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Nordic Nutrition Recommendations 2012

Integrating nutrition and physical activity

Part 5


norden

Nord 2014:007

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Calcium, phosphorus, magnesium, sodium as salt, potassium, iron, zinc, iodine, selenium, copper, chromium, manganese, molybdenum and fluoride

5th edition

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Nordic co-operation

Nordic co-operation is one of the world's most extensive forms of regional collaboration, involving Denmark, Finland, Iceland, Norway, Sweden, and the Faroe Islands, Greenland, and Åland.

Nordic co-operation has firm traditions in politics, the economy, and culture. It plays an important role in European and international collaboration, and aims at creating a strong Nordic community in a strong Europe.

Nordic co-operation seeks to safeguard Nordic and regional interests and principles in the global community. Common Nordic values help the region solidify its position as one of the world's most innovative and competitive.

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Secretary General's Preface

There has been an increasing interest in food and nutritional science in recent years. Food programmes are a staple of most television channels and cookbooks top the bestseller lists. At the same time, it can be a bit of a challenge to find your way through the jungle of advice on what we should eat facing the average consumer.

That is why we need a work like the Nordic Nutrition Recommendations, one of the most well-researched and thoroughly documented works within nutritional science worldwide. They give a scientific basis for formulating dietary guidelines and are an excellent example of what the Nordic countries can achieve when they work together.

The Nordic Council of Ministers funds the extensive scientific effort behind the Nordic Nutrition Recommendations. We do this as a means to inform the public debate on food-related matters. But maybe more importantly, the NNR also serve as the main reference point for the various national nutrition recommendations in the Nordic countries.

The Nordic Nutrition Recommendations are also the foundation for the criteria developed for the Nordic nutritional label the Keyhole, informing the shopping decisions of millions of consumers in the Nordic region on a daily basis.

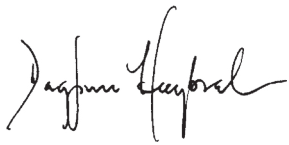
Finally, the NNR form part of the overall Nordic action plan *A better Life through Diet and Physical Activity.* In its aim to ensure the best-possible health for the population at large, this can be seen as an expression of the Nordic model, with its focus on an inclusive and holistic approach to society and the welfare of its citizens.

This is the fifth edition of the Nordic Nutrition Recommendations. As such, this publication is one of many examples of a long and fruitful Nordic co-operation over the last decades.

As a new step, we have decided to publish a free PDF version of the NNR along with a series of e-publications of individual chapters. The NNR will also for the first time ever be published as an e-book and they have thus entered the digital era.

I would like to thank the hundreds of scientists, experts and officials involved in compiling the Nordic Nutrition Recommendations and hope

that the quality of the work itself, as well as the many new forms of publication, will help ensure the widespread use that the NNR deserve.



Dagfinn Høybråten
Secretary General, Nordic Council of Ministers

Preface

The 5th edition of the Nordic Nutrition Recommendations, NNR 2012, has been produced by a working group nominated by the Working Group on Food, Diet and Toxicology (NKMT) under the auspices of the Nordic Committee of Senior Officials for Food Issues (ÄK-FJLS Livsmedel). The NNR 2012 working group was established in 2009 and consisted of Inge Tetens and Agnes N. Pedersen of Denmark; Ursula Schwab and Mikael Fogelholm of Finland; Inga Thorsdottir and Ingibjorg Gunnarsdottir of Iceland; Sigmund A. Anderssen and Helle Margrete Möltzer of Norway; and Wulf Becker (Chair), Ulla-Kaisa Koivisto Hursti (Scientific secretary), and Elisabet Wirfält of Sweden.

More than 100 scientific experts have been involved in this revision. Existing scientific evidence has been reviewed for setting dietary reference values (DRVs) that will ensure optimal nutrition and help prevent lifestyle-related diseases such as cardiovascular diseases, osteoporosis, certain types of cancer, type-2 diabetes, and obesity as well as the related risk factors for these diseases. The experts have assessed the associations between dietary patterns, foods, and nutrients and specific health outcomes. The work has mainly focused on revising areas in which new scientific knowledge has emerged.

Systematic reviews (SR) were conducted by the experts, with assistance from librarians, for the nutrients and topics for which new data of specific importance for setting the recommendations has been made available since the 4th edition. Less stringent updates of the reference values were conducted for the other nutrients and topics.

Peer reviewers for each nutrient and topic have also been engaged in the process of reading and commenting on the SRs and the updates conducted by the expert groups. A reference group consisting of senior experts representing various fields of nutrition science both within and outside the Nordic countries has also been engaged in the project. A steering group with representatives from national authorities in each country has been responsible for the overall management of the project.

All chapters were subject to public consultations from October 2012 to September 2013. The responses and actions to the comments by the NNR working group are published separately.

The SRs and the updates form the basis for deriving the DRVs. In the process of deriving the NNR 2012, emphasis has been put on the whole diet and the current dietary practices in the Nordic countries. This evaluation was performed by the NNR 2012 working group and was not part of the SRs conducted by the expert groups. The SRs were used as major and independent components – but not the only components – for the decision-making processes of the working group that was responsible for deriving the NNR 2012.

The SRs are published in the Food & Nutrition Research journal and the other background papers can be found on the Nordic Council of Ministers (NCM) website.

The 5th edition, the Nordic Nutrition Recommendations 2012, is published by the NCM and is also available in electronic form.

The following experts and peer reviewers have been engaged in performing SRs and chapter updates.

Systematic reviews

Calcium experts: Christel Lamberg-Allardt, Kirsti Uusi-Rasi and Merja Kärkkäinen, Finland.
Peer reviewers: Christian Mølgaard, Denmark and Karl Michaëlsson, Sweden.

Carbohydrates – including sugars and fibre experts: Emily Sonestedt, Sweden, Nina C Överby, Norway, Bryndis E Birgisdottir, Iceland, David Laaksonen, Finland.
Peer reviewers: Inger Björck, Sweden, Inge Tetens, Denmark.

Elderly experts: Agnes N Pedersen, Denmark, Tommy Cederholm, Sweden, Alfons Ramel, Iceland.
Peer reviewers: Gunnar Akner, Sweden, Merja Suominen, Finland, Anne Marie Beck, Denmark.

Fat and fatty acids experts: Ursula Schwab and Matti Uusitupa, Finland, Thorhallur Ingi Halldorsson, Iceland, Tine Tholstrup and Lotte Lauritzen, Denmark, Wulf Becker and Ulf Risérus, Sweden.
Peer reviewers: Jan I Pedersen, Norway, Ingibjörg Hardardottir, Iceland, Antti Aro, Finland, Jorn Dyerberg, Denmark, Göran Berglund, Sweden.

Folate experts: Cornelia Witthöft, Sweden, Georg Alfthan, Finland, Agneta Yngve, Norway.
Peer reviewers: Margaretha Jägerstad and Jörn Schneede, Sweden.

Food based dietary guidelines experts: Lene Frost Andersen, Norway, Asa Gudrun Kristjansdottir, Iceland, Ellen Trolle, Denmark, Eva Roos and, Eeva Voutilainen, Finland, Agneta Åkesson, Sweden, Elisabet Wirfält, Sweden.
Peer reviewers: Inge Tetens, Denmark, Liisa Valsta, Finland, Anna Winkvist, Sweden.

Infants and children experts: Agneta Hörnell, Sweden, Hanna Lagström, Finland, Britt Lande, Norway, Inga Thorsdottir, Iceland.
Peer reviewers: Harri Niinikoski, Finland, Kim Fleischer Michaelsen, Denmark.

Iodine experts: Ingibjörg Gunnarsdottir, Iceland, Lisbeth Dahl, Norway.
Peer reviewers: Helle Margrete Meltzer, Norway, Peter Lauerberg, Denmark.

Iron experts: Magnus Domellöf, Sweden, Ketil Thorstensen, Norway, Inga Thorsdottir, Iceland.
Peer reviewers: Olle Hernell, Sweden, Lena Hulthén, Sweden, Nils Milman Denmark.

Overweight and obesity experts: Mikael Fogelholm and Marjaana Lahti-Koski, Finland, Sigmund A Anderssen, Norway, Ingibjörg Gunnarsdottir, Iceland.
Peer reviewers: Matti Uusitupa, Finland, Mette Svendsen, Norway, Ingrid Larsson, Sweden.

Pregnancy and lactation experts: Inga Thorsdottir and Anna Sigridur Olafsdottir, Iceland, Anne Lise Brantsaeter, Norway, Elisabet Forsum, Sweden, Sjurdur F Olsen, Denmark.
Peer reviewers: Bryndis E Birgisdottir, Iceland, Maijaliisa Erkkola, Finland, Ulla Hoppu, Finland.

Protein experts: Agnes N Pedersen, Denmark, Jens Kondrup, Denmark, Elisabet Börsheim, Norway.
Peer reviewers: Leif Hambraeus and Ingvar Bosaeus, Sweden.

Vitamin D experts: Christel Lamberg-Allardt, Finland, Magritt Brustad, Norway, Haakon E Meyer, Norway, Laufey Steingrimsdottir, Iceland.
Peer reviewers: Rikke Andersen, Denmark, Mairead Kiely, Ireland, Karl Michaëlsson, Sweden, Gunnar Sigurdsson, Iceland.

Overviews

Alcohol experts: Anne Tjønneland and Janne Schurmann Tolstrup, Denmark.
Peer reviewers: Morten Grønbæk, Denmark and Satu Männistö Finland.

Fluid and water balance expert: Per Ole Iversen, Norway.

Vitamin B_6, Vitamin B_{12}: Chapters revised by the NNR5 working group.

Thiamin, Riboflavin, Niacin, Biotin, Pantothenic acid: Hilary Powers, United Kingdom. Evaluation of need for revision. Revised by the NNR5 working group.

Vitamin K expert: Arja T Erkkilä, Finland. Peer reviewer: Sarah L. Booth, USA.

Dietary Antioxidants expert: Samar Basu, France. Peer reviewer: Lars Ove Dragsted, Denmark.

Vitamin A: Håkan Melhus, Sweden. Evaluation of need for revision. Chapter revised by the NNR5 working group.

Vitamin E expert: Ritva Järvinen, Finland. Peer reviewer: Vieno Piironen, Finland.

Vitamin C expert: Mikael Fogelholm, Finland. Peer reviewer: Harri Hemilä, Finland.

Phosphorus expert: Christel Lamberg-Allardt, Finland. Peer reviewer: Susan Fairweather-Tait, United Kingdom.

Magnesium, Zink, Manganese experts: Ingibjörg Gunnarsdottir, Iceland, Helle Margrete Meltzer, Norway. Peer reviewer Lena Davidsson State of Kuwait.

Chromium, Molybdenum experts: Ingibjorg Gunnarsdottir, Iceland, Helle Margrete Meltzer, Norway.

Copper expert: Susanne Gjedsted Bügel, Denmark Peer reviewer: Lena Davidsson, State of Kuwait.

Sodium as salt and Potassium expert: Antti Jula, Finland. Peer reviewer: Lone Banke Rasmussen, Denmark.

Selenium experts: Antti Aro, Finland, Jan Olav Aaseth and Helle Margrete Meltzer Norway. Peer reviewer: Susanne Gjedsted Bügel, Denmark.

Fluoride expert: Jan Ekstrand, Sweden. Peer reviewer Pia Gabre, Sweden.

Physical activity experts Lars Bo Andersen, Danmark, Sigmund A Anderssen and Ulrik Wisløff, Norway, Mai-Lis Hellénius, Sweden. Peer reviewers Mikael Fogelholm, Finland, Ulf Ekelund, Norway.

Energy experts: Mikael Fogelholm and Matti Uusitupa, Finland. Peer reviewers: Ulf Holmbäck and Elisabet Forsum, Sweden.

Population groups in dietary transition expert: Per Wändell, Sweden. Peer reviewer: Afsaneh Koochek, Sweden.

Use of NNR experts: Inge Tetens, Denmark, Agneta Andersson, Sweden.

Sustainable food consumption expert: Monika Pearson, Sweden.

Librarians

The librarians have been responsible for literature searches in connection with the SRs, other database searches, and article handling.
Mikaela Bachmann, Sweden
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Susan Fairweather-Tait, United Kingdom
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Dag Thelle, Norway

Introduction

For several decades, the Nordic countries have collaborated in setting guidelines for dietary composition and recommended intakes of nutrients. Similarities in dietary habits and in the prevalence of diet-related diseases, such as cardiovascular diseases, osteoporosis, obesity and diabetes, has warranted a focus on the overall composition of the diet, i.e. the intake of fat, carbohydrate, and protein as contributors to the total energy intake. In 1968, medical societies in Denmark, Finland, Norway, and Sweden published a joint official statement on "Medical aspects of the diet in the Nordic countries" (Medicinska synpunkter på folkkosten i de nordiska länderna). The statement dealt with the development of dietary habits and the consequences of an unbalanced diet for the development of chronic diseases. Recommendations were given both for the proportion of fat in the diet and the fat quality, i.e. a reduced intake of total fat and saturated fatty acids and an increase in unsaturated fatty acids.

The Nordic Nutrition Recommendations (NNR) are an important basis for the development of food, nutrition, and health policies; for formulation of food-based dietary guidelines; and for diet and health-related activities and programmes. Previous editions mainly focused on setting dietary reference values (DRVs) for the intake of, and balance between, individual nutrients for use in planning diets for various population groups. The current 5th edition puts the whole diet in focus and more emphasis is placed on the role that dietary patterns and food groups play in the prevention of diet-related chronic diseases.

The NNR are intended for the general population and not for groups or individuals with diseases or other conditions that affect their nutrient requirements. The recommendations generally cover temporarily increased requirements, for example, during short-term mild infections or certain medical treatments. The recommended amounts are usually not suited for long-term infections, malabsorption, or various metabolic disturbances or for the treatment of persons with a non-optimal nutritional status. They are meant to be used for prevention purposes and are not specifically meant for treatment of diseases or significant weight reduction. The NNR do, however, cover dietary approaches for sustainable weight maintenance

after significant and intentional weight reduction. For specific groups of individuals with diseases and for other groups with special needs or diets, dietary composition might have to be adjusted accordingly.

After a thorough revision in which experts have reviewed a vast amount of scientific publications, most of the recommendations from the 4th edition (2004) remain unchanged. However, the RIs for vitamin D in children older than 2, adults, and the elderly ≥75 years of age and for selenium in adults have been increased. An emphasis has been put on the quality of fat and carbohydrates and their dietary sources. The recommendation for protein has been increased for the elderly ≥65 years of age. No recommended intakes have been set for biotin, pantothenic acid, chromium, fluoride, manganese, or molybdenum due to insufficient data, and this represents no change from the 4th edition.

The primary aim of the NNR 2012 is to present the scientific background of the recommendations and their application. A secondary aim is for the NNR 2012 to function as a basis for the national recommendations that are adopted by the individual Nordic countries.

The NNR 2012 are to be used as guidelines for the nutritional composition of a diet that provides a basis for good health. The basis for setting recommendations is defined for each individual nutrient using the available scientific evidence. In many cases, the values for infants and children are derived from adult data using either body weight or energy requirement as a basis for the estimations. As new scientific knowledge emerges with time, the NNR have to be reassessed when appropriate and should, therefore, not be regarded as definitive.

The NNR are based on the current nutritional conditions in the Nordic countries and are to be used as a basis for planning a diet that:

- satisfies the nutritional needs, i.e. covers the physiological requirements for normal metabolic functions and growth, and
- supports overall good health and contributes to a reduced risk of diet-associated diseases.

The NNR are valid for the average intake over a longer period of time of at least a week because the dietary composition varies from meal to meal and from day to day. The recommended intakes refer to the amounts of nutrients ingested, and losses during food preparation, cooking, etc. have to be taken into account when the values are used for planning diets.

The NNR can be used for a variety of purposes:

- as guidelines for dietary planning
- as a tool for assessment of dietary intake
- as a basis for food and nutrition policies
- as a basis for nutrition information and education
- as guiding values when developing food products

28 Calcium

Calcium mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	800	800	600	700	900
Average requirement	AR	500	500			
Lower intake level	LI	400	400			
Upper intake level	UL	2,500*	2,500*			

* EFSA 2012.

Introduction

The amount of calcium in the body at maturity is approximately 1,200 g and 1,400 g in adult women and men, respectively. Over 99% is found in teeth and bones, and the remainder is present as an easily exchangeable pool in the blood, extracellular fluid, and in all cells in the body. This free calcium plays vital roles in signal transduction both within and between cells, neuromuscular transmission, glandular secretion, and in a large number of enzymatic reactions. The concentration of calcium in plasma is kept constant within narrow limits (2.1–2.6 mmol/L). About half of this is in an ionised form and the other half is bound to albumin. Parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$) are the most important hormones in the regulation of calcium homeostasis. They contribute to the maintenance of a constant calcium concentration in the plasma by regulating the influx and efflux of calcium in the intestine, bones, and kidneys. Maintenance of a constant concentration of ionised calcium is of vital importance, and calcium homeostasis is probably the most tightly regulated homeostatic mechanism in the body.

In bones, calcium is almost exclusively in the form of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). Adult bone tissue undergoes continuous remodelling through resorption by osteoclasts and formation of new bone by osteoblasts. The rate of exchange of calcium between bone and the exchangeable

pool has been estimated to be about 700 mg/d. Bone formation exceeds bone resorption in children, and the rate of remodelling is higher in children than in adults and it is higher in trabecular bones than in cortical bones.

Dietary sources and intake

Milk and dairy products are main sources of calcium in the Nordic countries. Other sources of calcium are fish and fish products, especially when eaten with the bones intact. Pulses, nuts, seeds, and green vegetables have variable amounts of calcium. Mean calcium intakes are 995–1,417 mg/10 MJ.

Physiology and metabolism

In the intestine, dietary calcium is mixed with calcium in the digestive juices. From this mixture, absorption takes place mostly in the upper part of the ileum by passive diffusion or by an active energy requiring process. The latter is dependent on the action of $1,25(OH)_2D$, the hormonal form of vitamin D. Calcium absorption is thus decreased in vitamin D deficiency. The difference between dietary calcium and that lost in faeces is termed net absorption. True absorption is much higher because of reabsorption from, and secretion into, the intestinal juices. The per cent net absorption (or fractional absorption) increases with decreasing amounts of calcium in the diet and also with increased physiological needs such as during infancy, during puberty, and during pregnancy. This adaptation of calcium absorption according to varying intakes and varying physiological needs is of primary importance when assessing the dietary calcium requirement.

Balance studies have shown that when calcium intake is reduced, a period of up to several weeks of negative balance is observed in most individuals before a new steady state is reached (1). The ability to adapt might be reduced by advancing age (2). However, in the extensive balance study by Malm it was shown that adaptation in men might still be efficient at least up to the age of 70 (1). Thus calcium absorption per se seems to be unaffected by ageing (3).

The absorption of calcium can be inhibited by foods containing such factors as phytic acid and oxalic acid in plant foods and phosphates. Because calcium intake in the general Nordic population is generally sufficient and derived from a variety of dietary sources, and because of adaptation, these factors probably play only a minor role in an ordinary mixed diet. This situation might be different in populations with low calcium intake and

consuming large amounts of fibre-rich food such as unfermented bread (4). The net calcium absorption is reported to range from about 30% to 60% in infants and between 25% and 40% in older children depending on absolute intake (5). The net absorption is relatively high during puberty (about 34% from an intake of 925 mg/d (5)) and then declines to 20%–25% in adulthood and even lower at advanced age (4, 6). The varying degree of absorption, both because of adaptation and varying dietary compositions, add uncertainty to the use of net absorption estimates as a basis for determining requirements.

Calcium is lost from the body via the faeces, urine, and skin. Non-absorbed calcium is lost with faeces. In adults with intakes of about 1,000 mg, the loss amounts to about 70% to 80% of the intake, but an appreciable amount is recovered as calcium soaps. Loss via the skin and sweat is generally small, about 20–50 mg/d (7, 8). Under warm conditions or high physical activity, the loss might be appreciably greater.

Loss via urine varies appreciably from person to person. It is generally between 100 and 400 mg/d in adults and is relatively constant within individuals even if the intake varies. In the balance study by Malm (1), the urinary loss decreased from 231 mg/d to 201 mg/d (not significant) upon reduction of the intake from 940 mg/d to 450 mg/d. This finding indicates that the urinary loss of calcium is only affected to a minor degree by the intake and can almost be considered an individual constant. Adaptation to low intake thus does not involve the kidneys to any significant degree. Similar findings have been observed in children (9, 10).

Dietary factors such as intakes of sodium, potassium, and phosphorus as well as acid-base balance have been reported to affect calcium balance (11–14). The long-term effect on bone health, however, is unclear. Inactivity increases bone resorption and loss of calcium. Conversely, weight-bearing exercise contributes to higher bone mineral density (15–17). Post-menopausal women have a higher rate of bone resorption during the night than during the day (18).

Health effects of calcium intake

In connection with the formulation of NNR 2012, a systematic review (SR) was carried out to update the scientific evidence for requirements and for the favourable or harmful health effects of calcium (19). Medline and Swemed+ were searched for publications from 2000 to December 2011 and included all SRs that reported on calcium supplementation or habitual

dietary calcium intake on health outcomes. Meta-analyses, randomized controlled trials (RCTs), and cohort studies were included in a second search covering publications from May 2009 up to March 2011 and in an additional search covering studies until the end of 2011. The SR concentrated on studies reporting on independent effects of calcium, although few recent trials reported solely on the effects of calcium on health outcomes and most trials used calcium together with vitamin D compared to placebo.

