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DRAFT SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for chromium[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) considered the evidence for setting Dietary Reference Values for chromium. Trivalent chromium (Cr(III)) has been postulated to be necessary for the efficacy of insulin in regulating the metabolism of carbohydrates, lipids and proteins. However, the mechanism(s) for these roles and the essential function of Cr(III) in metabolism have not been substantiated. Criteria for essentiality of a trace element were considered. It was noted that attempts to create chromium deficiency in animal models have not produced consistent results, and that there is no evidence of essentiality of Cr(III) in animal nutrition. Evaluating the possibility of Cr(III) as an essential element for humans, the evidence from reported improvements associated with chromium supplementation in patients on total parenteral nutrition was considered to be the most convincing, but overall the data do not provide sufficient information on the reversibility of the possible deficiencies and the nature of any dose-response curve in order to identify a dietary requirement for humans. The Panel concludes that no Average Requirement and no Population Reference Intake for chromium can be defined. Several studies assessed the effect of chromium supplementation on glucose and/or lipid metabolism. In the only study for which information on total chromium intake was available, there was no difference in parameters of glucose metabolism of normoglycaemic subjects between the placebo and chromium-supplemented periods. The Panel considers that there is no evidence of beneficial effects associated with chromium intake in healthy subjects. The Panel concludes that the setting of an Adequate Intake for chromium is also not appropriate.

KEY WORDS

chromium, essentiality, Dietary Reference Value

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to review the evidence with regard to the setting of Dietary Reference Values for the European population, including chromium.

In 1993, the Scientific Committee for Food was unable to define a specific physiological requirement of chromium and did not propose Dietary Reference Values (DRVs) for chromium, but other authorities have subsequently proposed DRVs for chromium.

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 regulating the metabolism of carbohydrates, lipids and proteins. However, at present, the mechanism(s) for these roles and the essential function of chromium in metabolism have not been substantiated. The postulation of chromium's essentiality for humans was almost entirely based on case reports of patients on long-term total parenteral nutrition (TPN) who developed metabolic and neurological defects which were reported to respond to supplementation with trivalent chromium (Cr(III)). The Panel noted that the chromium concentrations in the TPN solutions which induced the presumed deficiency symptoms were not reported in all the patients studied. In the three studies in which the concentration of chromium in the TPN solution was reported, the daily chromium supply was between 5 and 10 µg; at an absorption efficiency of 5 % this amount of infused chromium is equivalent to an oral intake of 100-200 µg/day. The Panel notes that this intake is well above the estimated mean daily intakes in the 17 European countries for which data were available to perform an assessment of chronic dietary chromium intake. On the basis of these case reports, the Panel concludes that it is unclear whether deficiency of chromium has occurred in these patients and whether chromium deficiency occurs in healthy populations.

The Panel considered criteria for essentiality of a trace element and noted that attempts to create chromium deficiency in animal models have not produced consistent results, that there is no evidence of essentiality of Cr(III) as a trace element in animal nutrition, and that Cr(III) requirements could not be established for animal feed. The Panel considered that there is a possibility that Cr(III) is an essential trace element for humans, but that there is, as yet, no convincing evidence of this. The evidence from reported improvements associated with chromium supplementation in patients on TPN is arguably the most convincing, but overall the data do not provide sufficient information on the reversibility of the possible deficiencies and on the nature of any dose-response curve in order to identify a dietary requirement for humans. The existence and functional characterisation of a chromium-oligopeptide complex (chromodulin)) is still unclear.

The Panel concludes that no Average Requirement and no Population Reference Intake for chromium for the performance of physiological functions can be defined.

Nevertheless, as for fluoride, DRVs might be derived if a consistent dose-response relationship could be established between dietary chromium intake and a beneficial health outcome. A comprehensive search of the literature published between January 1990 and October 2011 was performed to identify relevant health outcomes upon which DRVs for chromium may potentially be based. Several studies that assessed the effect of chromium supplementation on glucose and/or lipid metabolism were retrieved in the literature search. In most studies chromium intake from the diet was not assessed, and information on total chromium intake is therefore not available. In one cross-over study for which total chromium intake was available, there was no significant difference in parameters of glucose metabolism between the placebo and chromium-supplemented periods in normoglycaemic subjects.

The Panel considered that there is no evidence of beneficial effects associated with chromium intake in healthy subjects. The Panel concludes that the setting of an Adequate Intake for chromium is also not appropriate.

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Background as provided by the European Commission

The scientific advice on nutrient intakes is important as the basis of Community action in the field of nutrition, for example such advice has in the past been used as the basis of nutrition labelling. The Scientific Committee for Food (SCF) report on nutrient and energy intakes for the European Community dates from 1993. There is a need to review and if necessary to update these earlier recommendations to ensure that the Community action in the area of nutrition is underpinned by the latest scientific advice.

In 1993, the SCF adopted an opinion on nutrient and energy intakes for the European Community.[4] The report provided reference intakes for energy, certain macronutrients and micronutrients, but it did not include certain substances of physiological importance, for example dietary fibre.

