis. Magnesium is present in mitochondria to carry out oxidative phosphorylation. The widespread involvement of magnesium in numerous physiological functions and its metabolic interaction with other minerals makes it difficult to relate magnesium deficiency to specific symptoms.

2.1.3 Absorption

At normal dietary intakes of magnesium, 20-60% is absorbed and the absorption is inversely proportional to the amount ingested. Magnesium absorption takes place in the distal small intestine, mainly (90%) in ionised form through a paracellular process in tight junctions which is driven by electrochemical gradients, but also by an active Mg-specific transport protein/channel, not yet very well defined (Fine et al., 1991). However, it is uncertain to what degree the composition of the diet influences absorption. In a study where a standard meal was supplemented with 0, 120, 243, 486 and 972 mg magnesium as magnesium acetate, it was shown that magnesium absorption was reduced from 65% at the lowest to 11% at the highest intake (Fine et al., 1991). Using a stable isotope single labelling method, Sabatier et al. (2003) found that a mean (SD) of 45.7% (4.6) of magnesium was absorbed from magnesium rich mineral water containing 30 mg of Mg/L.

Hypermagnesemia has been found in patients with impaired renal function in connection with high intake of supplementary magnesium salts which can result in serious neurological or cardiac symptoms. However, hypermagnesemia has not been found without impaired
renal function. In individuals without kidney impairment, the kidneys manage to maintain magnesium homeostasis across a wide range of dietary intakes.

Intake of large doses of magnesium salts from supplements will, because of low absorption rate, result in an osmotic laxative effect. While this effect is desired in certain pharmacological settings, diarrhea as a result of magnesium supplementation is considered the main adverse effect in subjects with no kidney impairment.

2.1.4 Occurrence

The earth’s crust contains approximately 2% magnesium and sea water up to 55 mmol/L (1.2-1.3 g/L). Magnesium is an alkaline metal and occurs as free cation Mg$^{2+}$ in aqueous solution, or as the mineral part of a large variety of compounds such as chlorides, carbonates and hydroxides. Dietary sources of magnesium include green leafy vegetables, legumes, whole grain cereals, dark chocolate, nuts, fish and seafood, banana and coffee. Water (hard) can contain magnesium which may contribute to total magnesium intake.

The body contains approximately 21-28 g of magnesium related to a healthy man weighing 70 kg. Forty to 45% of the body’s magnesium is intracellular in muscles and soft tissue, 1% being extracellular while the majority of magnesium is deposited in the skeleton (about 60%). The normal serum magnesium concentration is 0.7 to 1.0 mmol/L (1.8 to 2.3 mg/dL).

2.1.5 Interaction with calcium and zinc

In the report from EFSA (2015) to set dietary reference values (DRV) for magnesium, it is stated that balance studies performed in children and adults did not detect an interaction between magnesium and calcium balance, while a high zinc intake (53 mg/day) can affect magnesium balance negatively. Protein may increase magnesium absorption, while intake of fibre and oxalic acid had no effect on magnesium balance. Manganese is mentioned to interact with magnesium balance and to be interchangeable with magnesium in the energy metabolism. It is however concluded, that that data on interaction between magnesium and other minerals, proteins or fibre are limited and cannot be used for setting DRV for magnesium.

2.2 Previous reports on safe upper level for magnesium

2.2.1 Dietary reference intakes for Calcium, Phosphorous, Magnesium Vitamin D and Fluoride. Institute of Medicine (USA), 1997

In the report from the Institute of Medicine (IOM), USA, tolerable upper intake levels (ULs) for magnesium were established and it was stated that when magnesium is ingested as a naturally occurring constituent in food, no adverse effects have been demonstrated (IOM, 1997). However, adverse effects of excess magnesium intakes have been observed with intakes from non-food sources such as various magnesium salts used for pharmacological
purposes. The primary initial manifestation of excessive magnesium from non-food sources is diarrhea caused by an osmotic effect. Non-food sources of magnesium can also cause nausea and abdominal cramping. It had also been documented that magnesium is absorbed more efficiently from the normal concentrations found in food than it is from the higher doses found in non-food sources. The presence of food counteracts the osmotic effect of magnesium salts in the gut. It is not known if all magnesium salts induce diarrhea, but it was assumed that there were no major differences between the different magnesium salts.

Very large doses of magnesium salts (30 g for several days or a single dose of 465 g magnesium) used for pharmacological purposes have been shown to give serious adverse effects such as metabolic alkalosis, severe diarrhea and dehydration.

No UL was set for magnesium from natural food sources, since no adverse effects had been found. Mild diarrhea or other gastrointestinal symptoms resulting from use of magnesium salts were chosen as the most sensitive toxic manifestations of excess magnesium intake from non-food sources. A UL of 350 mg magnesium per day was set for adults and children > 8 years based on a lowest observed adverse effect level (LOAEL) seen in a study where 6 of 21 patients developed diarrhea while receiving 360 mg/day of magnesium chloride (Bashir et al., 1993). An uncertainty factor (UF) of 1 was chosen due to the very mild reversible nature of the adverse effects. It was also mentioned that some individuals of the population may encounter diarrhea or gastrointestinal symptoms from doses well tolerated by others. UL was set for children 1-8 years based on body weight since it was assumed that children are equally susceptible to the osmotic effect of non-food sources as adults. A summary of the ULs for various age groups in the IOM (1997) reports are given in Table 2.2.1-1.

Table 2.2.1-1: The IOM (1997) ULs for supplementary magnesium in various age groups in the USA.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>UL for supplementary magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>Not possible to establish</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>65 mg/day</td>
</tr>
<tr>
<td>4-8 years</td>
<td>110 mg/day</td>
</tr>
<tr>
<td>Children &gt;8 years, adolescents and adults</td>
<td>350 mg/day</td>
</tr>
<tr>
<td>Pregnant and lactating women</td>
<td>350 mg/day</td>
</tr>
</tbody>
</table>

Special considerations were given to individuals with impaired renal function, but magnesium from food was considered insufficient to cause adverse effects in this patient group.

Details about the literature search were not presented.

2.2.2 Opinion of the Scientific Committee on Food on the tolerable upper intake level of magnesium. Scientific Committee on Food (EU), 2001

As in the document from IOM (1997), the Scientific Committee on Food (SCF, 2001) defined mild diarrhea as the most sensitive non-desirable effect if magnesium supplements are taken for nutritional purposes. It was stated that (i) adaptation to higher oral doses is known, (ii)
that a mild laxative effect may be desirable, (iii) that a mild laxative effect has been frequently observed also in placebo groups, (iv) that a given daily dose of magnesium is better tolerated when it is divided into several portions, and (v) that the administration form (aqueous solution, capsules, tablets) may play a role. Twenty studies from 1984 to 2001 reporting mild diarrhea were included in the EFSA opinion. The results in the papers included in this SCF opinion are recited in Table 2.2.2-1.

Table 2.2.2-1: Results from papers included in SCF (2001) copied from SCF.

