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Assessment of iron 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

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Assessed and approved

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Competence of VKM experts

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

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the intake of iron in the Norwegian population in relation to tolerable upper intake levels (ULs). The existing maximum limit for iron in food supplements is 27 mg/day. VKM has also conducted scenario calculations to illustrate the consequences of amending the maximum limit to 5, 10, 20, 30, 40 or 50 mg/day.

Iron deficiency is one of the most common nutritional disorders in the world. Individuals with increased iron demand such as growing children and pregnant women, those who experience blood loss such as menstruating women are particularly at risk for the consequences or iron deficiency. Iron deficiency can lead to fatigue and anaemia.

The most common adverse effects of iron supplementation are reversible gastrointestinal symptoms. Chronic iron excess can lead to iron overload which is associated with several irreversible severe health outcomes such as cancers and cardiovascular diseases. Up to 1% of the population have a genetic trait that leads to accumulation of iron and renders them more vulnerable to iron excess.

An adult needs approximately 10 mg iron per day to overcome daily loss. The tolerable upper intake level (UL) for iron in adults range from 45 to 60 mg/day. However, all previous reports acknowledge the challenges in defining upper levels. The Expert Group on Vitamins and minerals (EVM), UK report provided a guidance level (GL) of 17 instead of a UL and the Nordic Nutrition Recommendations (NNR) (2012) suggested an UL of 60 mg/day, but did not suggest any clear upper levels for children. Institute of Medicine (IOM), US (2001) gives the most substantiated tolerable upper intake levels based on gastrointestinal effects, which is 40 mg/day for infants and children, regardless of age, and 45 mg/day for adolescents and adults. The Joint FAO/WHO Expert Committee on Food Additives 2003 (JECFA) also took the potential serious effects of iron overload into account and suggested a GL of 50 mg/day in adults or 0.8 mg/kg per day in children and adolescents.

Because the risks and consequences from overload are significant and potentially serious, VKM suggests that the GL from JECFA (2003) is used.

Using the GL from JECFA (2003), none of the suggested doses can be given to 2 or 4-year-old children, 9 year olds can add 5 mg iron from supplements, 13 year olds 20, and adults 30 mg without exceeding the guidance levels.

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

Sammendrag på norsk

Vitenskapskomiteen for mattrygghet har vurdert inntak av jern i den norske befolkningen i relasjon til øvre tolerable inntaksnivåer (UL). Den eksisterende maksimumsgrensen for jern i kosttilskudd er 27 mg/dag. VKM har også gjort scenarioberegninger for å illustrere konsekvensene av å endre denne maksimumsgrensen til 5, 10, 20, 30, 40 eller 50 mg/dag.

Jernmangel er en av de vanligste mangelsykdommene i verden. Personer med økt jernbehov som barn i vekst, gravide kvinner og individer med blodtap som menstruerende kvinner er spesielt utsatt for konsekvenser av jernmangel. Jernmangel kan føre til utmattelse og anemi.

De vanligste bivirkningene fra jerntilskudd er reversible gastrointestinale symptomer. Kronisk høyt jerninntak kan imidlertid føre til jernoverskudd som er forbundet med flere alvorlige irreversible negative helseeffekter som kreft og kardiovaskulære sykdommer. Opptil 1% av befolkningen er genetisk disponert for opphopning av jern i kroppen som gjør at de er sårbare for jernoverskudd.

En voksen trenger ca 10 mg jern per dag for å erstatte kroppens daglige tap av jern. De fastsatte tolerable øvre inntaksnivåene (UL) for jern hos voksne varierer fra 45 til 60 mg/dag. Men i alle de tidligere rapportene påpekes utfordringene i å fastsette øvre nivåer for jern. Ekspertgruppen for vitaminer og mineraler (EVM, 2003), UK foreslår et veiledende nivå (guidance level=GL) på 17 i stedet for et tolerabelt øvre inntaksnivå. I de nordiske ernæringsanbefalinger (NNR, 2012) er det foreslått et tolerabelt øvre inntaksnivå på 60 mg/dag for voksne, men det er ikke foreslått noen øvre nivåer for barn. Institute of Medicine (IOM, 2001), USA har etablert tolerable øvre inntaksnivåer for jern på 45 mg/dag for ungdom og voksne og 40 mg/dag for spedbarn og barn i alle aldre basert på kun gastrointestinale effekter. The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2003) inkluderte også de potensielle alvorlige negative helseeffektene av jernoverskudd i sin vurdering, og foreslo et foreløpig tolerabelt øvre inntaksnivå på 50 mg/dag hos voksne eller 0,8 mg/kg per dag hos barn og unge.

