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Assessment of dietary intake of chromium (III) in relation to tolerable upper intake level

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

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Assessment of dietary intake of chromium in relation to tolerable upper intake

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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 and Environment (Vitenskapskomiteen for mat og miljø, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), evaluated the intake of chromium. VKM has also conducted scenario calculations to illustrate the consequences of establishing maximum limit for chromium at 50, 125, 200 or 300 µg/day in food supplements. The former maximum limit for chromium of 125 µg/day in food supplements was revoked 30 May 2017.

Chromium is present in food and supplements mainly as trivalent chromium, Cr(III), whereas in drinking water, chromium is present mainly as Cr(VI). Trivalent chromium has been reported to be an essential trace element in that it has been postulated to be necessary for the efficacy of insulin in regulation of the metabolism of carbohydrates, lipids and proteins. However, no mechanisms for these roles have been identified. Absorption of Cr(III) from food has been estimated to range from 0.4 to 2.5%, depending among other factors on the chemical properties of the ingested source and the presence of other dietary components. Absorption efficiency of supplemental Cr(III) has been reported to be between 0.1 and 5.2%, and to vary between the chromium complex ingested.

In general, Cr(III) has very low toxicity by the oral route (ATSDR, 2012), and there are hardly any well-documented observations of toxicity after peroral intake in humans. In a series of animal repeat dose toxicity studies, the no observed adverse effect level (NOAEL) for general toxicity was consistently the highest dose tested (EFSA, 2014b).

Chromium is ubiquitous in foods, and rich sources include meat and meat products, oils and fats, breads and cereals, fish, pulses and spices.

There are no Norwegian recommendations for intake of chromium. The Nordic Nutrition Recommendations and the European Food Safety Authority (EFSA) concluded that no recommendations could be given for chromium due to lack of sufficient evidence (EFSA, 2014a; NNR Project Group, 2012). Furthermore, no tolerable upper intake levels (UL) have been established for chromium. However, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) suggested a tolerable daily intake (TDI) at 300 µg trivalent chromium per kg bodyweight per day based on a NOAEL in a rat study and an uncertainty factor at 1000. Due to uncertainty in the available data on developmental and reproduction toxicity, the EFSA Panel applied an uncertainty factor of 10 in addition to the default uncertainty factor of 100 for the extrapolations from rodents to humans and for human variability.

The chromium intake in Norway is not known, since Norwegian food composition data are not available. VKM has therefore based this evaluation upon intake data from EFSA. Values from EFSA are likely to be valid also for Norway. Median dietary chromium intakes were 28.6-44.0 µg/day (medians of lower and upper bound) in the category toddlers (1 to < 3 years), 55.4-76.2 µg/day in other children (3 to < 10 years), 52.1-69.4 µg/day in adolescents (≥10

to <14 years), 73.6-98.1 in adolescents (≥ 14 to <18 years) and 63.0-84.0 $\mu\text{g}/\text{day}$ in adults (18-65 years) (EFSA, 2014b). These values are 80-300 times lower than the suggested tolerable daily intake (TDI).

To illustrate the consequences of amending maximum limits for chromium to 50, 125, 200 or 300 μg per daily dose in food supplements, VKM has compared these levels and various intakes from food to the TDI at 300 $\mu\text{g}/\text{kg}$ bw per day.

Even with the highest level of supplemental intake and additional median levels as well as the 95 percentile intakes from food, the estimated exposure will be 16-48 times lower than the TDI of 300 $\mu\text{g}/\text{kg}$ bw per day in all age groups except for the 95th percentile intake in toddlers, where it will be about nine times lower.

VKM emphasises that the current assessment of maximum limits for Cr(III) in food supplements is merely based on published reports concerning upper levels from the WHO (1996), IOM (2001, USA), SCF (2003, EU), EVM (2003, UK), NNR (2012, Nordic countries), and EFSA (2014b). VKM has not conducted any systematic review of the literature for the current opinion, as this was outside the scope of the terms of reference from NFSA.

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food and Environment, chromium, food supplement, upper level, exposure.

Sammendrag på norsk

Vitenskapskomiteen for mat og miljø (VKM) har vurdert inntaket av krom i befolkningen på oppdrag fra Mattilsynet. VKM har også gjort scenarioberegninger for å illustrere konsekvensene av å endre maksimumsgrensen for krom i kosttilskudd til 50, 125, 200 eller 300 µg/dag. Tidligere maksimumsgrense var 125 µg/dag. Den ble opphevet 30. mai 2017.

I mat og kosttilskudd forekommer krom hovedsakelig som trivalent krom, Cr(III), mens seksvalent krom, Cr(VI), er den vesentligste formen i drikkevann. Trivalent krom har blitt rapportert å være et essensielt sporstoff ved at det har blitt hevdet å være nødvendig for insulinets effektivitet i regulering av metabolismen av karbohydrater, fett og proteiner. Mekanismen for denne rollen er imidlertid ikke kjent. Absorpsjon av Cr(III) fra mat kan variere fra 0,4 til 2,5 %, avhengig av blant annet av matvarenes kjemiske egenskaper og av andre komponenter i kosten. Absorpsjon av Cr (III) fra kosttilskudd er rapportert å være mellom 0,1 og 5,2 %, avhengig av kromforbindelsen.

Generelt er oralt Cr(III) lite toksisk (ATSDR, 2012), og det er knapt noen veldokumenterte observasjoner av toksiske effekter etter peroral inntak hos mennesker. I en serie toksisitetstudier med gjentatte doser i mus og rotter, var no observed adverse effect level, NOAEL - dvs. høyeste daglige dose i mg/kg kroppsvekt som ikke ga negative helseeffekter, konsekvent den høyeste dosen som ble testet (EFSA, 2014b).

Krom finnes i mange matvarer. Rike kilder inkluderer kjøtt og kjøttprodukter, fett og oljer, brød og andre kornprodukter, fisk, belgvekster og krydder.

Det er ikke gitt norske anbefalinger for inntak av krom. De nordiske næringsstoffanbefalingene og European Food Safety Authority (EFSA) konkluderte også med at det ikke er tilstrekkelig data til å gi næringsstoffanbefalinger for inntak av krom (EFSA, 2014a; NNR Project Group, 2012). Det er heller ikke fastsatt øvre tolerable inntaksnivåer (UL) for krom. EFSA-panelet for forurensninger i matvarer (CONTAM-panelet) foreslo imidlertid et tolerabelt daglig inntak (TDI) på 300 µg trivalent krom per kg kroppsvekt per dag basert NOAEL i en rottestudie og en usikkerhetsfaktor på 1000. På grunn av usikkerhet i dataene for utviklings- og reproduksjonstoksisitet, brukte EFSA-panelet en ekstra usikkerhetsfaktor på 10 i tillegg til standard usikkerhetsfaktoren på 100 for ekstrapoleringen fra gnagere til mennesker og for menneskelig variabilitet.