<table>
<thead>
<tr>
<th>Total Mg dose* (mg/day)</th>
<th>Diarrhea (n)</th>
<th>Doses per day</th>
<th>Administration form</th>
<th>Mean age (years)</th>
<th>Gender</th>
<th>Salt</th>
<th>Weeks</th>
<th>Ref.**</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0/130</td>
<td>3</td>
<td>Tablets</td>
<td>5.3-17.4</td>
<td>M,F</td>
<td>Asp.Cl</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>245</td>
<td>0/112</td>
<td>2</td>
<td>Granules</td>
<td>8.1 (4-12)</td>
<td>M,F</td>
<td>Asp.Cl</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>245</td>
<td>0/181</td>
<td>2</td>
<td>Granules</td>
<td>4-12</td>
<td>M,F</td>
<td>Asp.Cl</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>250</td>
<td>0/31</td>
<td>1</td>
<td>Tablets</td>
<td>58</td>
<td>F</td>
<td>Hydroxide</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>360</td>
<td>1/32</td>
<td>3</td>
<td>Granules</td>
<td>37 (18-65)</td>
<td>M,F</td>
<td>Pyrrolidine carboxylic acid salt</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>365</td>
<td>0/17</td>
<td>3</td>
<td>Tablets</td>
<td>52 (33-66)</td>
<td>M,F</td>
<td>Asp.Cl</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>365</td>
<td>0/39</td>
<td>3</td>
<td>Granules</td>
<td>40 (20-59)</td>
<td>M,F</td>
<td>Asp.Cl</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>365</td>
<td>1/278</td>
<td>3</td>
<td>Tablets</td>
<td>28 (20-38)</td>
<td>F</td>
<td>Asp.Cl</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>365</td>
<td>4/17</td>
<td>3</td>
<td>Tablets</td>
<td>71 (56-88)</td>
<td>nd</td>
<td>Lactate citrate</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>365</td>
<td>4/22</td>
<td>nd</td>
<td>Tablets</td>
<td>62</td>
<td>M,F</td>
<td>Hydroxide</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>384</td>
<td>1/25</td>
<td>6</td>
<td>Coated</td>
<td>21</td>
<td>F</td>
<td>Chloride</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>384</td>
<td>2/21</td>
<td>Divided</td>
<td>Coated</td>
<td>63 (42-73)</td>
<td>M,F</td>
<td>Chloride</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>400</td>
<td>2/20</td>
<td>nd</td>
<td>Coated</td>
<td>46 (26-65)</td>
<td>M,F</td>
<td>Chloride, oxide</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>476</td>
<td>18/50</td>
<td>2</td>
<td>Capsule</td>
<td>30 (21-50)</td>
<td>M,F</td>
<td>Oxide</td>
<td>8.5</td>
<td>14</td>
</tr>
<tr>
<td>480</td>
<td>2/12</td>
<td>nd</td>
<td>nd</td>
<td>16 (11-21)</td>
<td>M,F</td>
<td>Asp.Cl</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>480</td>
<td>2/37</td>
<td>2</td>
<td>Granules</td>
<td>28.5 ±4.5</td>
<td>F</td>
<td>Asp.Cl</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>500</td>
<td>2/20</td>
<td>3</td>
<td>Capsule</td>
<td>57</td>
<td>M,F</td>
<td>Oxide</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>576</td>
<td>0/5</td>
<td>3</td>
<td>Tablets</td>
<td>54 (38-75)</td>
<td>M,F</td>
<td>Oxide</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>970</td>
<td>Adaptation to doses</td>
<td>1-3</td>
<td>Tablets</td>
<td>50</td>
<td>M,F</td>
<td>Hydroxide</td>
<td>3x3</td>
<td>19</td>
</tr>
<tr>
<td>1095</td>
<td>8/8</td>
<td>nd</td>
<td>Tablets Granules Capsule</td>
<td>nd</td>
<td>M,F</td>
<td>Asp.HCl</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

*Referred to elemental Mg; nd = no data; M = males; F = females; Asp. = aspartate.


A LOAEL of 360/365 mg magnesium per day was found, while no laxative effect was found at 250 mg magnesium per day. Based on a NOAEL of 250 mg per day and an uncertainty factor of 1.0, UL was set at 250 mg for adults for readily dissociable magnesium salts (e.g.
chloride, sulphate, aspartate, lactate) and compounds like MgO in food supplements, water or added to food and beverages. This UL applies to adults, including pregnant and lactating women, and for children 4 years and older. No data was available for younger children, and consequently no UL was set for children younger than 3 years. It was pointed out that this UL was appropriate for adults and children >3 years with intact kidney function. It was also pointed out that most studies referred to a daily intake from two or more doses, for example 2 x 245 mg magnesium without reported diarrhea (Schimatschek and Rempis, 2001).

Toxic hypermagnesemia, presenting with hypotension or muscular weakness was seen at oral magnesium doses greater than 2500 mg, doses exceeding the UL by a factor of 10.

This UL was based on several German studies not found in MEDLINE. Details about the literature search were not presented.

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

In the toxicity chapter it was stated that no adverse effects had been associated with ingestion of magnesium as a naturally occurring substance in foods. Adverse effects had only been found with excessive magnesium intakes from various magnesium salts in supplements or drugs for pharmacologic /medical purposes (EVM, 2003). The primary effect of excessive ingestion of magnesium from non-food sources was osmotic diarrhea, and magnesium salt is used in pharmaceutical drugs because of its laxative effect.

In animal toxicity studies, the administration of magnesium had been through the intravenous route, which was not of value for the Expert Group on Vitamins and Minerals (EVM) risk assessment. In vitro genotoxicity tests were negative for magnesium chloride and magnesium sulphate. Mechanism for toxicity was not identified and no vulnerable groups were identified.

For the EVM risk assessment of magnesium in dietary supplements, seven experimental human studies were cited, see Table 2.2.3-1.

**Table 2.2.3-1:** Results from papers included in EVM (2003).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mg salt</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagy et al. 1998</td>
<td>Al-Mg hydroxy carbonate</td>
<td>1200 mg Mg/day, 20 patients for 6 weeks</td>
<td>No adverse effects</td>
</tr>
<tr>
<td>Randomised cross-over trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marken et al. 1989</td>
<td>MgO</td>
<td>486 mg Mg = 800 mg MgO, 50 healthy subjects for 60 days</td>
<td>18 of 50 reported diarrhea and 6 dropped out because of diarrhea</td>
</tr>
<tr>
<td>Randomised cross-over trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zemel et al. 1990</td>
<td>Mg aspartate</td>
<td>40 mmol =1000 mg Mg 500 x 2 in 13 patients with mild hypertension for 3 months</td>
<td>No effect on blood pressure and blood lipid concentration</td>
</tr>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Mg salt</td>
<td>Dose</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Paolisso et al. 1992 RCT</td>
<td>Mg pidolate (MAG 2)</td>
<td>16.2 mmol Mg/day =400 mg Mg in 25 young and 12 non-obese elderly diabetes mellitus patients for 4 weeks</td>
<td>No information about adverse effects</td>
</tr>
<tr>
<td>Bashir et al. 1993 RCT</td>
<td>MgO</td>
<td>384 mg Mg/day among 21 patients with stable heart failure for 6 weeks</td>
<td>Diarrhea was reported by 6 of 21 subjects</td>
</tr>
<tr>
<td>Stendig-Lindberg et al. 1993 Non-randomised uncontrolled trial</td>
<td>Mg as magnesium hydroxide</td>
<td>750 mg/day for 6 months followed by 226 mg/day for 18 months</td>
<td>No diarrhea was reported, but at the beginning Mg intake was increased stepwise so no diarrhea should occur</td>
</tr>
<tr>
<td>Altura et al. 1994 Uncontrolled trial</td>
<td>MgO</td>
<td>Diet was enriched with 452 mg magnesium per day among 18 healthy 13-38 year old males for 6 days</td>
<td>No adverse effects were reported</td>
</tr>
</tbody>
</table>