Ettersom risikoen for jernoverskudd er betydelig og konsekvensene potensielt alvorlige, foreslår VKM å bruke de foreløpige tolerable øvre inntaksnivåene fra JECFA (2003).

Vurdert opp mot de foreløpige tolerable øvre inntaksnivåene for de ulike aldersgruppene fra JECFA, kan ingen av de foreslåtte endringene av maksimumsgrensene gis til 2 eller 4 år gamle barn, 9-åringer kan ha 5 mg jern fra kosttilskudd, 13-åringer 20 mg og voksne 30 mg/dag uten å overskride de øvre inntaksnivåene.

Abbreviations and/or glossary

Abbreviations

AR – average requirement
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
GL – guidance level
LOAEL – lowest observed adverse effect level
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
IOM – Institute of Medicine, USA
RI – recommended intake
SD – standard deviation
TGL – temporary guidance level
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee For Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet]

Glossary

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

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

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.

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. $RI = AR + 2SD_{AR.}$

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 iron

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

	Minimum amount per recommended daily dose	Maximum amount per recommended daily dose
Iron (mg)	5	27

Permitted iron substances which may be used in the manufacture of food supplements are listed in Annex 2 in the food supplement regulation.

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 iron from the diet, including fortified products, in all age groups in the population above 1 year (mean, P5, P50 and P95).

VKM is also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for iron to 5, 10, 20, 30, 40 or 50 mg/day in food supplements, and to evaluate these scenarios against already established tolerable upper intake levels.

Assessment of iron

1 Introduction

Iron is a metal with an atomic mass of 55.8. It is present in biological systems as ferrous (Fe2+) and ferric (Fe3+) iron. Iron is an essential constituent of oxygen carriers, such as haemoglobin and myoglobin, and the iron contained within haem is essential for the redox reactions of numerous cytochromes.

Iron deficiency is one of the most common nutritional disorders in the world. Individuals with increased iron demand such as growing children and pregnant women, those who experience blood loss such as menstruating women are particularly at risk for the consequences or iron deficiency.

Low intake of iron and intake of foods containing inhibitors (tannins, phytates, calcium) may impair iron uptake/status. Several animal source foods such as red meat, liver, other internal organs, as well as pulses have moderate to high levels of iron. However, the bioavailability of iron varies substantially between different food sources. Chronic inflammation, particularly in the gut, may downregulate iron absorption and is considered to be an important cause of deficiency.

Iron deficiency causes reduced function of many iron dependent enzymes and proteins (Beard and Dawson, 1997). The most important effect of deficiency is poor physical performance from reduced levels of haemoglobin and myoglobin and lower activity of iron-dependent cytochromes. Deficiency might impair RNA synthesis and neurotransmitter metabolism. Iron deficiency anaemia may impair psychomotor development and cognitive performance (Grantham-McGregor and Ani, 2001).

Adults contain between 2.2 and 3.8 g of iron. In order to replenish the daily losses, an adult needs about 10 mg iron per day, assuming that only about 10% of the dietary iron is absorbed. The relative requirement in children is higher due to their higher metabolism and growth (Oski, 1993). Iron excretion via the kidneys is very low, and body iron is highly conserved. To avoid overload, iron metabolism is under tight homeostatic control that occur mainly in the gut. An exception is individuals who carry the genes for hereditary haemochromatosis who have an increased risk of iron accumulation.

Ferrous iron may increase oxidative stress, because reactive oxygen species may convert superoxide anions into highly reactive hydroxyl radicals (Mccord and Turrens, 1994). *In vitro* studies have demonstrated a relation between the intracellular free, iron pool and oxidative stress.