Inntak av krom fra kosten i Norge er ikke kjent ettersom det ikke finnes informasjon om innholdet av krom i den norske Matvaretabellen. VKM har derfor basert denne vurderingen på inntaksdata fra EFSA. Inntaksdataene fra EFSA vil trolig også være representative for norske forhold. I små barn, 1 til <3 år, var median inntak av krom fra kosten 28,6-44,0 µg/dag (medianer av lower bound og upper bound konsentrasjoner) i eldre barn, 3 til <10 år, var inntaket 55,4-76,2 µg/dag. I ungdom, ≥10 til <14 år, var inntaket av krom 52,1-69,4 µg/dag, og i ungdom, ≥14 til <18 år, var inntaket av krom 73,6-98,1, mens inntaket

blant voksne, 18-65 år, var 63,0-84,0 µg/dag (EFSA, 2014b). Disse inntaksnivåene er 80-300 ganger lavere enn det foreslåtte tolerable daglige inntaket (TDI).

For å illustrere konsekvensene av å endre maksimumsgrenser for krom til 50, 125, 200 eller 300 µg per daglig dose i kosttilskudd, har VKM lagt de ulike inntakene fra kosten til disse foreslåtte maksimumsgrensene og sammenlignet med det tolerable daglige inntaket (TDI) på 300 µg/kg kroppsvekt per dag.

Selv med den høyeste foreslåtte maksimumsgrensen i kosttilskudd vil krominntaket være 16-48 ganger lavere enn det tolerable daglig inntaket på 300 µg/kg kroppsvekt per dag i alle aldersgrupper unntatt de minste barna når vil legger til både mediant krominntak og inntak i 95-persentilen fra kosten. Hos de minste barna, 1 til <3 år, vil inntaket da være om lag ni ganger lavere enn tolerabelt daglig inntak.

VKM presiserer at denne vurderingen av maksimumsgrenser for krom i kosttilskudd er basert på publiserte rapporter om øvre inntaksnivåer fra WHO (1996), IOM (2001, USA), SCF (2003, EU), EVM (2003, Storbritannia), NNR (2012, de nordiske landene) og EFSA (2014b).

Ettersom mandatet i bestillingen fra Mattilsynet var å vurdere øvre inntaksnivå basert på allerede eksisterende rapporter, har VKM ikke gjennomført et eget systematisk litteratursøk for å vurdere det samlede kunnskapsgrunnlaget i denne vurderingen.

Abbreviations and/or glossary

Abbreviations

AI	– adequate intake
AOAC	– Association of Analytical Communities, an independent international standardization agency
ANS	– Panel in EFSA on Food Additives and Nutrient Sources Added to Food
AR	– average requirement
bw	– body weight
CI	– confidence interval
CONTAM	– Panel in EFSA on Contaminants in the Food Chain
DRI	– dietary reference intake
DRV	– dietary reference value
EAR	– estimated average requirement (IOM).
EFSA	– European Food Safety Authority
EVM	– Expert group on vitamins and minerals of the Food Standard Agency, UK
GSH	– reduced glutathion
GSSG	– oxidised glutathion
IOM	– Institute of Medicine, USA
IU	– international unit
LB	– lower bound
LOAEL	– lowest observed adverse effect level
MOE	– margin of exposure
NDA	– Panel in EFSA on Dietetic Products, Nutrition and Allergies
NFSA	– Norwegian Food Safety Authority [<i>Norw.</i> : Mattilsynet]
NNR	– Nordic Nutrition Recommendations
NOAEL	– no observed adverse effect level
NTP	– National Toxicology Program
OECD	– Organisation for Economic Co-operation and Development
PARNUTS	– foods for particular nutritional uses
PRI	– population reference intakes
RDA	– recommended dietary allowances
RI	– recommended intake
SCF	– Scientific Committee on Food
SUL	– safe upper intake level
TDI	– tolerable daily intake
UF	– uncertainty factor
UL	– tolerable upper intake level
UB	– upper bound
VKM	– Norwegian Scientific Committee for Food and Environment [<i>Norw.</i> : Vitenskapskomiteen for mat og miljø]

Glossary

The margin of exposure (MOE) is the ratio of the NOAEL to the estimated exposure dose.

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

Percentile is a term for visualising the low, medium and high occurrences of a measurement by splitting the whole distribution into one hundred equal parts. A percentile is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value (or score) below which 95 percent of the observations are found.

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

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

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

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

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

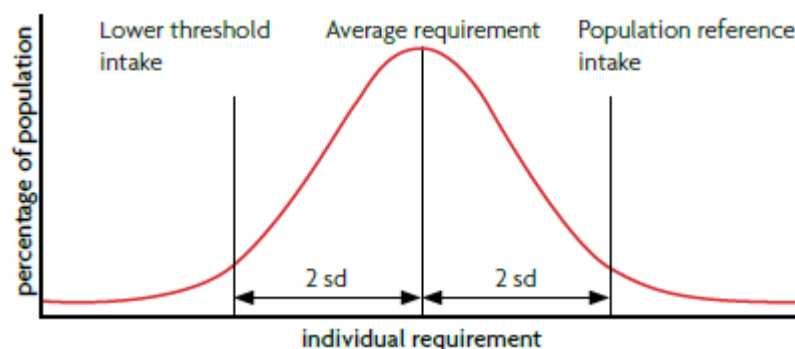


Figure 1: Population reference intake (PRI) and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010b).

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

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

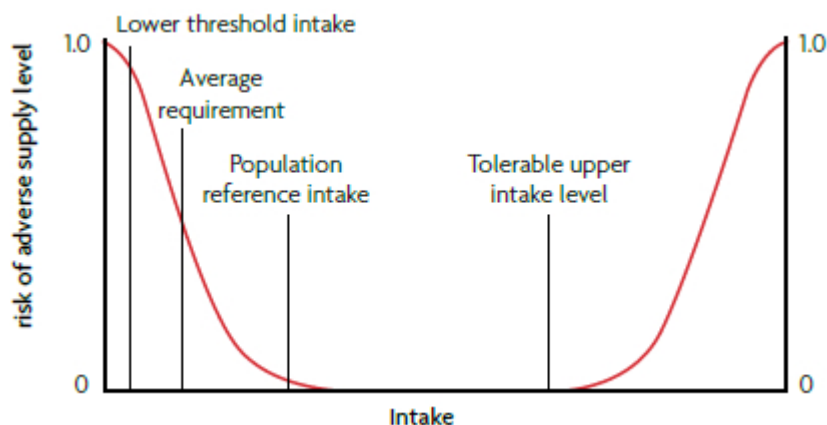


Figure 2: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake.