EVM (2003) concluded that there were insufficient data to establish a Safe Upper Level for magnesium although a few studies reported mild and reversible diarrhea in a small percentage of patients and healthy volunteers at doses in the magnitude of 384 to 470 mg/day. However, these symptoms were not observed in the majority of studies using similar or higher doses. A guidance level of 400 mg/day for supplemental magnesium was set because it was not expected to find any significant adverse effects at this level. According to the EVM (2003) report, an uncertainty factor for human variability was not needed because the value is derived from human studies, some of which reported no adverse effects at higher doses.

Details about the literature search were not presented.

### 2.2.4 A safe strategy for addition of vitamins and minerals to foods. (Denmark, 2005)

In an attempt to provide safe guidelines for food fortification with vitamins and minerals, the Danish Institute for Food and Veterinary Research proposed a model which included ULs for vitamins and minerals. In cases where no UL had been set, a guidance level was suggested. In this food fortification model, the Danish group adopted the UL set by SCF in 2001 of 250 mg magnesium per day (Rasmussen et al., 2006).

### 2.2.5 Summary of previous reports on magnesium

Magnesium intake from food sources has not been shown to cause any adverse effects in healthy people. Diarrhea has been established as the main adverse effect of magnesium given as magnesium salts in supplements. SCF established in 2001 a UL of 250 mg magnesium for supplemental use. This UL was based on several German studies not found in MEDLINE.
IOM suggested in 1997 an UL of 350 mg magnesium per day for adults and children > 8 years based on a LOAEL seen in a study where 6 of 21 patients developed diarrhea while receiving 360 mg/day of magnesium chloride (Bashir et al., 1993). Uncertainty factor (UF) was set to 1, because the adverse effect was reversible mild diarrhea and the study was performed in humans. UL was set for children 1-8 years based on body weight since it was assumed that children are equally susceptible to the osmotic effect of non-food sources of magnesium as adults.

EVM (2003) set a guidance level (GL) of magnesium salts at 400 mg per day based on mild diarrhea seen in patients and healthy volunteers at levels of 384 to 470 mg/day. However, these symptoms were not observed in the majority of studies using similar or higher doses. The potential implications for vulnerable groups such as infants and older people need to be addressed by further studies.

Conclusions from previous reports on UL for magnesium are summarised in Table 2.2.5-1.

**Table 2.2.5-1:** Conclusions from previous reports on UL for magnesium.

<table>
<thead>
<tr>
<th>Previous reports</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCF (2001), EU</td>
<td>UL for Mg in supplements was set at 250 mg based on a NOAEL for observed mild diarrhea in adults and children &gt; 3 years. No UL was set for children 1-3 years.</td>
</tr>
<tr>
<td>IOM (1997), USA</td>
<td>The UL for Mg for adolescents and adults was established at 350 mg/day based on a LOAEL of 360 mg /day and a UF very close to 1.0. UL for children 1-3 years = 65 mg/day and for children 4-8 years = 11 mg/day based on body weight.</td>
</tr>
<tr>
<td>EVM (2003), UK</td>
<td>A guidance level of 400 mg/day of supplemental Mg was set. Infants and older people have to be addressed further.</td>
</tr>
<tr>
<td>Rasmussen et al. (2006), Denmark</td>
<td>Adopted the UL set by the SCF in 2001.</td>
</tr>
</tbody>
</table>
2.3 Recommended intakes of magnesium

Recommendations for intake of magnesium have been given by several authorities. Table 2.3-1 summarises recommendations from NNR, 2012 and EFSA, 2015. Recommendations from IOM, USA are from 1997, and considered to be too old as NNR and EFSA have more updated knowledge.

Table 2.3-1: Overview of recommended intakes (RI) for magnesium from NNR Project Group (2012).

<table>
<thead>
<tr>
<th>Age groups</th>
<th>mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-23 months</td>
<td>85</td>
</tr>
<tr>
<td>2 - 5 years</td>
<td>120</td>
</tr>
<tr>
<td>6 - 9 years</td>
<td>200</td>
</tr>
<tr>
<td>Females 10 ≥75 years (including lactating and pregnant women)</td>
<td>280</td>
</tr>
<tr>
<td>Men 10 - 13 years</td>
<td>280</td>
</tr>
<tr>
<td>Men 14 ≥75 years</td>
<td>350</td>
</tr>
</tbody>
</table>

Table 2.3-2: Overview of adequate intakes (AI) for magnesium from EFSA (2015).

<table>
<thead>
<tr>
<th>Age groups</th>
<th>mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - &lt;3 years</td>
<td>170</td>
</tr>
<tr>
<td>3 - &lt;10 years</td>
<td>230</td>
</tr>
<tr>
<td>Females 10 - &lt;18 years</td>
<td>250</td>
</tr>
<tr>
<td>Females ≥18 years (including lactating and pregnant women)</td>
<td>300</td>
</tr>
<tr>
<td>Men 10 - &lt;18 years</td>
<td>300</td>
</tr>
<tr>
<td>Men ≥18 years</td>
<td>350</td>
</tr>
</tbody>
</table>

The Nordic recommendations will be used in the risk characterisation in this VKM opinion. The Nordic recommendations are the basis for and equal to the Norwegian recommendations for magnesium.

2.4 Literature searches

A systematic search for published literature with no restriction on publication year was performed in MEDLINE and EMBASE in order to retrieve any human studies on adverse effects caused by magnesium. Both databases were searched to ensure comprehensive study retrieval. The literature search was performed by the panel coordinator in the secretariat on 11 September 2015.

In addition, a systematic literature search was performed in MEDLINE and EMBASE on 10 November 2015, aiming at identifying relevant animal studies with magnesium. Titles and abstracts were searched for the period 2001 to present.

We also searched MEDLINE for human studies on the interaction between magnesium supplements and absorption of other divalent cations.

The search strategies for the searches are shown in Appendix 1.
2.4.1 Publication selection

The study types for inclusion in this opinion were systematic reviews and meta-analyses of human studies, randomised controlled trials and prospective cohort studies presenting data for magnesium supplementation in at least one subgroup. The criteria for inclusion were:

- Magnesium in relation to health outcomes was the main objective (or one of the main objectives) in the article.
- Results for magnesium could be separated from results from other constituents in supplements.
- Study population representative for the general population.

The literature search for human studies identified 2042 articles, and the literature search for animal studies identified 364 articles. It may be some overlap of articles between the two searches.

Study titles and abstracts were independently reviewed by the two authors according to the above mentioned inclusion criteria. Titles were selected if chosen by one of the experts and resulted in 37 full text publications which were examined in full text.