Bone health

Children

The NNR SR (19) identified one high-quality SR (20, 21) and one low-quality meta-analysis that covered effects on bone health in children (22). The SR by Winzenberg et al. included 19 RCTs of calcium supplementation either with calcium supplements or dietary calcium in doses of 300–1,200 mg/d compared with placebo over a treatment period of at least three months. The studies included healthy children aged 3 to 18 years (the mean ages of the studies were 4–17 years) from Europe, Israel, the US, China, and Africa, and bone outcomes were measured after at least six months of follow-up. Calcium was provided in the studies as various calcium compounds, milk extracts, or milk minerals. The combined results showed a small, but significant, increase in bone mineral density (BMD) in the upper limb, but this seems mainly have been driven by studies including children from Hong Kong and the Gambia with habitually low calcium intakes. However, the results did not differ by baseline dietary calcium intake when using higher or lower values than the median value (794 mg/d) of the individual study means as the cut-off. The authors state that the finding is unlikely to result in a clinically significant decrease in fracture risk.

A low-quality meta-analysis by Huncharek et al. (22) included 12 RCTs from Hong Kong, the US, Europe, and Israel on the effects of calcium/dairy supplementation on bone health. The calcium supplements in the studies ranged from 300 mg/d to 1,300 mg/d, and the studies used bone mineral content (BMC) in grams as the primary outcome. Initial pooling of 12 RCTs (2,460 subjects) yielded a summary mean difference in BMC of 2.05 g (95% CI: −3.26 to 7.36 g) between the calcium-supplemented and placebo arms. Due to the heterogeneity of the pooled data, the calculated summary mean difference in BMC was considered to be of dubious validity (19). Baseline calcium intakes in studies from Europe and the US were

700–1,200 mg/d, thus an additional intake may have had limited effect on bone health measures.

In an 18-month RCT, 96 girls aged 11–12 years were randomised to receive a calcium supplement or placebo as a beverage (23). Baseline calcium intake was 636 mg/d. After 18 months, the calcium intake was 946 mg/d in the intervention group and remained at the baseline level in the control group (mean 658 mg/d). There were no group differences in BMC or BMD measures at 18 months in intention to treat analyses. However, the absolute gains in BMC were generally significantly greater at most sites, e.g. lumbar spine region (~5% at 18 mo), and bone resorption markers and PTH were significantly lower in the intervention group. At follow-up 42 months after the start of the study, the differences between groups were no longer evident. Vitamin D intake and status were not reported.

The results from RCTs show no or only small effects on bone mineral measures after increasing calcium intakes by 300–1,200 mg/d above habitual intakes (20–23). However, habitual calcium intakes were in general relatively high (> 700 mg/d), and this might have influenced the results. The study by Lambert et al. (23) indicates that an intake of around 900 mg/d would lead to small increases in BMC and BMD compared to an intake of about 600 mg/d in prepubescent girls aged 11–12 years.

Uusi-Rasi et al. (19) concluded that it is likely that calcium intake is a necessary, but not sufficient, condition for the development of a strong skeleton. Adequate vitamin D intake might be a crucial factor when assessing the role of calcium intake because vitamin D status interacts with calcium uptake and metabolism.

Pregnancy and foetal growth

The NNR SR (19) did not identify any SRs regarding calcium intake and bone health during pregnancy. One RCT and one prospective study, both of low methodological quality, that assessed bone health in the offspring were included. The RCT included healthy primiparous women (< 20 weeks gestation) with calcium intakes below 600 mg/d. The results showed that supplementation with 1,500 mg/d compared to placebo throughout the rest of the pregnancy did not impact on foetal somatic and skeletal growth, nor on neonatal characteristics and anthropometric measurements at delivery (24). In a prospective study, Yin et al. (25) found no significant association between maternal calcium intake in the third trimester of pregnancy and bone mass in children at 16 years of age. Calcium intake was assessed with a food frequency questionnaire and mean intake was high at 1,670 mg/d.

In summary, the available data are insufficient to draw conclusions on potential associations between calcium intake during pregnancy and bone health in the offspring (19).

Adults

After puberty and throughout most of adulthood, bone mass is consolidated and calcium requirements are relatively stable. Peak bone mass – the maximum amount of bone that can be accumulated – is reached in early adulthood (26, 27). The peak bone mass that can be attained is affected by genetic background and by lifestyle factors such as physical activity and total calcium intake.

Bone is a dynamic tissue, and a number of clinical studies suggest that increasing bone mass early in life has a transient effect but does not confer protection against later bone loss and osteoporosis (28). The total calcium content of bone at maturity is approximately 1,200 g in women and 1,400 g in men (29, 30). In men, this level remains relatively constant until the onset of age-related bone loss later in life, and in women until the onset of menopause. Caucasian women appear to lose as much as 3%–10% of their trabecular bone per year during the first few years after menopause and about 1% of their cortical bone per year during the first decade after menopause. After this accelerated bone loss period, the loss again levels off during the postmenopausal years. Lifetime losses can reach 30% to 40% of peak bone mass among women and 20% to 30% among men (31).

Women

The NNR SR did not identify any SR published since 2000 reporting on the effects of calcium supplementation on bone health in premenopausal women (19). For postmenopausal women, the SR by Uusi-Rasi et al. (19) included one high-quality (32) meta-analysis, one low-quality (33) meta-analysis) regarding calcium intake and bone health (bone mass and fractures).

The meta-analysis by Chung et al. (32) covered studies from a previous review by Cranney et al. (34). Trials using calcium supplements only and trials with calcium plus vitamin D were analysed together. The supplements typically provided 500–1,200 mg calcium per day and 10–20 µg vitamin D_3 per day. Chung et al. (32) concluded that there was no evidence to change the findings by Cranney et al. (34) that there is good evidence that combined vitamin D_3 and calcium supplementation results in small increases

in BMD of the spine, total body, femoral neck, and total hip. However, no trials that included an intervention group with calcium supplement alone were included.

Men

Data evaluating the effect of calcium intake on bone health in men are scarce and inconclusive (19). Only one low-quality SR was identified (35) that covered assessment of BMD by five prospective and nine cross-sectional studies. Results were inconsistent regarding the association between calcium intake (dietary or supplements) and subsequent bone loss.

Conclusions

In postmenopausal women, calcium supplementation of 500–1,200 mg/d increased BMD in most studies. Calcium plus vitamin D_3 supplementation resulted in small increases in BMD of the spine, femoral neck, and total hip. The data evaluating the effect of calcium intake on bone health in men are scarce and inconclusive.

Fractures

The NNR SR (19) included one high-quality SR (32), one high-quality meta-analysis (36), two low-quality meta-analyses (33, 37), and one low-quality cohort study (38) on the association between calcium intake and fractures. Data reporting the effects of calcium supplementation on bone fractures in children were not identified.

The SR by Chung et al. (32) covered studies from a previous review by Cranney et al. (34) and two additional RCTs identified among studies published after that up to 2009. The SR by Cranney et al. (34) concluded that calcium supplementation (500–1,600 mg/d) with vitamin D (10–20 µg/d, mainly as D_3) is effective in reducing fractures and falls in institutionalized populations, but that evidence for reducing falls in postmenopausal women and older men was inconsistent. However, the only trial that included an intervention group with calcium supplement alone showed no effect on secondary fracture risk (39). This was a secondary prevention.

The meta-analysis by Tang et al. (36) included 29 randomised trials on the effects of supplementation with calcium or calcium in combination with vitamin D on fractures and bone loss. Seventeen trials reported all types of fractures as an outcome. In total 64,897 individuals 50 years or older, 92% of them women, were included. In 16 trials, participants received

calcium-only supplements (500–1,200 mg/d). Effect of supplementation with calcium only on fracture risk showed a borderline significant reduced risk (relative risk (RR) = 0.90, 95% CI: 0.80–1.00). The difference in RR between calcium-only supplementation and calcium combined with vitamin D was small (0.90 vs. 0.87) and not significant. Risk reduction was significantly higher with doses at or above 1,200 mg/d than with lower doses in individuals who were elderly (> 70 years), had low dietary calcium intake (< 700 mg/d), or were compliant with calcium supplementation (> 80%).

The remaining studies included in the SR by Uusi-Rasi et al. (19) did not show any consistent association between calcium intake from the diet or from supplements and fracture risk (33, 37, 38). The meta-analysis of Bischoff-Ferrari et al. (37) included five RCTs that provided 800–1,600 mg/d calcium as a supplement. The pooled results from these studies showed no reduction in hip fracture risk with calcium supplementation, and there was even the possibility of an increased risk. In a Swedish prospective cohort study by Warensjö et al. (38), calcium intakes in the lower quintile (< 751 mg/d) were associated with an increased risk of any fractures and hip fracture as well as osteoporosis compared to the third quintile (882–992 mg/d). Intakes in the upper quintile (> 1,137 mg/d) did not further reduce the risk of fractures but were instead associated with an increased risk of first-ever hip fracture.

In summary, the evidence that calcium supplementation alone reduces fracture incidence is *limited and inconclusive* (19). Calcium supplementation in combination with vitamin D might be effective in reducing fractures in institutionalized populations, but the effect in the general population is unclear.

Pregnancy related outcomes

The NNR SR included two high-quality SRs (40, 41) and one good-quality SR (42) on the effects of calcium during pregnancy (19).

Offspring

The SR by Buppasiri et al. (40) reviewed 21 RCTs involving 16,602 pregnant women. Results showed a significant increase in birth weight of about 65 g (95% CI: 16–114 g) in children whose mothers had used calcium supplements ranging from 300–600 mg/d to 1,000–2,000 mg/d during pregnancy compared to babies of non-supplemented women (19 trials, 8,287 women). However, no significant differences were found for the

proportions of low birth weight infants between the two groups. Dietary calcium intakes were not reported so total intakes cannot be estimated.

In the SR by Bergel et al. (42), including two RCTs and three observational studies, no consistent effect was found on blood pressure in infants. However, in children aged 1–9 years, higher maternal calcium intake (dietary or from supplements) was associated with lower systolic blood pressure (mean 1.92 mmHg, 95C% CI: 0.71–3.14 mmHg). Calcium intakes from supplements were 2 g/d in the RCTs, and the mean total intake was 1.7 g/d in the included observational study. No association with diastolic blood pressure was found. The SR by Hofmeyr et al. (41) included one RCT that found that calcium supplementation with 2 g/d during pregnancy was associated with lower risk of having systolic blood pressure greater than the 95th percentile in children at 5–9 years of age compared to placebo (RR = 0.59, 95% CI: 0.39–0.91). Reported dietary intake at baseline was about 450 mg/d.

In conclusion, there is *probable* evidence for an association between supplemental calcium intakes during pregnancy and birth weight. Because there is no information on total calcium intakes, the relevance with respect to setting DRVs is limited.

No conclusions can be drawn with respect to effects on blood pressure in the offspring.

Mother

Hofmeyr et al. (41) also included 13 randomized trials comparing calcium supplementation of at least 1 g per day (typically 1.5–2 g/d) during pregnancy with a placebo. Meta-analysis of 12 trials including 15,730 women showed that the risk of high blood pressure was reduced by 35% (RR = 0.65, 95% CI: 0.53–0.81), and the effect was greatest in women with low baseline calcium intake (as defined by the trial authors or, if not defined, a mean intake < 900 mg/d). High blood pressure was defined as diastolic blood pressure ≥ 90 mmHg, or an increase in diastolic blood pressure of 15 mmHg or more or an increase in systolic blood pressure of 30 mmHg or more. In four small trials with women at high risk of developing pre-eclampsia (568 women), the risk of preeclampsia was reduced by 55% (RR = 0.45, 95% CI: 0.24–0.83).

The results on preterm birth were inconsistent. Hofmeyr et al. (41) reported that the overall average risk of preterm birth was reduced in the calcium supplementation group (11 trials, 15,275 women: RR = 0.76, 95% CI: 0.60–0.97). The SR by Buppasiri et al. (40) found no statistically signifi-

cant differences between women who received calcium supplementation and non-users for preterm births < 37 weeks gestation (RR = 0.90; 95% CI: 0.73–1.11; 12 studies with 15,615 women) or < 34 weeks gestation (RR = 1.11; 95% CI 0.84–1.46; 3 trials with 5,145 women).

In summary, There is *suggestive* evidence that calcium supplementation during pregnancy reduces the risk of developing hypertension. However, the effect seems to be dependent on baseline calcium intake, which was not specified, and this limits the interpretation of the results.

Lactation

The NNR SR did not identify any SR regarding calcium intake and lactation (19).

Cancer

The NNR SR (19) included nine articles of which two were SRs of high quality (32, 43) and three were cohort studies of good quality (44–46).

Breast cancer

The SR by Chung et al. (32) concluded that higher calcium intakes were associated with a lower risk of breast cancer in premenopausal women only. In the prospective cohort study by Hjartaker et al. (44) including 64,904 Norwegian women, calcium intakes in the upper category (> 800 mg/d, 4th quartile) tended to be associated with lower risk of pre-menopausal breast cancer compared to the lower category (< 550 mg/d). Mean follow-up was 8.6 years.

Colorectal cancer

Calcium intake as a supplement (1,200–2,000 mg/d), alone or with other agents, was associated with lower risk of recurrence of colorectal adenomas in two SRs of RCTs (43, 47).

The high-quality SR by Chung et al. (32) included the SR by Weingarten et al. (43), 19 prospective cohort studies, and one nested case-control study. The studies included men and women older than 45 years, and follow-up time ranged from 1.4 years to 11.3 years. Of the five cohort studies and the nested case-control study with good methodological quality, two of the cohort studies showed a significant inverse association between total calcium intake and risk of colorectal cancer. In general, risk reductions were observed in intake categories above the lower reference category in

the cohort, which varied between about 500 mg/d and 800 mg/d. Five of the cohort studies included Nordic populations in which calcium intakes in the low and high categories were 500–860 mg/d and 740- >1,420 mg/d, respectively, among women and 760–1,180 and 1,070- >1,950 mg/d, respectively, among men (48–52). Results were mixed, and three studies showed an inverse association (48, 50, 51).

Prostate cancer

The SR by Chung et al. (32) included 12 prospective cohort studies among men with mean ages ranging from 53 years to 67 years. Five studies found a higher risk (adjusted OR 1.2–2.2) among subjects in the highest calcium intake categories (quintile/quartile, 921 to >2,000 mg/d) compared to subjects in the lowest intake categories (455–1,000 mg/d). Seven studies did not find an association between calcium intake and the risk of prostate cancer. Only one cohort study included Nordic populations (heavy smokers in Finland) in which calcium intakes in the low and high reference categories were 1,000 mg/d and ≥ 2,000 mg/d, respectively (53). The results of that study showed an increased risk of prostate cancer with increasing calcium intakes during a mean of 17 years follow-up.

Other cancers

No significant associations were found with endometrial cancer in a low-quality SR (54), with lung cancer in a good-quality prospective cohort study (46), or with total cancer in the SR by Chung et al. (32).

Summary

The NNR SR concluded that there is *suggestive* evidence that higher calcium intakes might be associated with a decreased risk of colorectal cancer (19). Higher calcium intakes have also been associated with an increased risk of prostate cancer. Based on the SR by Chung et al. (32) the evidence is *limited-suggestive*. The evidence for an association with total cancer is sparse and *inconclusive*. The interpretation of the findings is complicated by large variations in habitual calcium intakes in the study populations, the use of calcium-containing supplements, and differences in dietary assessment methods.

Cardiovascular outcomes

The NNR SR included 13 studies (6 SRs, 1 meta-analysis, 3 RCTs, and 3 cohort studies) that addressed different types of cardiovascular outcomes (19). The methodological quality of the SRs was generally high or good except for one (55). Two of the RCTs (56, 57), the meta-analysis (58), and two of the cohort studies (59, 60) were graded as low quality.

Cardio-metabolic markers

Calcium intake and calcium supplementation were not significantly associated with progress of aortic valve calcification, coronary artery calcification (CAC) (59), serum lipids (57, 59), atherosclerosis vascular disease (61), abdominal aortic calcification, or coronary aortic calcification (56). All studies were of low quality.

Blood pressure

Results from three SRs of high quality showed that calcium supplementation lowered systolic blood pressure by 2–4 mmHg in hypertensives and in pregnant women, but no significant effect was seen among normotensives (32, 41, 62). Doses varied from approximately 400 mg/d to 2,000 mg/d with most studies using 1,000 mg/d to 1,500 mg/d.

Cardiovascular disease events

In the SR by Uusi-Rasi et al. (19), calcium intake or calcium supplementation was not significantly associated with stroke (58, 60), cardiovascular events (55), or cardiovascular disease mortality (63). In one study (58), calcium supplementation was associated with increased risk of myocardial infarction but not in the others (55, 61).

Summary

The SR by Uusi-Rasi et al. (19) did not find any consistent evidence for an association between calcium intake and cardiovascular outcomes. The low-quality meta-analysis by Bolland et al. (58) suggested an upward trend in cardiovascular events in older people receiving calcium supplements. However, cardiovascular events were not a primary outcome, the studies were small, and the event frequency was low. Doses ranged mainly from 1,000 mg/d to 1,200 mg/d, but total calcium intake was not reported. The adverse events might, therefore, be associated with calcium intakes of 2,000 mg/d or more. The implications for habitual calcium intakes from

foods are probably limited. No increase in cardiovascular events was found in the good-quality studies (61, 63) or in the low-quality SR of RCTs by Wang et al. (55). The results of the high-quality SR by Dickinson et al. (62) showed that calcium supplementation might improve some vascular risk factors, such as blood pressure, in hypertensives.

Diabetes

The NNR 2012 SR (19) identified one SR of low methodological quality that had type-2 diabetes as an outcome (64). The results showed that a higher calcium intake from supplements, with or without vitamin D or dairy, was associated with reduced risk of type-2 diabetes.

Obesity and body weight control

The NNR SR (19) included three SRs, of which two were of high methodological quality (32, 65) and one was of low quality (66). Two RCTs of low quality were also included (57, 67). No consistent association was found. In the SR by Onakpoya et al. (65), which included seven RCTs with 794 subjects in total, calcium supplementation was associated with a mean difference of –0.74 kg body weight and –0.93 kg body fat compared to placebo. Interventions included calcium supplements of 1,000–1,500 mg/d with a duration of 6–24 months.

The evidence for an effect of calcium intake on body weight is *inconclusive*.

Total mortality

The NNR SR (19) included two SRs, one of high methodological quality (32) and one of low quality (58). The SR by Chung et al. (32) showed no association between calcium intake and mortality from cardiovascular causes. In the SR by Bolland et al. (58), including 15 RCTs, calcium supplementation was not associated with total mortality, but an increased risk of cardiovascular death was observed. In three prospective studies, higher calcium intake was associated with about a 10% to 25% decreased risk in all-cause mortality (60, 63, 68).

In conclusion, no consistent association was found between calcium intake and total mortality or death from various causes.

Requirement and recommended intake

It has been difficult to reach agreement on what should be considered the physiological requirement of calcium. This is because we have no clear deficiency criteria at low intakes due to the slow turnover of bone. When assessing the dietary requirement for calcium, one condition is that vitamin D status should be sufficient because vitamin D influences calcium bioavailability.

In NNR 2004, calcium requirements and recommendations were based on different criteria for various age and sex groups. For children and adolescents, recommendations were based on calcium retention in the skeleton during growth in addition to the requirement for losses in faeces, urine, skin, and sweat. For adults, data from balance studies were used and supplemented with evidence regarding the role of calcium in maintaining a healthy skeleton and preventing fractures.

Children and adolescents

Because over 99% of body calcium is in the skeleton, an adequate calcium intake during the growth period might be critical in maximising BMC. During growth, bone formation exceeds bone resorption. The NNR 2004 reported that the estimated net retention in the skeleton was 160 mg/d during the first year of life, between 70 mg/d and 150 mg/d during the period of 1–10 years of age, and 250 mg/d and 300 mg/d during pubertal growth for girls and boys, respectively (69). These estimates are in line with a recent longitudinal study in adolescent Caucasian boys and girls aged 9–18 years that measured calcium accrual in the skeleton (70). Boys accrued bone mass equivalent to 175 mg calcium per day with a maximum accrual of 296 mg per day at age 14. Girls accrued 122 mg calcium per day with a maximum 235 mg per day at age 13. A previous study in Danish children 6–19 years old found that median annual calcium accretion in pubertal stage III (median age 13 years) was 220 mg/d in girls and 317 mg/d in boys, which were close to the maximum annual BMC increase (71).

Controlled balance studies have been used to estimate calcium needs during growth. The studies have generally been of short duration (2–6 weeks) and measured net retention of calcium calculated from intake and losses in urine and faeces (72–76). Adaptation to low calcium intakes is generally efficient in children and adolescents (72, 73). At intakes of 300–400 mg/d, fractional absorption was around 60% compared to 26%–43% at intakes of 1,200–1,400 mg/d. However, the total absorbed amount is

higher at higher intakes. Maximal net calcium retention has been reported to occur at intakes of 1,100–1,500 mg/d in children aged 9–18 years (74).

A limitation of these studies for setting DRVs is that adaptation, especially to lower intake levels, had probably not yet taken place. Other factors also influence bone growth and calcium accretion, including vitamin D status and physical activity. Insufficient vitamin D status can impair calcium absorption from the gut, but the serum 25OHD concentration below which a significant effect occurs is uncertain. According to the US Institute of Medicine (77) report, an effect is generally seen at serum 25OHD concentrations below 30 nmol/L (77), but a level of 20 nmol/L is reported by Lips (78). Data on vitamin D status are, however, reported in relatively few of the studies.