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

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

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

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

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

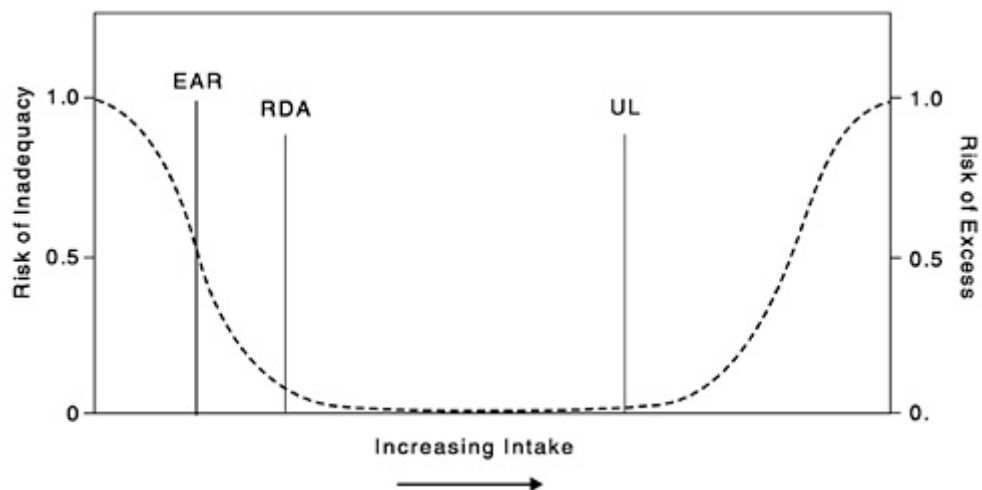


Figure 3: Dietary reference intakes.

NNR -Recommended Intake (NNR Project Group, 2012)

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

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

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

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

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

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

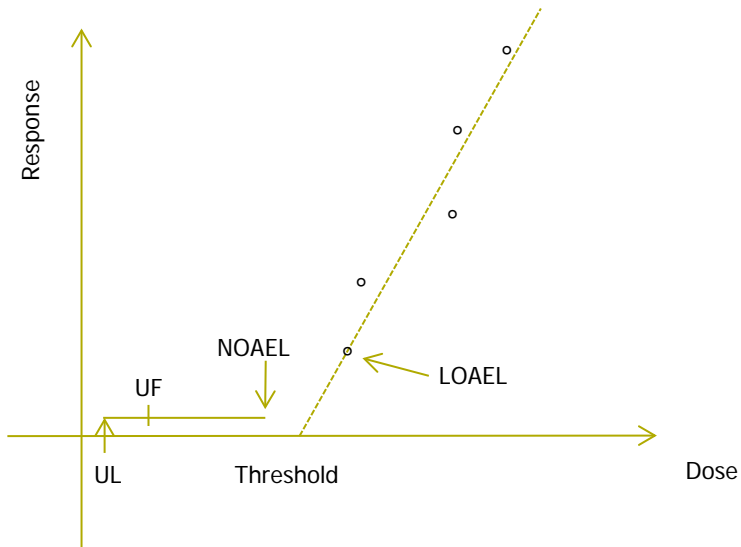


Figure 4: Derivation of Upper Intake Level (UL)

UF: Uncertainty factor

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

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

Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented into 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. The European Commission started to establish common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

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 national maximum and minimum limits in the food supplement regulation were established a long time before the food supplement directive was adopted, and the limits were consequently not established in accordance with the criteria for limits set in the food supplement directive. Maximum limits for vitamins and minerals which were not already revised according to the criteria in article 5 in the food supplement directive, were therefore repealed from 30 May 2017.

Maximum limits for levels of vitamins and minerals in food supplements shall be set on 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.

Norwegian authorities will as soon as possible, when it exists a scientific basis, and pending establishment of common maximums limits in the EU, establish new national maximum limits for those vitamins and minerals where limits were repealed 30 May 2017.

Assessment of chromium

The Norwegian Food Safety Authority will consider establishing a new national maximum limit for chromium in the food supplement regulation.

The former maximum limit for chromium was 125 µg per daily dose, but was repealed from 30 May 2017. The minimum limit and permitted chromium substances that may be used in the manufacture of food supplements, are listed in annex 1 and 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 and Environment (VKM) to assess the intake of chromium from the diet, including fortified products, in all age groups in the population above 1 year (mean intakes, median, P5, P95).

As there is no data on chromium in the Norwegian food composition data base (KBS), VKM is requested to evaluate if other relevant intake data can be used - included the EFSA Scientific Opinion on Dietary reference values for chromium (2014).

VKM is also requested to evaluate the consequences of establishing a maximum limit for chromium in food supplements of 50, 125, 200 or 300 µg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

Assessment chromium

1 Introduction

Chromium is ubiquitous, occurring in water, soil and biological systems. Also in the diet chromium is ubiquitous. Foods rich in chromium include meat and meat products, oils and fats, breads and cereals, fish, pulses and spices.

Chromium has an atomic mass of 51.9961 Da and occurs in each of the oxidation states from -2 to +6, with +6 being the state most often studied. Chromium compounds with oxidation states below +3 are reducing, and above +3 are oxidising. Because of the high energy needed to oxidise the +3 form to the +6 form, oxidation does not occur in biological systems (EFSA, 2014a).

Absorption of Cr(III) from food has been estimated to range from 0.4 to 2.5%, depending among other factors on the chemical properties of the ingested source and the presence of other dietary components. Absorption efficiency of supplemental Cr(III) has been reported to be between 0.1 and 5.2%, and to vary to a limited extent between the chromium complex ingested. Vitamin C has been reported to enhance the absorption of chromium in women (EFSA, 2014a).

Absorbed Cr(III) binds to plasma proteins such as transferrin, and less than 5% is present in an unbound form. Chromium is then transported to the liver, and accumulates mainly in the liver and spleen, but can also be found in other soft tissues and bone. Urine is the main excretory route for chromium. Faecal chromium is mainly unabsorbed chromium. No markers of chromium body burden have been identified (EFSA, 2014a).

Trivalent chromium has been reported to be an essential trace element in that it has been postulated to be necessary for the efficacy of insulin in regulation of the metabolism of carbohydrates, lipids and proteins. However, no mechanisms for these roles have been identified. The physico-chemical properties of Cr(III) do not support ligand exchange and transitions on oxidation states, as would be expected if Cr(III) were to be catalytic; rather it has been argued that Cr(III) influences the conformation of insulin and its interaction with its peripheral receptors. A circulating complex of Cr(III) and an oligopeptide of aspartate, glycine, cysteine and glutamate, named low-molecular weight Cr-binding substance or chromodulin (Chen et al., 2011) has been proposed as the means by which Cr(III) mediates responses to insulin. However, the Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) in the European Food Safety Authority (EFSA) found that chromodulin's existence and function is unclear as is the functional essentiality of Cr(III) (EFSA, 2014a).