No animal studies were found relevant for inclusion. In vitro studies were excluded, as were position papers, conference abstracts/summaries and editorial comments.

Nor were we able to find any relevant human studies on the interaction between magnesium and other minerals.

A final total of 13 publications were identified and included in the results in this report (see Figure 2.4.1-1).
Figure 2.4.1-1: Flowchart for the literature search for supplemental magnesium and associated health outcomes and the subsequent selection of publications.

The majority of the RCTs retrieved in the literature search investigated possible beneficial effects of magnesium. The study design of these "effect" studies might not be suitable for detecting possible negative health effects, but are, however the best at hand.

2.5 Human studies investigating supplementary magnesium and adverse health effects

Mild diarrhea is the most frequently reported adverse health effect in the literature included from our literature searches. A total of 13 studies are included; 10 randomised controlled trials, one open-labelled trial, one high-dose magnesium study and one meta-analysis.

2.5.1 Randomised controlled trials

An overview of the results in the included randomised controlled trials is given in Table 2.5.1-1.
Table 2.5.1-1: Overview of all randomised controlled trials included in this opinion.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participant characteristics</th>
<th>Country</th>
<th>No. Subjects</th>
<th>Dose</th>
<th>Main endpoint</th>
<th>Length of follow-up</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supakatisant and Phupong (2015)</td>
<td>Pregnant women with leg cramps</td>
<td>Thailand</td>
<td>43</td>
<td>300 mg</td>
<td>Leg cramp frequency</td>
<td>4 weeks</td>
<td>Nausea and diarrhea: non-significant increase in the Mg group, 17 total</td>
</tr>
<tr>
<td>Park et al. (2015)</td>
<td>Postmenopausal breast cancer survivors</td>
<td>USA</td>
<td>88/88</td>
<td>800-1200 mg</td>
<td>Hot flashes</td>
<td>8 weeks</td>
<td>Increased incidence of diarrhea in the magnesium arms</td>
</tr>
<tr>
<td>Simental-Mendia et al. (2014)</td>
<td>18-65 years old with prediabetes</td>
<td>Mexico</td>
<td>31</td>
<td>380 mg</td>
<td>High sensitivity-CRP</td>
<td>3 months</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Abbasi et al. (2012)</td>
<td>Elderly with insomnia, mean age 65 years</td>
<td>Iran</td>
<td>23</td>
<td>500 mg</td>
<td>Sleep time</td>
<td>8 weeks</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Guerrero-Romero and Rodriguez-Moran (2011)</td>
<td>Non diabetics</td>
<td>Mexico</td>
<td>53</td>
<td>650 mg</td>
<td>Insulin resistance</td>
<td>3 months</td>
<td>3 experienced slight abdominal pain and diarrhea in magnesium vs. 1 in placebo</td>
</tr>
<tr>
<td>Roffe et al. (2002)</td>
<td>46 patients with leg cramps</td>
<td>UK</td>
<td>1st step n= 29 and 17, then crossover</td>
<td>One liquid infusion 300 mg</td>
<td>Count of leg cramps. Adverse events were recorded 3 times during the study</td>
<td>4 weeks (total length 12 weeks)</td>
<td>Twelve patients encountered new diarrhea during treatment and 5 during placebo, the difference was significant. No significant difference in other adverse events</td>
</tr>
<tr>
<td>Attias et al. (1994)</td>
<td>Young, healthy men undergoing 2 months with basic military training</td>
<td>Israel</td>
<td>150</td>
<td>167 mg</td>
<td>Noise-induced permanent hearing threshold</td>
<td>2 months</td>
<td>Adverse events are given in a table. Tinnitus, headache and dizziness somewhat higher in placebo group while nausea and stomachache were somewhat higher in treatment group, but not significantly. Study supported by Casella Med. Artesan Pharma GmbH.</td>
</tr>
<tr>
<td>Reference</td>
<td>Participant</td>
<td>Country</td>
<td>No. Subjects</td>
<td>Dose</td>
<td>Main</td>
<td>Length</td>
<td>Adverse effect</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------</td>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Purvis et al. (1994)</td>
<td>Patients with non-Insulin dependent diabetics.</td>
<td>USA</td>
<td>16</td>
<td>384 mg/day in the treatment period. A cross-over study with 6 weeks either on Mg or placebo and then switch after 2 weeks washout period</td>
<td>Blood pressure, serum glucose and blood lipid status. Occurrence of any side effects was documented</td>
<td>6 weeks</td>
<td>Four patients reported changes in bowel habits, increased frequency or diarrhea during the active phase (4 of 28=14%). Two patients had the same effect during placebo period. Headache, constipation, fatigue, increased energy and improved sight, but not any difference between active treatment and placebo period</td>
</tr>
<tr>
<td>Haga (1992)</td>
<td>17 patients with mild to moderate hypertension and 8 age matched normotensive controls.</td>
<td>Japan</td>
<td>17</td>
<td>600 mg</td>
<td>Blood pressure</td>
<td>2 weeks</td>
<td>No diarrhea or other side effect were encountered in patients or controls</td>
</tr>
<tr>
<td>Facchinetti et al. (1991)</td>
<td>32 women (24-39 y) with premenstrual syndrome (PMS)</td>
<td>Italy</td>
<td>32</td>
<td>3x120 mg=360 mg/day from 15th day of the menstrual period until onset of menstruation</td>
<td>PMS score and Mg concentrations in different cell compartments. Side effects reported by participants</td>
<td>4 months</td>
<td>One woman left the study because of headache and one because of diarrhea</td>
</tr>
</tbody>
</table>

**Oral magnesium for relief in pregnancy-induced leg cramps: a randomised controlled trial.** Supakatisant and Phupong, 2015

Eighty-six pregnant women with leg cramps were randomised to receive 300 mg magnesium or placebo daily for 4 weeks. The main outcome was symptoms of leg-cramps (Supakatisant and Phupong, 2015). Adverse effects such as nausea, vomiting and diarrhea were self-reported. There were 17 who experienced mild gastrointestinal symptoms in the magnesium group and 7 in the placebo group. These differences were borderline statistically significant. No serious adverse effects were observed.

**North Central Cancer Treatment Group N10C2 (Alliance): a double-blind placebo-controlled study of magnesium supplements to reduce menopausal hot flashes.** Park et al., 2014

Postmenopausal women with a history of breast cancer and bothersome hot flashes were randomised to 800 or 1200 mg magnesium daily or a placebo for 8 weeks (Park et al., 2015). The 289 US women were randomised to the three groups in a 1:1:1 ratio. An increased incidence of diarrhea and a corresponding lower incidence of constipation were reported in the magnesium arms compared with the placebo. The authors do not mention...
whether or not these differences were statistically significant. The authors stated that there "were no significant toxicity differences between the three study arms" and referred to the "Common Terminology Criteria for Adverse Events version 4".

**Oral Magnesium Supplementation Decreases C-reactive Protein Levels in Subjects with Prediabetes and Hypomagnesemia: A Clinical Randomized Double-blind Placebo-controlled Trial. Simental-Mendia et al., 2014**

Sixty-two men and women aged 18-65 years with prediabetes and hypomagnesemia were randomised in a 1:1 ratio to receive 380 mg elemental magnesium or placebo per day for 3 months (Simental-Mendia et al., 2014). The main outcome was C-reactive protein (CRP) concentration. All but two individuals completed follow up in each group. There is no description on any adverse effects.