Since then new scientific data have become available for some of the nutrients, and scientific advisory bodies in many European Union Member States and in the United States have reported on recommended dietary intakes. For a number of nutrients these newly established (national) recommendations differ from the reference intakes in the SCF (1993) report. Although there is considerable consensus between these newly derived (national) recommendations, differing opinions remain on some of the recommendations. Therefore, there is a need to review the existing EU Reference Intakes in the light of new scientific evidence, and taking into account the more recently reported national recommendations. There is also a need to include dietary components that were not covered in the SCF opinion of 1993, such as dietary fibre, and to consider whether it might be appropriate to establish reference intakes for other (essential) substances with a physiological effect.

In this context the EFSA is requested to consider the existing Population Reference Intakes for energy, micro- and macronutrients and certain other dietary components, to review and complete the SCF recommendations, in the light of new evidence, and in addition advise on a Population Reference Intake for dietary fibre.

For communication of nutrition and healthy eating messages to the public it is generally more appropriate to express recommendations for the intake of individual nutrients or substances in food-based terms. In this context the EFSA is asked to provide assistance on the translation of nutrient based recommendations for a healthy diet into food based recommendations intended for the population as a whole.

Terms of reference as provided by the European Commission

In accordance with Article 29 (1)(a) and Article 31 of Regulation (EC) No. 178/2002,[5] the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

In the first instance the EFSA is asked to provide advice on energy, macronutrients and dietary fibre. Specifically advice is requested on the following dietary components:

- Carbohydrates, including sugars;

[4] Scientific Committee for Food. Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food, 31st series. Office for Official Publication of the European Communities, Luxembourg, 1993.

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1-24.

- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;
- Protein;
- Dietary fibre.

Following on from the first part of the task, the EFSA is asked to advise on population reference intakes of micronutrients in the diet and, if considered appropriate, other essential substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

Finally, the EFSA is asked to provide guidance on the translation of nutrient based dietary advice into guidance, intended for the European population as a whole, on the contribution of different foods or categories of foods to an overall diet that would help to maintain good health through optimal nutrition (food-based dietary guidelines).

ASSESSMENT

1. Introduction

In 1993, the Scientific Committee for Food (SCF) published an opinion on nutrient and energy intakes for the European Community but was unable to define a specific physiological requirement of chromium (SCF, 1993). Thereafter, other authorities have proposed DRVs for chromium (see Appendix A). A labelling reference value has also been set (SCF, 2003a).

This evaluation is limited to trivalent chromium (Cr III) because it is the form of chromium naturally occurring in food (Kovacs et al., 2007; Novotnik et al., 2013; EFSA CONTAM Panel, 2014).

During the assessment process for health claims pursuant to Article 13 of Regulation (EC) No 1924/2006,[6] the Panel assessed claims on chromium and maintenance of normal blood glucose concentrations, and on chromium and contribution to normal macronutrient metabolism with a favourable outcome (EFSA NDA Panel, 2010). These claims were substantiated in light of the general consensus, which was available at that time among authoritative bodies, on the essentiality of chromium. In the context of the present Opinion on DRVs for chromium, the NDA Panel considered in detail the criteria for essentiality and functionality of chromium when assessing the need for a dietary intake of chromium

2. Definition/category

2.1. Chemistry

Chromium is ubiquitous, occurring in water, soil and biological systems. It has an atomic mass of 51.9961 Da and occurs in each of the oxidation states from -2 to +6, with +3, and +6 being the most often studied in relation to human health (Eckhert, 2014). Chromium compounds with oxidation states below +3 are reducing, and above +3 are oxidising. The high energy needed to oxidise the trivalent to the hexavalent form of chromium results in the fact that oxidation does not occur in biological systems.

Chromium has generally been measured with atomic absorption spectroscopy (AAS), although this method does not allow the determination of the relative concentrations of Cr(III) and Cr(VI) without initial separation of individual species. A great variety of separation techniques have been used; these include the use of chelating and ion-exchange resins, chelation-extraction with organic solvents, and co-precipitation. The traditional methods of speciation analysis by AAS with pre-concentration by co-precipitation allow the achievement of specificity and sensitivity equivalent to those obtained by means of the more recent separation by high performance liquid chromatography (HPLC) with inductively coupled plasma-mass spectrometric detection (ICP-MS) (Gomez and Callao, 2006).

For quantification of chromium in food samples ICP-MS has been used (Pacquette et al., 2011, 2012). The AOAC Official Method 990.08 for quantifying total chromium in food and water is based on inductively coupled plasma – atomic emission spectroscopy and does not discriminate between Cr(III) and Cr(VI) (EFSA, 2009). There is a large amount of published data on total chromium content in food, but a lack of data as to the presence of Cr(VI) in food (EFSA CONTAM Panel, 2014). The reliability of chromium data for biological and food samples measured before the 1980s has been questioned because of low sensitivity of the methods used as well as contamination (Anderson et al., 1983a; SCF, 2003b).

[6] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

2.2. Postulated function of chromium

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 regulating the metabolism of carbohydrates, lipids, and proteins. However, at present, the mechanism(s) for these roles have not been substantiated: the physico-chemical properties of trivalent chromium 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 considers that chromodulin's existence and function is unclear as is the functional essentiality of trivalent chromium.