Quantification methods of chromium in food are discussed in EFSA (2014a) and EFSA (2014b). The Association of Analytical Communities (AOAC) Official Method 990.08 for

quantifying chromium in food and water does not discriminate between Cr(III) and Cr(VI). It should be noted that the reliability of chromium data for biological and food samples measured before 1980s has been questioned because of low sensitivity of the methods used as well as contamination issues.

In general, Cr(III) has very low toxicity by the oral route (ATSDR, 2012), and there are hardly any well-documented observations of toxicity after peroral intake in humans. In a series of animal repeat dose toxicity studies, the no observed adverse effect level (NOAEL) for general toxicity was consistently the highest dose tested (EFSA, 2014b). There are some conflicting results regarding developmental and reproductive toxicity, with the lowest observed adverse effect levels (LOAELs in the order of 30 mg/kg bw per day when effects were observed). The extensive literature on genotoxicity of Cr(III) also provides some conflicting results, with largely negative results in bacterial assays and mixed results in mammalian cell assays. EFSA concluded that Cr(III) is not carcinogenic in experimental animals (EFSA, 2014b).

2 Recommendations and tolerable upper intake levels

2.1 Recommendations

There are no Norwegian recommendations for intake of chromium. The Nordic Nutrition Recommendations (2012) concluded that no recommendations could be given for chromium due to lack of sufficient evidence (NNR Project Group, 2012).

In 2014, EFSA issued an opinion on Dietary Reference Values (DRVs) for chromium (EFSA, 2014a). EFSA concluded that data are insufficient for deriving Average Requirements (ARs) or Population Reference Intakes (PRIs) for chromium. Furthermore, EFSA noted that there is no convincing evidence for a role of chromium in human metabolism and physiology, and no proof that chromium is an essential trace element, nor could chromium be linked to any beneficial health effects in healthy, normoglycaemic people. The EFSA NDA Panel therefore found that the setting of an Adequate Intake (AI) for chromium is not appropriate (EFSA, 2014a). AIs for chromium were given in the report Dietary Reference Intakes from Institute of Medicine (IOM, 2001), USA. AI for adults were set to 25 µg/day for women and 35 µg/day for men.

2.2 Tolerable upper intake levels

World Health Organization (WHO, 1996)

In a report of a re-evaluation of the role of trace elements in human health and nutrition, it is stated that trivalent chromium has such a low toxicity that deleterious effects of excessive intake of this form of chromium do not readily occur, and that the relatively non-toxic nature of chromium as found in food indicates that the tolerable limit for chromium is quite high. Further, it is stated that "Findings that supplements of 125-200 µg of chromium/day, in addition to the usual dietary intake, can in some cases reverse hypoglycaemia and impaired glucose tolerance, and improve both circulating insulin levels and the lipid profile, suggest that the upper limit of the safe range of population mean intakes could be above 250 µg/day". However, until more is known about chromium, it was found appropriate that supplementation of this element should not exceed this amount.

Institute of Medicine (IOM, 2001), USA

It is stated that the limited studies on renal, hepatic, reproductive, and DNA damaging effects of chromium III do not provide dose-response information or clear indications of a

LOAEL or a NOAEL. Thus, there are insufficient data to establish a tolerable upper intake level (UL) for soluble chromium III salts.

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

It is said that overall, there are insufficient data from human or animal studies to derive a safe upper level for chromium, although the oral toxicity of poorly absorbed trivalent chromium appears to be low.

The study by Anderson et al. (1997) was cited to indicate that 15 mg/kg bw/day chromium (as chromium chloride) was not associated with adverse effects in the rat. Based on this study, and allowing uncertainty factors of 10 for inter-species variation and 10 for inter-individual variation, a total daily intake of about 0.15 mg/kg bw/day (or 10 mg/person/day) would be expected to be without adverse health effects. This value was said to be used for guidance purposes and applied to trivalent chromium only.

Scientific Committee on Food (SCF, 2003)

The Scientific Committee on Food (SCF) stated that data on the oral toxicity of trivalent chromium are limited. Doses up to 15 mg chromium/kg bw/day did not show adverse effects in a feeding study with chromium chloride and chromium picolinate in rats for 20 weeks (Anderson et al., 1997).

In mice, doses of 250 to 1250 mg/kg body weight chromium chloride decreased fertility significantly and reduced body weights in males (Elbetieha and AlHamood, 1997).

Human data on trivalent chromium were found to be limited. No adverse effects were reported in a number of supplementation trials, in which subjects received up to 1 mg chromium/day, mostly as picolinate for several months. These trials, however, were mainly studies of efficacy and not designed to find potential toxic effects.

The limited data from studies on subchronic, chronic, and reproductive toxicity on soluble trivalent chromium salts and the available human data were found not to give clear information on the dose response relationship. Therefore, a tolerable upper intake level could not be derived.

The US Institute of Medicine also concluded that the data from animal and human studies were insufficient to establish an UL for soluble chromium (III) salts (IOM, 2001).

VKM mini-review (VKM, 2007), Norway

VKM refers to a study on rats by Anderson et al. (1997) (see below), and a proposal by the UK Expert Group on Vitamins and Minerals (EVM, 2003). Based on this study, EVM had concluded that allowing for an uncertainty factor of 100, a dose of chromium of

0.15 mg/kg bw/day, or 9 mg in a 60 kg person, would be expected to be without adverse health effects. VKM then goes on citing a later study in rats by (Scibior and Zaporowska, 2007). In this study, 0.3 mg chromium/kg bw/day resulted in a significant decrease in kidney GSH (reduced glutathione) concentration and GSH/GSSG (oxidised glutathione) ratio in both liver and kidney, indicating that chromium has pro-oxidative effects. Based on the results from the GSH study, VKM found that it could not be ruled out that an intake of chromium much lower than 9 mg/day for adults proposed by EVM may represent a health risk. VKM therefore encouraged a more restrictive guidance level for chromium, and with the GSH study in mind stated that, for the time being, the guidance level for upper intake should be maximum 1 mg/day for an adult.

European Food Safety Authority, ANS Panel (EFSA, 2010a and c)

Safety of trivalent chromium as a added nutrient

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) delivered a scientific opinion re-evaluating the safety of chromium(III) as a nutrient added to foods for particular nutritional uses (PARNUTS) and foods intended for the general population (including food supplements) (EFSA, 2010c). The background was the doubt raised in some studies about the safety of chromium(III) picolinate. The opinion therefore focused on chromium(III) picolinate in relation to the (then) current recommendations regarding Cr(III) intake, rather than on performing a full general re-evaluation of the levels of Cr(III) intake that should not be exceeded. Based on the facts i) that maximum intake levels of up to 250 µg/day for supplemental intake as suggested by the WHO (1996) would be in the same order of magnitude as the exposure resulting from normal dietary intake ii) that in vitro, at high concentrations, chromium(III) might cause DNA damage, iii) that this DNA damage is not reflected in in vivo genotoxicity assays performed according to standard Organisation for Economic Co-operation and Development (OECD) protocols and in National Toxicology Program (NTP) studies, iv) that chromium(III) is not carcinogenic, v) that there is a large margin of safety of 4 to 5 orders of magnitude between a daily intake of 250 µg/day, equivalent to 4.1 µg/kg bw per day for a 60 kg person, and the NOAEL of 300 mg/kg bw/day for chromium(III) calculated from the NOAEL for chromium(III) picolinate in the long-term NTP studies in mice and rats, the EFSA Panel concluded that the safety of chromium(III) as a nutrient added to PARNUTS and foods intended for the general population (including food supplements) is not of concern, provided that the intake of chromium(III) from these sources does not exceed 250 µg/day, the value established by the WHO (1996) for supplemental intake of chromium that should not be exceeded.