Adverse effects of oral iron preparations at therapeutic dose levels of 50-220 mg/day include nausea, vomiting, heartburn, epigastric discomfort, diarrhoea and intractable constipation (Blot et al., 1981; Brock and Curry, 1985; Brock et al., 1985; Coplin et al., 1991; Frykman et al., 1994; Ganzoni et al., 1974; Hallberg et al., 1966; Liguori, 1993; Reddaiah et al., 1989). The adverse effects in the upper gastrointestinal tract depend on the local iron concentrations and are due to irritation of the mucosa, alteration of gastrointestinal motility and/or rapid transfer of iron into the circulation (Cook et al., 1990). Adverse gastrointestinal effects (i.e. nausea, epigastric discomfort, constipation) have been reported after short-term oral dosage at 50 mg or lower daily of supplemental non-haem iron preparations, particularly if taken without food.

A particularly sensitive subpopulation (up to 1% of the population) are homozygotes for hereditary haemochromatosis, and are susceptible to iron overload even at normal dietary iron intakes. Such individuals should avoid iron-supplements and iron-fortified foods. The majority of homozygotes are not diagnosed or identified, and they are not aware of their greater susceptibility until sufficient iron has accumulated to produce consequences such as liver failure, cardiovascular diseases and diabetes mellitus.

There are some indications that iron overload also in a general population lead to hepatomegaly, hepatic fibrosis, and hepatoma in addition to joint inflammation, diabetes mellitus, cardiomyopathy, and cardiac failure. Although a proportion of the population has serum ferritin levels indicative of elevated iron stores (above 200 µg/L for women and 300 µg/L for men), the point at which an elevated serum ferritin level becomes associated with an increased risk of adverse effects is not known. The risk of adverse effects from iron overload in the general population, including those heterozygous for hereditary haemochromatosis, is considered to be low and the causality is inconclusive.

1.1 Recommendations

The recommended intake (RI) for different age and life stages are listed in the table below. These values were first recommended by NNR in 2004 and reiterated in 2012. The values are defined by two standard deviations above the average requirement. There are no recommendations for the first 6 months of life as infants do not seem to need extra iron even when they are exclusively breastfed. The recommended intakes of iron are given in Table 1.1-1.

Table 1.1-1 RI of iron according to age and gender (NNR Project Group, 2012).

Age group	Iron, mg/day Females	Iron, mg/day Males
6-11 mo	8	8
12-23 mo	8	8
2-5 y	8	8
6-9 y	9	9
10-13 y	11	11
14-17 y	15	11
18-30 y	15	9
31-60 y	15	9
61-74 y	9	9
≥ 75 y	9	9
Pregnant		
Lactating	15	

2 Tolerable upper intake levels

The tolerable upper intake levels for iron have been evaluated by IOM (2001), JECFA (2003), EVM (2003), EFSA (2004), Rasmussen et al., 2004 and in NNR (2012).

Institute of Medicine (IOM, 2001), USA

In its report from 2001, IOM arrived on an UL of 40 mg/day for children (including all age groups 0-13 years), and 45 mg/day in adolescents and adults. Gastrointestinal side effects were selected as the critical adverse effects on which to base the UL. Gastrointestinal distress is not serious compared with other possible adverse effects from iron overload such as cirrhosis, vascular disease and cancer. The evidence of non-gastrointestinal adverse effects of iron was, however, considered inconclusive. The report stated that the evidence is insufficient to definitively exclude iron as a risk factor for potential severe adverse effects such as cirrhosis, vascular disease and cancer. The relatively high doses for children and adolescents were justified by increased demand. The UL was based on a LOAEL of 70 mg/day (60 from supplements and 10 from foods) based on GI symptoms and used an uncertainty factor of 1.5. Because of the self-limiting nature of the observed GI effects, a higher UF was not justified.

Based on studies in infants and young children with up to 30 mg supplemental non-hem iron without any GI symptoms and additional 10 mg iron from other foods a NOAEL at 40 mg was suggested for infants and children. IOM stated that there was little uncertainty regarding the range of intakes that was likely to induce GI effects in infants and young children, and a UF of 1 was specified. For adolescents, IOM applied the same UL as for adults.

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

The UK EVM 2003 report had difficulties establishing an UL but generated a GL from several prospective studies and arrived at a LOAEL of 50 mg/day based on GI symptoms and used an uncertainty factor of 3. This GL was set to 17 mg/day.