The essentiality of Cr(III) has been questioned both for animals (Woolliscroft and Barbosa, 1977; EFSA, 2009; Di Bona et al., 2011) and humans (Anonymous, 1988; Stearns, 2000, 2007; Vincent and Love, 2012). The case for the essentiality of dietary Cr(III) for humans was uncertain when the SCF considered the element twenty years ago (SCF, 1993); then, as now, the postulation of its essentiality was almost entirely based on case reports of patients on long-term total parenteral nutrition (TPN) who developed metabolic and neurological defects which were reported to respond to Cr(III) supplementation. These case reports are described below (Section 2.2.1.1).

2.2.1. Health consequences of deficiency and excess

2.2.1.1. Deficiency

Jeejeebhoy et al. (1977) described a female receiving long-term TPN for 3.5 years when she exhibited impaired glucose tolerance, weight loss, ataxia, peripheral sensory neuropathy, elevated plasma fatty acid concentrations, reduced respiratory quotient and abnormalities in nitrogen metabolism. Blood chromium concentration was reported to be 0.55 µg/L (normal range according to the authors: 4.9-9.5 µg/L) and hair chromium concentration 154-175 ng/g (normal range according to the authors: > 500 ng/g). The TPN solution contained chromium as a contaminant and provided 5.3 µg chromium/day. The symptoms were reported to be reversed following the addition of 250 µg/day of chromium to the TPN solution for two weeks. Afterwards the patient was maintained on a TPN solution that contained an added amount of 20 µg/day of chromium.

In a second case report it was stated that a woman receiving TPN (chromium concentration in TPN solution was not reported and chromium contamination could not be ruled out) for five months after complete bowel resection developed severe glucose intolerance, weight loss and a metabolic encephalopathy-like confusional state. The serum chromium concentration was reported to be 5 µg/L (normal range according to the authors: 5-90 µg/L). All symptoms were reported to be reversed by chromium supplementation of 150 µg/day for 3-4 days. Supplementation continued for approximately 1.5 months until the patient's death from sepsis (Freund et al., 1979).

Brown et al. (1986) reported that chromium supplementation reversed the development of unexplained hyperglycaemia and glycosuria in a 63-year-old female during a TPN regimen of several months' duration (providing 6 µg/day of chromium). Initially 200 µg/day of chromium chloride was added to the TPN for 14 days. Following this initial intervention the patient thereafter received 26 µg/day of chromium in the standard TPN formula and glycosuria resolved. The patient was discharged on home TPN with 32 µg/day of chromium, with no hyperglycaemia, neuropathy or encephalopathy reported in the following year.

An 8-year-old boy had received TPN containing an added 3 µg/day of chromium for more than two years when the addition of chromium to the TPN was discontinued because one of two serum measurements indicated an elevated serum chromium concentration. One year later a mild neuropathy developed while glucose tolerance was normal. Despite serum chromium still exceeding the upper range of normal according to the authors, chromium was again added to the TPN solution (3 µg/day), but the peripheral neuropathy persisted at follow-up assessments at three and ten months. It was estimated that the TPN solution without the addition of chromium provided 4 µg/day of chromium (Kien et al., 1986).

Another case study by Verhage et al. (1996) reported on a 40-year-old man who had undergone multiple intestinal resections over 11 years as a result of Crohn's disease and received TPN for six months while recovering from an injury to the bowel. The TPN solution was reported to provide 5 µg/day of chromium with an estimated additional 2.4-10.5 µg/day of chromium by contamination from the component solutions (Ito et al., 1990). After five months, the patient began to experience hyperesthesia in his hands and feet, postural tremor, unsteady gait, and muscle weakness which was initially attributed to one of the medications. Concomitantly, multiple hyperglycaemic episodes with blood glucose concentrations ranging from 16-24 mmol/L were experienced by the patient, who required exogenous insulin and a reduction in the dextrose load of the TPN. Serum chromium (0.084 µmol/L, 4.4 µg/L) was reported as being above their "reference range". In the hospital the TPN formula was switched to one which contained 10 µg/day of chromium as chromium chloride; this solution also differed in its content of most vitamins and minerals. After 12 days an additional 250 µg/day of chromium as chromium chloride was added to the TPN solution for 14 days. Within four days the patient had an improvement in gait, paresthesia and postural tremor. Serum chromium concentration increased to 1.7 µmol/L (88.4 µg/L) and fractional glucose clearance during intravenous glucose tolerance test normalised.