Safety of chromium picolinate as a source of chromium

This report was focused on the safety of picolinate, and the aim was not to re-evaluate the general intake level of Cr(III) not to be exceeded. The EFSA ANS Panel concluded that the use of chromium(III) picolinate as a source of chromium added for nutritional purposes to PARNUTS and foods intended for the general population (fortified foods and food

supplements) would not be of concern provided that the amount of total chromium did not exceed 250 µg/day, the value established by the WHO (1996) for supplemental intake of chromium that should not be exceeded (EFSA, 2010a).

European Food Safety Authority, (EFSA, 2014b)

Risk related to public health related to the presence of chromium in food and drinking water

The EFSA Panel in on Contaminants in the Food Chain (CONTAM Panel) derived a tolerable daily intake (TDI) of 0.3 mg/kg bw per day for Cr(III) from the lowest NOAEL identified in the extensive NTP chronic (2-year) oral toxicity study in mice and rats (EFSA, 2014b; NTP, 2010). Under the assumption that all chromium in food is Cr(III), the mean and 95th percentile dietary exposure across all age groups in Europe were found to be well below the TDI and therefore does not raise concerns for public health. In the case of drinking water, the EFSA CONTAM Panel considered all chromium in water as Cr(VI). However, the CONTAM Panel noted that to improve the risk assessment, there is a need for data on the content of Cr(III) and Cr(VI) in food and drinking water.

Nordic Nutrition Recommendations (NNR Project Group, 2012)

It is stated: "Trivalent chromium has generally low toxicity, no adverse effects were observed [in the scientific literature] at intakes of 1,000–2,000 µg/d. Due to the lack of adequate data, the EU Scientific Committee on Food has not suggested a Tolerable Upper Intake Level (UL) for chromium (III) salts. The same conclusion was reached by the U.S. Food and Nutrition Board and the UK Expert Group on Vitamins and Minerals."

2.2.1 Summary tolerable upper intake levels

Table 2.2.1-1 Overview of suggestions for intake levels in adults not to be exceeded set by various authorities.

Authority	Intake levels not to be exceeded*		Based on	NOAEL	UF
WHO, 1996	250 µg/day				
SCF, 2003	-		-	-	-
IOM, 2001	-		-	-	-
EVM, 2003	150 µg/kg bw/day (or 9000 µg/60 kg person)		Anderson et al., 1997, in the rat	15 mg/kg bw/day	100
VKM, 2007	1000 µg/day		Based on EVM, plus a newer publication		900

Authority	Intake levels not to be exceeded*		Based on	NOAEL	UF
EFSA, 2010c	250 µg/day		Follows WHO, 1996	300 mg/kg bw day NTP rat studies**	Margin of safety 4-5 orders of magnitude
EFSA, 2010a	250 µg/day		Follows WHO, 1996	300 mg/kg bw/day NTP rat studies**	
NNR, 2012	-		-	-	-
EFSA, 2014b	TDI 300 µg/kg bw per day		NTP 2-year toxicity studies in rats	300 mg/kg bw/day NTP rat studies	1000

*various suggestions for intake levels not to be exceeded, none of them an UL, see report summaries above.

**referred to in the discussion of the safety of the recommendations of levels not to be exceeded, but not used as a basis for arriving at the suggestion of the 250 µg/day dose.

3 Chromium(III) intakes

No Norwegian data on chromium intakes are available. The most recent and comprehensive data available on chromium(III) intake are found in the EFSA opinion on chromium in food and drinking water (EFSA, 2014b). This report gives mean and 95th percentile dietary exposure estimates ($\mu\text{g}/\text{kg}$ bw per day) for Cr(III) in food and Cr(VI) in water calculated for each of 26 dietary surveys from 17 European countries, as well as summary estimates (median and 95th percentile).

To obtain data on chromium levels in foods, EFSA published a call in which European national food authorities and similar bodies, research institutions, academia, feed and food business operators and any other stakeholders were invited to submit data. A total of 81 247 analytical results on chromium were made available. About 80% of the samples reported had been collected in Germany. After Germany, Cyprus, Slovakia and Ireland were the countries where the highest number of samples had been collected. To secure an appropriate quality of the data used in the subsequent exposure assessment, the initial chromium concentration dataset was evaluated applying a number of data cleaning and validation steps (EFSA, 2014b).

The food consumption data were from the EFSA Comprehensive European Food Consumption Database (EFSA, 2011), based on data provided by EU member states and the food consumption data for children obtained through an EFSA Article 36 project (Huybrechts et al., 2011). For calculating the chronic dietary exposure to Cr(III), food consumption and body weight data at the individual level were accessed in the Comprehensive Database.

The EFSA CONTAM Panel (EFSA, 2014b) noted that there is a lack of data on the presence of Cr(VI) in food, and decided to consider all the reported analytical results in food as Cr(III). This assumption was based on recent speciation work by Kovacs et al. (2007) and Novotnik et al. (2013), on the fact that food is overall a reducing medium that would likely cause Cr(VI) to be reduced to Cr(III), and that oxidation of Cr(III) to Cr(VI) would not be favoured in such a medium. In contrast, in drinking water chromium may easily be present in the hexavalent state, not only due to anthropogenic contamination events, but also because water treatment facilities use strong oxidants to make water potable.

Thus, reported analytical results for total chromium in food were assumed to be as Cr(III), as it was assumed that the Cr(VI) present in water, in food is completely reduced to Cr(III). These assumptions were also made for water-based foods (following the FoodEx classification) (EFSA, 2011) like 'fruit and vegetable juices', 'soft drinks' and 'alcoholic beverages'. However, certain foods are prepared with water to be consumed (coffee, tea infusions, and dry infant and follow-on food), and an incomplete reduction of the Cr(VI) present in this water into Cr(III) may happen if the foods are ingested immediately after their preparation. In these cases, the occurrence data on Cr(III) reported for dry foods were used with appropriate dilution factors to estimate the exposure to Cr(III). For each country,

estimates of dietary exposure to Cr(III) were calculated per dietary survey and age class. Because different methodologies were used between surveys to collect data, direct country-to-country comparisons can be misleading. Complete data for the surveys used and the results can be found in the EFSA CONTAM Panel 2014 opinion (EFSA, 2014b). The EFSA report also gives detailed data on the contribution of the different food categories to the chromium (III) intake in the various age groups. Lower-bound (LB) and upper-bound (UB) values were given for the population groups toddlers (≥ 12 months to ≤ 36 months old), other children (≥ 36 months to < 10 years old), adolescents (≥ 10 years to < 18 years old), adults (≥ 18 years to < 65 years old), elderly (≥ 65 years to < 75 years old) and very elderly (≥ 75 years old) (Table 3-1).