Results from the SR by Winzenberg et al. (20, 21) included in the NNR SR (19) showed that calcium supplementation among children with a mean age ranging from 4 years to 17 years was associated with a small increase in the upper limb BMD and total body BMC, but the long-term effects on future risk for fractures were uncertain. Overall, baseline dietary calcium intake was relatively high with a median of the individual study means of 794 mg/d. The 18-month study by Lambert et al. (23) showed some improvements in BMC and BMD at a mean intake of about 950 mg/d compared to around 650 mg/d among girls aged 11–12 years. At follow-up 42 months after the start of the study, the differences were no longer evident. Vitamin D intake or status was not reported.

The US IoM (77) used a factorial approach for setting an estimated average requirement (EAR) among children and adolescents up to 18 years of age. Based on several studies, mean calcium accretion or retention estimates were 100 mg/d for infants and 100–210 mg/d for older children up to 18 years (70, 76, 79, 80). However, the resulting EARs are dependent on estimates of fractional absorption and losses via urine, faeces, and skin. Ideally, results from more long-term studies on balance and bone development should be used to establish EARs.

In NNR 2004, no average requirements (ARs) were established. The recommended intake (RI) for children 1–5 years of age was set to 600 mg/d based on estimates for calcium accretion and absorption. The SR by Uusi-Rasi et al. (19) concluded that no strong evidence has emerged to support a change in the recommendation. In the study by Lynch et al. (76), net calcium retention was estimated to be 160 mg/d at an average intake of 550 mg/d. An advantage of this study is that calcium intake during the study period did not differ from the previous habitual calcium intake. The

calcium accretion in the skeleton during this period has been estimated to be 100–120 mg/d (c.f. (76)). Adding losses in sweat of about 30 mg/d results in a net balance of 130 mg/d. An intake of about 500 mg/d is estimated to cover the average requirement and an intake of 600 mg/d the majority. Thus the RI is maintained in NNR 2012.

In NNR 2004 the RI for the age group 6–9 years was set to 700 mg/d. There are limited new data for this age group. In the study by Vatanparast et al. (70), calcium accretion was 100–120 mg/d among boys and 88–99 mg/d among girls aged 9–10 years and these are similar to the estimates for younger children. The IoM used an estimated calcium accretion of 140–160 mg/d for children aged 4–8 years and set an EAR of 800 mg/d and an RDA of 1,000 mg/d. However, these data were based on short-term balance studies and no data on skeletal accretion were reported (80, 81).

Because there is no new strong scientific evidence, the RI of 700 mg/d is maintained in NNR 2012.

Calcium retention is very high during puberty, and the maximum rate of retention coincides with the maximum growth velocity. In the study by Vatanparast et al. (70), mean skeletal calcium accrual among children aged 9–18 years was 121 mg/d and 175 mg/d for girls and boys, respectively. Maximum accrual occurred between ages 14 and 16 among boys (236–296 mg/d) and between ages 12 and 14 among girls (164–235 mg/d), which is in line with a study on Danish children and adolescents (71). Peak bone mass is generally attained during late adolescence (82–84). In the study by Magarey et al. (83), 94% of peak bone mass was attained in girls and 86% in boys at 17 years of age.

Adaptation to the increased demand for calcium is very efficient during puberty (72, 85), and this efficient absorption was one reason for setting the RI for this age group at 900 mg/d in NNR 2004. The SR by Winzenberg et al. (20, 21) showed that a higher calcium intake in the form of supplements was associated with some improvement in bone health indicators, but the long-term effects on future risk for fractures are uncertain. Because calcium absorption appears to be more efficient up to age 24 than in later life (86, 87) the RI of 900 mg/d in NNR 2012 should cover the entire age group of 10–20 years.

Potential interaction of high calcium intakes with iron absorption and iron status was considered in NNR 2004 when setting the RI for adolescents. However, available data do not support a major role for calcium in long-term iron status (88, 89).

Adults

The results from two classical balance studies among Norwegian men (1) and Peruvian men (90) show that humans can adapt to very low calcium intake levels. In the study by Malm (1), calcium balance was monitored in men aged 20–79 years fed controlled diets with two different calcium levels. The diet was based on the Norwegian standard for an "ideal" diet and consisted of common Norwegian foods. The calculated macronutrient composition was protein 14 E%, fat 28 E%, and carbohydrates 58 E%. Thirty-nine men were monitored for several months (mean 7 months) with a mean calcium intake of 940 mg/d (sd 38 mg/d). All except one were in positive balance. The intake was gradually reduced to a mean of 460 mg/d (sd 58 mg/d) in 26 men monitored for several months (mean 7 months). All except three adapted to this lower level of intake. It should be noted that 20 of the men went through a transient period of more or less marked negative balance before they again reached balance. This indicates that adaptation in most individuals is a slow process. In the study by Hegsted (90), 10 male prisoners aged 30–56 years adapted to a low habitual calcium intake and were in balance at intakes of 300–400 mg/d. However, the latter study has limited relevance for the current dietary circumstances in the Nordic countries.

Long-term balance studies in women similar to those in men have not been performed, and it is not clear if women after menopause are at or near balance at the same low levels of calcium intake as in men. Some balance studies indicate that this is not the case (91). However, most of these balance studies have been of short duration and it is not clear if the individuals were adapted to the actual intakes. The bone loss in early menopause due to lack of oestrogen is not appreciably altered by calcium supplementation. However, supplementation studies are difficult to interpret because they alter the rate of bone remodelling in the short term. If they are not of long enough duration (about 4 years), any lasting effect on bone density cannot be evaluated. Most of the supplementation studies included in the NNR SR (19) have been of shorter duration.

The US IoM based their RDAs on intakes of calcium that promote bone maintenance and maintain calcium balance (77). The RDA was set to 1,000 mg/d for the age group 19–50 years based on short-term (minimum 18 days) controlled metabolic ward studies (92). A possible additional limitation is the low vitamin D content of the experimental diets (mean 2.9 µg/8.4 MJ). For the age group 51–70 years, the RDA was set to 1,000 mg/d for men and 1,200 mg/d for women. The higher RDA for

women was based on data from intervention studies suggesting a positive effect on BMD and reduced risk of fractures (36). However, the report states that the meta-analysis by Tang et al. (36) "is compromised by the inability to study a true dose-response relationship; many studies were grouped at the 1,200 mg/d level of intake and could not be used to reveal the effects at lower levels of intake". Data on total calcium intake were missing for several of the included studies. For adults older than 70 years, the RDA was set to 1,200 mg/d for both men and women.

The RI for calcium in NNR 2004 of 800 mg/d was based on long-term balance studies (1) in combination with epidemiological and clinical studies (10, 93–96). Evidence from subsequent supplementation studies or epidemiological studies does not indicate that a higher calcium intake would confer additional health benefits (19).

The NNR 2004 did not set an AR for adults. The results from the balance study by Malm (1) indicate that a mean intake of about 500 mg/d maintained long-term balance in men. In NNR 2004 the lower intake level (LI) was set to 400 mg/d, which is also maintained in NNR 2012.

There are some observations that supplementation with calcium alone in doses > 1,000 mg/d above the usual intake might increase the risk for cardiovascular events and fractures, although results are controversial. The NNR SR concluded that there is *limited-suggestive* evidence that higher calcium intakes are associated with a decreased risk of colorectal cancer. The WCRF/ACIR concluded that calcium probably protects against colorectal cancer. Higher calcium intakes have also been associated with increased risk of prostate cancer, but the evidence is *limited-suggestive*. No association with total cancer was found. The interpretation of these findings is complicated by large variations in habitual calcium intakes in the study populations, the use of calcium-containing supplements, and differences in dietary assessment methods (19, 32, 97).

The evidence that increasing calcium intake in the form of supplements alone reduces fracture incidence is *inconclusive*. Combined supplementation with calcium (500–1,600 mg/d) and vitamin D (10–20 µg/d) has, on the other hand, been shown to reduce the risk of fractures in elderly women living in institutions (19).

The RI of 800 mg/d from NNR 2004 is maintained in NNR 2012 because no strong evidence to change it has emerged. An intake of 500 mg/d is used as the AR.

Pregnancy and lactation

Adaptation is very efficient during pregnancy, and this might be connected to the increased serum levels of 1,25-dihydroxyvitamin D during pregnancy (98–101). Studies among women with low (about 400 mg/d) or high (700–900 mg/d) intakes have shown that both groups increase calcium absorption during pregnancy and that retention corresponds to the amount of calcium deposited in the foetus (98, 99). Supplementation with extra calcium in addition to that in the diet was not shown to influence the retention among women with high calcium intakes (1,300–1,400 mg/d) (102).

The NNR SR concluded that there is *suggestive* evidence that calcium supplementation during pregnancy reduces the risk of developing hypertension and *probable* evidence for an effect on birth weight. However, the effect seems to be dependent on baseline calcium intake, and because total intake was not given the relevance for setting DRVs is limited. The SR did not identify any studies that investigated calcium intake and bone health in pregnancy. In one RCT, calcium supplementation of 1,500 mg/d during pregnancy in women with dietary intakes below 600 mg/d did not impact foetal somatic or skeletal growth or neonatal characteristics and anthropometric measurements at delivery compared to placebo (24). A prospective study showed no significant association between maternal calcium intake in the third trimester and bone mass in their offspring at 16 years of age, although mean calcium intake was high at 1,670 mg/d (25).

In NNR 2004, the recommended calcium intake during pregnancy was set to 900 mg/d because many young women might become pregnant before termination of skeletal growth. This recommendation is maintained in NNR 2012 because no new data supporting a change have emerged (19).

Calcium absorption during lactation does not appear to increase above normal (101, 103, 104). The extra calcium needed for milk production appears to be provided by increased bone resorption combined with renal conservation of calcium (103, 105, 106). These adaptive changes are not influenced by calcium intake. The bone loss resulting from calcium mobilisation is regained when ovarian function is resumed and menstruation reappears.

Based on available data, the NNR 2004 concluded that there was no need for additional calcium intake above that of pregnant women (107), and the RI was set to 900 mg/d. This recommendation is maintained in NNR 2012 because no strong evidence to change it has emerged (19).

Reasoning behind the recommendation

The recommendations for calcium are maintained in NNR 2012 because no strong scientific evidence to change them has emerged.

Upper intake levels and toxicity

The NNR SR did not identify any dose-response data that could be used to evaluate the safety limits of an upper intake level (19). The SR included clinical outcomes, such as all-cause mortality, cancer, and cardiovascular events. Calcium/dairy intake was not associated with an increased risk of total mortality. In cohort studies, all-cause mortality was lowest in subjects in the highest calcium intake category (60, 63, 68). Results for cancer showed either no relation or a protective effect for high calcium intake categories. Prostate cancer was an exception with inconsistent results. Observational studies, however, suggested an increased risk of prostate cancer among men with high daily calcium intakes of above 2,000 mg (45, 108).

The European Food Safety Authority (EFSA) re-evaluated the previous Tolerable Upper Intake Level (UL) for calcium of 2,500 mg/d for adults including pregnant and lactating women (109). Additional placebo-controlled human intervention studies in adults showed that total daily calcium intakes of 2,500 mg from both diet and supplements are tolerated without adverse effects. Health outcomes evaluated were risk of nephrolithiasis, cardiovascular disease, and prostate cancer. Due to lack of data, ULs for infants, children, and adolescents were derived from the UL for adults.

The US IoM used the risk of kidney stone formation to set the UL to 2,500 mg/d and 2,000 mg/d among adults 18–50 years and older than 50 years, respectively (77). The report stated that limited new information was available since the previous report from 1997 (110). For younger age groups, ULs were derived from those of adults after accounting for needs for growth and development.

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29 Phosphorus

Phosphorus mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	600	600	470	540	700
Average requirement	AR	450	450			
Lower intake level	LI	300	300			
Upper intake level	UL	3,000	3,000			

Introduction

Phosphorus plays an essential role in many biological processes. Phosphorus-containing compounds have important roles in bone mineralization, cell structure, cellular metabolism, regulation of subcellular processes, and maintenance of acid-base homeostasis. In biological systems, phosphorus is present as phosphate (1).

The total amount of phosphorus in the body is 800–1200 g, 85% of which is in the skeleton and the rest evenly distributed in all tissues. Phosphate is the most abundant anion in the human body and comprises about 1% of the total body mass. It is predominantly an intracellular anion, and in the skeleton phosphate is generally complexed with calcium in the form of hydroxyapatite. In soft tissue and cell membranes, phosphorus exists mainly as phosphate esters and to a lesser extent as phosphoproteins and free phosphate ions. In the extracellular fluid, about one-tenth of the phosphorus content is bound to proteins, one-third is complexed to sodium, calcium, and magnesium, and the remainder is present as inorganic phosphate (1, 2). Serum phosphate concentration varies with age, with the highest concentration in infants. The concentrations decline towards adulthood, and the normal range in adults is 0.8–1.5 mmol/L (1).

Dietary sources and intake

Meat, milk, grain products, and legumes are high in phosphorus and contribute the largest amounts to the total dietary phosphorus intake in an average diet in the Nordic countries. The bioavailability of phosphorus differs among food sources. Some forms of dietary phosphorus are less bioavailable, especially the phosphorus in the phytic acid found in the outer layer of cereal grains. The actual bioavailability depends on the way these grain products are processed and the amount of residual phytate. Little is known about phosphorus bioavailability from different food sources, but inorganic phosphate salts such as additives used in food processing are readily hydrolysed in the gastrointestinal tract and absorbed (3–5).

Diets in the Nordic countries contain 1.560–1.940 mg/10MJ. The intake from food additives is largely unknown, but it is likely to be of significant importance.

Physiology and metabolism

The understanding of phosphorus homeostasis has increased dramatically in the past 5–10 years with the discovery of two new compounds, Klotho and fibroblast growth factor 23 (FGF23). The FGF23-Klotho system regulates body phosphorus content together with parathyroid hormone (PTH). After ingestion of phosphorus, both PTH and FGF23 are released, the former from the parathyroid glands and the latter from bone, probably from osteocytes (1).

Dietary phosphate is absorbed by the epithelium of the duodenum and jejunum in the small intestine via both passive diffusion, which depends on the amount of phosphorus in the intestine, and an active sodium-dependent process that is regulated by calcitriol (1,25-dihydroxyvitamin D_3. Calcitriol in turn is regulated by serum phosphate such that a decrease in phosphate concentration leads to an increase in the synthesis of calcitriol. Phosphate absorption is thought to depend on the function of sodium-dependent phosphate transporters. The most highly expressed phosphate transporter in the small intestine is NaPiIIb, and the activity of NaPiIIb is regulated by calcitriol (1).

Net absorption from a mixed diet has been reported to vary between 55% and 70% in adults and between 65% and 90% in infants and children. There is no evidence for a dose-response relationship (3).

The kidney is the major organ involved in the regulation of short-term phosphate homeostasis. PTH, FGF-23, and dietary phosphate are considered to be the major regulators of NaPiIIa, which is the main sodium-dependent phosphate transporter in the kidney. Brush border membrane expression of NaPiIIa is reduced within minutes in response to PTH and within 2 h in response to altered dietary phosphate load (1, 6). There is little phosphate reabsorption in the proximal straight tubule in the presence of PTH. An increase in PTH enhances the urinary excretion of phosphorus by removing the sodium phosphate co-transporter from the apical membrane of the proximal tubule, whereas FGF23 and its cofactor, Klotho, shut down the synthesis of the sodium phosphate co-transporter. FGF23 and Klotho also decrease the synthesis of calcitriol and this leads to a decrease in intestinal phosphate absorption. As a result of these events, more phosphorus is excreted in the urine and less phosphorus is absorbed from the intestine and the serum phosphorus level is reduced (1, 7). Other factors that can affect the renal handling of phosphate include bicarbonate concentrations, sodium reabsorption rates, and the effects of other hormones such as growth hormone and insulin (8).

Chronic phosphorus insufficiency results in impaired bone mineralization, rickets, and osteomalacia. In addition to these skeletal defects, the clinical consequences of phosphorus insufficiency include problems with the nervous system, muscle tissue, and kidney function. Low dietary phosphorus intake is rare, and intestinal absorption of phosphorus is very efficient. Renal regulation of phosphorus excretion is the most important step in phosphorus homeostasis and this is also a very efficient process. Although vitamin D deficiency or resistance decreases phosphorus absorption, hypophosphataemia due to low intestinal absorption is rare and only becomes apparent when phosphorus deprivation has continued for a long time, such as in the case of diarrhoea (9).

Requirement and recommended intake

The exact requirement for phosphorus is not known, but 400 mg daily is considered adequate for adults to maintain a plasma concentration of 0.8 mmol/L.

The EU Scientific Committee for Food suggested that phosphorus intakes should correspond on a molar basis with those of calcium and, therefore, proposed an average requirement (AR) of 400 mg/d and a population reference intake of 550 mg/d (10).

The US Food and Nutrition Board (FNB) has set the Estimated Average Requirement (EAR) for phosphorous at 580 mg/d for both men and women aged 19–70 years using serum inorganic phosphorus level as the criterion (11). The RDA (Recommended Dietary Allowance) is 700 mg/d for both genders after applying a coefficient of variation of 10%. For adolescents 9–18 years of age, the RDA is 1,250 mg phosphorus per day based on both dietary data and estimated additional needs during growth (11).

In NNR 2004, the recommended intake (RI) for phosphorus was 600 mg per day for both men and women. There are no substantial new data since then to indicate that these values should be changed. This intake level adheres to the view that an equimolar relationship between calcium and phosphorus is used as a basic principle for recommendations (1 mmol calcium = 40 mg, 1 mmol phosphorus = 30.9 mg). The RI values for children are also maintained and are based on the same considerations.

Reasoning behind the recommendation

The recommendations for phosphorus are maintained in NNR 2012 because no strong scientific evidence to change them has emerged.

Upper intake level and toxicity

Excessive phosphorus is toxic to the body by causing kidney and bone damage, vascular calcification, and premature ageing (12). The harmful effects of phosphorus are well documented in patients with chronic kidney disease (CKD) in which excess phosphorus results in vascular disease and bone loss. Over the last 5–10 years, new effects of increased serum phosphorus concentrations and high phosphorus intake on the vascular system and the skeleton have been observed in healthy populations with no kidney disease. Excessive dietary phosphorus intake might be one cause of mildly elevated serum phosphorus concentrations in persons with relatively normal kidney functions (7).

The potential adverse effects of phosphorus intakes at the high end of the range of habitual intakes on bone metabolism have been investigated and debated in recent decades (5, 13). A high-phosphorus diet produces mild hyperparathyroidism and reduces calcitriol concentrations. Moreover, it has been demonstrated in experimental settings in animals and humans that high-phosphorus diets increase bone resorption and decrease bone formation – at least in combination with low calcium diets. Some

cross-sectional studies have indicated that phosphorus intake, especially as food-additive phosphorus, is associated with higher PTH concentrations and could be deleterious to bone health (9, 14). However, results from a meta-analysis of 12 RCTs on phosphate supplementation with study periods ranging from 1 to 56 days showed that supplemental dietary phosphate was associated with decreased calcium in the urine and increased calcium retention (15).

The use of food additives containing phosphorus in the food industry is widespread. It has been estimated that phosphorus added during processing can represent an average daily intake of 500 mg/d in the US. This value ranges from 300 mg/d to 1,000 mg/d depending on individual food preferences (1). There are no corresponding estimates in the Nordic countries.

There is also a discussion as to whether data on phosphorus in food composition databases might underestimate the contribution from phosphate additives. This is not a problem specific for phosphorus, and the ability to accurately capture dietary intakes is related to the food coverage in the database and the proportion of values based on chemical analysis as well as to the dietary assessment method used.

Hyperphosphataemia and abnormal mineral metabolism have been recognized as risk factors in the development of vascular calcification in patients with CKD and are associated with increased mortality in both pre-dialysis and dialysis patients (16, 17). In the general population, phosphorus concentrations in the upper quartile of the normal range are also associated with increased cardiovascular and all-cause mortality (18, 19).

Some studies have shown that the risk of end-stage renal disease and mortality increases with increasing serum phosphorus within the normal range (20). Whether this is related to dietary intake of phosphorus is unclear. No significant association between dietary phosphorus intake and mortality was seen in subjects with moderate CKD during a mean follow-up of 6.5 years in the US NHANES III study (21). Dietary intake, however, was assessed with only one 24-h recall. Results from another prospective study among patients with cardiovascular disease with normal or moderate CKD showed decreased risk of cardiovascular events with increasing levels of urinary phosphorus excretion after a median of 7.4 years follow-up (22). There was no significant association with all-cause mortality.

Cardiovascular calcification is not only the result of precipitation of calcium and phosphate. Recent studies have documented that high phosphate is one factor that triggers the differentiation of vascular smooth muscle cells into osteoblast-like cells (18). Even transient increases of

serum phosphate concentrations, e.g. post-prandial hyperphosphataemia, can promote endothelial dysfunction (23, 24).

The US FNB set a Tolerable Upper Intake level (UL) of 4,000 mg/d in 1997 (11). A subsequent evaluation by the European Food Safety Agency (EFSA) was published in 2006. The EFSA concluded that there was not enough scientific evidence (in 2005) to establish a UL but stated that normal, healthy persons can tolerate intakes up to at least 3,000 mg/d (3).

In NNR 2004, the UL was set to 4,000 mg/d based on the evaluation by the US FNB (11). In NNR 2012, a provisional UL of 3,000 mg/d is used based on the EFSA evaluation. Given the recent observations of possible adverse health effects, a re-evaluation of the UL should be considered.

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30 Magnesium

Magnesium mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	280	350	120	200	280
Average requirement	AR	–	–			
Lower intake level	LI	–	–			
Upper intake level	UL	–	–			

Introduction

Magnesium is a divalent ion and is involved in a range of biochemical reactions and cellular functions. The metabolism and requirements for magnesium are still poorly understood.