Tsuda et al. (1998) observed a 35-year-old man who was admitted to the hospital complaining of muscle weakness of the limbs and a progressive rise in serum creatine phosphokinase. He had been on TPN for 13 years as a result of chronic idiopathic intestinal pseudo obstruction. Selenium and chromium concentrations of the initial TPN solution were not reported. A muscle biopsy revealed myopathic changes with mild variation in size and regeneration of muscle fibres and muscle cell necrosis. Selenium deficiency was suspected as serum concentrations were low (0.1 µg/dL, normal range reported to be 9.7–16.0 µg/dL), and supplementation of 100 µg/day of selenium was administered for 99 days. After three months, the muscle weakness and serum creatine phosphokinase concentrations began to ameliorate. However, as the muscle weakness did not completely resolve and serum selenium concentrations were still low (3.9 µg/dL), supplementation with selenium was increased to 200 µg/day. On the 62nd hospital day there were elevated serum glucose concentrations (200-300 mg/dL), and glycosuria was found during and after administration of the TPN solution. Serum chromium concentrations were not detectable and an infusion with 200 µg chromium/day was initiated. After two weeks, the concentration of plasma insulin in response to an intravenous glucose tolerance test improved, but the concentration of plasma glucose did not. Therefore, 200 µg of chromium was added to the standard TPN solution every two weeks. About two months later, the serum glucose concentration decreased to within the normal range.

Chromium supplementation of the TPN solution of five acute-care patients receiving TPN only upon hospital admission provided inconclusive results, with two patients showing a possible benefit through a decrease in the amount of insulin needed to control blood glucose, and three patients reporting a slight or no benefit in terms of amount of insulin needed to control blood glucose (results not given) (Wongseelashote et al., 2004).

No symptoms have been reported in apparently healthy subjects that can be related to low chromium intakes (Stearns, 2007).

The Panel notes that the chromium concentrations in the TPN solutions given before the occurrence of presumed deficiency symptoms were not reported in all the patients studied. In the three studies in which the concentration of chromium in the TPN solution was reported the daily chromium supply was between 5 and 10 µg; at an absorption efficiency of 5 % this amount of infused chromium is equivalent to an oral intake of 100-200 µg/day. The Panel notes that this amount is above the estimated median daily intakes in the 17 European countries for which data were available to perform an assessment of chronic dietary chromium intake (see Section 3). The Panel concludes that it is unclear on the basis of these case reports whether deficiency of chromium could be considered the only cause of glucose intolerance in these patients, whether deficiency of chromium has occurred in these patients and whether chromium deficiency occurs in healthy populations.

The essentiality of Cr(III) for humans has been questioned based on the criteria required for essential inorganic elements (Stearns, 2000). The traditional criteria for essentiality for human health are that absence or deficiency of the element from the diet produces either functional or structural abnormalities and that the abnormalities are related to, or a consequence of, specific biochemical changes that can be reversed by the presence of the essential trace element (WHO, 1996; Mertz, 1998). Criteria that need to be considered in assessing the essentiality include (1) absence from the diet causes reproducible and consistent functional and structural abnormalities; (2) reintroduction or addition to intakes reverses or prevents these abnormalities; (3) the abnormalities associated with deficiencies are accompanied by specific biochemical, and physiological, changes; (4) these biochemical and physiological changes are prevented or reversed by preventing or curing the deficiency. Implicit in these criteria are the needs for organisms to have systems to ensure the acquisition, systemic regulation and utilisation of the trace element, as well as a means to prevent its excessive acquisition (IPCS, 2002).

Considering the above-mentioned criteria, the Panel notes that attempts to create chromium deficiency in animal models have not produced consistent results (Woolliscroft and Barbosa, 1977; EFSA, 2009; Di Bona et al., 2011). In 2009, the EFSA FEEDAP Panel concluded that symptoms of chromium deficiency in animals have not been demonstrated in experimental conditions or observed in the field. The FEEDAP Panel considered that there is no evidence of essentiality of Cr(III) as a trace element in animal nutrition and consequently, that Cr(III) requirements could not be established for animal feed (EFSA, 2009). The Panel considers that the failure to create an unambiguous laboratory model of Cr(III) deficiency is a particular obstacle to establishing Cr(III) as an essential trace element; this might be due to, amongst other things, a particularly low requirement for dietary Cr(III), environmental and dietary contamination arising from the ubiquity of Cr(III), variations on the profile of metabolic substrates in the experimental diets used, and the possibility that Cr(III) is not an essential trace element. The data from reported improvements associated with chromium supplementation in patients are not sufficiently well characterised to provide sufficient information on the reversibility of the possible deficiencies and the nature of any dose-response curve in order to identify a dietary requirement for humans.

2.2.1.2. Excess

Owing to limited data the SCF (2003b) was unable to set a Tolerable Upper Intake Level (UL). It was stated that in a number of limited studies there was no evidence of adverse effects associated with supplemental intake of chromium up to a dose of 1 mg/day.

The CONTAM Panel of EFSA recently derived a Tolerable Daily Intake (TDI) of 300 µg Cr(III)/kg body weight per day from the lowest No Observed Adverse Effect Level (NOAEL) identified in a chronic oral toxicity study in rats (EFSA CONTAM Panel, 2014).

2.3. Absorption, distribution, metabolism and excretion

In humans, absorption efficiency of supplemental chromium has been reported to be between 0.1 and 5.2 % (Donaldson and Barreras, 1966; Anderson et al., 1983a; Offenbacher et al., 1986; Gargas et al., 1994; Kerger et al., 1996) and to vary depending on the chromium complex ingested (Kerger et al., 1996; DiSilvestro and Dy, 2007). Absorption of trivalent chromium from food has been estimated to range from 0.4 to 2.5 % (SCF, 2003b), depending, among other factors, on the chemical properties of the ingested source and on the presence of other dietary components.