Mean chronic dietary exposure values across age classes, countries and surveys, ranged from 0.6 $\mu\text{g}/\text{kg}$ bw per day (minimum LB) to 5.9 $\mu\text{g}/\text{kg}$ bw per day (maximum UB). The 95th percentile dietary exposure ranged from 1.1 $\mu\text{g}/\text{kg}$ bw per day (minimum LB) to 9.4 $\mu\text{g}/\text{kg}$ bw per day (maximum value UB). A tendency was observed for higher exposure values to be found for toddlers and other children compared to the older age groups. Median dietary chromium intake values were 80-300 times lower than the suggested tolerable daily intake (TDI) of 300 $\mu\text{g}/\text{kg}$ bw per day (EFSA 2014b).

Table 3-1 Summary statistics of the chronic exposure assessment ($\mu\text{g}/\text{kg}$ bw per day) for Cr(III) across European dietary surveys. Estimates were rounded up to one decimal place. Source: EFSA, 2014b.

Age groups	Mean dietary exposure ($\mu\text{g}/\text{kg}$ bw per day)					
	Min LB	Median LB	Max LB	Min UB	Median UB	Max UB
Toddlers	2.3	2.4	4.6	3.1	3.7	5.9
Other children	1.6	2.4	3.5	2.1	3.3	4.9
Adolescents	0.9	1.2	2.1	1.2	1.6	2.5
Adults	0.8	0.9	1.2	1.0	1.2	1.6
Elderly	0.6	0.8	1.0	1.0	1.1	1.4
Very elderly	0.7	0.8	1.2	1.0	1.1	1.5
	95th percentile dietary exposure ($\mu\text{g}/\text{kg}$ bw per day)					
	Min LB	Median LB	Max LB	Min UB	Median UB	Max UB
Toddlers	3.4	4.5	5.9	4.5	6.7	9.0
Other children	2.9	4.2	7.3	3.7	5.6	7.9
Adolescents	1.7	2.4	4.1	2.3	2.9	4.8
Adults	1.2	1.5	2.0	1.7	2.0	2.6
Elderly	1.1	1.3	1.5	1.6	1.7	2.0
Very elderly	1.2	1.6	1.8	1.7	2.0	2.3

In absolute numbers, median dietary chromium intakes were 28.6-44.0 µg/day (medians of lower and upper bound) in toddlers, 55.4-76.2 µg/day in other children, 52.1-69.4 µg/day in adolescents (≥10 to <14 years), 73.6-98.1 in adolescents (≥14 to <18 years) and 63.0-84.0 µg/day in adults (EFSA, 2014b) (adolescent values calculated from relative intake for age group 10-18 years).

Due to the limited and incomplete consumption information in the Comprehensive Database on fortified foods, PARNUTS and food supplements was excluded from the dietary exposure calculations. Intakes from this food group were calculated separately by an approach used previously by the EFSA ANS Panel (EFSA, 2010a). Levels per serving equal to 12 µg of Cr(III) from fortified foods and 300 µg of chromium from PARNUTS had been proposed by the ANS Panel. No use levels were proposed for food supplements, but the EFSA ANS Panel noted that levels up to 600 µg/day Cr(III) could be consumed from supplements. Using these values, the typical exposure due to supplemental intake in the EFSA study would be about 10 times higher than that obtained from food intake. One might possibly argue that for Norway, data from the Nordic countries would be more valid than data collected from all over Europe, because Norwegian dietary habits might be more similar to the other Nordic countries than to eating habits in Eastern and Southern European countries. However, comparing the data from the European dataset (Table 3-1) to the Nordic countries (Table 3-2), it is found that mean dietary exposure to Cr(III) across all the different European surveys shows a fairly similar range as the data from the Nordic surveys (0.6 to 5.9 µg/kg bw per day *vs.* 0.8 to 3.7) (minimum LB to maximum UB). The largest difference between the Nordic countries dataset and the all-European dataset was seen for the maximum UB. Similarly, the 95th percentile dietary exposure data showed a similar range in the Nordic and the European datasets (1.1 to 9.0 µg/kg bw per day *vs.* 1.2 to 8.4) (minimum LB to maximum UB) (Table 3-2).

Table 3-2 Mean and 95th percentile (P95) chronic dietary exposure to Cr(III) (µg/kg bw per day) for population groups in lower-bound (LB) and upper-bound (UB) scenario in the Nordic countries (data from EFSA, 2014b)*.

	Toddlers		Other children		Adolescents		Adults	
	Mean	P95	Mean	P95	Mean	P95	Mean	P95
DK	-	-	1.87-2.79	2.92-4.24	1.01-1.53	1.71-2.53	0.78-1.13	1.22-1.75
FI/1	2.37-3.70	5.07-8.44	2.35-3.57	4.20-5.99	-	-	-	-
FI/2	-	-	-	-	-	-	0.77-1.15	1.37-2.02
FI/3	-	2.22-3.02	3.72-4.61	-	-	-	-	-
SE/1	-	-	-	-	-	-	1.00-1.33	1.68-2.18
SE/2	-	-	2.47-3.37	5.33-6.32	1.62-2.11	3.33-3.99	-	-

DK: Denmark; FI: Finland SE: Sweden.

*Data for elderly and very elderly not included.

In conclusion, VKM will base its evaluation upon the larger European dataset generated by the EFSA CONTAM Panel, which is likely to be valid also for Norway.

4 Assessment of the intakes of chromium

4.1 Evaluation of chromium intakes, including scenarios with supplementation

Toxicity of trivalent chromium and establishment of a TDI for Cr(III)

The EFSA CONTAM Panel (EFSA, 2014b) established a TDI of 300 µg/kg bw per day for Cr(III) based on the NOAEL determined in a 2-year US National Toxicology Program study in rats (NTP, 2010) where no adverse effects were observed even at the highest dose tested. Due to the uncertainty in the available data on developmental and reproduction toxicity, the EFSA CONTAM Panel applied an uncertainty factor of 10 in addition to the default uncertainty factor of 100 for the extrapolations from rodents to humans and for human variability.