Dietary sources and intake

Magnesium is found in abundance in green, leafy vegetables, legumes, and whole grain cereals. Magnesium concentrations are especially high in dark chocolate, nuts, and coffee. "Hard" water contains more magnesium than "soft" water and can contribute to total magnesium intake. The average dietary intake ranges from 354–479 mg/d (see the chapter on Dietary intake in Nordic countries).

Physiology and metabolism

The content of magnesium in the body is regulated by absorption and excretion. At normal dietary intakes, 20–60% is absorbed and this percentage is inversely proportional to the amount of magnesium ingested (1, 2). It is uncertain to what degree the composition of the diet influences absorption (3). Plasma concentrations are probably regulated via the kidneys and are kept within a narrow range of 0.75–0.95 mmol/L. When magnesium intake is low, kidney excretion is reduced.

A large number of biochemical and physiological processes are regulated by magnesium. Magnesium is necessary for energy-dependent membrane transport, gene regulation, sustained electrical potential in nerves and cell membranes, and for transmission of neuromuscular impulses.

The total body content of magnesium in an adult is estimated to be 20–28 g with 40–45% being intracellular in muscles and soft tissue, 1% being extracellular, and the remainder being found in the skeleton. Although humans do not have a true storage organ for magnesium, approximately one-third of skeletal magnesium is in equilibrium with plasma magnesium levels and functions as a buffer to maintain extracellular magnesium concentrations.

Magnesium depletion is very unusual in the absence of dietary restriction or some disorder causing magnesium loss from the body. Magnesium depletion is usually secondary to another disease process or to a therapeutic agent. The physiological manifestations of severe magnesium depletion include hypokalaemia and hypercalcaemia, neuromuscular hyperexcitability, electrocardiographic abnormalities, and cardiac arrhythmias. Adverse heart rhythm changes have been observed after 78 days of magnesium depletion with a daily magnesium intake of 101 mg (4).

Therapeutic use of magnesium in heart arrhythmia conditions (5–7) and to reduce the risk of eclampsia in women with pre-eclampsia (8–12) has received wide scientific attention in recent years. The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth has also been established (13). However, no studies have been conducted to show a preventive potential of high- versus low-magnesium diets in relation to reducing the risk of these conditions in the general population.

Requirement and recommended intake

Magnesium research has been hampered by the lack of good biomarkers of magnesium status in the body (14). At present, useful data that could contribute to the development of evidence-based dietary recommendations is limited, especially for specific vulnerable population groups such as infants, children and adolescents, pregnant women, and the elderly (14). Epidemiological studies have reported a relationship between low magnesium intake and increased risk of cardiovascular disease, hypertension, stroke, colorectal tumour risk, obesity, and type 2 diabetes (15–25). However, at present the results are difficult to interpret because it is not

possible to tell whether the observed associations are primarily attributable to magnesium intake itself or to other constituents of magnesium-rich food. High quality randomised controlled trials in this area are scarce (14).

Adults. In the absence of functional indicators of magnesium status, the only basis we have for evaluating requirements are balance studies. Because absorption of magnesium varies with the dietary intake, it seems possible to adapt to a low intake through more effective absorption. The U.S. Food and Nutrition Board (26) set an Estimated Average Requirement (EAR) for magnesium of 255 mg/d for women and 330 mg/d for men aged 19–30 years. The RDA (Recommended Dietary Allowance) is 310 and 400 mg/d for women and men, respectively. For adults aged 31–70 years the RDA for women is set at 320 mg/d and for men at 420 mg/d in this age group.

Data from 27 balance studies where pooled by Hunt and Johnson in 2006 (27) at the U.S. Department of Agriculture, and they suggested that the previously estimated EAR by the U.S. Food and Nutrition Board might have been too high. Neutral magnesium balance was predicted at a magnesium intake of 165 mg/d, and neither age nor sex affected the relation between magnesium intake and output (27). Data were reported for adults only.

The EU Scientific Committee for Food (28) considered 150–500 mg/d to be an acceptable range of magnesium intake based on observed intakes.

In the NNR 2004 (29) the recommended intakes (RI) were 350 mg/d and 280 mg/d for men and women (including pregnant and lactating women), respectively. There are no substantial new data since then indicating that these values should be changed (14, 27, 30).

Infants and children. The magnesium content in human breast milk is 23–47 mg/L (30), and this concentration is relatively constant during the first 12 months of lactation (31). For children, the RI values from 2004 are maintained (29).

Upper intake levels and toxicity

Excessive magnesium intake (0.5–5 g/d) gives diarrhoea, but otherwise no negative symptoms are observed when kidney function is normal.

The U.S. Food and Nutrition Board (26) has set a Tolerable Upper Intake level (UL) of 350 mg/d from supplements. This level is based on

the lowest observed adverse effect levels. The EU Scientific Committee for Food (28) has derived a maximum daily intake of 250 mg based on similar data. The UL does not include magnesium normally present in foods and beverages.

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31 Sodium as salt

Population goal	Adults and children > 10 y	Children 2–9 y
Sodium Salt	2.4 g/d 6 g/d	0.5 g/MJ 3–4 g/d

Introduction

Salt is nutritionally equivalent to sodium chloride (NaCl) and is used as a food ingredient or condiment. Sodium is also found in unprocessed foods but usually in very low concentrations. One gram of salt corresponds to about 0.4 g sodium, and 1 g sodium is equivalent to 2.5 g salt. One millimole of sodium corresponds to 23 mg and is equivalent to about 58 mg sodium chloride.

Dietary sources and intake

The main sources of sodium in the diet are processed foods such as bread, cheese, spreads, meat and fish products (1). The contribution of sodium from added salt in cooking and at the table varies but on average this intake constitutes approximately 10% to 20% of the total salt intake (1, 2). Data on the total dietary intake of sodium in Nordic populations are scarce. According to national food balance sheets, the daily amount of salt available for consumption in the Nordic countries is estimated to be 10 g to 12 g per person. Estimations of the sodium intake from national dietary surveys among adults generally show somewhat lower values. Average dietary sodium contents calculated from national dietary surveys among adults were 3.9 g/d (9.8 g salt) in men and 2.9 g/d in women (7.3 g salt) in Denmark, 3.7 g in men (9.3 g salt) and 2.7 g in women (6.8 g salt) in Finland, 3.8 g in men (9.1 g salt) and 2.6 g in women (6.5 g salt) in Iceland, and 3.6 g (9.0 g salt) in men and 2.7 g (6.9 g salt) in women in Sweden (1–6).

The contribution from discretionary salt intake – such as that from extra salt added to meals, etc. – is generally not included in these estimates. Data from Finnish population studies suggest that sodium intake assessed from dietary records and 24 h and 48 h dietary recalls are valid and give similar estimates of the mean level of sodium intake as determinations of 24 h urinary sodium (1). Results from 24 h urine collections in different population groups show wide variations ranging from about 7 g to 12 g of salt per day (7–10).

Physiology and metabolism

The sodium ion is essential for a number of metabolic processes in the cell and is involved in the regulation of the acid-base balance, the osmotic pressure in the extracellular fluid volume (ECV), blood volume, nerve function, and the transport of glucose and certain amino acids (11).

The body pool of sodium in an adult is approximately 100 g. About half is found in the ECV and 10% is found in the cells. The rest is mainly bound in the skeleton, of which half is exchangeable and thereby functions as a store for the body fluids.

The absorption of sodium is effective and generally amounts to more than 90% of the dietary intake. The excretion of sodium mainly occurs through the kidneys where it is effectively regulated depending on sodium and fluid intake. Losses through the skin in the Nordic climate are generally not more than 1 mmol/d (12). Small amounts of sodium (0.1–8 mmol) are also lost daily in the faeces (13). During profound sweating or in massive diarrhoea or vomiting, the extrarenal loss might become clinically significant. Healthy kidneys can retain almost all of the sodium in the body because the tubule cells reabsorb up to 99.5% of the sodium. Healthy kidneys can also excrete large amounts of sodium. This requires a sufficient water supply, however, because the urine can only be concentrated to a limited degree. The daily excretion through the kidneys and skin is normally 100–200 mmol.

Requirement

Dietary sodium deficiency does not normally occur in the Nordic countries. Acute deficiency, however, can develop in connection with heavy sweating in combination with large fluid intakes devoid of sodium or in connection with prolonged vomiting and diarrhoea without a compensatory salt

supply. Clinical symptoms include muscle seizures, loss of appetite, and circulation disturbances. Severe deficiency can result in coma and death.

Among adults, sodium balance can be maintained at intakes as low as 10 mmol (230 mg) per day, which corresponds to about 0.6 g of salt. An intake of 25 mmol (575 mg) per day, corresponding to about 1.5 g salt, is set as the estimated lower intake level and accounts for variations in physical activity and climate (11).

Salt and blood pressure

From a public health perspective, the role of sodium as dietary salt in the regulation of blood pressure has received the most interest. The relationship between salt and blood pressure has been studied since Kempner's classic observations during the 1930s and 1940s (14). He treated diabetics and hypertensive patients with a salt-restricted rice and fruit diet containing less than 2 grams of salt per day and found that blood pressure was drastically reduced among most of these patients.

Cross-sectional population studies

Population studies have shown that hypertension is rare in populations with a very low salt intake (< 2 g/d) and that blood pressure does not normally rise with age in these populations (15, 16). In areas with very high salt intakes (30–35 g/d), severe hypertension has been reported among 30%–35% of the population (15). In the large, multi-centre Intersalt study (16), the relationship between 24 h sodium and potassium excretion and blood pressure was investigated. The study included 10,000 men and women aged 20–59 years from 52 centres around the world. The median sodium excretion varied from 0.2 mmol/d to 242 mmol/d between centres. In four centres with very low sodium excretion, blood pressure was low and no age-related increase in blood pressure was observed. In the other 48 centres, sodium excretion was related to the increase in blood pressure with age but not to median blood pressure or prevalence of high blood pressure. Potassium excretion was found to be inversely related to blood pressure on an individual basis, while the sodium to potassium ratio showed a pattern similar to that of sodium. Increased body mass index and heavy alcohol intake were strongly related to increased blood pressure.

Law et al. (17) analysed published data on blood pressure and sodium intake from 24 different communities (47,000 subjects) throughout the world, including those of the Intersalt study. Allowance was made for

differences in blood pressure between economically developed and underdeveloped communities to minimise overestimation of the association through confounding with other determinants of blood pressure. The authors found that blood pressure was higher on average in the developed communities, but the association with sodium intake was similar in both types of community. A difference in sodium intake of 100 mmol/24 h was associated with an average difference in systolic blood pressure that ranged from 5 mmHg at 15 to 19 years of age to 10 mmHg at 60 to 69 years of age. The differences in diastolic blood pressure were about half as great. The authors concluded that the association of blood pressure with sodium intake is substantially larger than is generally appreciated and increases with age and initial blood pressure. Data from within-population studies also generally support such an association (17, 18).

In the EPIC-Norfolk (the European Prospective Investigation into Cancer in Norfolk) study with 23,104 community-living adults aged 45 years to 79 years, the mean systolic and diastolic blood pressure increased as the ratio of urinary sodium to creatinine increased and differences of 7.2/3.0 mmHg for systolic/diastolic blood pressure between the top and bottom quintiles were observed (19). This trend was independent of age, body mass index, smoking, and the ratio of urinary potassium to creatinine and was consistent by sex and history of hypertension.

Clinical trials

Several meta-analyses of clinical trials of dietary salt reduction have been published (17, 19–22), and these differ in scope and inclusion criteria. Law et al. (17) analysed 68 crossover and 10 randomised controlled trials of salt reduction among normotensives and hypertensives that included studies published up to 1989. They found that the blood pressure lowering effect of salt restriction was related to the duration of the study and that less of an effect was seen in trials lasting less than 4 weeks. The authors concluded that in people aged 50 to 59 years, a reduction in daily sodium intake of 50 mmol (approximately 3 g of salt) would, after a few weeks, lower systolic blood pressure by an average of 5 mmHg and by 7 mmHg in those with high blood pressure (170 mmHg). The diastolic blood pressure would be lowered by about half as much.

Midgley et al. (20) analysed 56 trials published between 1966 and 1994. These studies had randomised the allocation of subjects into a control group or to various dietary sodium intervention groups, had monitored sodium excretion, and had both systolic and diastolic blood

pressure as outcome measures. All papers in the analysis were selected by blinded review of the methods sections. Several of these studies, including some published before 1990, were not included in the analysis by Law et al. (17). The mean reduction in daily urinary sodium excretion was 95 mmol/d (range 71–119 mmol/d) in 28 trials with 1,131 hypertensive subjects, and 125 mmol/d (range 95–156 mmol/d) in 28 trials with 2,374 normotensive subjects. In hypertensive subjects, a reduced urinary sodium excretion of 95 mmol/d was associated with a reduction in systolic blood pressure by 5.9 mmHg (95% CI: 4.1–7.8 mmHg) and in diastolic blood pressure by 3.8 mmHg (95% CI: 2.9–4.8 mmHg). In normotensive subjects, the corresponding changes for a reduced urinary sodium excretion of 125 mmol/d were a reduction of 1.6 mmHg (95% CI: 0.9–2.4 mmHg) for systolic and 0.5 mmHg (non-significant; 95% CI: 0.1–1.2 mmHg) for diastolic blood pressure. A weakness of the analysis of trials on normotensives was the short duration of the trials (on average 14 days), although the authors state that there was a tendency for a greater blood pressure reduction in trials with a shorter duration (< 2 weeks). This is in contrast with the findings of Law et al. (17, 18) and could be due to problems of compliance in some of the more long-term studies. Trials on normotensive subjects involved mainly young subjects, while the trials on hypertensives mainly involved middle-aged or older subjects. The decreases in blood pressure were larger in trials on older hypertensive individuals than in trials on younger patients, but no data were given for normotensives.

Graudal et al. (21) published another meta-analysis including 58 randomised trials on dietary sodium restriction among hypertensives and 56 trials among normotensives published between 1966 and 1997. In the 58 trials of hypertensive persons (the exact criteria for hypertension was not stated), a reduced urinary mean sodium excretion of 118 mmol/24 h was associated with a significant reduction in systolic blood pressure of 3.9 mmHg and a reduction in diastolic blood pressure of 1.2 mmHg. In the 56 trials of normotensive persons, a reduced mean sodium excretion of 160 mmol/24 h was associated with a significant average reduction in the systolic blood pressure of 1.2 mmHg, but only a non-significant reduction in the diastolic blood pressure of 0.26 mmHg was observed. In this study, the trials on normotensives also had a short duration with a mean of only 8 days and included younger subjects (mean age 27 years) with a mean systolic blood pressure of 120 mmHg. This limits the relevance of the results for public health action. The mean duration of trials of hypertensives

was 28 days and the mean age of the subjects was 49 years, which was comparable to the analysis by Midgley et al. (20).

The meta-analysis by Cutler et al. (22) included 23 trials published up to mid-1994. The lower number of trials included was due to stricter inclusion criteria. The combined weighted data showed that a decrease in sodium excretion of 100 mmol/24 h (5.8 g salt) was associated with a reduction in systolic blood pressure of 4.8 mmHg in hypertensives and 2.3 mmHg in normotensives. The corresponding figures for diastolic blood pressure were 2.5 mmHg and 1.4 mmHg, respectively.

The meta-analysis by Geleijnse et al. (23) only included randomised controlled trials with a duration greater than 2 weeks, and 40 trials published between 1966 and 1991 were included. A median reduction in sodium excretion of 77 mmol/24 h (4.5 g salt) was associated with a 2.5 mmHg reduction in systolic blood pressure and a reduction of 2.0 mmHg in diastolic blood pressure. Reductions were more pronounced in hypertensives, and the same tendency was seen in older subjects. A subsequent meta-analysis including trials with a duration of 4 weeks or more with a similar reduction in sodium excretion (74–78 mmol/24 h) found a 5.0 mmHg reduction in systolic blood pressure and a 2.7 mmHg reduction in diastolic blood pressure among hypertensives. Corresponding figures for subjects with normal blood pressure were 2.0 mmHg and 1.0 mmHg, respectively (24, 25). A dose-response relationship was observed with a systolic/diastolic blood pressure reduction of 7.2/3.8 mmHg among hypertensives and a reduction of 3.6/1.7 mmHg among normotensives per 100 mmol/24 h (5.8 g salt) reduction in sodium excretion.

Only a few studies have examined the long-term effects on blood pressure of sodium restriction. Jula et al. (26) studied the effects on blood pressure and serum lipids of a non-pharmacological treatment based mainly on sodium restriction in a 12 month controlled randomized study with 91 middle-aged untreated and mildly hypertensive men and women. The estimated daily sodium intakes, calculated from 24 h urine samples, decreased in men from 227 mmol to a mean level of 105 mmol and in women from 129 mmol to 63 mmol. After 12 months of non-pharmacological treatment, the mean weight in men was 1.9 kg lower and in women 0.3 kg higher compared to the mean weight at baseline. In the treatment group, energy derived from fat decreased in men by 4% and in women by 3% reflecting decreased intake of saturated and monounsaturated fats. The net blood pressure decrease (the difference in changes between the treatment and control group) during the 12 months was 8.2 mmHg for systolic and

5.8 mmHg for diastolic blood pressure in men and 9.5 mmHg for systolic and 5.6 mmHg for diastolic blood pressure in women. All changes were significant. In the treatment group, LDL-cholesterol also decreased by 6.8% in men and by 12.1% in women.

In the DASH trials (Dietary Intervention to Stop Hypertension), the effects of various controlled diets on the blood pressure of adult Americans with normal or moderately elevated blood pressure were studied (27, 28). The study by Sacks et al. (28) assessed the influence of sodium intake on blood pressure in 412 subjects who were randomly assigned to follow either a control diet typical of the sodium intake in the US or to follow the DASH diet. In both groups, a second randomization was done and the subjects followed their assigned diets at three sodium levels for 30 days in random order in a crossover design. The subjects were selected among adults 22 years or older who were not taking antihypertensive medication and who had a systolic blood pressure ranging from 120 mmHg to 160 mmHg and a diastolic blood pressure ranging from 80 mmHg to 95 mmHg. The control diet had a fat composition corresponding to the usual American diet (36 E% total fat, 14 E% saturated fat) but a low content of fruits, vegetables, and dairy products. The DASH diet was rich in fruits, vegetables, and low-fat dairy products but low in edible fats, snacks, and sweets and had a low content of total fat (25 E%), saturated fat (7 E%), and cholesterol. The content of calcium, potassium, and magnesium in the control diet was lower than in the average US diet but was higher in the DASH diet. The intake of dietary fibre was similar in both groups. Within the assigned diets, sodium levels were adjusted to provide a daily intake of 150 mmol (high, about 9 g salt), 100 mmol (intermediate, about 6 g salt), and 50 mmol (low, about 3 g salt) for 30 consecutive days each, in random order. The estimated sodium intakes, calculated from 24 h urine samples, indicated a sodium intake of 141–144 mmol (about 8 g salt) during the high sodium phase and an intake of 64–67 mmol (about 4 g salt) during the low sodium phase and an intake of 106–107 mmol (about 6 g salt) during the intermediate sodium phase. Reducing the sodium intake from the high to the intermediate level significantly reduced the systolic blood pressure by 2.1 mmHg during the control diet and by 1.3 mmHg during the DASH diet. A further reduction from the intermediate to the low level caused additional reductions of 4.6 mmHg while on the control diet and 1.7 mmHg while on the DASH diet. A regression analysis of these data showed that a reduction in the sodium intake of 100 mmol per day would lead to a reduction in the systolic blood pressure of about 3 mmHg in the

DASH group and of about 7 mmHg in the control group. Corresponding values for diastolic blood pressure were 1.5–2 mmHg and about 3 mmHg, respectively. The effects of sodium were observed in normotensive and hypertensive subjects, subjects of different ethnicities, and in both women and men, and the effects were not dependent on weight (28, 29).

An aspect that was only partly addressed in the meta-analyses was the relationship between the sodium intake and the age-related change in blood pressure. Data from the Intersalt study strongly indicated a relationship between the median daily urinary sodium excretion and the difference in blood pressure with age (30). In within-population analyses, an individual 24 h urinary sodium excretion increase of 100 mmol was associated with a 3–6 mmHg higher systolic and 0–3 mmHg higher diastolic blood pressure. Associations were larger at 40–59 years of age than at younger ages. In cross-population analyses, a median 24 h sodium excretion greater than 100 mmol was associated with 5–7 mmHg higher median systolic and 2–4 mmHg higher median diastolic blood pressure. At age 55, the estimated mean increases in systolic and diastolic blood pressure were 10–11 mmHg and 6 mmHg, respectively, compared to the values at age 25. This indicates a strong age-related effect of high sodium intakes on blood pressure. In the DASH trial, the blood pressure reduction was higher in older (> 45 years) than in younger subjects, e.g. a 100 mmol reduction in sodium excretion was associated with a 6 mmHg lower systolic blood pressure among older non-black subjects (29).

The DASH trials clearly showed an effect of sodium restriction ranging from 2–5 g/d on blood pressure that was independent of other dietary and lifestyle factors. An important finding was that the blood pressure reduction was larger in the control group than in the DASH group. This implies that the benefits of sodium restriction are more pronounced among persons consuming a diet that is less than optimal in terms of fat, fruit, and vegetable intake (which is similar to the current dietary patterns in the Nordic countries) than among those already consuming a diet in line with the general nutrition recommendations. A limitation of the study was the relatively short duration (30 days) and the fact that the study excluded subjects with low blood pressure (systolic blood pressure < 120 mm Hg) and high blood pressure (systolic blood pressure > 160 mm Hg). However, the blood pressure lowering effect of dietary salt reduction on hypertensives is well documented, and the proportion of the adult population with systolic blood pressure below 120 mm Hg is small, especially among the middle-aged and older.