Vitamin C has been reported to enhance the absorption of chromium (given as chromium chloride) in women (Offenbacher, 1994). In rats, phytate reduced and oxalate enhanced ^{51}Cr absorption (Chen et al., 1973).

Following absorption, trivalent chromium binds to plasma proteins such as transferrin (Hopkins and Schwarz, 1964; Sayato et al., 1980), and only small amounts (~ 5 %) are present in an unbound form (Lim et al., 1983). Chromium is then transported to the liver where it is sequestered; uptake by the spleen, soft tissue, and bone also occurs. In humans, intravenously injected ^{51}Cr was found to accumulate mainly in the liver and spleen, but also in soft tissues and bone (Lim et al., 1983). Chromium has been reported to be also present in the skin, heart, brain, kidneys, pancreas, and testes (Schroeder, 1968; Sumino et al., 1975).

Urine is the main excretory route for absorbed chromium, with small amounts being excreted in perspiration and bile (Ishihara and Matsushiro, 1986). The majority of faecal chromium consists of unabsorbed chromium (Donaldson and Barreras, 1966; Offenbacher et al., 1986). Mean chromium concentrations in mature human milk from small groups of women in Europe have been found to be highly variable ranging from 0.14-10.8 µg/L (Appendix B).

2.4. Biomarkers

Urinary chromium excretion has been reported to be unrelated to chromium intakes ranging between about 10 and 60 µg/day (Anderson and Kozlovsky, 1985). Chromium supplementation (182-200 µg/day) for 8 to 12 weeks significantly increased serum/plasma chromium concentrations in men and women (Anderson et al., 1985; Offenbacher et al., 1985; Anderson et al., 1987; Lukaski et al., 1996; Lukaski et al., 2007). Supplementation also significantly increased urinary chromium excretion in men and women (Anderson et al., 1982b; Anderson et al., 1991; Uusitupa et al., 1992; Hallmark et al., 1996; Kerger et al., 1996; Lukaski et al., 1996; Kato et al., 1998; Campbell et al., 2002; Lukaski et al., 2007). The Panel notes that studies addressing dose-response relationships are lacking.

Hair has been considered to reflect past fluctuations in chromium intake of individuals provided that standardised procedures for sample collection have been followed (Hambidge et al., 1972b, 1972a).

The Panel concludes that serum/plasma and urinary chromium concentrations reflect changes in chromium intake after chromium supplementation but that it is unknown whether these changes also reflect habitual dietary chromium intakes.

No markers of chromium body burden have been identified.

3. Dietary sources and intake data

Chromium is ubiquitous in the diet. Foods rich in chromium include meat and meat products, oils and fats, breads and cereals, fish, pulses and spices.

Currently, chromium (III) chloride and its hexahydrate, chromium (III) sulphate and its hexahydrate and chromium (III) picolinate may be added to both foods[7] and food supplements,[8] and chromium (III) lactate trihydrate and chromium (III) nitrate may be added to food supplements[8] only. Directive 2006/141/EC on infant and follow-on formulae does not set minimum and maximum levels for chromium.[9]

Chronic dietary chromium intake has recently been estimated for various age groups using food consumption and body weight data at the individual level available from 26 dietary surveys carried out in 17 EU countries. Median dietary chromium intakes were 30.1-42.9 µg/day (medians of lower and upper bound) in young children (12 months to < 36 months), 54.3-71.2 µg/day in children (36 months to < 10 years), 63.5-83.4 µg/day in adolescents (10 years to < 18 years) and 57.3-83.8 µg/day in adults (≥ 18 years) (EFSA CONTAM Panel, 2014).

The main contributors to dietary chromium intake among children, adolescents and adults were the food categories "Milk and dairy products", "Bread and rolls", "Chocolate (cocoa) products" (except for adults ≥ 65 years) and "Non-alcoholic beverages". For example for adults (18 years to < 65 years), the main contributors to dietary chromium intake were the food categories "Bread and rolls" (median 14 %), "Milk and dairy products" (median 8 %), "Non-alcoholic beverages" (median 7 %), and "Meat and meat products (including edible offal)" (median 7 %). The food categories "Chocolate (Cocoa) products" (median 6 %), "Vegetables and vegetable products (including fungi)" (median 6 %) and "Potatoes and potato products" (median 5 %) also contributed to chromium intake. Whereas the high contribution of "Chocolate (cocoa) products" was mainly due to their high Cr(III) concentration, for other foods the contribution to dietary chromium intake was rather because such foods (e.g. bread and rolls) are highly consumed (EFSA CONTAM Panel, 2014).

4. Criteria on which to base Dietary Reference Values

The Panel notes that there is no convincing evidence for a role of chromium in human metabolism and physiology. The Panel also notes that there is no evidence that the general population is chromium-deficient, or has Cr(III)-responsive metabolic defects. The Panel therefore considers that there is no proof that chromium is an essential trace element. The Panel concludes that an Average Requirement for the performance of physiological functions cannot be derived.