**The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. Abbasi et al., 2012**

In this randomised, double-blind, placebo controlled trial 250 mg elemental magnesium was given to older people with insomnia twice daily for 8 weeks (Abbasi et al., 2012). There was no mention of adverse effects, however there were only 3 who did not complete the study which was apparently due to lack of compliance to the supplements or that they did not adhere to the protocol.

**Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. Guerrero-Romero and Rodriguez-Moran, 2011**

Non-diabetic individuals with low serum magnesium levels were randomised in a 1:1 ratio to receive 650 mg magnesium or placebo daily for three months. The main outcome of the trial was "the ability of beta-cells to compensate for variations in insulin sensitivity in non-diabetic individuals with significant hypomagnesaemia" (Guerrero-Romero and Rodriguez-Moran, 2011). There were 3 adverse events in the magnesium group and 1 in the placebo group. There were no severe adverse events, but they do not mention how adverse events were observed or recorded.

**Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps. Roffe et al., 2002**

In this study 46 patients completed the 12 weeks study plan with 2 weeks run-in period, 4 weeks randomised treatment/placebo, 2 weeks wash-out period and 4 weeks randomised treatment/placebo (Roffe et al., 2002). The treatment consisted of 300 mg magnesium in sachets which were to be dissolved in water for one drink. Sixty-eight patients were included, but 21 dropped out before completion and of these 4 because of diarrhea while on magnesium treatment and one on placebo. Of the patients who completed the study 12 patients in the treatment group got new diarrhea, while 5 got new diarrhea during placebo
period. The difference in new reported diarrhea cases was statistically significant. Otherwise there were no differences in reported adverse events during treatment and placebo periods.

**Oral Magnesium intake reduces permanent hearing loss induced by noise exposure. Attias et al., 1994**

In a placebo controlled double-blind study, hearing loss during two months of training was investigated in 300 healthy military recruits. One hundred and fifty participants were randomised to receive 167 mg Mg-aspartate and 150 recruits received Na-aspartate in a daily drink (Attias et al., 1994). No serious adverse events were reported during the study. Symptoms reported in the treatment and placebo groups were tinnitus, headache, dizziness, nausea, stomachache, vomiting, diarrhea and weakness. Only stomachache was more frequently reported in the treatment group (17 vs. 9 cases).

**Effect of oral magnesium supplementation on selected cardiovascular risk factors in non-insulin-dependent diabetics. Purvis et al., 1994**

In a double-blind crossover study the effect of 385 mg/day of a sustained-release Mg chloride tablet compared with identical-appearing placebo were investigated for six weeks in 28 patients with non-insulin dependent diabetes mellitus (NIDDM) patients with two weeks of wash-out period in between (Purvis et al., 1994). Reported side effects were relatively infrequent, with altered bowel habits as the most common side effect. Four patients in the treatment group and two patients in the placebo group complained about increased frequency of stools or diarrhea, while one patient complained about constipation in the treatment group. Two patients in the treatment group and three patients in the placebo group complained about headache.

**Effects of dietary magnesium supplementation on diurnal variations of blood pressure and plasma Na⁺, K⁺ - ATPase activity in essential hypertension. Haga, 1992**

Seventeen patients with mild-to-moderate essential hypertension and 8 age matched controls were given 600 mg MgO orally three times per day (200 mg Mg x3) for 2 weeks. No diarrhea or other side effects were encountered (Haga, 1992).

**Oral magnesium successfully relieves premenstrual mood changes. Facchinetti et al., 1991**

In a double-blind randomised study 32 women with confirmed premenstrual syndrome (PMS) symptoms were randomised to receive Mg pyrrolidone carboxylic acid or placebo for two menstrual cycles (Facchinetti et al., 1991). After two periods all women received Mg pyrrolidone carboxylic acid for another two periods. The Mg pyrrolidone carboxylic acid was administered three times per day 3 x 120 mg from day 15 in the menstrual cycle until the start of the next menstrual period. Two women dropped out of the study; one due to diarrhea and one due to headache, but the authors commented that the treatment was well tolerated.
2.5.2 Other studies

2.5.2.1 Systematic reviews and meta-analyses

Most of the meta-analyses including magnesium have focused on parenteral magnesium and many have not reported adverse effects. Only one meta-analysis fulfilled the inclusion criteria.

Effect of magnesium therapy on nocturnal leg cramps: a systematic review of randomised controlled trials with meta-analysis using simulations. Sebo 2014

Seven RCTs between 1995 and 2012 with a total of 361 participants were included in this analysis, all comparing magnesium to placebo. The objective of the meta-analysis was to evaluate the effect of magnesium therapy on nocturnal leg cramps. Three of these trials included only pregnant women (Sebo et al., 2014). The doses of elemental magnesium were in all but one trial between 300 and 360 mg per day. One trial provided 1800 mg per day. Adverse effects identified in these trials were summarised in a separate table and consisted mainly of different gastrointestinal symptoms. Overall gastrointestinal side effects were slightly more common with magnesium therapy than with placebo. The authors did not pool these events and attempt to perform an overall statistical analysis. In none of the individual studies was the frequency of adverse events significantly higher in the magnesium group compared to the placebo groups. No serious or life-threatening adverse reaction was reported in relation to magnesium treatment.

2.5.2.2 Other studies – not RCTs or systematic reviews

An overview of other studies included in this report is given in Table 2.5.2.2-1.

Table 2.5.2.2-1: Overview of other uncontrolled trials included in this report.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participant characteristics</th>
<th>Country</th>
<th>Number in treatment group</th>
<th>Dose</th>
<th>Main endpoint</th>
<th>Length of follow-up</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quaranta et al. (2007)</td>
<td>Patients with a history of PMS</td>
<td>Italy</td>
<td>41</td>
<td>250 mg slow releasing Mg ions (patented) Sincrmag - Zambon Group</td>
<td>Effect of PMS syndromes; Nervous tension, mood swing, irritability, anxiety' Adverse events were monitored at each visit by the physician.</td>
<td>3 months observation s and 3 months treatment.</td>
<td>Vertigo was reported in one patient during treatment period.</td>
</tr>
<tr>
<td>Morris et al. (1987)</td>
<td>6 healthy were given a high dose of MgSO₄ to evaluate urinary excretion</td>
<td>USA</td>
<td>6</td>
<td>13.9 g MgSO₄ given as 3.5 g in hourly increments</td>
<td>Urinary excretion</td>
<td>1 day</td>
<td>An increase in urinary excretion of magnesium, 6.9 percent after 72 hours, showing low absorption. All participants experienced mild to moderate diarrhea.</td>
</tr>
</tbody>
</table>
Pilot study of the efficacy and safety of a modified-release magnesium 250 mg tablet (Sincromag®) for the treatment of premenstrual syndrome. Quaranta et al., 2007

In this uncontrolled open-label study 41 women, aged 18–45 years, with high score on PMS symptoms were given a modified-release 250 mg magnesium tablet during three menstrual cycles (from day 20 until the start of the next menstrual period) (Quaranta et al., 2007). The tablets were effective in reducing PMS. During the study 18 women experienced a total of 72 adverse events; however none of these are listed in the article and the authors described them as non-treatment related. One woman experienced vertigo, which the authors described as a possible treatment related effect. No serious event occurred during the study and none of the women discontinued the study because of adverse events. Measurements evaluated were blood pressure, heart rate and a gynecological examination. One woman had symptoms of disease (possible endometrioma) at the last examination.