Observational population studies and population-based intervention studies

In Finland, salt intake decreased by 40% from the 1970s to 2002 along with a decrease in the intake of saturated fats and an increased intake of fruits and vegetables (10, 31). The dietary changes were associated with a 10–20 mmHg and 6–10 mmHg decrease in population systolic and diastolic blood pressure, respectively, and with a 70% decrease in stroke and coronary heart disease mortality (32–34). In a Portuguese population-based intervention study, sodium intake was reduced by dietary advice (35). The mean dietary intake of salt decreased by approximately 40% (from approximately 20 g/d to 11.5 g/d) as estimated by food consumption data, but estimations based on urinary sodium to creatinine ratios indicated a lower reduction of approximately 25% (5 g salt) after one year and 9% (2 g salt) after 2 years. After 2 years of intervention, the systolic and diastolic blood pressure had both decreased by approximately 5 mmHg. The systolic blood pressure rose in the control community, and after 2 years there was a 13/6 mmHg difference in systolic/diastolic blood pressure between the intervention and control communities.

Salt intake and blood pressure among children

The blood pressure of children living in industrialized countries rises with age, and this increase is more rapid in children of hypertensive parents than in children of normotensive parents (36–39). In the Finnish STRIP study (39), systolic blood pressure of children living in southwestern Finland increased with age along with sodium intake and by the age of 10 years their systolic blood pressure exceeded that of adults in populations consuming low-sodium diets. The mean daily sodium intake was 1,500 mg at the age of 13 months and 3,000 mg at the age of 15 years. Similar levels of salt intake by children have been reported in other countries (40, 41). Childhood blood pressure tracks with adult blood pressure (42, 43) and predicts early atherosclerosis in adolescence (44) and adulthood (44, 45).

A randomised trial among 476 Dutch newborn infants studied the effect of a low-sodium (average 120 mg/d) or a normal-sodium (average 330 mg/d) diet on blood pressure during the first 6 months of life (46). The sodium intake in the low-sodium group was approximately the same as the intake of breastfed infants, whereas the intake in the normal group was similar to the sodium intake of infants fed commercial infant formula. At the end of the trial, systolic blood pressure in the low-sodium group was 2.1 mmHg lower than in the control group. The authors also measured

blood pressure in 167 children from the original cohort (35% of the original study participants) after 15 years of follow-up. The adjusted systolic blood pressure at follow-up was 3.6 mmHg lower and the diastolic pressure was 2.2 mmHg lower in adolescents who as infants had been assigned to the low-sodium group compared with those assigned to the control group. One meta-analysis of controlled trials has been carried out to assess the effect of reducing salt intake on blood pressure in children and adolescents (47). Ten trials with 966 participants were included. Among adolescents (the mean ages for the participants in the individual trials ranged from 8 to 16 years), a reduction in salt intake by 42% corresponded to a reduction in systolic blood pressure of 1.2 mmHg (95% CI: 0.6–1.8 mmHg) and a reduction in diastolic blood pressure of 1.3 mmHg (95% CI: 0.7–1.9 mmHg) after a median duration of 4 weeks. In the three trials with infants, sodium excretion was reduced by 54% and systolic blood pressure was decreased by 2.5 mmHg (95% CI: 0.9–4.0 mmHg) after a median duration of 20 weeks.

Other dietary factors and blood pressure

A number of dietary factors, including alcohol, potassium, calcium, magnesium, and fatty acid composition, as well as levels of physical activity have been associated with blood pressure (see respective chapters).

Salt and morbidity and mortality

Cardiovascular disease (CVD)

A number of prospective cohort studies have investigated the association between dietary salt intake and the risk of stroke and other cardiovascular events. A systematic review and meta-analysis of prospective studies published between 1996 and 2008 assessed the relation between habitual salt intake and stroke or total cardiovascular events (48). The analysis included 19 independent cohorts with a total of 177,025 participants and over 11,000 vascular events. Follow-up varied between 3.5 years and 19 years. A higher salt intake of approximately 5 g per day was associated with a 23% higher incidence of stroke and a 14% higher incidence of total cardiovascular events. Study populations included both men and women, and salt intake was estimated using various dietary assessment methods and/or 24 h urine samples. Most of the included studies showed an increased risk of stroke and CVD. One of the included studies reported an increased risk of myocardial infarction in association with a lower sodium intake among male hypertensive subjects who had been treated with

blood pressure reducing drugs (49). The trend for women was the opposite, although not significant. The sodium intake was measured using a single 24 h urine sample that was collected 5 days after the subjects had been asked to avoid consumption of foods with a high salt content. One can, therefore, question whether the assessment provided a representative measure of the subjects' usual sodium intake. The results could also have been biased due to confounders, such as alcohol, not being accounted for.

In another study, Alderman et al. (50) reported a significant negative correlation between sodium intakes estimated by 24 h recalls and all-cause mortality and CVD mortality in a follow-up of the first National Health and Nutrition Examination Survey (NHANES I) study in the US. Based on these results, the authors concluded that sodium restriction might lead to negative health effects and that advice to reduce sodium intake in the general population is not justified. A critical examination of the data (51), however, favoured the opposite interpretation because the authors also found a positive correlation between the sodium content of the diet expressed as mg/kcal and mortality. A major weakness of the NHANES I data was the low energy intake. When the study population was classified according to sodium density (mg Na/kcal), the energy intakes were more comparable among the quartiles indicating that underreporting was more evenly distributed. The energy-adjusted sodium intakes are, therefore, more reliable, and in the absence of 24 h urine data only these data can be used with some confidence in the analysis of a possible relationship between sodium intake and mortality. The result of this analysis, which the authors briefly mention, is that there is a weak, but significant, positive association between the sodium content of the diet and both all-cause mortality and CVD mortality.

In another study from the NHANES I cohort (included in the above-mentioned meta-analysis (48), a 100 mmol higher sodium intake among overweight persons was associated with a 32% increase in stroke incidence, an 89% increase in stroke mortality, a 44% increase in coronary heart disease mortality, a 61% increase in CVD mortality, and a 39% increase in mortality from all causes (52). Dietary sodium intake was, however, not significantly associated with CVD risk in non-overweight persons. The limitations of the study are the same as for the earlier mentioned study by Alderman et al. (50) on the same population.

Subsequent prospective studies have shown J-shaped (53), positive (54, 55), or inverse associations between sodium intake or excretion and CVD (56). The study by Cook covers a prospective follow-up of 2,275 adults

with prehypertension aged 30 to 54 years not assigned to active sodium restriction in two intervention trials (TOPH I and II). The association between urinary sodium and potassium (the mean of three to seven 24 h urine collections) and CVD events (n=193) during 10 to 15 years of post-trial follow-up showed a non-significant trend for an increased CVD risk across sex-specific quartiles of urinary sodium excretion, but a significant trend for an increased risk across quartiles of the sodium to potassium excretion ratio was evident (RR = 1.00, 0.84, 1.18, and 1.50 for each quartile, respectively; p = 0.04 for trend). The study by O'Donnell (53) included two cohorts with 28,880 patients at high risk of CVD aged ≥ 55 years followed for a mean of 56 months. Compared with a baseline sodium excretion of 4 g/d to 5.99 g/d, sodium excretion of greater than 7 g/d was associated with an increased risk of all cardiovascular events, and a sodium excretion of less than 3 g/d was associated with increased risk of cardiovascular mortality and hospitalization for congestive heart failure. The 24 h urinary sodium excretion was estimated from morning urines, which adds some uncertainty to the risk estimates in this study.

The multi-centre study by Stolarz-Skrzypek (56) included 3,681 participants without CVD, of which 2,096 were normotensive. During a median of 7.9 years, 84 CVD deaths occurred. Risk of CVD death decreased with increasing baseline 24 h sodium excretion tertiles of 107 mmol/d, 168 mmol/d, and 260 mmol/d. The study by Yang investigated all-cause, cardiovascular, and ischemic heart disease (IHD) mortality in a nationally representative sample of 12,267 US adults from the third NHANES. After a mean follow-up of 14.8 years, a total of 2,270 deaths, including 825 CVD and 443 IHD deaths, had occurred. A 1,000 mg/d higher sodium intake was associated with a 20% increased risk for all-cause mortality. A higher sodium-potassium ratio was also associated with an increased risk of all-cause mortality and CVD mortality when comparing the highest and lowest quartiles. The findings did not differ by sex, ethnicity, body mass index, hypertension status, or physical activity. Dietary sodium intake was measured by a single 24 h recall that was calibrated with data from a subgroup with two valid recalls.

A Cochrane Review included seven randomized controlled trials with a follow-up of at least 6 months that included a total of 6,250 participants and 665 deaths (57). Results from meta-analyses performed separately for normotensive and hypertensive subjects did not find any benefits of reduced dietary salt reduction for the prevention of CVD. One of the included trials included subjects suffering from severe heart failure (58). The

participants were severely salt and water depleted due to being medicated with large doses of diuretics and being put on fluid restriction of 1,000 mL per day. A re-analysis of these studies combined the data for hypertensives and normotensives and excluded the study performed with subjects suffering from severe heart failure (59). This new analysis showed that a decrease in salt intake of 2–2.3 g per day decreased cardiovascular events by 20% ($p < 0.05$) and all-cause mortality non-significantly by 5%–7%.

A previous review of controlled studies, published from 1984 to 1995, in which the sodium intake was restricted did not reveal any evidence of adverse effects of moderate sodium restriction (60). The analysis included 20 randomised intervention studies with at least 6 months follow-up using urinary excretion data.

The review by Perry (61) concluded that available studies suggest that sodium intake is independently related to left ventricular hypertrophy, a condition that is associated with increased risk of coronary mortality. Long-term sodium restriction decreases left ventricular hypertrophy in hypertensive subjects (62, 63).

Cancer

The WCRF/AICR concluded that there is probable evidence that total intake of salt and sodium is associated with stomach cancer (64). A meta-analysis of seven prospective cohort studies found an increased risk with dietary intakes categorised as "high" or "moderately high" compared to "low" intakes (65). The meta-analysis included 10 cohorts, 268,718 participants, and 1,474 events with a follow-up of at least 4 years. The categorisation of intakes was based on reported tertiles or middle and extreme quintiles.

Other outcomes

Several studies have indicated a positive relationship between sodium excretion and calcium excretion and that sodium intake might play a role in the aetiology of osteoporosis and kidney stones (66).

Recommended intake

According to epidemiological studies, hypertension is practically non-existent in populations with low salt intake, and a lower sodium intake will attenuate the usual age-related increase in blood pressure. Data from individual trials and meta-analyses of previous trials show that reduction of sodium decreases blood pressure and that the effect is greater among

hypertensive subjects. The magnitude of the blood pressure decrease upon sodium restriction also depends on the dietary composition. The effect seems to be more pronounced when the diet is less optimal with respect to energy-providing nutrients, dietary fibre, potassium, and calcium as well as with respect to other dietary constituents such as those provided by fruits and vegetables.

Observational studies suggest that population blood pressures and cardiovascular morbidity and mortality have declined together with decreased salt intake. Blood pressure is a strong independent risk factor for CVD, and a lower sodium intake is associated with decreased risk of CVD morbidity and mortality. It has been estimated that the cardiovascular benefits of reduced salt intake are on par with the benefits of population-wide reductions in tobacco use and would be highly cost-effective (67).

Adults

There is a progressive dose-response relationship between sodium intake and blood pressure. Any recommendations on the sodium intake have to be compatible with the overall dietary recommendations, and also account for public health considerations, rather than on a precise estimate of an optimal intake. Based on an overall evaluation of the available data, a limitation of sodium intake to about 2.4 g/d – corresponding to about 6 g salt (NaCl) – is feasible at the population level.

Children

Blood pressure rises with age beginning in early childhood and systolic blood pressure may, with increasing sodium intake, already by the age of 10 years exceed that of adults in populations consuming low-sodium diets. Blood pressure measured in childhood tracks with the level measured in adulthood and predicts early atherosclerosis in adulthood. The available data suggest that a reduction in sodium intake at a young age is associated with lower blood pressure in later life. Following a lifelong salt-reduced diet beginning in early childhood is recommended. It is also prudent to limit sodium intake in childhood in order to avoid preference for a diet with a high salt content.

The recommended sodium intake for children up to 10 years age is set to 0.2 g per MJ (0.5 g NaCl/MJ), which is based on the energy-adjusted recommended levels for adult women.

Pregnancy and lactation

Pregnancy and lactation are associated with a small increase in the physiological requirements for sodium by about 0.07 g or 3 mmol per day (pregnancy) and 0.12 g or 5.2 mmol per day (full lactation). These amounts are small and can apparently be handled by the body's homeostatic system. There is a lack of evidence to suggest that sodium requirements during pregnancy and lactation differ significantly from that of non-pregnant women.

International expert reports

As early as 1982, a WHO report on prevention of CVD (68) recommended that salt intake should not exceed 5 g/d. This recommendation was based on various clinical and epidemiological data. Since then, several international and national expert bodies including the WHO (69), the US Food and Nutrition Board (70), the American Heart Association (71, 72), and a British Expert Panel (73) have published recommendations to limit salt intake to 6 g/d among adults. The British Expert Panel also set recommendations for children and adolescents. A joint report from three German institutes recommends that salt intake in the German population should be reduced to between 3.5 g/d and a maximum of 6 g/d (74). The importance of population-wide sodium reduction as a means to prevent CVD and stroke has been pointed out by the American Heart Association (75) and the British National Institute for Health and Clinical Excellence (76).

Reasoning behind the recommendation

There is a progressive dose-response relationship between sodium intake and blood pressure. Results from both prospective cohort studies and randomised controlled trials generally show that sodium intake is positively associated with an increased risk of stroke and cardiovascular events and mortality among the general adult population. A precise lower threshold for intakes associated with health benefits is difficult to assess, but intakes of 4 g/d to 6 g/d for adults have been recommended internationally. Based on an overall evaluation of the available data, a limitation of the sodium intake to about 2.4 g/d – corresponding to 6 g salt (NaCl) – is feasible at the population level in the Nordic countries. Thus, the recommendation in NNR 2004 is maintained.

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32 Potassium

Potassium g/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	3.1	3.5	1.8	2.0	2.9/3.3
Lower intake level	LI	1.6	1.6			
Upper intake level	UL	– [a]	– [a]			

[a] Not established.

Introduction

Most of the potassium in the body (98%) is found in the cells, and potassium is quantitatively the most important intracellular cation. Extracellular potassium, which constitutes the remaining 2%, is important for regulating the membrane potential of the cells and is necessary, therefore, for nerve and muscle function, blood pressure regulation, etc. Potassium also participates in the acid-base balance. 1 mmol potassium is equivalent to 39 mg.

Dietary sources and intake

Important potassium sources in the Nordic diets are potatoes, fruits and berries, vegetables, and milk and dairy products. The average dietary intake ranges from 3.6 g/10 MJ to 4.8 g/10 MJ (see chapter on intake of vitamins and minerals in the Nordic countries).

Physiology and metabolism

The absorption of potassium is efficient and about 90% of the dietary potassium is normally absorbed from the gut. The potassium balance is primarily regulated by renal excretion in urine. A small amount can be lost in sweat.

Potassium deficiency can develop as a consequence of increasing losses from the gastrointestinal tract and kidneys, such as that which occurs during prolonged diarrhoea or vomiting, and in connection with the use of laxatives or diuretics. Potassium deficiency due to low dietary intake alone is very uncommon due to the widespread occurrence of potassium in foods. Treatment with diuretics without potassium compensation or potassium-sparing diuretics can, however, lead to deficiency. Hyperaldosteronism, hereditary defects in renal salt transporters such as Bartter's syndrome and Gitelman's syndrome, and excessive consumption of liquorice increase sodium retention and potassium excretion and can lead to hypokalaemia. Symptoms of potassium deficiency are associated with disturbed cell membrane function and include muscle weakness and disturbances in heart function that can lead to arrhythmia and heart seizure. Mental disturbances such as depression and confusion can also develop.

About 800 mg/d (20 mmol) of potassium is lost via the gastrointestinal tract, urinary excretion, and sweat, and an intake of 1.6 g/d (40 mmol) is needed to avoid low plasma levels and loss of total-body potassium in adults (1). The potassium intake can affect sodium balance, and low potassium intakes of 10–30 mmol/d can induce sodium retention and an increase in blood pressure in both normotensive and hypertensive subjects (2–4).

Potassium and blood pressure

In the Intersalt study, a 30–45 mmol increase in urinary potassium excretion was associated with a 2–3 mm Hg lower systolic blood pressure (5). An inverse relationship between blood pressure and potassium excretion and the K/Na ratio in urine was also observed (6). A number of studies of both normotensive and hypertensive subjects indicate that an increased potassium intake in the form of supplements can lower blood pressure and increase urinary sodium excretion (7–12). However, a clear dose-response effect was not observed, and not all studies showed a beneficial effect (9). The lack of a clear dose-response could be due to factors such as differences in the duration of the studies, initial blood pressure, sodium intake, habitual diet, race, and age.

Two meta-analyses of randomised trials with potassium supplementation showed a significant reduction in blood pressure (7, 8). In the study by Whelton and co-workers (8), 33 studies conducted between 1981 and 1995 with a mean duration of five weeks (range of 4 days to 3 years) were included. The average net increase in potassium excretion from baseline

was 54 mmol/d. Potassium supplementation was associated with a mean decrease in systolic blood pressure of 4.4 mm Hg (95% CI: -2.2 to -6.6) and a mean decrease in diastolic blood pressure of 2.5 mm Hg (95% CI: -0.1 to -4.9) among hypertensive individuals. Corresponding figures for normotensive subjects were decreases of 1.8 mm Hg (95% CI: -0.6 to -2.9) and 1.0 mm Hg (95% CI: 0.0 to -2.1), respectively, but the changes were not significantly different between hypertensives and normotensives. The blood pressure lowering effect of potassium supplementation was greater in trials with a higher urinary sodium excretion indicating the close interrelationship between sodium and potassium in this respect. Using urinary excretion data for potassium, the average intake of potassium in the supplemented groups was estimated at 4.5–5 g/d. In a subsequent meta-regression analysis including 27 randomised controlled trials with potassium supplementation with a duration of more than 2 weeks (mean 6 weeks), an increased median potassium excretion of 44 mmol/d was associated with a 2.4 mm Hg (95% CI: -1.08 to -3.75) decrease in systolic blood pressure and a 1.6 mm Hg (95% CI: -0.50 to -2.65) decrease in diastolic blood pressure (7). Reductions were larger among hypertensives than among normotensives.

A review and meta-analysis included six RCT studies published between 1986 and 1991 with a duration of at least 8 weeks that included participants over 18 years of age with elevated blood pressure and with no changes in medication during the follow-up (9). The intervention arms included increased potassium intake from foods (one study) and from supplements as potassium chloride (four studies), potassium citrate, or potassium bicarbonate (one study). A meta-analysis of five eligible studies including 483 participants showed overall non-significant reductions in systolic and diastolic blood pressures. However, studies with doses less than 100 mmol were associated with significant decreases in both systolic and diastolic blood pressure. The authors concluded that the small number of participants in two high quality trials, the short duration of follow-up, and the unexplained heterogeneity between the trials made the evidence for an effect on blood pressure inconclusive (9). Another meta-analysis of 10 RCTs in hypertensives (556 patients) with high salt intake found that supplementation with potassium reduced both systolic and diastolic blood pressure by 9.5 mmHg and 6.4 mmHg, respectively (13). High salt intake was defined as >170 mmol/d (9.9 g NaCl) or "high salt intake" and follow-up was 8–16 weeks. Potassium dose was not stated.

Two subsequent RCTs among normotensives have found significant

reductions in systolic and diastolic blood pressure of 5–8 mmHg and 4–6 mmHg, respectively, after four to six weeks supplementation with potassium salts (23–30 mmol/d, 900–1,200 mg) (11, 14). No significant effects were, however, seen in two other RCTs (15, 16). In the study by Berry et al (15), potassium intake was increased by increased intake of fruit and vegetables (20–40 mmol/d, 780–1,560 mg) or potassium citrate (40 mmol/d) during six weeks. In the study by Matthesen et al. (16) subjects received daily supplements of potassium chloride of 100 mmol/d (3.9) during between four weeks. A RCT in 144 patients with mild to moderate essential hypertension but otherwise healthy showed that supplementation with potassium aspartate (30 mmol/d) significantly reduced both office and 24-h blood pressure compared to placebo (17).

Most of the RCTs have used potassium chloride supplements. Some studies have investigated the effect of other potassium salts, such as citrate, but the results are conflicting with respect to any differential effects on blood pressure (14, 15, 17–19).

Potassium and cardiovascular disease

An inverse association between potassium intake and the risk of stroke has been shown in most cohort studies. The association between dietary potassium intake and incidence of cardiovascular disease (CVD) was assessed in a systematic review and meta-regression analysis of 11 prospective cohort studies published from 1966 through 2009 including 15 cohorts with 247,510 men and women with a follow-up of 5–19 years (20). Potassium intake was assessed by 24-h dietary recall in two studies, a food frequency questionnaire in six studies, and 24-h urinary excretion in three studies. In a pooled analysis, a 1.64-g (42 mmol) per day increase in potassium intake was associated with a 21% lower risk of stroke (RR: 0.79; 95% CI: 0.68 to 0.90). There was also a trend toward lower risk of CHD and total CVD. The results of the meta-analysis are supported by subsequent studies (21), and an interaction between potassium and sodium intake has been shown in some studies (21, 22).