Nevertheless, as for fluoride (EFSA NDA Panel, 2013), DRVs might be derived if a consistent dose-response relationship could be established between dietary chromium intake and a beneficial health outcome. A comprehensive search of the literature published between January 1990 and October 2011 was performed as preparatory work for this assessment, to identify relevant health outcomes upon which DRVs for chromium may potentially be based (Mullee et al., 2012).

Several studies have assessed the effect of chromium supplementation on glucose and/or lipid metabolism. Many of these included men and women with impaired glucose tolerance. In most studies chromium intake from the diet was not assessed and information on total chromium intake is therefore not available (Hopkins et al., 1968; Riales and Albrink, 1981; Anderson et al., 1983b; Offenbacher et al., 1985; Potter et al., 1985; Anderson et al., 1987; Press et al., 1990; Boyd et al., 1998; Hermann et al., 1998; Kato et al., 1998; Cefalu et al., 1999; Joseph et al., 1999; Amato et al., 2000; Bahijri, 2000; Volpe et al., 2001; Gunton et al., 2005; Anton et al., 2008; Krikorian et al., 2010; Yazaki et al., 2010; Kim et al., 2011; Masharani et al., 2012). The Panel considers that no conclusions can be drawn from

[7] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26.

[8] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51.

[9] Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, OJ L 401, 30.12.2006, p.1.

these supplementation studies performed mainly in subjects with impaired glucose tolerance with regard to an effect of total dietary chromium intake on glucose metabolism in healthy populations.

Anderson et al. (1991) carried out a randomised double-blind placebo-controlled cross-over trial in 17 men and women aged 22 to 65 years supplemented with 200 µg of chromium as chromium chloride or placebo daily for four weeks, with a one-week washout period in between. From four weeks before and throughout the supplementation phase subjects were on a fixed diet containing less than 20 µg chromium/day. The diet was given as a four-day rotating menu and duplicate daily food composites were taken 16 times during the study. Individuals with 90-minute blood glucose concentrations > 5.56 but < 11.1 mmol/L were designated hyperglycaemic (n = 8) and individuals with concentrations < 5.56 mmol/L comprised the normoglycaemic group (n = 9). Subjects had a mean body mass index of ~24 kg/m^2. Blood glucose, insulin and glucagon concentrations after an oral glucose tolerance test were reported to be significantly lower at the end of the chromium-supplemented period compared to the placebo period in the hyperglycaemic subjects only, while there was no difference in the normoglycaemic subjects.

The Panel considers there is no evidence of beneficial effects associated with chromium intake in healthy normoglycaemic subjects.

The Panel therefore concludes that the setting of an Adequate Intake for chromium is not appropriate.

CONCLUSIONS

The Panel concludes that the derivation of an Average Requirement and a Population Reference Intake for chromium for the performance of physiological functions is inappropriate. The Panel also considered health outcomes that may be associated with chromium intake and concludes that there is no evidence of beneficial effects associated with chromium intake in healthy subjects. The Panel concludes that the setting of an Adequate Intake for chromium is also not appropriate.

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APPENDICES

Appendix A. Overview of Dietary Reference Values and recommendations

Several national authorities have considered chromium when setting DRVs, but few have actually derived values for chromium.

Adults

The Nordic countries (Nordic Council of Ministers, 2014), WHO/FAO (2004), the Health Council of the Netherlands (2000), and the SCF (1993) did not derive DRVs for chromium for adults.

The German-speaking countries (D-A-CH, 2013) based their Adequate Intake (AI) on the estimated adult requirement of 20 µg/day by WHO (1996), which was thought to be sufficient for all physiological functions but not for body reserves. Adding a certain requirement for body reserves and in the absence of satisfactory data, an AI range for adults of 30-100 µg/day was derived.

The US Institute of Medicine (IOM, 2001) considered that the mean chromium content of 22 adult diets designed by nutritionists was 13.4 µg/1 000 kcal (Anderson et al., 1992). Taking into account energy intake estimates of 1 850 kcal for women and 2 800 kcal for men aged 19-30 years (Briefel et al., 1995), AIs of 25 µg/day and 35 µg/day were derived for women and men, respectively, aged 19-50 years. For women and men aged over 50 years AIs were set at 20 µg/day and 30 µg/day, considering energy intake estimates of 1 500 kcal for women and 2 100 kcal for men aged 50-70 years.

The French Food Safety Agency (Afssa, 2001) acknowledged that in a previous edition an AI range for chromium of 50-200 µg/day was proposed considering the absence of clinical signs of deficiency for an intake of 50 µg/day and the absence of toxicological effects for an intake of up to 200 µg/day. With the aim to set a narrower AI range and considering the problems with chromium analysis prior to the 1980s, AIs between 55 and 70 µg/day were set for women and men, respectively.

The UK Committee on Medical Aspects of Food (COMA) (DH, 1991) did not set a Reference Nutrient Intake (RNI) for chromium but considered that a safe and adequate level of intake for adults was above 20 µg/day.

Infants and children

The Nordic countries (Nordic Council of Ministers, 2014), WHO/FAO (2004), the Health Council of the Netherlands (2000), and the SCF (1993) did not derive DRVs for chromium for children and adolescents.