Joint Expert Committee on Food Additives (JECFA/WHO, 2003)

The report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) from 2003 suggests a provisional maximum tolerable daily intake at 0.8 mg/kg bw per day for adults (men and women). This was because “Normal individuals have taken supplements of 50 mg Fe/day (ferrous iron) for long periods of time without any adverse effects”. The evaluation applied to iron from all sources except for iron oxides used as coloring agents, supplemental iron taken during pregnancy and lactation and supplemental iron for specific clinical requirements. For adults, they used a GL of 50 mg/day which was close to 0.8 mg/kg for an adult of 70 kg.

Scientific Committee for Food (SCF, 2003), EU

In 2003, the Scientific Committee for Food (SCF) did not set an UL for iron due to lack of data. They concluded that "Based on estimates of current iron intakes in European countries, the risk of adverse effects from high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole, except for those homozygous for hereditary haemochromatosis. However, intake of iron from food supplements in men and postmenopausal women may increase the proportion of the population likely to develop biochemical indicators of high iron stores. Some groups at special risk for poor iron status, such as menstruating women or children, could benefit from additional iron intake and/or improved availability of dietary iron."

Rasmussen et al. (Denmark, 2006)

In a review published in 2006, Rasmussen and co-workers suggested temporary guidance levels (TGL) for several minerals and vitamins (Rasmussen et al., 2006). They expressed a concern with the ULs for iron proposed by the IOM in 2001, because these ULs were based merely on the risk for acute GI symptoms and did not include the potential risk for other more serious adverse effects. They therefore suggested using the values generated by the JECFA from 2003 at 50 mg/day for adults and 0.8 mg/kg bw per day for children and adolescents. Rasmussen et al. suggested the use of body surface area ratios to establish TGLs for younger age groups, and these TGLs for children and adolescents are therefore substantially lower than the ULs suggested by IOM. VKM endorsed the Rasmussen/JECFA approach in a report from 2006 and later revised in 2013 (VKM, 2013).

Nordic Nutrition Recommendations (NNR Project Group, 2012)

The Nordic Nutrition Recommendation report arrived on a LOAEL-based UL of 60 mg/day for adults. The NNR report from 2012 concludes "Although it is not possible to establish a cause-effect relationship between iron and diseases, it seems prudent at least in sub-populations such as adult males, post-menopausal women, and heterozygotes for haemochromatosis to avoid an intake of iron above the current recommendation, which already provides for the highest need". The report also argues: "Based on homeostatic control of iron absorption and the risk of biochemical iron overload, the UL might occur at intake levels between 10 mg/day and 30 mg/day of additional iron over and above typical dietary intakes." For adults, they set the UL at 60 mg/day because "...regular intake of 60 mg/day in a fertile woman has been calculated to lead to biochemical iron overload...". Thus, their choice of UL was not based studies that have estimated safety from observation of adverse events. NNR did not suggest any ULs for children and adolescents.

2.1 Summary and discussion upper levels

Table 2.1-1 summarises available upper intake levels.

Table 2.1-1: Upper intake levels from JECFA, IOM and NNR.

Age group	JECFA (2003) (TGL) mg/day	IOM (2001) (UL) mg/day	NNR (2012) UL mg/day
Children 1 yr	10	40	
Children 2 yr	10	40	
Children 4 yr	14	40	
Children 9 yr	20	40	
Children 13 yr	30	40	
Women	50	45	60
Men	50	45	60

Because the TGLs suggested by JECFA/Rasmussen take the risk of chronic illnesses from iron overload into account, and because the TGLs for children and adolescents are based on the commonly used body surface area ratios VKM will use these values in the current report. It should also be noted that ethnic Norwegians have a relatively high risk of having hemochromatosis which also serve as an argument for our choice of relatively low upper intake levels in all age groups.

3 Intakes and scenarios iron

In the terms of reference, VKM is requested to assess the intake of iron from the diet, including fortified products, in all age groups in the population above 1 year. VKM is also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for iron in food supplements to 5, 10, 20, 30, 40 or 50 mg/day in food supplements.