Evaluation – risk characterisation

Under the assumption that all chromium in food is Cr(III) and all chromium in water Cr(IV), the mean dietary exposure to Cr(III) across all age groups and surveys (minimum LB of 0.6 µg/kg bw per day and maximum UB of 5.9 µg/kg bw per day) as well as the 95th percentile exposure (minimum LB of 1.1 µg/kg bw per day and maximum UB of 9.0 µg/kg bw per day) are below the TDI by a factor of more than 10. The CONTAM Panel concluded that the current dietary exposure to Cr(III) does not raise concern from a public health point of view.

Regarding the vegetarian population, although based on limited consumption data, the dietary exposure to Cr(III) was found by the EFSA CONTAM Panel to be similar to that estimated for the general population. The CONTAM Panel concluded that the dietary exposure of vegetarians is well below the TDI of 300 µg Cr(III)/ kg bw per day.

Exposure scenarios

VKM was requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for chromium to 50, 125, 200 or 300 µg/day in food supplements. The results are shown in Table 4.1-1 and 4.1-2 (without possible contribution from fortified foods and PARNUTS). Even with the highest level of supplemental intake, median intake levels as well as the 95th percentile intake will be less than one tenth of the TDI of 300 µg/kg bw per day, except for toddlers where the 95th percentile intake for UB plus 300 µg supplementation will be nine times lower than the TDI. A daily serving of Cr(III)-fortified food estimated at 12 µg Cr(III) (see Section 3) will not change this.

Table 4.1-1 Mean exposure to Cr(III)(µg per day) from the diet and with different additional intake scenarios from supplements*.

	Median LB	Median UB	LB+ 50	UB+ 50	LB+ 125	UB+ 125	LB+ 200	UB+ 200	LB+ 300	UB+ 300	TDI ** (µg)
Toddlers 1-3 years	28.6	44.0	78.6	94.0	153.6	169.0	228.6	244.0	328.6	344.0	3600
Other children 3-10 years	55.4	85.5	105.4	135.5	180.4	210.5	255.4	285.5	355.4	385.5	6900
Adolescents 10-14 years***	52.1	69.4	102.1	119.4	177.1	194.4	252.1	269.4	352.1	369.4	13000
Adolescents 14-18 years***	73.6	98.1	123.6	148.1	198.6	223.1	273.6	298.1	373.6	398.1	118400
Adults 18-65 years	63.0	84.0	113.0	134.0	188.0	209.0	263.0	284.0	363.0	384.0	21000
Elderly 65-75 years	56.0	77.0	106.0	127.0	181.0	202.0	256.0	277.0	356.0	377.0	21000
Very elderly ≥ 75 years	56.0	77.0	106.0	127.0	181.0	202.2	256.0	277.0	356.0	377.0	21000

*LB = Lower bound, UB = Upper bound

**EFSA default weight for toddlers 11.9 kg; other children 23.1 kg; adolescents 10 to <14 years, 43.4 kg; adolescents 14 to <18 years 61,3 kg; adults, elderly and very elderly 70 kg. TDI 300 µg/kg bw per day.

*** Cr(III) diet intake values based on relative intake for age group 10 to <18 years.

Table 4.1-2 P95 exposure to Cr(III)(µg per day)from the diet and with different additional intake scenarios from supplements*.

	Median LB	Median UB	LB+ 50	UB+ 50	LB+ 125	UB+ 125	LB+ 200	UB+ 200	LB+ 300	UB+ 300	TDI **
Toddlers 1-3 years	53.6	79.7	103.6	129.4	178.6	204.4	253.6	279.4	353.6	379.4	3600
Other children 3-10 years	97.0	129.4	147.0	179.4	222.0	254.4	297.0	329.4	397.0	429.4	6900
Adolescents 10-14 years	104.2	125.9	154.2	175.9	229.2	250.9	304.2	325.9	404.2	425.9	113000
Adolescents 14-18 years	147.1	177.8	197.1	227.8	272.1	302.8	347.1	377.8	447.1	477.8	18400
Adults 18-65 years	105.0	140.0	155.0	190.0	230.0	265.0	305.0	340.0	405.0	440.0	21000
Elderly 65-75 years	91.0	119.0	141.0	169.0	216.0	244.0	291.0	319.0	391.0	419.0	21000
Very elderly ≥ 75 years	112.0	140.0	162.0	190.0	237.0	265.0	312.0	340.0	412.0	440.0	21000

*LB = Lower bound. UB = Upper bound

**EFSA default weight for toddlers 11.9 kg; other children 23.1 kg; adolescents - 10 to <14 years, adolescents 14 to <18 years 61,3 kg; 43.4 kg; adults, elderly and very elderly 70 kg. TDI 300 µg/kg bw per day. Cr(III) values based on relative intake for age group 10 to <18 years.

5 Uncertainties

Uncertainty regarding how well the European food consumption studies and analytical data used by EFSA (2014b) reflect the true European average.

Uncertainty regarding how well the European food consumption studies used by EFSA (2014b) reflect food consumption in Norway.

Uncertainty whether there are subpopulations in Norway e.g. ethnic minorities that deviate strongly from the average Norwegian (and European) population with regard to dietary habits.

Uncertainty regarding how well chromium level analyses of foods used by EFSA (2014b) represent chromium levels in foods consumed in Norway – there is an uncertainty about regional differences in chromium content in foods.

Uncertainty due to the lack of appropriate consumption data for fortified foods, foodstuffs for particular nutritional use (PARNUTS) and food supplements.

Uncertainty about the adequacy of the extra uncertainty factor of 10 added due to the uncertainty about developmental and reproduction toxicity.

Uncertainty because the NOAEL was the highest dose tested.

Due to the large proportion of left-censored data, LB values reported will tend to underestimate, and UB levels will tend to overestimate dietary exposure.

Uncertainty about the contribution of stainless steel containers, processors and utensils to Cr(III) levels in foods as consumed – data on foods as consumed are virtually absent from the dataset used by EFSA.

Uncertainties about the assumption that all Cr in foods is Cr(III) and all Cr in water is Cr(VI), and the content of Cr(III) (and Cr(VI)) in water-based foods and drinks.

Uncertainty because of the absence of human studies on possible long-term adverse effects of chronic high Cr(III) intake.

6 Answers to the terms of reference

The Norwegian Food Safety Authority (NFSA, Mattilsynet) has requested the Norwegian Scientific Committee for Food and Environment (VKM) to assess the intake of chromium from the diet, including fortified products, in all age groups in the population above age 1 year.

EFSA has published summary as well as individual study estimates for Cr(III) intakes based on 26 dietary surveys from 17 European countries and analytical data on Cr(III) (EFSA, 2014a). There were six Nordic studies included; from Denmark (1 study), Sweden (2 studies) and Finland (3 studies), but none from Norway. VKM considers that the summary data from this European study are valid also for Norway. Intake data (median lower and upper bound with max and min values) as well as the corresponding P95 data for the relevant standard EFSA age groups are given in Table 3-1.