The German-speaking countries (D-A-CH, 2013) concluded that although breast milk concentrations are low (Anderson et al., 1993), exclusively breast-fed infants are adequately supplied. In view of the low absorption efficiency, the AI was considered to extend over a relatively wide range. Estimated values for infants and children were extrapolated downwards from the adult AI range assuming equally wide relative ranges and age-related energy intakes.

For infants aged 7 to 12 months, the IOM (2001) set an AI based on chromium intake from human milk and complementary foods. The average concentration of chromium in human milk was estimated to be 0.25 µg/L (Casey and Hambidge, 1984; Casey et al., 1985; Engelhardt et al., 1990; Anderson et al., 1993; Mohamedshah et al., 1998) and the average volume of milk intake assumed to be 0.6 L/day (Heinig et al., 1993). The amount of chromium ingested via breast milk and balanced meals (Anderson et al., 1992) was estimated to be 5.5 µg/day, which was therefore set as the AI for infants aged 7 to 12 months. In the absence of information on the chromium content of children's diets, for children aged one to 18 years the AIs were set using data extrapolated from the adult AI. Because urinary excretion of chromium is increased with exercise (Anderson et al., 1982a; Anderson et al., 1984; Anderson et al., 1988) metabolic weight ($kg^{0.75}$) was used for extrapolation, resulting in AIs ranging from 11-35 µg/day depending on age and sex (see Table 1).

Afssa (2001) indicated that no signs of deficiency had been seen in young children, apart from severe protein-energy malnutrition and TPN and that chromium concentrations in breast milk are very low, between 0.1-1.6 µg/day and with no variation between stages of lactation. They also considered the previous COMA (DH, 1991) estimates for an optimal intake of 0.1-1 µg/kg body weight per day, and set AIs between 25 and 50 µg/day for infants, children and adolescents.

The UK COMA (DH, 1991) did not set an RNI but considered that a safe and adequate level of intake for children and adolescents was between 0.1 and 1.0 µg/kg body weight per day.

Table 1: Overview of Dietary Reference Values for chromium for children and adults

	D-A-CH (2013)	Afssa (2001)	IOM (2001)
Age (months)	4-<12		7-12
AI (µg/day)	20-40		5.5
Age (years)	1-<4	1-3	1-3
AI (µg/day)	20-60	25	11
Age (years)	4-<7	4-6	4-8
AI (µg/day)	20-80	35	15
Age (years)	7-<15	7-9	
AI (µg/day)	20-100	40	
Age (years)	15-<19	10-12	9-13
AI			
Boys (µg/day)	30-100	45	25
Girls (µg/day)	30-100	45	21
Age (years)		13-19	14-18
AI			
Boys (µg/day)		50	35
Girls (µg/day)		50	24
Age (years)	≥ 19	20-65	19-50
AI			
Men (µg/day)	30-100	65	35
Women (µg/day)	30-100	55 (a)	25
Age (years)		> 65	≥ 51
AI			
Men (µg/day)		70	30
Women (µg/day)		60 (b)	20

(a): 20-55 years
(b): > 55 years
AI, Adequate Intake

Pregnancy and lactation

The Nordic countries (Nordic Council of Ministers, 2014), the German-speaking countries (D-A-CH, 2013), WHO/FAO (2004), the Health Council of the Netherlands (2000), the SCF (1993), and the UK COMA (DH, 1991) did not derive (separate) DRVs for chromium for pregnant and lactating women.

Because of a lack of data to estimate the additional chromium requirement during pregnancy, IOM (2001) determined the AI by extrapolating from the AI for non-pregnant adolescent girls and adult women. A median gestational weight gain of 16 kg was added to the reference weight for adolescent girls and adult women for extrapolation. For pregnant girls aged 14 to 18 years the AI was set at 29 µg/day and for pregnant women aged 19 to 50 years the AI was 30 µg/day. For lactating women, the AI was estimated on the basis of the chromium intake necessary to replace chromium secreted in human milk plus the AI for non-lactating women. Based on a milk chromium concentration of 0.25 µg/L and a mean secreted volume of 0.78 L/day during the first six months of lactation, chromium losses with breast milk were assumed to amount to 200 ng/day. Taking into account an absorption efficiency of 1 %, a chromium intake of 20 µg/day was considered for replacement of these losses. For lactating girls aged 14 to 18 years the AI was thus set at 44 µg/day, and for women aged 19 to 50 years the AI was 45 µg/day.

Afssa (2001) recommended to increase chromium intake by 5 µg/day for pregnant women during the third trimester, resulting in an AI of 60 µg/day. For breastfeeding women, Afssa (2001) did not recommend any additional chromium intake and advised the same intake as for non-pregnant, non-lactating women.