3.1 Short description of the Norwegian dietary surveys

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

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

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

9- and 13-year-old children/adolescents: "Ungkost 3" is based on a 4-day food intake registration with a webbased food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 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 iron in the Norwegian population

Intakes of iron in the various age groups and in groups of users of iron supplements are presented in tables in Appendix I. The tables in Appendix I also include calculations for P25 and P75. Iron intake from fortified products is not included in the calculations, but are evaluated to be very low.

Adults

The mean intake of iron from the diet alone is 11.2 mg/day (median 10.6 mg/day) in adults (n=1787). Intake of iron in the 5th percentile (P5) is 5.6 mg/day and in the 95th percentile (P95) is 18.7 mg/day.

In Norkost 3, 222 participants (12%) reported use of supplements containing iron. Their mean total intake of iron including that from food supplements is 26.1 mg/day (median 19.8 mg/day), P5 intake is 9.8 mg/day and P95 intake is 69.9 mg/day.

Mean intake of iron from supplements alone in adults reporting use of supplements containing iron is 14.5 mg/day (median 7.0 mg/day), P5 intake is 2.5 mg/day and P95 intake is 54.8 mg/day.

13-year-olds (n=687)

The mean intake of iron from the diet alone is 8.4 mg/day (median 8.0 mg/day) in 13-year-olds. The P5 intake is 4.3 mg/day and the P95 intake is 13.6 mg/day.

In Ungkost 3 (13-year-olds), 25 participants (4%) reported use of supplements containing iron. Their mean total intake of iron including that from food supplements is 16.1 mg/day (median 13.4 mg/day).

Mean intake of iron from supplements alone in 13-year-olds reporting use of supplements containing iron is 7.4 mg/day (median 6.7 mg/day).

9-year-olds (n=636)

The mean intake of iron from the diet alone is 7.9 mg/day (median 7.6 mg/day) in 9-year-olds. The P5 intake is 4.4 mg/day and the P95 intake is 12.3 mg/day.

In Ungkost 3 (9-year-olds), 13 participants (2%) reported use of supplements containing iron. Their mean total intake of iron including that from food supplements is 13.7 mg/day (median 13.0 mg/day).

Mean intake of iron from supplements alone in 9-year-olds reporting use of supplements containing iron is 6.1 mg/day (median 4.5 mg/day).

4-year-olds (n=399)

The mean intake of iron from the diet alone is 6.6 mg/day (median 6.4 mg/day) in 4-year-olds. The P5 intake is 3.9 mg/day and the P95 intake is 9.7 mg/day.

In Ungkost 3 (4-year-olds), 16 participants (4%) reported use of supplements containing iron. Their mean total intake of iron including that from food supplements is 14.4 mg/day (median 10.7 mg/day).

Mean intake of iron from supplements alone in 4-year-olds reporting use of supplements containing iron is 7.3 mg/day (median 3.0 mg/day).

2-year-olds (n=1674)

The mean intake of iron from the diet alone is 7.1 mg/day (median 6.5 mg/day) in 2-year-olds. The P5 intake is 3.6 mg/day and the P95 intake is 12.0 mg/day.

In Småbarnskost 2007, 80 participants (5%) reported use of supplements containing iron. Their mean total intake of iron including that from food supplements is 13.6 mg/day (median 11.0 mg/day), P5 intake is 5.8 mg/day and P95 intake is 37.3 mg/day.

Mean intake of iron from supplements alone in 2-year-olds reporting use of supplements containing iron is 6.6 mg/day (median 4.5 mg/day), the P5 intake from supplements is 1.3 mg/day and the P95 intake is 31.3 mg/day.

3.3 Scenario calculations for iron

For scenario calculations VKM used the intake of iron at the P5 and at the P95 from food alone to calculate iron intake and added the suggested supplementation levels from NFSA (5, 10, 20, 30, 40 and 50 mg iron per day).

Table 3.3-1 Calculated total iron intakes for various age groups in scenarios with 5, 10, 20, 30, 40 and 50 mg as supplements added to the P5 intake from food alone (mg/day).