In an intervention trial, the effect of using potassium-enriched salt on cardiovascular mortality was investigated (22a). Five kitchens at a veteran's retirement home in Taiwan were randomized into two groups, and the 1,981 veterans assigned to those kitchens were given either potassium-enriched salt (n = 768) or regular salt (n = 1,213) for approximately 31 months. One hundred three CVD-related deaths were observed during the

follow-up. A 17% lower urinary sodium-to-creatinine ratio and a 76% higher urinary potassium-to-creatinine ratio in the experimental group were associated with a significant reduction in CVD mortality (HR: 0.59; 95% CI: 0.37 to 0.95).

In controlled intervention studies using diets designed to meet recommended levels of fat, fat quality, and dietary fibre similar to those in NNR 2004 (23), the dietary potassium intakes (estimated from urinary potassium excretion) in these diets have all been around 3–4 g/d (24–26). In these studies, blood pressure reductions were observed both with and without changes in sodium intake.

Requirement and recommended intake

The recommended intake of potassium in NNR 2004 (23) was based mainly on data on the effect of potassium on blood pressure (5–12, 24–27). Several clinical trials and cohort surveys published since that time support the finding that a diet rich in potassium alone, or in combination with calcium and magnesium, might have a favourable effect on blood pressure and might reduce the risk of stroke and other cardiovascular endpoints (20). The reference values in NNR 2012 are kept unchanged compared to NNR 2004 (23) because there are no new data to justify any major changes.

The recommended intakes are set at 3.5 g/d (90 mmol) for men and 3.1 g/d (80 mmol) for women. The figure for women also includes pregnant and lactating women. It should be pointed out that potassium intakes somewhat over and above these values might have further beneficial effects. The reference values for children and adolescents are extrapolated from adult values based on needs for growth and adjusted for body weight. The lower intake level (LI) is estimated to be 1.6 g/d (40 mmol) for adults.

Reasoning behind the recommendation

The recommended intake of potassium in NNR 2004 was based mainly on data on the effect of potassium on blood pressure. Data from clinical trials and cohort studies published since that time support the finding that a diet rich in potassium alone, or in combination with calcium and magnesium, might have a favourable effect on blood pressure and might reduce the risk of stroke and other cardiovascular endpoints. The reference values are kept unchanged compared to NNR 2004 because there are no new scientific data to justify any major changes.

Upper intake levels and toxicity

Potassium chloride has been associated with acute poisoning in humans. Case reports have described heart failure, cyanosis, and cardiac arrest after ingestion of high doses of potassium chloride tablets. Gastrointestinal effects have also been described after chronic ingestion of potassium chloride in case studies and supplementation studies. These effects include abdominal pain, nausea and vomiting, diarrhoea, and ulceration of the oesophagus, stomach, duodenum, and ileum. The occurrence and severity of the effects depend on a number of factors of which formulation of the preparation, dose, and gut transit time seem to be the most important. Slow release, wax-coated potassium chloride tablets appear to induce more lesions than microencapsulated tablets (28).

Dietary potassium has not been associated with any negative effects in healthy subjects. Prolonged high potassium intakes from diet and potassium-containing salt substitutes might, however, cause hyperkalaemia and affect heart function in subjects with renal insufficiency or impaired kidney function (28, 29). The available data are insufficient to set an upper level for dietary potassium. A British expert group proposed an intake of 3.7 g/d from supplements as an upper guidance level for adults. Supplemental intakes up to this level are generally not associated with overt adverse effects, but certain preparations might induce mild lesions of the gastrointestinal mucosa. It seems prudent to include potassium from potassium-containing mineral salt in this figure.

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33 Iron

Iron mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	15 / 9[1]	9	8	9	11
Average requirement	AR	10 / 6[1]	7			
Lower intake level	LI	5[1]	7			
Upper intake level	UL	60	60			

[1] post menopause.

Introduction

Iron deficiency anaemia (IDA) is the most common micronutrient deficiency across the globe (1), and many population groups have high iron requirements but insufficient iron intake or absorption to meet their needs. The relative iron requirement is greatest in infants and young children (aged 6–24 months) and adolescents (aged 12–16 years) because of the rapid growth rates in these age groups. During childbearing years, women also have increased needs for iron because of iron losses due to menstrual bleeding and the transfer of iron to the foetus during pregnancy. Iron overload can also occur, and people with hereditary haemochromatosis are those most likely to be affected. The prevalence of this condition is much higher than previously assumed, and up to 7 per 1000 Caucasians of Northern European descent are homozygous for the C282Y mutation in the HFE gene as recently reported by Thorstensen et al (2).

Dietary sources and intake

Recent dietary surveys in the Nordic countries show that iron intake among adult men and women ranges from 11 to 14 mg/d on average with a considerably lower intake among women than men. The average intake in Iceland is 9.4 mg/d among women and 12.5 mg/d among men between

the ages of 18 and 80 years old, but the intake of women of childbearing age is 10.2 mg/d (3) and the intake of 6-year-olds was recently shown to be 11.1 mg/d (4). In Finland, the figures for adults are 13.2 mg/d for men and 10.0 mg/d for women after the fortification of wheat flour was ceased (5). The figures for Swedish adolescents are 14 mg/d for boys and 9 mg/d for girls compared to 12.3 mg/d and 10.4 mg/d for adult men and women, respectively (6). The majority of iron in the Nordic diet comes from cereal products, some of which, for example breakfast cereals, are iron-fortified. However, the bioavailability of that iron seems to be low and today fortification of cereals in Finland, Sweden, and Denmark has ceased. Lower proportions of iron have traditionally come from iron-rich foods such as a variety of meats and lean meat.

To ensure a higher absorption of iron from the diet, people with high iron needs, such as adolescent girls and women of childbearing age, can increase the bioavailability of iron by several means. For these vulnerable groups, foods with factors that enhance iron absorption, such as vitamin C, should be included in meals containing iron. Examples of such foods are fresh vegetables or vegetable salad, fresh fruits and berries, and fruit juice. Meat, fish, and poultry contain a factor (MPF-factor) that also enhances iron absorption from food. In addition, these groups of people should avoid foods that inhibit iron absorption. A significant inhibitor of iron absorption is the calcium found in cow's milk and other dairy products, and these foods should be consumed in moderation. However, cow's milk is an important source of several nutrients and should not be eliminated from the diet simply due to its effect on iron absorption. The influence of enhancing and inhibiting factors on iron absorption is most noticeable in single-meal studies, and studies on whole diets over longer time periods have shown varying effects, and sometimes no effect, on iron absorption.

Physiology and metabolism

Iron is essential to virtually all living organisms. The most important biological characteristic of iron is its ability to alternate between two oxidation states – ferrous iron (Fe^{2+}) and ferric iron (Fe^{3+}) – that can donate or accept one electron, respectively. Due to the poor solubility of ferric iron at physiological pH and the ability of ferrous iron to reduce oxygen intermediates to harmful free radicals, all organisms have developed binding molecules (chelators) to transport and store iron and to control its reactivity (7, 8).

Iron has many vital functions in the body, the most significant of which

is to form the oxygen-binding part of haemoglobin (Hb) that transports oxygen from the lungs to the tissues. Iron is also found in myoglobin, the oxygen-binding protein in muscle fibre. Iron is an important component of many enzymes that transfer oxygen and electrons in a variety of metabolic pathways in the liver, brain, and endocrine organs. For example, iron is necessary for the function of cytochromes that are part of a series of enzymes that couples energy to ATP formation during oxidative phosphorylation.

The human body can store iron as ferritin and haemosiderin that are storage proteins in the liver, spleen, and bone marrow. Minute amounts of ferritin are also found in plasma in an iron-free form, and the serum ferritin level (s-ferritin) is considered to reflect the size of the body's iron stores.

Absorption and bioavailability

Iron homeostasis is maintained through absorption. Compared to many nutrients, however, iron is poorly absorbed by the human body and iron metabolism in the human body does not have an associated excretory pathway. As an aid to maintaining iron homeostasis, the body produces absorption regulators. An example of such a regulator is the small peptide hepcidin that is encoded by the HAMP-17 gene and is predominantly expressed in the liver (9). Absorption in the intestine depends on the iron status of the body, the amount and type of iron in the diet, and the composition of the meal (10).

Iron in foods exists as either haem iron or non-haem iron. Haem iron constitutes about 10% of the total iron in the Nordic diet and is mainly found in meat where it accounts for about half of the total iron content. Iron in grains and other plant-derived foods is in the form of non-haem iron. Haem iron is generally more efficiently absorbed than non-haem iron and it is not subjected to the same regulatory mechanisms. Absorption is increased in subjects with iron deficiency compared with normal subjects, and this demonstrates that absorption depends on the body's iron stores (11). About 25% of the total amount of haem iron is usually absorbed from food and is in general not affected by other food components, although reduced bioavailability of haem iron due to interaction with calcium has been reported (12). The absorption of non-haem iron depends on the composition of meals. Absorption of non-haem iron is enhanced by ascorbic acid with the most pronounced effects at moderate intakes of up to 100 mg/d of ascorbic acid (13, 14), but a less pronounced effect is seen in complete diets compared to single meals (15). It is still unclear to what extent organic acids other than ascorbic acid promote absorption. Iron absorption is also

enhanced by the MFP-factor found in meat, fish, and poultry (16). A possible explanation for enhanced absorption because of muscle protein in e.g. meat is that partially digested peptides, cysteine and histidine residues from muscle proteins, bind iron and form complexes that are soluble and available for absorption. The enhancing effect of muscle tissue on iron absorption is mainly protein related but this indicates that other factors might also play a role in enhancing iron absorption (17).

The absorption of non-haem iron is inhibited by phytates and their metabolites, iron-binding polyphenols such as tannins, and calcium (12, 18–20). Manganese in larger amounts than can be obtained from food can compete with iron for absorption in the intestines (21).

Copper and zinc are divalent metals, and it has been suggested that a high iron intake can influence intestinal absorption of these two minerals and potentially lead to deficiencies. Copper is believed to use the same transporter protein as iron, divalent metal transporter 1, but zinc is believed to use specific zinc transporter proteins (22). A recent study in mice reported the modulation of iron absorption through hypoxia/HIF-2 that is independent of hepcidin and duodenal iron levels but is reflective of overall body copper status (23). In a systematic review (SR) undertaken for the Nordic Nutrition Recommendations, no conclusive evidence could be found with regard to the effect of iron supplementation on zinc and copper absorption (24). Intervention studies by Domellöf and co-workers (25) and Harvey and co-workers (26) gave supplemental iron to breastfed infants or pregnant women and found no significant effects on zinc or copper levels. Troost et al investigated the effects of a single dose of 100 or 400 mg iron versus placebo in 55-year-old ileostomy subjects and found lower zinc absorption but no difference in copper absorption after iron administration (27).

The effects of enhancing and inhibiting factors on absorption can be seen in studies on different diets. Fruits and vegetables rich in vitamin C and meat can counteract the effect of inhibiting factors (28). Tea and coffee to a lesser extent, drunk with a meal reduce the absorption of non-haem iron because of the iron-binding polyphenols that they contain. Even cocoa diminishes absorption for the same reason, but it also contains considerable amount of phytates. A SR concluded that there was suggestive evidence that tea drinking might have a negative impact on iron nutrition in individuals with marginal iron stores (24). There is no reason to advice against tea in conjunction with meals for the general population, but in subpopulations at increased risk of IDA it could be considered advisable

to drink tea only between meals. The SR concluded that tea drinking has only a marginal impact on iron status in the Nordic countries because tea drinking is not very widespread and most people in these countries have adequate iron stores.

Phytic acid is mainly found in unprocessed fibre-rich products. Part of the phytic acid is degraded during the leavening of bread. Low pH, which can be obtained, for example, with a lasting sourdough leavening or if acetic acid is added to the dough, increases the probability of phytic acid breakdown and iron absorption increases (10, 19). Calcium, however, reduces the breakdown of phytates during dough fermentation and baking (12). Calcium also has a direct inhibiting effect on both haem and non-haem iron absorption indicating a mucosal rather than luminal effect (12). Measurements from single meals showed that 40 mg calcium did not reduce iron absorption, but one glass of milk (165 mg calcium) caused a 50% reduction in iron absorption. There was a dose-dependent effect up to a consumption of 300 mg calcium in the meal, and higher quantities of calcium did not cause any further reduction in the absorption of iron. Other experiments that evaluated iron absorption from the diet showed that iron absorption was reduced by about 40% when milk was drunk with an iron-rich meal compared to when water was drunk with such a meal (29, 30). Supplemental calcium has also been shown to reduce iron absorption substantially when taken with meals (31).

The influence of enhancing and inhibiting factors on iron absorption appears to be most apparent in single meal studies, and studies of whole diets show varying results. Two-week studies comparing iron absorption from a whole diet containing either enhancing or inhibiting factors of absorption found about two times higher iron absorption from the diet with the enhancing factors (32). Algorithms for calculating the absorption of iron have also been developed for adults (33, 34). The algorithm of Hallberg and Hulten (34) predicts the effects of dietary factors known to influence iron status based on their content in consumed foods with consideration taken of the interactions between individual factors such as phytate, polyphenols, ascorbic acid, meat, fish and seafood, calcium, eggs, soy protein, and alcohol (34).

Hunt and Roughead found no effect of enhancing and inhibiting components in iron-replete men over time and concluded that their subjects homeostatically adapted to a diet of high or low iron bioavailability to maintain body iron stores (35). Another study on subjects with normal iron stores showed long-term calcium supplementation with meals had no effect on iron status, but short-term supplementation decreased iron

absorption (36). A study on complete diets for 5-day periods reported no effect from calcium intake or the intake of animal foods and vitamin C on the absorption of non-haem iron in 14 subjects with normal iron status (37). Cook and Reddy found that the facilitating effect of vitamin C on iron absorption from a complete diet was far less pronounced than that seen in single meals (15).

Despite the varying results from studies on whole diets, subjects with poor iron status seem to benefit from a diet rich in factors enhancing iron absorption.

Iron deficiency and iron deficiency anaemia

Development

When iron supply is inadequate, the development of iron deficiency (ID) proceeds continuously from normal iron status to iron deficiency anaemia (IDA), a serious health concern. Initially body iron stores diminish, which is reflected in a decreasing concentration of s-ferritin. When iron can no longer be obtained from stores, iron deficiency in tissues develops and this leads to increasing levels of transferrin and transferrin receptors (TfR). This in turn leads to reduced transferrin saturation and a higher concentration of erythrocyte protoporphyrin, which is often assayed as an increasing serum level of zinc protoporphyrin (ZPP) because zinc is incorporated into the protoporphyrin molecule in the absence of iron (38). Finally the Hb level starts to decrease, and if the negative iron balance is not corrected anaemia develops. Anaemia is defined as a level of Hb two standard deviations below the mean of the population. Iron status variables in iron-replete individuals and those with IDA overlap (39, 40). Indications of the effect of iron deficiency on the formation of red blood cells, e.g. reduced mean cell (corpuscular) volume (MCV), can be seen before stores are completely emptied (41–43).

Effects of iron deficiency

ID can lead to various symptoms. Serious consequences of ID are anaemia (IDA), reduced work capacity, and impaired cell-mediated immunological defence. Altered temperature regulation has also been noted in connection with ID (44). Of particular concern is the suggestion that severe IDA seems to affect children's mental development and cognitive functions. These effects might even be irreversible depending on the age of the child, the severity and duration of the deficiency, and the child's socioeconomic environment (38, 45–49). ID without anaemia has also been shown to be associated with lower scores in cognitive tests (50, 51). In summary, ID

and IDA are associated with poor physical, cognitive, and behavioural performance, impaired neurodevelopment and growth inhibition in children, hypertension, and reduced immune function (50–54).

Assessment and indicators of iron status

Several indicators are used for the detection of ID, but s-ferritin is considered to be the best single indicator of iron status and is also the most widely used (55). S-ferritin levels are a good indication of the size of the iron stores in the absence of infection and inflammation, and the WHO recommends 12 mg/L as the cut-off for children below the age of 5 years and 15 mg/L for males and females 5 years and older (56). These cut-offs are based on global criteria that also include various races and countries, including developing countries. Lower s-ferritin values have been used as cut-off values for ID in infants and young children, e.g.10 mg/L in the Euro-Growth study (57), and this reference value was also used for US children up to 5 years of age in a nationwide study (58). Scientists from different countries have used values <12 mg/L as the cut-off for s-ferritin in adolescence (58–64). Other indicators of iron status are s-transferrin levels (total iron binding capacity, TIBC), transferrin saturation (s-iron/TIBC), and s-TfR levels (serum transferrin receptor). Transferrin saturation is less useful for detecting ID due to diurnal variations in s-iron, and s-TfR is considered among most sensitive indicator of functional iron depletion (65). The level of transferrin saturation is, however, very useful as a screening variable for hereditary haemochromatosis (56). In recent years, s-Tfr/s-ferritin has also been used as an indicator of iron status in scientific studies (59, 60). Free erythrocyte protoporphyrin (or ZPP) and MCV become abnormal relatively late in the development of ID (65) so alone they would be relatively insensitive indicators of iron deficiency and are not often used in studies on iron status.

Anaemia is defined as a reduced concentration of Hb. According to the WHO, Hb <110g/L should be used to diagnose anaemia in infants and children from 6 months up to 5 years of age and 115 g/L in children up to 11 years of age (56). Higher values are recommended for children aged 12–14 years and in adult women (120 g/L) and men (130 g/L), but during pregnancy the cut-off is lowered to 110 g/L. However, reference values for Hb (and also for other iron status variables) are still not sufficiently validated in infants and young children. In clinical practice as well as in research, the commonly used cut-off levels to identify ID and IDA in infants (Hb <110 g/L and s-ferritin <10–12 mg/L) are, in fact, extrapolated from

older age groups and there are indications that they might not be appropriate (66). Emond et al suggested a cut-off of 97 g/L for Hb in 8-month-old infants (67). Others have used cut-offs of 105 g/L (68, 69) and 100 g/L (66, 70) in similarly aged infants.

IDA is defined as Hb concentrations below a given cut-off in addition to abnormal iron status indicators. The number of iron status indicators used for diagnosis, as well as their cut-offs used for indicating iron deficiency, varies (Table 34.1.). Sometimes only s-ferritin is used, but some studies have used the approach that the individual is diagnosed with IDA when two out of three iron status indicators are below (or above) a given cut-off together with a concentration of Hb below the cut-off.

Table 34.1. Cut-off values for different iron status indicators

Indicator	Units	Adults		Children and adolescents	Infants aged 4/6/9 months[c]
		Males	Females		
Haemoglobin (Hb)	g/L	<130 [a]	<120 [a]	<105 [b]<110 [a]	<105/105/100 <105 [d]
Serum ferritin	mg/L	<15 [a]	<15 [a]	<12 [a, i, j]	<20/9/5
Mean cell volume (MCV)	fL [k]	<80 [c, e, f]	<80 [e, f]	<74 [g]	<73/71/71
Serum transferrin receptors (TfR)	mg/L	>8.5 [f, h]	>8.5 [f, h]	>8.5 [f, h]	>11/11/11
Free erythrocyte protoporphyrin	mg/dL erythrocyte	>70 [e]	>70 [e]	>80 [e]	
Transferrin saturation	%	<16 [e]	<16 [e]	<12 [e]	
Total iron binding capacity (TIBC)	mg/dL	>400 [e, f]	>400 [e, f]		
Zinc protoporphyrin (ZPP)	mmol/mol				>75/75/90

a WHO (56).
b Thorsdottir et al (75).
c Domellof et al (66).
d Michaelsen et al for 9-month-olds (68).
e Expert Scientific Working Group (55).
f The US recommendations (14).
g Gill et al (149).
h Baynes (65).
i Samuelson et al (59).
j Samuelson et al (60).
k fL, is 10^{-15} L.

Prevalence of iron deficiency and iron deficiency anaemia

Globally, it is estimated that about 25% of pre-school children have IDA (71). In studies from Norway, Sweden, and Iceland published in the years 2004, 2008, and 2011, the prevalence of ID and anaemia was relatively low, and ID (s-ferritin <12 mg/L) in 12-month-olds was 10%, 18%, and 6%, respectively (72–74). In a Norwegian study published in 2004, 13% of two-year-olds had s-ferritin <12 mg/L (72), but at the age of two years iron status generally improves. Poorer iron status at one and two years of age has been related to faster growth from birth (75, 76), but other reasons, such as nutrient imbalance, cannot be excluded (72). Iron status in young children seems to have improved since the 1990s, and a report on iron status in the 1990s in the Nordic countries can be found in chapter 34 in NNR 2004 (77). In a Danish study, 5% of 9-month-old infants had anaemia (defined as Hb <105 g/L) and 20% had Hb <110 g/L, but no cases of IDA were found (68). In the 1990s, the prevalence of Finnish children aged 3–4 years with Hb <110 g/L was 4% (78). The prevalence of ID among adolescents and adults varies from study to study in the Nordic countries (77). In Norway, ID was found in 5%–18% and 6%–30% of 13- to 15-year-old Norwegian boys and girls, respectively (79). In a Swedish longitudinal study from 15 to 21 years of age, s-ferritin concentrations <12 mg/L were found in 2%–3% of males and in 18%–26% of females (60). Studies have found ID in 10%–22% of Nordic women of childbearing age and IDA in 0%–17% of pregnant Nordic women (77, 80).

Only a few studies have been conducted on iron status in elderly populations in the Nordic countries, and very few of these are recent studies. The prevalence of low Hb among the elderly (>65 years) has been found to be 0%–5%. ID is relatively uncommon in 70-year-olds, and even more uncommon in healthy 80- and 85-year-olds, but high iron stores (s-ferritin >300 mg/L) have been observed in 8.7% of elderly men and 3.7% of elderly women (77, 81).