VKM is also requested to conduct scenario estimations to illustrate the consequences of establishing maximum limits for chromium to 50, 125, 200 or 300 µg/day. The outcomes are given in 4.1-1 (median (of individual study means) exposure lower and upper bound) and 4.1-2 (95th percentile exposure levels). Even with the highest level of supplemental intake, median intake levels as well as the 95th percentile intake will be less than one tenth of the TDI of 300 µg/kg bw per day (except for toddlers where the 95th percentile intake for UB plus 300 µg supplementation will be about nine times lower than the TDI). This conclusion is not changed even if a daily serving of Cr(III)- fortified foods estimated at 12 µg Cr(III) as discussed under Section 3 is added.

VKM emphasises that the current assessment of maximum limits for Cr(III) in food supplements is merely based on published reports concerning upper levels from the WHO (1996), IOM (2001, USA), SCF (2003, EU), EVM (2003, UK), NNR (2012, Nordic countries), and EFSA (2014b). VKM has not conducted any systematic review of the literature for the current opinion, as this was outside the scope of the terms of reference from NFSA.

7 Data gaps

- Data on Cr(III) levels in foods consumed in Norway
- Dietary information for some population subgroups, e.g. ethnic minorities
- Appropriate consumption data for fortified foods, foodstuffs for particular nutritional use (PARNUTS) and food supplements
- More reliable data on developmental and reproduction toxicity
- Identification of a LOAEL, because the NOAEL that was basis for the TDI was the highest dose tested
- Quantitative data below the present limit of quantification
- Data about the contribution of stainless steel containers, processors and utensils to Cr(III) levels in foods as consumed
- Human studies on possible long-term adverse effects of chronic high Cr(III) intake

8 References

Chen Y, Watson HM, Gao J, Sinha SH, Cassady CJ and Vincent JB, 2011. Characterization of the organic component of low-molecular-weight chromium-binding substance and its binding of chromium. *Journal of Nutrition*, 141, 1225-1232.

Anderson R.A., Bryden N.A., Polansky M.M. (1997) Lack of toxicity of chromium chloride and chromium picolinate in rats. *J Am Coll Nutr* 16:273-9.

ATSDR. (2012) Toxicological profile for chromium, in: P. H. S. Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, (Ed.), Atlanta, Georgia, USA.

Chen Y., Watson H.M., Gao J.J., Sinha S.H., Cassady C.J., Vincent J.B. (2011) Characterization of the Organic Component of Low-Molecular-Weight Chromium-Binding Substance and Its Binding of Chromium. *Journal of Nutrition* 141:1225-1232. DOI: 10.3945/jn.111.139147.

EFSA. (2010a) Safety of chromium picolinate as a source of chromium. *EFSA Journal* 12:49. DOI: 10.2903/j.efsa.2010.1883.

EFSA. (2010b) Scientific Opinion on principles for deriving and applying Dietary Reference Values. *EFSA Journal* 8:1458.

EFSA. (2010c) Scientific Opinion on the safety of trivalent chromium as a nutrient added for nutritional purposes to foodstuffs for particular nutritional uses and foods intended for the general population (including food supplements). *EFSA Journal* 8:49. DOI: 10.2903/j.efsa.2011.2097.

EFSA. (2011) Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. *EFSA Journal* 9:34. DOI: 10.2903/j.efsa.2011.2097.

EFSA. (2014a) Scientific Opinion on Dietary Reference Values for chromium. *EFSA Journal* 12:25. DOI: 10.2903/j.efsa.2014.384.

EFSA. (2014b) Scientific Opinion on the risks to public health related to the presence of chromium in food and drinking water. *EFSA Journal* 12:261. DOI: 10.2903/j.efsa.2014.3595.

Elbetieha A., AlHamood M.H. (1997) Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: Effect on fertility. *Toxicology* 116:39-47. DOI: Doi 10.1016/S0300-483x(96)03516-0.

EVM. (2003) Safe Upper Levels for Vitamins and Minerals, in: E. G. o. V. a. Minerals (Ed.), Food Standard Agency, London, UK.

Huybrechts I., Sioen I., Boon P.E., Ruprich J., Lafay L., Turrini A., Amiano P., Hirvonen T., De Neve M., Arcella D., Moschandreas J., Westerlund A., Ribas-Barba L., Hilbig A., Papoutsou S., Christensen T., Oltarzewski M., Virtanen S., Rehurkova I., Azpiri M., Sette S., Kersting M., Walkiewicz A., Serra-Majem L., Volatier J.L., Trolle E., Tornaritis M., Busk L., Kafatos A., Fabiansson S., De Henauw S., Van Klaveren J.D. (2011) Dietary exposure assessments for children in Europe (the EXPOCHI project): rationale, methods and design. *Arch Public Health* 69:4. DOI: 10.1186/0778-7367-69-4.

IOM. (2000) Introduction to Dietary Reference Intakes, in: N. A. Press (Ed.), Institute of Medicine, Washington D.C.

IOM. (2001) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc Institute of Medicine, National Academies Press, Washington, D.C.

Kovacs R., Beni A., Karosi R., Sogor C., Posta J. (2007) Investigation of chromium content in foodstuffs and nutrition supplements by GFAAS and determination of changing Cr(III) to Cr(VI) during baking and toasting bread. *Food Chemistry* 105:1209-1213. DOI: 10.1016/j.foodchem.2007.02.030.

NNR Project Group. (2012) Nordic Nutrition Recommendations 2012, Nordic Council of Ministers, Copenhagen Denmark.

Novotnik B., Zuliani T., Scancar J., Milacic R. (2013) Chromate in food samples: an artefact of wrongly applied analytical methodology? *Journal of Analytical Atomic Spectrometry* 28:558-566. DOI: 10.1039/c3ja30233d.

NTP. (2010) NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chromium Picolinate Monohydrate (CAS No. 27882-76-4) in F344/N Rats and B6C3F1 Mice (Feed Studies), in: D. o. H. a. H. Services (Ed.), US National Toxicology Programme, Research Triangle Park, North Carolina, USA.

SCF. (2003) Opinion on the Scientific Committee on Food on the Tolerable Upper Intake Level of trivalent chromium, Scientific Committee on Food, Brussels, Belgium. pp. 18.

Scibior A., Zaporowska H. (2007) Effects of vanadium(V) and/or chromium(III) on L-ascorbic acid and glutathione as well as iron, zinc, and copper levels in rat liver and kidney. *Journal of Toxicology and Environmental Health-Part a-Current Issues* 70:696-704. DOI: 10.1080/15287390601187906.

VKM. (2007) Comments from the Norwegian Scientific Committee for Food Safety, Panel on Nutrition, dietetic products, Novel Food and Allergy (Panel 7) on the setting of maximum limits for vitamins and minerals in foods, Vitenskapskomiteen for mattrygghet, Oslo, Norway.

WHO. (1996) Trace elements in human nutrition and health, World Health Organization, Geneva, Switzerland.