Age group	Intake in P5 from food	Including 5 mg from suppl	Including 10 mg from suppl	Including 20 mg from suppl	Including 30 mg from suppl	Including 40 mg from suppl	Including 50 mg from suppl
Adults	5.6	10.6	15.6	25.6	35.6	45.6	55.6
13 years	4.3	9.3	14.3	24.3	34.3	44.3	54.3
9 years	4.4	9.4	14.4	24.4	34.4	44.4	54.4
4 years	3.9	9.9	13.9	23.9	33.9	43.9	53.9
2 years	3.6	8.6	13.6	23.6	33.6	43.6	53.6

Table 3.3-2 Calculated total iron intakes for various age groups in scenarios with 5, 10, 20, 30, 40 and 50 mg as supplements added to the P95 intake from food alone (mg/day).

Age group	Intake in P95 from food	Including 5 mg from suppl	Including 10 mg from suppl	Including 20 mg from suppl	Including 30 mg from suppl	Including 40 mg from suppl	Including 50 mg from suppl
Adults	18.7	23.7	28.7	38.7	48.7	58.7	68.7
13 years	13.6	18.6	23.6	33.6	43.6	53.6	63.6
9 years	12.3	17.3	22.3	32.3	42.3	52.3	62.3
4 years	9.7	14.7	19.7	29.7	39.7	49.7	59.7
2 years	12.0	17.0	22.0	32.0	42.0	52.0	62.0

4 Assessment of the intakes of iron

We will use the TGL from JECFA/Rasmussen of 50 mg/day in adults and 0.8 mg/kg bw per day in all other age groups. This approach takes the risk of chronic illnesses from iron overload into account and was endorsed by VKM in 2006 (VKM, berikningsrapporten).

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

Using the TGLs for iron from JECFA/Rasmussen et al. (2004) at 50 mg/day or 0.8 mg/kg bw per day, the TGLs will be exceeded without including iron from supplements in 2 and 4-year-olds, 9-year-olds can add 5 mg iron from supplements, 13-year-olds up to 20 mg, and adults up to 30 mg.

5 Uncertainties

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

The percentile estimates of dietary intake are prone to random error due to the limited number of participants in the dietary surveys. There is most uncertainty 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 rates limit the representativeness of the participants compared with the background population in Norway and give rise to systematic errors in the estimated exposure data. For example, the participation rates among 13-, 9- and 4-year-olds in the dietary surveys were 53%, 55% and only 20%, respectively, while the participation rate among adults was 37%. 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.

The terms of reference has been to assess the intake in Norway in relation to already established tolerable upper intake levels. These tolerable upper levels from various authorities have been established between 2001 and 2011, and new scientific evidence may have emerged after this. No literature search has been conducted for this VKM assessment.

Only IOM has concluded with an UL while the other reports concluded that there was not sufficient data to conclude. For the determinations of the ULs for iron from EFSA, NNR, JECFA, IOM and EVM have not reached the same conclusions, indicating uncertainty regarding establishment of these ULs both for adults, and even more for children and adolescents. We chose the approach suggested by JECFA/Rasmussen because the suggested limits (TGL) from this report took into account the chronical and irreversible adverse effects of iron overload which the report from IOM did not.

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 iron from the diet, including fortified products, in all age groups in the population above 1 year (mean, P5, P50 and P95).

VKM was also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for iron (to 5, 10, 20, 30, 40 and 50 mg/day, as an example) in food supplements.

JECFA suggested a GL of 0.8 mg per kg per day in all children and adolescents and 50 mg/day in adults, VKM endorsed this TGL in 2006. VKM here chose this approach because the suggested limits (GL) took into account the chronical and irreversible adverse effects of iron overload. VKM here used these limits and estimated at what dose of iron the 95 percentile intake of iron from food was exceeded.

The two highest (40 or 50 mg/day) maximum limits for iron in food supplements listed in the terms of reference from NFSA will exceed the GL for iron. For adolescents, this limit will be exceeded at doses above 20 mg/day, for nine year olds at 10 mg and in younger children the TGL is exceeded without supplements.

Table 6-1 An overview of the conclusions for iron according to doses in supplements.
Green: No exceedance of the GL.
Red: Exceedance of the GL.

Doses in supplements / Age group	5 mg/day	10 mg/day	20 mg/day	30 mg/day	40 mg/day	50 mg/day
Adults						
13 years						
9 years						
4 years						
2 years						

7 Data gaps

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

In the chapter 5 we refer to the uncertainties setting ULs for iron. This refers to few clinical studies evaluating high intakes and different clinical endpoints.