Absorption of magnesium from orally administered magnesium sulfate in man. Morris et al., 1987

Six healthy men were given a single dose of 3.48 g Mg SO₄ in 100 ml water x 4 in one hour intervals after a light breakfast, corresponding to a total magnesium dose of 13.9 g. Urinary excretion was followed for 3 consecutive days (Morris et al., 1987). The baseline excretion of magnesium was correlated with that of creatinine and sulfate. The authors concluded that a laxative dose of magnesium is poorly absorbed. All of the subjects experienced mild or moderate diarrhea.

2.5.3 Summary human studies investigating supplementary magnesium and adverse health effects

In our literature search we found six randomised controlled trials (RCT) and two clinical studies reporting on adverse events in conjunction with use of magnesium supplementation. All of these were in adults and none lasted for longer than 4 months. Diarrhoea and other mild gastrointestinal symptoms were the only adverse effects that had been observed. We were not able to identify any studies in children.

The adverse effects were graded as mild and reversible and most common were diarrhea, upset stomach, bloating, nausea, and headache. The doses used in these studies ranged from 167 to 1200 mg/day and duration varied from 2 weeks to 4 months. Although, increased frequency of diarrhea was reported in most studies, there was no significant difference between treatment group and placebo group in any of the studies. There was a non-significant higher frequency of gastrointestinal symptoms in the magnesium group compared with the control group in one study (Supakatisant and Phupong, 2015).
3 Magnesium intake

In the terms of reference from the Norwegian Food Safety Authority, VKM is requested to estimate the intake of magnesium from the diet, in all age groups in the population above 1 year. VKM is also requested to estimate the intake of magnesium from drinking water, and to assess the risk for a too low intake in some population groups.

Estimated intakes of magnesium in the Norwegian population are described below. More details are presented in tables in Appendix 2. The appendix tables also include estimates for a wider range of percentiles than those described in the text.

3.1 General description of food consumption surveys

The estimated intakes of magnesium presented in this opinion are based on data from the national food consumption surveys for young children (2-year-olds), children and adolescents (4-, 9-, and 13-year-olds) and adults (18 to 70 years). The national food consumption surveys have been 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:

"Småbarnskost 2007" in 2-year-old children is based on a semi-quantitative food frequency questionnaire (FFQ). 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 (participation rate 56%) (Kristiansen et al., 2009).

"Ungkost 2000" in 4-, 9- and 13-year-olds is based on a 4-day food intake registration with a pre-coded food diary. Food amounts were presented in predefined household units or as portions estimated from photographs. The study in 4-year olds was conducted in 2001, and 391 children participated (Polestad et al., 2002). The study in 9- and 13-year-olds was conducted in 2000 and 810 9-year old children and 1005 13-year old adolescents participated (Øverby and Andersen, 2002).

"Norkost 3" 2010-11 in adults 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 925 women and 862 men aged 18 to 70 years participated (participation rate 37%).

The daily intake of magnesium from diet and supplements in these surveys was computed by using food databases in the software system (KBS) developed at the Institute of Basic Medical Sciences, Department of Nutrition, at the University of Oslo. The food databases are
mainly based on various versions of the official Norwegian food composition table (Rimestad et al., 2000) and are continuously updated with data on new food items.

In this chapter, all values are given in milligrams, because this is the norm when setting recommendations or estimating intake in the KBS system.

3.2 Estimated intakes in various age groups

The intakes summarised in this chapter are given in tables in Appendix 2.

In adults (n=1787)

The mean intake of magnesium from the diet alone is 391 mg/day (median 373 mg/day) in adults. Intake of magnesium in the 5th percentile (P5) is 209 mg/day and in the 95th percentile (P95) is 635 mg/day.

In Norkost 3, 238 participants (13%) have reported that they use supplements with magnesium. Their mean total intake of magnesium including from food supplements is 490 mg/day (median 469 mg/day), P5 intake is 264 mg/day and P95 intake is 807 mg/day.

Mean intake of magnesium from supplements alone in adults reporting to use supplements including magnesium is 100 mg/day (median 67 mg/day), P5 intake is 9 mg/day and P95 intake is 300 mg/day.

In women (n=925), the mean intake of magnesium from the diet alone is 346 mg/day (median 333 mg/day) in adults. The P5 intake is 188 mg/day and the P95 intake is 558 mg/day.

The mean total intake of magnesium including from food supplements among women (n=151) (users of supplements including magnesium only) is 462 mg/day (median 446 mg/day), P5 intake is 253 mg/day and P95 intake is 761 mg/day.

In men (n=862), the mean intake of magnesium from the diet alone is 440 mg/day (median 420 mg/day) in adults. The P5 intake is 243 mg/day and in the P95 intake is 687 mg/day.

The mean total intake of magnesium including from food supplements among men (n=87) (users of supplements including magnesium only) is 537 mg/day (median 519 mg/day), P5 intake is 267 mg/day and P95 intake is 880 mg/day.

In 13-year-olds (n=1005)

The mean intake of magnesium from the diet alone is 247 mg/day (median 232 mg/day) in 13-year-olds. The P5 intake is 123 mg/day and the P95 intake is 410 mg/day.
In Ungkost 2000 (13-year-olds), 91 participants (9%) have reported that they use supplements with magnesium. Their mean total intake of magnesium including from food supplements is 308 mg/day (median 288 mg/day), P5 intake is 174 mg/day and P95 intake is 493 mg/day.

Mean intake of magnesium from supplements alone in 13-year-olds reporting to use supplements including magnesium is 61 mg/day (median 56 mg/day), P5 intake is 18 mg/day and P95 is 139 mg/day.

In 9-year-olds (n=810)

The mean intake of magnesium from the diet alone is 237 mg/day (median 231 mg/day) in 9-year-olds. The P5 intake is 138 mg/day and the P95 intake is 361 mg/day.

Mean intake of magnesium from supplements alone in 9-year-olds reporting to use supplements including magnesium is 53 mg/day (median 56 mg/day), P5 intake is 18 mg/day and P95 is 75 mg/day.

In 4-year-olds (n=391)

The mean intake of magnesium from the diet alone is 186 mg/day (median 179 mg/day) in 4-year-olds. The P5 intake is 115 mg/day and the P95 intake is 279 mg/day.

Mean intake of magnesium from supplements alone in 4-year-olds reporting to use supplements including magnesium is 54 mg/day (median 56 mg/day), P5 intake is 18 mg/day and P95 is 80 mg/day.

In 2-year-olds (n=1674)

The mean intake of magnesium from the diet alone is 230 mg/day (median 221 mg/day) in 2-year-olds. The P5 intake is 131 mg/day and the P95 intake is 361 mg/day.