Requirement and recommended intakes

In the recent SR on the health effects of iron intake, it was concluded that there is no reason to alter the NNRs on iron intake from those in NNR 2004. The SR suggested that advice on iron supplements should be given to pregnant women and to parents of low birth weight infants (24).

The recommended daily intakes of iron for adult men, post-menopausal

women, and children are based on the amounts needed to cover basic losses and growth for approximately 95% of the individuals in each age group. The lower intake level (LI) of iron for adults is the same in NNR 5 as in NNR 2004. That level was also suggested by UK's Scientific Advisory Committee on Nutrition (SACN) 2010, which generally defined lower intake levels as two standard deviations below the average requirement (AR) (82).

Women's requirements for iron during childbearing years are not normally distributed, which makes decision-making on recommended intakes more difficult. The recommendation in NNR 5 is an intake that meets the iron needs of approximately 90% of menstruating teenage girls and women and is similar to what was recommended in NNR 2004.

Iron stores of vegetarians are lower than non-vegetarians, but the incidence of IDA has been shown to be similar (83, 84). However, vegetarians and athletes, especially female athletes, are two groups that might deserve special attention with respect to their iron needs.

Children and adolescents

Children and adolescents need iron to cover basic losses and for growth. Full-term infants have iron stores sufficient to cover their needs during the first 4–6 months of life. The concentration of iron in human milk is low and is similar to that in cow's milk (0.3–0.4 mg/L), but this low level is to some extent counteracted by the high bioavailability of iron in human milk (14). An infant's blood Hb concentration falls rapidly after birth, and iron is transferred from Hb to iron stores, which also helps to ensure that the full-term, normal birth weight, healthy, breastfed infant is virtually self-sufficient with regard to iron during the first 4–6 months of life. A recent randomized controlled trial found lower s-ferritin concentrations in 6-month-olds who had been exclusively breastfed for 6 months than those given small amounts of complementary food from 4 months of age. However, none of the infants had clinically low values that were significantly below the reference values (85). Healthy, full-term infants in a developed country who were either exclusively breastfed or given infant formula with only 1.6[1] mg iron/L did not develop ID during the first 6 months of life (86, 87). Infants, therefore, seem to have no need for extra iron from birth to 6 months even though their body weight doubles during this time.

All formula-fed infants theoretically have higher iron requirements due

1 Infants who are not breastfed during the first 6 months should be fed an iron-fortified infant formula. Infant formulas that are not fortified with iron should not be used.

to the lower bioavailability of iron from formula compared to breast milk. Even though an iron concentration of about 1.5 mg/L in infant formula would be sufficient, much higher levels of fortification have traditionally been used. In Europe, infant formulas are usually iron fortified to a level of 4–8 mg/L (88). The growth and development of the central nervous system (CNS) is rapid during early childhood and iron is critical for this process. Several case-control studies in children have shown a consistent association between IDA in early childhood and long-lasting poor cognitive and behavioural performance, and an association between early ID and later developmental scores has also been observed in the Nordic setting (50, 51). Meta-analysis including preventive trials in high-risk groups, mostly in low-income countries, and therapeutic trials in children with diagnosed IDA show limited but suggestive evidence that preventive iron supplementation of infants might improve psychomotor development (89). There is no evidence, however, for preventive iron supplementation before 6 months of life and beneficial effects on cognition or psychomotor development in healthy, breastfed infants of normal birth weight in low-risk populations such as the Nordic countries.

Based on the above evidence, no recommendation is given for the first 6 months[1]. In addition, there is evidence to suggest that during the first 6 months infants might not down-regulate their absorption of iron as efficiently as children and adults so excessive iron intake should be avoided in this age group. The recent SR, however, suggested that low birth weight infants (<2,500 g) should be given supplemental iron at a dosage of 1–2 $mg \cdot kg^{-1} \cdot d^{-1}$ from week 6 to at least 6 months of age (24). This is supported by a meta-analysis from 1992 (90), a randomized trial testing different amounts of supplemental iron to marginally low birth weight infants (91), and the WHO recommendation that iron supplements should be given to all low birth weight infants (92). Studies have shown that infants with higher growth rates are at greater risk of iron deficiency that is thought to be due to more rapidly depleted iron stores from birth that coincides with greater weight gain (93). It is well known that birth weight can influence iron endowment at birth (94). Low birth weight infants often have low iron stores at birth and they tend to grow faster, and this can increase the risk of developing ID and IDA. Infants who are born weighing between 2,000 g and 2,500 g represent 3%–5% of all infants in affluent countries (91). It has been previously reported that delayed umbilical cord clamping after birth can have a beneficial effect on the infant's iron status even up to 6 months of age (95, 96).

After the first 6 months of life, the requirement for exogenous iron is high and the infant now becomes dependent on iron-rich complementary foods (97). High intake of cow's milk (>300–500 mL/d) might be associated with ID (24, 75), and it seems prudent, therefore, to avoid such high intakes of cow's milk in infants and toddlers. This is supported by the reduced prevalence of ID at 12 months in infants after new recommendations suggesting the avoidance of cow's milk before 12 months of age and instead using iron-fortified formula (74). The basic iron requirements are similar from 7 months to 5 years of age, and the Nordic iron recommendation is 8 mg/d for children in this age range. This amount of iron, mainly provided by iron-fortified phytate-rich cereals, protects against ID late in infancy and also improves iron status in toddlers (76, 78, 98). A higher recommendation would require a diet unrealistically dense in iron for that age group and much denser than for older children and adults. For children 6–9 years old, the iron recommendation is 9 mg/d.

Table 34.2. shows the iron needs of adolescents and adults calculated from daily needs and losses using Nordic body weight values. The need for iron is relatively high in adolescence because it is a period of rapid growth. For 10- to 13-year-old boys, an iron intake of 9 mg/d meets the requirements of 95% of the population given a 15% absorption rate, and for 14- to 17-year-old boys about 12 mg/d is needed to meet their requirements (Table 34.2.). For boys aged 10–17 years, the Nordic recommendation of iron is 11 mg/d.

In addition to their requirement for growth and basal losses, adolescent girls need iron to cover losses during menstruation. Table 34.2. shows the total iron need for menstruating girls and women estimated by the sum of basal losses, the need for growth in adolescent girls, and menstrual losses. The iron need of 95% of 10- to 13-year-old pre-menarchal girls is 9 mg/d (Table 34.2.). The variation in menstrual losses is shown and used to estimate the 50th (median), 90th, and 95th percentiles of total iron need, with both basal losses and need for growth kept constant (Table 34.2.). The median daily iron requirement of adolescent girls is 10 mg, but 19 mg/d is required to satisfy the need of 95% of adolescent girls when assuming that the absorption rate is 15% (Table 34.2.). The iron need of about 90% of post-menarchal girls aged 10–17 years is satisfied by 14 mg/d (Table 34.2.). The 90th percentile of need represents the recommended intake and is justified by the fact that those in the top 5th percentile of iron need probably have a higher absorption rate than 15%. However, there will always be some small proportion of girls and women

with higher iron needs that must be satisfied with iron supplements. The recommended intake is 15 mg/d for 14- to 17-year-old girls and 11 mg/d for 10- to 13-year-old girls.

Women of childbearing age

The daily iron requirement is high among women during childbearing years because of blood loss during menstruation. This loss is highly variable between women, for example, it is diminished by contraceptive pills while contraceptive sponges enhance menstrual blood loss (99). The daily iron amount required to meet the need of 50% and 95% of adult women is 9 mg/d and 19 mg/d, respectively, given a 15% absorption rate (see Table 34.2.). The iron need for about 90% of women is satisfied by 15 mg/d. By the same criteria discussed for menstruating girls, the 90th percentile is chosen to represent the recommended intake because the top 5th percentile probably has a higher absorption rate than 15%. The recommended iron intake is 15 mg/d for women of childbearing age.

Table 34.2. Iron needs of adolescents and adults calculated from daily needs and losses

Age (years)	Weight (kg)	Need for growth (mg/d)	Basal losses (mg/d)[1]	Menstrual losses (mg/d)[2]			Total iron need (mg/d)			Necessary intake of iron from foods to cover 50%, 90%, and 95% of the iron need of groups on a diet for which iron absorption is assumed to be 15% (mg/d)		
	mean		median	median	90%	95%	median	90%	95%	50%	90%	95%
Boys												
10–13	37.5[5]	0.55	0.53				1.08		1.35	7		9
14–17	57[5]	0.60	0.80				1.40		1.75	9		12
Men												
18+	76[6]		1.05				1.05		1.37	7		9
Girls												
10–13[8]	38.5[5]	0.55	0.54				1.09		1.36	7		9
10–13	38.5[5]	0.55	0.54	0.46[3]	1.05	1.69[4]	1.55	2.14[7]	2.78[7]	10	14	19
14–17	53.5[5]	0.30	0.75	0.46[3]	1.05	1.69[4]	1.51	2.1[7]	2.74[7]	10	14	18
Women 18+	62[6]		0.87	0.48[3]	1.35	1.90	1.35[2]	2.22[7]	2.77[7]	9	15	19
Women after menopause	62[6]		0.87				0.87		1.13	6		8

1 Basal losses are estimated to be 0.014 mg·kg^{-1}·d^{-1} (105).
2 Evaluated from the amount of menstrual blood in ml/28 days (99, 105). For girls, the median and 90% intakes are based on reference (78) and the 95% intake on reference (11, 12). Menstrual losses for girls are assumed to be the same in both age groups. Haemoglobin concentration is calculated as 135g/L and it is assumed that 1 g of haemoglobin contains 3.34 mg iron. Menstrual iron loss (mg) = [blood loss (mL)/28 days × 135 g Hb/L × 3.34 mg iron/g Hb)/ (1000 mL/L)].
3 Calculated with a median blood loss of 28.4 mL for adolescent girls and 30 mL for adult women every 28 days (99, 105).
4 Calculated from the equation in the US recommendations derived from a fitted log normal distribution with a Monte Carlo simulation [ln (blood loss) = 3.3183 + 0.6662(SD)] (14).
5 Children weights 1973–1977 (77).
6 Mean weight of men and women aged 15–80 years (6).
7 Sum of basal losses, need for growth, and 90th and 95th percentiles of menstrual losses, respectively. It is assumed that there is no distribution in values for basal losses and need for growth.
8 Not menstruating.

The calculated estimates in Table 34.2. assume that blood losses in menstruation are the same as in the 1960s, although it is known that oral contraceptive use today is higher, which might mean less blood loss and, therefore, lower requirements (100). However, a recent study by Hunt et al showed slightly higher daily total iron excretion by menstruating and postmenopausal women (101) than the NNR estimates, and this would mean higher requirements. The levels in that study were average losses, not medians as shown in Table 34.2., and this might partly explain the difference (101). Also, data on body weight, e.g. growth of children and adolescents, indicate that the average weight of the different age groups

of the population is slightly higher than used in Table 34.2. (102), but the reference weights chosen are based on Nordic healthy weights before the current obesity epidemic. Even if these factors were to be taken into consideration, they would not change the estimates for necessary intake from foods as shown in Table 34.2.

As discussed earlier in this chapter under 'Absorption and bioavailability', the composition of meals can affect the absorption of iron, especially in iron-deficient individuals. It is difficult to put together a menu that contains enough iron to meet the needs of almost all women if the recommendations of the proportions of energy-giving nutrients and fibre are to be maintained and iron-fortified products are not used. It can, therefore, be important for some women to improve the bioavailability of the iron consumed by evaluating meal compositions. Two small studies looking at iron status markers in women with low iron stores support the recommendation of 15 mg/d. One studied iron intake between 11.5 and 13.9 mg/d over 8 weeks that maintained iron status independently of a fish or a meat diet (103). Supplementation with approximately 15 mg iron in a fruit-based meal every day appeared sufficient to substantially improve iron status over 16 weeks (104).

Pregnancy and lactation

Maternal iron need during pregnancy increases slowly as the pregnancy progresses because of growth and maintenance of the foetus and uterus, the increase in red blood cell count, and the expected iron losses when giving birth. According to Hallberg, the total iron requirement is 1,040 mg during pregnancy, of which 840 mg goes to the foetus or is lost while giving birth (105). During the first trimester of pregnancy, iron intake must cover basal losses. Iron demand increases during the second trimester and is greatest during the third trimester. Even though iron absorption increases during the last two thirds of pregnancy, for some women the amount of iron in food is not enough to satisfy the greatly increased iron demand that takes place during pregnancy. The US recommendation during pregnancy is 27 mg/d (24). Studies by Milman et al (106), Makrides et al (107), and Sandstad et al (108), and supported by other studies, provide probable evidence that supplementing with 40 mg iron/d from week 18–20 of gestation, without any knowledge of s-ferritin values, will achieve prevention of ID in more than 90% and IDA in more than 95% of women at delivery and at 6–8 weeks postpartum (24). Supplementation with 40 mg iron/d from week 18–20 of gestation might be adviced. The

supplementation could either be given as a general prophylaxis of 40 mg iron/d to all pregnant women or as an individual prophylaxis of 60 mg iron/d or 40 mg iron/d depending on whether s-ferritin is below 30 mg/L or between 30 mg/L and 70 mg/L measured early in pregnancy or before 15 weeks of gestation. Both regimens would prevent ID and IDA at delivery and at 6–8 weeks postpartum in more than 90% and 95% of cases. There is, however, no evidence that maternal iron supplementation has any effect on the offspring in the Nordic countries (24).

During the first months of lactation, menstruation has often not yet resumed and, therefore, the need for iron during lactation might be less than usual (109). This is the basis for the lower US recommendations for lactating women compared to other women of the same age (14). The median iron needs are assumed to be the sum of basal losses and iron secretion in human milk with no menstrual losses. However, women may have low iron stores postpartum and many women in the Nordic countries breastfeed their infants for quite a long time – greater than six months – and menstrual losses can start within the partial breastfeeding period. Therefore, 15 mg/d is recommended for lactating women, which is the same as for women of childbearing age who are not pregnant.

Post-menopausal women and adult men

Older women and adult men have to replenish basal losses of iron. Minimum iron intake has not changed since the NNR 1989 and varies from 5 mg/d to 7 mg/d depending on body size. As shown in Table 34.2., the median need is 6 mg/d for post-menopausal women and 7 mg/d for adult men and the requirements of the 95th percentile are met by a dietary intake of 8 mg/d or 9 mg/d, respectively. The recommended intake of iron is 9 mg/d for both post-menopausal women and adult men.

Upper intake levels and toxicity

Under physiological conditions, iron status is almost exclusively regulated by adaptation of intestinal iron absorption to demand and this process is well described for both deficiency and supply via food. Several studies indicate that this regulation operates up to the level of an additional 10–15 mg iron/d (11, 14, 40, 110, 111). However, Fleming and co-workers found that an additional iron intake of >30 mg iron per day was associated with an increased risk of high iron stores that are defined as plasma-ferritin >300 mg/L or >200 mg/L in elderly men and women,

respectively (112). Thus, the homeostatic regulation of iron absorption in elderly people seems able to prevent iron overload at a total iron intake of 17.5–25 mg/d (10 mg/d habitual dietary intake + 7.5–15 mg/d), but not at a total intake of 40 mg/d (10 mg/d habitual dietary intake + 30 mg/d). Theoretical calculations of prolonged intake of pharmaceutical iron and s-ferritin levels showed that ingestion of an extra 60 mg iron/d over 5 years or more would risk building up excessive iron stores in a fertile non-pregnant woman with a body weight of 63 kg (113). Long-term effects of high iron (12 mg/L) infant formula from 6 to12 months of age in healthy, non-anaemic infants were found in a follow-up at 10 years of age as lower scores for visual-motor integration (114). This negative effect seemed to be limited to those infants who were initially iron-replete but suggests possible adverse effects of excessive iron intake during late infancy. NNR 5 set the upper limit (UL) for iron for non-pregnant adults at 60 mg/d. It is not possible to set an UL for infants, but infant formulas should not provide more than 8 mg/L (88).

Acute effects of iron overload

Ingestion of an acute overdose of pharmaceutical iron preparations causes mucosal erosion in the stomach and intestine. Young children are especially at risk (115). Due to damage to the intestinal mucosa, non-controlled iron absorption can be high and cause acute systemic symptoms such as shock due to vascular dilatation, capillary leakage, and heart failure. Iron can also damage organs such as the liver, pancreas, kidney, CNS, and red blood cells (115).

Nausea, vomiting, heartburn, and epigastric discomfort, along with constipation and occasionally diarrhoea, are common side effects of oral therapeutic doses of iron (116–118). The mechanisms are mucosal irritation, alteration of gastrointestinal motility, and the rapid transfer of iron into the circulation. The occurrence of side effects of therapeutic iron is dependent on the dose and the luminal iron concentration. The lower dose level associated with such acute effects seems to be 50–60 mg iron/d (116, 117).

Chronic effects of iron overload

Because iron absorption is homeostatically regulated, at least in adults, the risk of iron overload from dietary iron is mainly limited to individuals with hereditary (primary) haemochromatosis, a relatively common disorder in the Nordic countries with a reported frequency of homozygosity for

the C282Y mutation ranging from 0.20% to 0.75% (2, 119). In primary haemochromatosis, iron absorption is increased 2 to 3 times in homozygotes due to a genetic defect in the HFE gene. Three mutations have been described, and for the two most common, C282Y and H63D, the frequencies of homozygotes are about 0.4% and 2%, respectively, in Scandinavia (2, 119, 120). Individuals who are heterozygous for the C282Y mutation do not appear to respond abnormally to dietary iron and, therefore, do not need to change their diet to prevent accumulation of iron in the body (121). Homozygosity for the C282Y mutation is most often associated with clinical signs of haemochromatosis and risk of developing serious symptoms even at the iron levels normally present in the diet. These symptoms include hepatomegaly, hepatic fibrosis, and hepatoma in addition to joint inflammation, diabetes mellitus, cardiomyopathy, and cardiac failure. The treatment is phlebotomy. If untreated, the risk of symptoms is five times higher in men than in women due to a constantly higher loss of iron among women via menstrual bleeding. The penetrance of the C282Y mutation, which is the most frequent one leading to haemochromatosis, has been estimated to be between 1% and 25% depending on the study design and the endpoints used (122).

Studies have found moderate and slight liver fibrosis in several cases with hepatic iron concentrations of 51 mmol/g to 240 mmol/g dry weight (123, 124). Hepatic fibrosis and iron concentration have also been correlated to s-ferritin levels. In the study by Bell et al, a dose response curve for severity of fibrosis and s-ferritin was found, and s-ferritin was mostly above 1000 mg/L in those with liver fibrosis (124). The median s-ferritin concentration for the mildest form of fibrosis was 858 mg/L with values as low as 520 mg/L. Åsberg et al found a clear correlation between hepatic iron and s-ferritin with quite a wide distribution (123). To keep hepatic iron below 400 mmol/g of dry weight, the limit for s-ferritin would be about 250 mg/L. In this study, 4 of 12 patients with moderate liver fibrosis had s-ferritin concentrations below 1000 mg/L and ranged from 311 mg/L to 629 mg/L.

Earlier reports have described secondary haemochromatosis caused by high intake of iron, e.g. as part of a habitual intake of iron-contaminated beer or as pharmaceutical iron, over a period of several years. Iron doses thought to stimulate secondary haemochromatosis might exceed 150 mg/d (77).

Iron and risk of cardiovascular disease

In the NNR 2004 a possible relationship between iron overload and cardiovascular disease was discussed, but no stable or causal relationship between iron and risk of cardiovascular disease had been established (77). In the recent SR (24), an association between both hypertension and cardiovascular disease was explored. The evidence for a relationship between haem iron intake and cardiovascular disease was determined to be suggestive based on the SACN report of 2010 that evaluated iron and cardiovascular disease and iron and health (82). This relationship between iron overload and cardiovascular disease has also been shown in the Iowa women's health study cohort in women using more than 10 g of alcohol per day and even more clearly in women using more than 30 g of alcohol per day (125). Some studies have indicated a protective effect of iron intake against high blood pressure, but no conclusions (24) could be drawn about associations between high iron intake and lower blood pressure either as intake during pregnancy *vs.* blood pressure in the offspring (126, 127) or as intake *vs.* blood pressure in adults (128, 129).

Iron and risk of cancer

According to a recent meta-analysis, individuals carrying the C282Y haemochromatosis mutation have an increased risk of hepatocellular carcinoma (130). Regarding extra-hepatic malignancies in the general population, there were studies cited in NNR 4 indicating an increased risk of colon cancer and other cancers related to high iron stores (77). However, a causal relationship between iron and extra-hepatic cancer could not be established. Several new studies have examined the possible relationship between dietary iron intake and various forms of cancer (131–140). However, no convincing evidence that dietary iron intake is associated with increased risk of colon cancer, lung cancer, breast cancer, oesophageal cancer, or other cancers could be found (24).

Iron and risk of diabetes

Based on the SR undertaken for NNR 5, there is probable evidence for an association between haem iron intake and type 2 diabetes (T2D) as well as gestational diabetes mellitus (GDM). Three recent large epidemiological studies have examined the association between iron intake and T2D (141–143). The studies reported similar figures for the lowest and the highest quintile of haem iron intake and they arrived at the exact same relative risk for T2D (RR = 1.28). No effect or an inverse effect on the risk

of T2D was seen for non-haem iron and for total iron intake. Two case studies looking mainly at the association between markers of iron stores and risk of T2D (144, 145) also found that cases with T2D had the highest intake of haem iron.