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Appendix I

Summary tables of the intake of iron for all age groups

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

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

	Adults (n=1787)	13 years (n=687)	9 years (n=636)	4 years (n=399)	2 years (n=1674)
Iron from diet alone, mean	11.2	8.4	7.9	6.6	7.0
Iron from diet alone, median	10.6	8.0	7.6	6.4	6.5
Iron from diet alone, P5	5.6	4.3	4.4	3.9	3.6
Iron from diet alone, P25	8.3	6.3	6.3	5.2	5.1
Iron from diet alone, P75	13.5	10.0	9.3	7.7	8.5
Iron from diet alone, P95	18.7	13.6	12.3	9.7	12.0

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

	Adults (n=222)	13 years (n=25)	9 years (n=13)	4 years (n=16)	2 years (n=80)
Total iron from diet and supplements, mean	26.1	16.1	13.7	14.4	13.6
Total iron from diet and supplements, median	19.8	13.4	13.0	10.7	11.0
Total iron from diet and supplements, P5	9.8	-	-	-	5.8
Total iron from diet and supplements, P25	14.9	-	-	-	8.7
Total iron from diet and supplements, P75	26.5	-	-	-	13.4
Total iron from diet and supplements, P95	69.9	-	-	-	37.3
Iron from supplements alone, mean	14.5	7.4	6.1	7.3	6.6
Iron from supplements alone, median	7.0	6.7	4.5	3.0	4.5
Iron from supplements alone, P5	2.5	-	-	-	1.3
Iron from supplements alone, P25	5.0	-	-	-	1.4
Iron from supplements alone, P75	14.0	-	-	-	4.5
Iron from supplements alone, P95	54.8	-	-	-	31.3

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

	Women (n=925)	Girls 13 years (n=355)	Girls 9 years (n=341)
Iron from diet alone, mean	9.9	7.7	7.4
Iron from diet alone, median	9.5	7.4	7.1
Iron from diet alone, P5	4.9	4.1	4.1
Iron from diet alone, P25	7.4	6.0	6.0
Iron from diet alone, P75	11.8	9.2	8.4
Iron from diet alone, P95	16.7	11.9	11.6

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

	Women (n=137)	Girls 13 years (n=15)	Girls 9 years (n=8)
Total iron from diet and supplements, mean	27.8	16.4	11.8
Total iron from diet and supplements, median	18.4	13.4	11.3
Total iron from diet and supplements, P5	9.3	-	-
Total iron from diet and supplements, P25	14.5	-	-
Total iron from diet and supplements, P75	27.0	-	-
Total iron from diet and supplements, P95	106.0	-	-
Iron from supplements alone, mean	17.4	7.1	5.1
Iron from supplements alone, median	7.0	6.7	4.5
Iron from supplements alone, P5	1.3	-	-
Iron from supplements alone, P25	5.0	-	-
Iron from supplements alone, P75	14.0	-	-
Iron from supplements alone, P95	100.0	-	-

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

	Men (n=862)	Boys 13 years (n=332)	Boys 9 years (n=295)
Iron from diet alone, mean	12.6	9.1	8.5
Iron from diet alone, median	12.2	8.7	8.2
Iron from diet alone, P5	6.3	4.9	4.8
Iron from diet alone, P25	9.5	6.9	6.7
Iron from diet alone, P75	14.9	10.8	9.8
Iron from diet alone, P95	20.5	14.8	13.3

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

	Men (n=85)	Boys 13 years (n=10)	Boys 9 years (n=5)
Total iron from diet and supplements, mean	23.2	15.5	16.6
Total iron from diet and supplements, median	21.4	13.6	16.4
Total iron from diet and supplements, P5	10.8	-	-
Total iron from diet and supplements, P25	16.9	-	-
Total iron from diet and supplements, P75	25.6	-	-
Total iron from diet and supplements, P95	52.5	-	-
Iron from supplements alone, mean	9.8	10.9	7.6
Iron from supplements alone, median	7.0	10.7	6.7
Iron from supplements alone, P5	2.5	-	-
Iron from supplements alone, P25	5.0	-	-
Iron from supplements alone, P75	10.5	-	-
Iron from supplements alone, P95	34.7	-	-