In Småbarnskost 2007 only 10 participants (0.5%) have reported to use supplements with magnesium. Their mean total intake of magnesium including from food supplements is 266 mg/day (median 269 mg/day).
3.3 Estimated intake from water

According to data from the Norwegian Waterworks Registry, the magnesium concentrations in water from Norwegian Waterworks are generally low (NFSA). Mean (SD) magnesium concentration in 45 waterworks in 2014 was 2.4 (2.6) mg/L water. A mean intake of water between 2-3 L per day would give a total intake of magnesium of 4.8 to 7.2 mg per day from water. The range varied from 0.3 to 11 mg magnesium/L. Assuming an intake of water of 2-3 L per day, the highest magnesium concentration would give an additional intake of 22 to 33 mg magnesium, contributing with 8-12% of the RI for women. However, about 60% of the waterworks had a magnesium concentration below 2 mg/L, indicating water as a poor source for magnesium and that the contribution is negligible for the majority of the population.

3.4 Intakes below the recommendations for magnesium

VKM is also requested to assess the risk for a too low intake of magnesium in the various age groups. The recommendations for magnesium intakes are summarised in chapter 2.3.

The proportion of participants with magnesium intakes below the recommendations in the various age groups are as follows:

- 2-year-olds: 5% have an intake from food and supplements below the recommendations at 120 mg magnesium per day.
- 4-year-olds: 5% have an intake from food and supplements below the recommendations at 120 mg magnesium per day.
- 9-year-olds: 30% have an intake from food and supplements below the recommendations at 200 mg magnesium per day.
- 13-year-olds: 70% have an intake from food and supplements below the recommendations at 280 mg magnesium per day.
- Adult, women: 25% have an intake from food and supplements below the recommendations at 280 mg magnesium per day.
- Adult, men: 25% have an intake from food and supplements below the recommendations at 350 mg magnesium per day.
4 Risk characterisation

4.1 Establishment of a safe upper level or tentative safe upper level for magnesium in food supplements

Available evidence from RCTs that have monitored adverse effects from magnesium supplements is limited. Readily dissociable magnesium salts in food supplements may cause osmotic diarrhoea which is the most frequently reported adverse effect. We were not able to identify a NOAEL where the gastrointestinal effects did not occur. However, the reported gastrointestinal adverse effects are considered relatively mild.

Previous reports have arrived on ULs or guidance levels (GLs) for supplemental magnesium ranging from 250 SCF (2001) to 400 mg per day (EVM, 2003).

The most recent report from EVM in 2003 proposed a GL for supplemental magnesium at 400 mg per day, although this dose could cause reversible osmotic diarrhoea. At this intake it has been reported in randomised controlled trials that magnesium supplementation caused diarrhea. The EVM report also included an evaluation of in vitro genotoxicity studies which were negative for magnesium chloride and magnesium sulphate. Two of the previous reports (IOM, 1997; SCF, 2001) used an uncertainty factor of 1, which was chosen due to the very mild and reversible nature of the adverse effects. The third report concluded that no uncertainty factor was needed (EVM, 2003). More severe adverse effects such as reversible hypotension and muscular weakness have been reported only at doses of 2500 mg magnesium per day or higher.

In 2001, SCF established a UL for magnesium at 250 mg/day for readily dissociable supplemental magnesium salts. The UL from SCF (2001) was based on a NOAEL at 250 mg/day were no diarrhea was reported. We have however not been able to find the research reports constituting the basis for this NOAEL. The UL from SCF (2001) is below the recommended intakes for adults.

The evaluation from IOM (1997) arrived at an UL of 350 mg magnesium per day, based on a LOAEL showing more frequently reported mild diarrhea at a level of 360 mg/day compared with occurrence in the placebo group.

In our literature search we have not been able to identify significant new evidence regarding adverse effects of magnesium.

Since the critical endpoint (gastrointestinal symptoms) is mild, rapidly reversible and no NOAEL could be identified, VKM finds it appropriate to base the UL for magnesium salts in food supplements on the LOAEL from IOM (1997). For the same reason, an uncertainty factor at 1 may be applicable for establishing a UL for magnesium salts in food supplements.
VKM therefore suggests a UL of 350 mg per day for magnesium salts in adults which is in accordance with the approach in IOM (1997) (corresponding to 5 mg/kg bw per day in a 70 kg adult). This UL will also cover the RI for the adult population.

We found no evidence that children are more susceptible to magnesium supplementation than adults. When extrapolating ULs based on body weights from EFSA’s guidance document for default values (EFSA, 2015), we arrive at ULs for children somewhat below recommended intakes for the various age categories. Taking into consideration that some children and several adolescents have intakes of magnesium below the recommendations, VKM suggests that the ULs for children equals the recommendations for each age group. The suggested ULs for magnesium in food supplements from VKM are listed in Table 4.1-1.

**Table 4.1-1:** Suggested ULs for magnesium salts in food supplements.

<table>
<thead>
<tr>
<th>Age group</th>
<th>ULs (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-3 years</td>
<td>85</td>
</tr>
<tr>
<td>Children 3-10 years</td>
<td>120-200</td>
</tr>
<tr>
<td>Children (10-&lt;14 years)</td>
<td>280</td>
</tr>
<tr>
<td>Adolescents (14-&lt;18 years)</td>
<td>280</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>350</td>
</tr>
</tbody>
</table>

Except patients with renal failure, no groups have been reported to be at a particularly high risk of adverse health effects from magnesium supplements.

**4.2 Evaluation of high magnesium intakes**

 Reported use of magnesium supplementation was 13% in the adult population and about 10% among children and adolescents. The 95 percentile among the adults were 300 mg/day of supplemental magnesium and 139 mg/day among 13-year-old adolescents, 75 mg/day among 9-year-old children and 80 mg/day among the 4-year-old children.

These intake calculations of magnesium supplementation are below the suggested ULs for all age groups.

**4.3 Evaluation of low magnesium intakes**

According to the estimated intakes, 25% of adult women and men had intakes below the recommendations. Almost the same percentage was below RI among the 9-year-old children; while as many as 70% of the adolescents (13-year-olds) had an intake below RI. It should also be noted that the intakes have been estimated differently for the different age categories and calculations might not have the same validity.

**4.4 Special groups**

Magnesium homeostasis might be impaired in patients with renal failure and this patient group is accordingly at risk of acute hypermagnesemia if their intake of magnesium is high.
We were not able to identify other groups who are particularly susceptible to adverse effects from magnesium supplements or who has a high intake of magnesium.
5 Uncertainties

We were not able to identify randomised, placebo-controlled trials that have supplemented with magnesium for more than 4 months. Thus, data on long-term use of this nutrient is not available. The clinical trials were designed to investigate the positive and not negative effects of magnesium. Adverse effects have been reported, but most often based on self-report in questionnaires and have focused on gastrointestinal symptoms due to osmotic diarrhea.

It should be noted that the intakes have been estimated based on various dietary surveys for the different age categories and a comparison of estimates across age groups can be misleading. The estimated intakes in the higher and lower percentiles are always associated with a higher degree of uncertainty than mean or median intakes. Data from "Ungkost 2000" are old, and the use of food supplements may have changed in children and adolescents.