Appendix B. Chromium concentration of human milk from healthy mothers

Reference	Country	n (number of samples)	Total maternal intake (µg/day) Mean (range)	Stage of lactation	Chromium concentration (µg/L)			Comments
					mean ± SD	median ± SD	range	
Abdulrazzaq et al. (2008)	United Arab Emirates	209 (205)	Not reported	<1 week-80 weeks	0.689 ± 0.517	0.591	0.000-2.527	
Anderson et al. (1993)	USA	17	41.08 ± 0.416 [(a)]	60 days	0.178 ± 0.021 [(a, b)]			
Aquilio et al. (1996)	Italy	8	Not reported	2-6 days 12-16 days 21 days	1.1 ± 0.4 1.1 ± 0.2 1.2 ± 0.5			
Bougle et al. (1992)	France	(8)	Not reported	1-88 days	1.2 ± 0.4 [(c)]			
Casey and Hambidge (1984)	USA	17 6 26 23 9 (overall 255)	Not reported	0-14 days 15-28 days 1-3 months 4-6 months 7+ months overall	0.29 ± 0.09 0.27 ± 0.13 0.28 ± 0.11 0.26 ± 0.12 0.46 ± 0.41 0.30 ± 0.17		0.06-1.56	
Casey et al. (1985)	USA	11 (109)	Not reported	Day 1 Day 2 Day 3 Day 4 Day 5 Day 8 ± 2 (6-10) Day 14 ± 3 Day 21 ± 3 Day 23 ± 3 Overall	0.24 ± 0.08 0.23 ± 0.08 0.23 ± 0.06 0.25 ± 0.08 0.34 ± 0.11 0.27 ± 0.05 0.22 ± 0.09 0.28 ± 0.11 0.26 ± 0.07 0.27 ± 0.10		0.12-0.53	
Clemente et al. (1982)	Italy	21 (123)	Not reported	Mature (≥15 days)		≤ 0.3	≤ 0.3-876	
Cocho et al. (1992)	Spain	(21)	Not reported	1-10 days >10 days Overall	1.80 ± 0.75 1.25 ± 0.74 1.56 ± 0.78		0.45-3.00 0.27-2.27 0.27-3.00	

Reference	Country	n (number of samples)	Total maternal intake (µg/day) Mean (range)	Stage of lactation	Chromium concentration (µg/L) mean ± SD	median ± SD	range	Comments
Deelstra et al. (1988)	Belgium	(9) (7) (10)	Not reported	0-3 days 5-10 days 30-60 days	0.18 ± 0.34 0.21 ± 0.06 0.14 ± 0.05		0.09-0.34 0.15-0.33 0.10-0.23	
Kumpulainen and Vuori (1980)	Finland	10 (10) 5 (5) 5 (5)	30	8-18 days 47-54 days 128-159 days	0.43 ± 0.13 0.39 ± 0.21 0.34 ± 0.12			
Kumpulainen et al. (1980)	Finland	5 (5) 4 (5)	34-40 21-38	6-8 weeks 17-22 weeks	(0.19-0.69) ± (0.02-0.06) [a, d] (0.24-0.54) ± (0.01-0.06) [a, d]			
Mohamedshah et al. (1998)	USA	6	400 µg ^{53}Cr (as Cr chloride) for 4 days; dietary intake not reported	1-2 months	0.09-0.46 [d] No ^{53}Cr detected		0.05-1.06 [b]	
Okolo et al. (2001)	Nigeria	45	Not reported	6.1 months	110			
Parr et al. (1991)	Guatemala Hungary Nigeria Philippines Sweden Zaire	(51)	Not reported	3 months		1.17 ± 0.14 0.78 ± 0.21 4.35 ± 1.78 3.46 ± 0.60 1.48 ± 0.57 1.07 ± 0.55		
Wappelhorst et al. (2002)	Germany, Poland, Czech Republic	19 (536)	256 ± 187 [e] Median: 206	3-68 weeks	10.8	10.8	3.1-19.4	
Yamawaki et al. (2005)	Japan	(1 166)	Not reported	1-5 days 6-10 days 11-20 days 21-89 days 90-180 days 181-365 days Summer Winter Overall	17 ± 10 35 ± 54 45 ± 53 50 ± 33 76 ± 54 25 ± 17 67 ± 39 51 ± 52 59 ± 47			According to Yoshida et al. (2008), the results of this study are not reliable, since no evaluation of analytical values using standard reference materials was performed.

Reference	Country	n (number of samples)	Total maternal intake (µg/day) Mean (range)	Stage of lactation	Chromium concentration (µg/L)			Comments
					mean ± SD	median ± SD	range	
Yoshida et al. (2008)	Japan	79 (64) [f]	Not reported	5-191 days	1.73 ± 2.57	1.00	<0.1-18.67	

(a): mean ± SE
(b): calculated using atomic mass of chromium (see Section 2.1)
(c): mean ± SEM
(d): individual means
(e): mean ± SD
(f): 15 samples were below the limit of detection (<0.1 µg/L)

ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
AR	Average Requirement
COMA	Committee on Medical Aspects of Food Policy
Cr(III)	Trivalent chromium
D-A-CH	Deutschland- Austria- Confoederatio Helvetica
DRV	Dietary Reference Value
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization
IOM	U.S. Institute of Medicine of the National Academy of Sciences
NNR	Nordic Nutrition Recommendations
PRI	Population Reference Intake
RNI	Reference Nutrient Intake
SCF	Scientific Committee for Food
SD	Standard deviation
SEM	Standard error of the mean
TPN	Total parenteral nutrition
UL	Tolerable Upper Intake Level
WHO	World Health Organization