There is also indications that intake of magnesium may interact with the uptake of other divalent cations such as zinc, calcium and iron. However, there is little experimental data from human populations regarding these interactions.
6 Conclusions with answers to the terms of reference

Previous reports have arrived on ULs (or guidance levels) from 250 (SCF, 2001) to 400 mg (EVM, 2003) magnesium per day in food supplements. In 2001, SCF established a UL for magnesium at 250 mg/day. The UL from SCF (2001) was based on a NOAEL at 250 mg/day where no diarrhea was reported. VKM has not been able to verify this NOAEL.

Since the critical endpoints (gastrointestinal symptoms) are mild, rapidly reversible and no NOAEL could be identified, VKM finds it appropriate to base the UL for magnesium salts in food supplements on the LOAEL from IOM (1997). For the same reason, an uncertainty factor of 1 may be applicable for establishing a UL for magnesium salts in food supplements.

VKM therefore suggests a UL of 350 mg per day for magnesium salts in adults which is in accordance with the approach in IOM (1997) (corresponding to 5 mg/kg bw per day in a 70 kg adult). This UL will also cover the RI for the adult population.

VKM suggests that the ULs for children equal the recommended intakes for each age group:

<table>
<thead>
<tr>
<th>Age group</th>
<th>ULs (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-3 years</td>
<td>85</td>
</tr>
<tr>
<td>Children 3-10 years</td>
<td>120-200</td>
</tr>
<tr>
<td>Children (10-&lt;14 years)</td>
<td>280</td>
</tr>
<tr>
<td>Adolescents (14-&lt;18 years)</td>
<td>280</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>350</td>
</tr>
</tbody>
</table>

The intake of magnesium from the diet seems adequate for children. According to the estimated intakes, about 25% of adult women and men will have intakes of magnesium below the recommendations. Almost the same percentage was below the recommended intakes among the 9-year-old children; while as many as approximately 70% of the adolescents had an intake of magnesium below the recommendations. It should be noted that the intakes have been estimated based on various dietary surveys for the different age categories and a comparison of estimates across age groups can be misleading and has a high degree of uncertainty.

Concentration of magnesium in water is low and about 60% of the waterworks had a magnesium concentration below 2 mg/L, indicating water as a negligible source of magnesium.
7 Data gaps

There is a lack of studies of adverse effects as primary outcomes of magnesium in humans and there are no studies that have supplemented for longer than four months.

We were not able to identify any studies that have examined the effect of magnesium supplements in children. There are also lack of studies examining whether magnesium supplements interacts with the uptake of other nutrients, especially divalent cations, from the gut.

The dietary data is to a large extent collected from an ethnic Norwegian population and extrapolation to other population groups should be done with caution.
8 References


Appendix 1

Search strategy for human studies

Database: Embase <1974 to 2015 September 10>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>

1. magnesium.ti. (43439)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (9460797)
3. 1 and 2 (7555)
4. (conference abstract* or letter* or editorial*).pt. (4714936)
5. 3 not 4 (7007)
6. limit 5 to (danish or english or norwegian or swedish) (6375)
7. limit 6 to human (3580)
8. remove duplicates from 7 (2042)

Search strategy for animal studies

Database: Embase <1974 to 2015 Week 45>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>

1. magnesium.ti. (43724)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (9586455)
3. 1 and 2 (7638)
4. (conference abstract* or letter* or editorial*).pt. (4800084)
5. 3 not 4 (7077)
6. limit 5 to (danish or english or norwegian or swedish) (6438)
7. limit 6 to animals (1566)
8. remove duplicates from 7 (999)
9. limit 8 to yr="2001 -Current" (364)
Appendix 2

The tables summarises intakes from magnesium containing supplements alone (users only) and total intakes from both diet and supplements. In adults the intakes are also estimated separately for women and men as the recommendations are not equal for the genders.

Table 1: Estimated magnesium intakes from diet alone in various age groups (mg/day).

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=1787)</th>
<th>13 years (n=1005)</th>
<th>9 years (n=810)</th>
<th>4 years (n=391)</th>
<th>2 years (n=1674)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg from diet alone, mean</td>
<td>391</td>
<td>247</td>
<td>237</td>
<td>186</td>
<td>230</td>
</tr>
<tr>
<td>Mg from diet alone, median</td>
<td>373</td>
<td>232</td>
<td>231</td>
<td>179</td>
<td>221</td>
</tr>
<tr>
<td>Mg from diet alone, P5</td>
<td>209</td>
<td>123</td>
<td>138</td>
<td>115</td>
<td>131</td>
</tr>
<tr>
<td>Mg from diet alone, P25</td>
<td>295</td>
<td>186</td>
<td>191</td>
<td>156</td>
<td>180</td>
</tr>
<tr>
<td>Mg from diet alone, P75</td>
<td>465</td>
<td>294</td>
<td>271</td>
<td>210</td>
<td>269</td>
</tr>
<tr>
<td>Mg from diet alone, P95</td>
<td>635</td>
<td>410</td>
<td>361</td>
<td>279</td>
<td>361</td>
</tr>
</tbody>
</table>

Table 2: Estimated total magnesium intakes in various age groups using magnesium supplements (users only), and magnesium intakes from supplements alone (users only) (mg/day).

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=238)</th>
<th>13 years (n=91)</th>
<th>9 years (n=72)</th>
<th>4 years (n=34)*</th>
<th>2 years (n=10)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mg from food and supplements, mean</td>
<td>490</td>
<td>308</td>
<td>297</td>
<td>235</td>
<td>266</td>
</tr>
<tr>
<td>Total Mg from food and supplements, median</td>
<td>469</td>
<td>288</td>
<td>293</td>
<td>228</td>
<td>269</td>
</tr>
<tr>
<td>Total Mg from food and supplements, P5</td>
<td>264</td>
<td>174</td>
<td>197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Mg from food and supplements, P25</td>
<td>386</td>
<td>242</td>
<td>254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Mg from food and supplements, P75</td>
<td>575</td>
<td>338</td>
<td>236</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Mg from food and supplements, P95</td>
<td>807</td>
<td>493</td>
<td>422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg from supplements alone, mean</td>
<td>100</td>
<td>61</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg from supplements alone, median</td>
<td>67</td>
<td>56</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg from supplements alone, P5</td>
<td>9</td>
<td>18</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg from supplements, P95</td>
<td>300</td>
<td>139</td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No percentiles due to less than 60 consumers.
Table 3: Estimated total magnesium intakes in men and women using magnesium supplements (users only) (mg/day).

<table>
<thead>
<tr>
<th></th>
<th>Men, N3 (n=87)</th>
<th>Women; N3 (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mg from food and supplements, mean</td>
<td>537</td>
<td>462</td>
</tr>
<tr>
<td>Total Mg from food and supplements, median</td>
<td>519</td>
<td>446</td>
</tr>
<tr>
<td>Total Mg from food and supplements, P5</td>
<td>267</td>
<td>254</td>
</tr>
<tr>
<td>Total Mg from food and supplements, P25</td>
<td>434</td>
<td>359</td>
</tr>
<tr>
<td>Total Mg from food and supplements, P75</td>
<td>611</td>
<td>545</td>
</tr>
<tr>
<td>Total Mg from food and supplements, P95</td>
<td>880</td>
<td>761</td>
</tr>
</tbody>
</table>