High intake of haem iron before or during pregnancy seems to increase the risk of developing GDM (146, 147). The studies on the association between haem iron intake and T2D and GDM adjusted their data for many confounders, but the facts that haem iron intake is closely related to the intake of red or processed meat and that subjects with high haem iron intake had significantly less healthy behaviour in terms of diet, physical activity, smoking, and BMI (142), as well as an absence of an effect of total iron intake, suggest that there are other dietary or lifestyle factors rather than iron that increase the risk of T2D. Haem iron intake might be an indirect marker of T2D development, but a meta-analysis found that the intake of both unprocessed and processed red meat was positively associated with T2D risk after adjustment for age, BMI, and lifestyle such as smoking (148). The association between haem iron and T2D could, therefore, be related to the increased risk of T2D that is associated with the intake of red meat.

There is probable evidence for the association of haem iron intake with the risk of T2D and GDM even though these associations might not be causal. Because there is no evidence that total iron intake is associated with increased risk of T2D, this does not have any implication for recommended daily intakes of iron.

There is no conclusive evidence for an association between iron intake and type1 diabetes (24).

Reasoning behind the recommendation

Requirements and recommendations for iron were based on calculations including the body's estimated basal loss of iron (taking body size into account), the requirements for growth of a child, an adolescent and fetus and maternal growth in pregnancy, and the estimated menstrual losses of a woman in fertile age. Varying absorption of different groups depending on possible iron status was taken into account. The recommendations of iron in NNR 2012 are maintained unchanged from NNR 2004 since no strong scientific evidence to change has emerged.

Upper level of iron intake

Epidemiological data on the association between iron and the risk of cardiovascular disease, cancer, or diabetes do not permit the establishment of any dose-response relationships with dietary iron. Consequently, a quantitative UL for iron intake cannot be set on this basis, nor is it possible to directly derive a limit based on liver fibrosis or increased hepatic iron and s-ferritin concentrations. However, it seems clear that an s-ferritin level above 300 mg/L, which is often referred to as "biochemical iron overload" when caused by increased iron stores, is associated with an increased risk of slight liver fibrosis. Based on homeostatic control of iron absorption and the risk of biochemical iron overload, the UL might occur at intake levels between 10 mg/d and 30 mg/d of additional iron over and above typical dietary intakes. A regular intake of 60 mg/d in a fertile woman has been calculated to lead to biochemical iron overload, and a quantitative UL for iron intake in addition to habitual dietary iron is set to 10 mg non-haem iron per day in order to avoid such overload. Based on the above evidence, the UL for total iron intake is 60 mg/d.

Although it is not possible to establish a cause-effect relationship between iron and diseases, it seems prudent at least in sub-populations such as adult males, post-menopausal women, and heterozygotes for haemochromatosis to avoid an intake of iron above the current recommendation, which already provides for the highest need.

Studies indicate possible adverse effects of high iron intake during late infancy. Infant formulas, therefore, should not provide more than 8 mg/L of iron.

Maintaining an iron intake below the UL would also protect against the local intestinal toxicity that is a side effect of therapeutic iron. The lower dose level of iron associated with such acute side effects seems to be in the range of 50–60 mg/d.

The UL and intake advice do not apply to individuals receiving iron prophylaxis and pharmaceutical iron preparations under medical supervision, such as pregnant women (for whom a supplement should be considered in the amount of 40 mg/d from week 18–20 of gestation) and low birth weight infants.

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34 Zinc

Zinc mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	7	9	6	7	8/11
Average requirement	AR	5	6			
Lower intake level	LI	4	5			
Upper intake level	UL	–	–			

Introduction

The biochemical role of zinc (Zn^{2+}) is as an essential part of more than 300 enzymes involved in synthesis, metabolism, and turnover of proteins, carbohydrates, lipids, nucleic acids, and some of the vitamins such as vitamin A. Well known zinc-containing enzymes include superoxide dismutase, alkaline phosphatase, and alcohol dehydrogenase. Zinc is essential for normal function of the immune system and normal DNA synthesis and cell division and protects proteins and lipids from oxidative damage. Dietary intake of zinc has also been related to maintenance of normal bone density, cognitive function, fertility and reproduction, metabolism of fatty acids, acid-base metabolism, vitamin A metabolism, and vision (1, 2).

Dietary sources and intake

Good sources of zinc are meat, milk and milk products, and whole-grain cereals. The intake of zinc in the Nordic countries is approximately 12–14 mg/10 MJ (see the chapter on Intake of Vitamins and minerals in Nordic countries).

Physiology and metabolism

Absorption of zinc is dependent on the dose and occurs mainly in the upper part of the small intestine. Absorbed zinc is transported in the blood, mostly bound to albumin. The majority of body zinc – estimated to be between 2 g and 4 g in adults – is located within cells. Approximately two thirds of the body's zinc is located in muscle tissue and one third is found in bone tissue. Plasma zinc only represents 0.1% of total body zinc.

High concentrations of zinc are found in parts of the eye and in prostate liquid. Zinc is excreted through the kidneys, skin, and gastrointestinal tract. Strong homeostatic mechanisms keep the zinc content of tissues and fluids constant over a wide range of intakes through changes in excretion and absorption. The molecular mechanisms involved in this regulation, however, are not fully understood.

Well-defined clinical zinc deficiency has only been reported in a limited number of cases that are related to incomplete total parenteral nutrition, malabsorption, and the use of drugs. Estimates based on evaluation of zinc intakes and diet composition in different parts of the world suggest that the populations of many countries in Asia and Africa are at high risk for developing zinc deficiency and that the risk is low in European countries and North America (1). The clinical manifestations of severe zinc deficiency are growth retardation, delayed sexual maturation, skin lesions adjacent to the body orifices, hair loss, and behavioural disturbances (3). These clinical signs have almost exclusively been observed in subjects with an inborn error in zinc transport (acrodermatitis enteropathica) and in adolescents subsisting on diets with a presumably very low availability of zinc. The consequences of moderate and mild zinc deficiency are still unclear.

In a meta-analysis of randomized controlled trials by Brown and coworkers (4) covering the years 1966–2001, zinc supplementation was associated with increases in both height and weight. The responses were greater in children with low initial weight-for-age z-scores. However, results from a more recent meta-analysis did not show any improvements in linear growth in intervention studies including zinc supplementation only (5). Studies published after those included in the study by Brown et al. accounted for the difference, possibly reflecting improvements in zinc status in many parts of the world (5). Further, zinc has successfully been used as a pharmacological agent to treat chronic diarrhoea in countries where zinc deficiency is prevalent (6). Zinc plays a role in the synthesis and action of insulin and seems to stimulate insulin action and insulin

receptor tyrosine kinase activity, but the role of zinc supplementation in the prevention of type 2 diabetes mellitus remains unclear (7). Further studies are also needed to assess potential benefits and risks of maternal zinc supplementation on pregnancy and lactation outcomes (8).

Requirement and recommended intake

Adults

The only biomarker recommended by WHO/UNICEF/IAEA/IZiNCG (9) to assess the zinc status of populations (not individuals) is measurement of serum or plasma zinc concentration. Serum zinc concentrations fall sharply when dietary zinc intakes are less than ~ 2 to 3 mg/d, but rise slightly but continuously when intakes are greater, reaching plateau when intakes reach ~ 25 to 30 mg/d (10), However, because the plasma zinc concentration is also influenced by factors unrelated to zinc status, such as food intake, infection, and tissue anabolism or catabolism the measurement cannot be used for estimating zinc requirements. In addition, the activities of the zinc-dependent enzymes explored so far have not proven sensitive enough to identify optimal or desired levels of zinc intake. In populations in which signs of zinc deficiency have been observed, reliable food intake data are usually not available. Consequently, zinc requirements have to be estimated by the factorial method, i.e. estimates of the daily losses of zinc and the corresponding amount of zinc to be ingested to replace these losses. Additional zinc is needed during periods of tissue growth. The use of the factorial method to estimate zinc requirements is complicated by a strong homeostatic regulation of body zinc – primarily through changes in endogenous zinc excretion – and by the pronounced impact of diet composition on zinc absorption and potentially also on the excretion of zinc. At zinc intakes close to zero, total endogenous zinc losses through urine, faeces, and skin are on the order of 0.5–0.6 mg/d (8, 11), and a daily intake of 10–15 mg of zinc results in losses of >4 mg/d. During the first few days on low zinc intakes, before adaptive mechanisms have become fully operational, zinc losses are approximately 1.0 mg/d and 1.4 mg/d for women and men, respectively (8, 11).

The dietary requirement is dependent of the efficiency of absorption. Fractional zinc absorption is dependent on zinc content; when intakes are increased, fractional absorption decreases. However, the relationship is not linear and the amount of zinc absorbed increases when zinc intake increases. Superimposed on the relationship between intake and fractional

absorption is the effect of enhancing and inhibiting components in the diet (12). At low intakes of zinc in diets with no inhibitors, the fractional absorption can be >50% (13), but at more common intakes 15–40% is absorbed depending on the composition of the diet. Phytic acid, which is present in cereals and leguminous plants, inhibits zinc absorption, and animal protein counteracts this inhibition (14, 15). From a cereal-based meal with a high content of phytic acid, 10–15% of the zinc is absorbed, but 20–40% can be absorbed from meals based on animal protein sources depending on the zinc content. In some foods, the negative effect of phytic acid is partly counteracted by a high zinc content.

A number of single-meal studies using radioisotope techniques have been undertaken to identify the dietary factors affecting absorption and their relative impact. Relatively few studies have measured zinc uptake from total diets with realistic compositions, and the techniques used in these studies are based on the use of stable zinc isotopes that are typically added in amounts that account for 20% or more of the total zinc content.

The U.S. Food and Nutrition Board (16) set the recommended daily allowance (RDA) was set to 11 mg/d for men and 8 mg/d for women. Although the absolute numbers are similar to those of other expert reports and the approach used is the same factorial method, they have introduced a somewhat different concept in the calculations. The data used are almost exclusively derived from total diet studies using semi-synthetic basic diets or blended low zinc foods with added zinc and stable zinc isotopes for the absorption estimates. The FNB used a three-step approach to estimate the average requirement of zinc. First, the losses of zinc via routes other than the intestine are estimated. These losses are regarded as constant over the range of intake that encompasses zinc requirements. For men, the estimates for losses via kidneys and sweat, integumental losses, and losses in semen are estimated to be 0.63, 0.54, and 0.1 mg/d, respectively. For women, menstrual zinc losses are estimated to be 0.1 mg/d and losses via kidneys and skin are estimated to be 0.44 mg/d and 0.46 mg/d, respectively. Thus, total losses via these routes are 1.27 mg/d and 1.0 mg/d for men and women, respectively. The second step, and the new concept, is the use of the relationship between the quantity of zinc absorbed and the excretion of endogenous zinc via the intestine. In the stable isotope/balance studies used for this calculation, the data suggest a linear relationship between absorbed zinc and intestinal (endogenous) excreted zinc. The constant losses via other routes are added and the point where the absorbed zinc is equal to the sum of the endogenous intestinal excretion and the

other losses is taken as the minimum requirement for absorbed zinc (i.e. the physiological requirement), which is 3.84 mg/d for men and 3.3 mg/d for women. The same studies are then used to calculate the amount of zinc that has to be ingested to give this amount of absorbed zinc. These calculations give an EAR of zinc of 9.4 mg/d and 6.8 mg/d for men and women, respectively. In the third step, a coefficient of variation of 10% is used as an estimate of the inter-individual variations and the RDA is set to 11 mg/d and 8 mg/d. Thus, the major differences in the U.S. estimates compared to other reports are a much higher estimate of the physiological requirement, the use of estimates of the endogenous intestinal losses, a higher estimate of the fractional absorption, and a smaller figure for the inter-individual variations.

In NNR 2004 (17), the following estimates were made. For the estimate of the endogenous losses and routes other than the intestine, the Food and Nutrition Board figures (16) have been used although it should be noted that the majority of the studies quoted in that report were performed at a time when reference urine samples were not available for quality control purposes. Losses via kidneys, skin, and semen or menses are thus set at 1.27 mg/d for men and 1.0 mg/d for women. Endogenous intestinal losses are estimated to be 1.4 mg/d for both genders based on the observed losses at low intakes (1–5 mg/d). Thus, 2.67 mg/d and 2.4 mg/d for men and women, respectively, have to be absorbed in order to replace these losses. At these levels of intake, absorption from a mixed animal and vegetable protein diet more realistic for Nordic conditions is assumed to be 40%. The average dietary requirement of zinc is, therefore, 6.4 mg and 5.7 mg for men and women, respectively. Using an inter-individual variation in requirement of 15%, the recommended intakes were set to 9 mg/d for men and 7 mg/d for women. This recommended intake probably has a high safety margin because the ability of the body to adapt to lower intakes appears to be substantial.

In NNR 2012, the RIs from 2004 are kept unchanged, since no new scientific data that justify a change has emerged.

Lower intake level

Balance studies with a combination of a semi-synthetic formula based on egg white and low zinc foods have shown that an intake of 4.4 mg/d or 4.6 mg/d for 35 days or 10 weeks do not give any indications of an impaired zinc status or the need for adaptation based on plasma levels and zinc excretion in urine (18, 19). The latter study also showed no changes

in exchangeable zinc pool mass during the low intake diet. These data are used as the basis for the lower limit of zinc intake.

Children

Data on endogenous losses of zinc at different intakes are almost completely lacking for children. In relation to body weight, children appear to have larger losses of zinc than adults. The need of zinc for growth is a daily intake of approximately 175 mg/kg during the first month and then a daily intake of approximately 30 mg/kg for the next 9–12 months (20). For growing children, the need for zinc is based on basal losses of 0.1 mg/kg and a zinc content in new tissue of 30 mg/kg. For adolescents, growth is assumed to result in an average zinc content in new tissue of 23 mg/kg due to an increase in fat tissue with a lower zinc content than that in younger children. The physiological requirements for rapidly growing adolescents can, therefore, be increased by 0.3–0.4 mg/d. Applying the same principles as for adults, the recommended daily zinc intake varies from 2 mg in the youngest age group to 12 mg for adolescent boys. In NNR 2012, the RIs from 2004 are kept unchanged.

Pregnancy and lactation

The total need for zinc during pregnancy for the foetus, placenta, and other tissues is approximately 100 mg (21). This additional need for zinc in pregnancy can be met by an increase in zinc intake or by adjustment in zinc homeostasis. There is no evidence that pregnant women increase their intake of zinc, so homeostatic adjustments in zinc utilization must be the primary mechanism for meeting the additional zinc demands for reproduction (21). It is assumed that an increased efficiency of zinc absorption or other metabolic changes occur during pregnancy and these changes ensure that the requirement for zinc can be met with an unchanged intake. However, studies in this area are inconclusive and there are some that show increased absorption during pregnancy (22) and other studies that have found no significant increase in fractional absorption (23). The results from the latter study might reflect inadequate power of the study design. The U.S. recommendations from 2001 for zinc intake in pregnancy (16) are based on this reference. In NNR 2012, the RIs are based on an increase in the physiological requirement by 0.7 mg/d with adjustment for absorption. With adjustment for absorption, the additional dietary intake is set to 2 mg/d.

Ortega and co-workers (24) showed lower zinc concentration in the breast milk of women consuming less than 7.5 mg/d of zinc during the

third trimester. Zinc content in breast milk is approximately 2.5 mg/L in the first month of lactation and thereafter falls to approximately 0.7 mg/L after 4 months (20). Theoretically this means that the zinc requirement of lactating women is double that of non-lactating women. A fractional increase in zinc absorption of up to 70–80% has been shown for lactating women compared with non-lactating postpartum or never-pregnant women (23, 25). Release of zinc from bone tissue could also be an explanation why zinc concentrations in breast milk are relatively independent of the mother's zinc intake and do not seem to result in zinc deficiency of the mother even after a long period of lactation. An elevated intake corresponding to the zinc content in breast milk is recommended for women lactating for a long time, i.e. a physiological need of 1.7 mg/d. With adjustment for absorption, the additional dietary intake is set to 4 mg/d.

Reasoning behind the recommendation

The recommended daily intake in NNR 2004 (17) was based on estimated zinc requirements by the factorial method, i.e. estimates of the daily losses of zinc and the corresponding amount of zinc to be ingested to replace these losses. Additional zinc is needed during periods of tissue growth. In NNR 2012 the reference values are kept unchanged compared to NNR 2004 because there are no new scientific data to justify any major changes.

Upper intake levels and toxicity

The risk of excessive intake of zinc from food alone is very low. Symptoms of acute toxicity from excessive intake occur at intakes of gram quantities of zinc and are related to consumption of dietary supplements. Reduced activity of copper-containing enzymes has been observed with zinc intakes of 50 mg/d, and with slightly higher daily intakes of ≥150 mg more pronounced signs of impaired copper metabolism have been observed along with negative changes in immune defence and blood lipids (26–28). More recent studies in which strictly controlled intakes of copper and zinc were given showed that at zinc intakes of 50 mg/d no adverse effects on a wide range of relevant indicators of copper status could be observed (29–32). Based on these data, the EU Scientific Committee on Food set an uncertainty factor of 2 and arrived at an upper level of 25 mg zinc per day for adults and for children and adolescents the upper levels are extrapolated on a surface area basis (33). In recent years, zinc has been provided in

therapeutic trials (75–150 mg/d) for a few weeks up to few months. Zinc lozenges administered within 24 hours of onset of symptoms have been shown to reduce the duration and severity of the common cold in otherwise healthy people (34). However, there is a potential for zinc lozenges to produce side effects and further studies are needed to determine possible risks associated with long-term use of therapeutic doses of zinc for prevention of the common cold (34).

In NNR, no ULs intake limits are set for zinc.

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35 Iodine

Iodine µg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	150	150	90	150	120
Average requirement	AR	100	100			
Lower intake level	LI	70	70			
Upper intake level	UL	600	600			

Introduction

Iodine deficiency is considered to be one of the most common nutritional disorders in the world and the most common cause of goitre (1, 2). In Sweden and Finland, goitre in adults and cretinism in children due to iodine deficiency was common during the first decades of the 1900s. The introduction of iodine fortification of salt resulted in a sharp decrease in the prevalence of these ailments (3). In 2000, mandatory iodisation of table salt and bread salt was introduced in Denmark as a response to studies showing low iodine status and goitre in certain population groups (4, 5). In 2004–2005, urinary iodine excretion had increased significantly in all age groups compared with the excretion levels before mandatory iodine fortification (6). However, salt iodisation has not been required to reduce goitre in all of the Nordic countries. Before 1950, there was endemic iodine deficiency in Norway with goitre prevalence as high as 80% in certain inland areas (7). Iodine fortification of cow fodder resulted in a relatively high concentration of iodine in milk and dairy products, and high levels of consumption of these products led to eradication of endemic goitre (8). Iceland has long been known for its high iodine status that is believed to be due to high levels of fish consumption (9).

Dietary sources and intake

In plants, iodine occurs predominantly in inorganic forms and the iodine content varies with the iodine content in the environment. The iodine content in sea-plants is higher than in plants grown on land. The iodine content of milk and milk products varies considerably depending on the concentration of iodine in the animal fodder and the use of iodine-containing disinfectants in connection with milking. The iodine content is generally higher in winter milk than in summer milk (10). The iodine in drinking water varies considerably between regions and can be a significant iodine source in some locations (3, 11). Fish, especially marine fish and shellfish, generally have high iodine contents. Eggs can also be an important iodine source depending on the iodine concentration in the chicken feed.

Iodised table salt is available in Denmark, Sweden, Finland, and Norway and contributes to iodine intake. The concentration of iodine present in iodised salt varies from 5 µg/g to 50 µg/g, and Denmark also fortifies the salt used in bread (5, 6, 12). Iodised salt is not commonly used in Iceland (13), and in Norway the iodisation of cow fodder has been more important for iodine intake than iodised table salt (10, 14).

The dietary intake of iodine is difficult to assess in dietary surveys because data for iodised table salt and drinking water are commonly lacking. An overview of studies on iodine intake and excretion in the Nordic countries published from the year 2000 to 2010 is given in the NNR systematic review (SR) (15) that covered studies on health effects of dietary iodine intake.

Physiology and metabolism

Iodine is essential for a number of animal and plant species. Only vertebrates, however, have developed a thyroid gland for the synthesis, storage, and secretion of the iodine-containing hormones thyroxine (T4) and its biologically active form triiodothyronine (T3) (16). The utilisation of iodine in the thyroid gland occurs via active uptake of iodide (the iodide concentration is approximately 30 times higher in the gland than in plasma), incorporation of iodine in thyroglobulin and iodine tyrosine, and secretion of the iodine thyronines triiodothyronine and thyroxine. The thyroid-stimulating hormone (TSH) from the pituitary gland regulates the formation of the thyroid hormones.

The thyroid hormones regulate cellular metabolism. The mechanism of

action is not completely known, but protein synthesis of enzymes necessary for increased metabolic activity increases in response to these hormones. The thyroid hormones also increase the size and number of mitochondria – a sign of increased ATP-production.

Dietary iodine is generally efficiently absorbed as iodide, although some sources of iodine, such as seaweed and protein-bound iodine, are absorbed less efficiently (17, 18). For a mixed diet that provides about 200 µg/d of iodine, about 90% of the iodine is excreted in the urine (18). Faecal losses vary, but are in general only 10–20 µg/d. Small amounts are also lost through the skin. Iodine absorption and utilisation can be affected by goitrogens, mainly sulphur-containing glucosides (glucosinolates). These are dietary constituents that can inhibit the uptake of iodine into the thyroid gland (e.g. thiocyanates) or interact with hormone production (e.g. goitrins) (17). These compounds occur in *Brassica* species such as cabbage, Brussels sprouts, turnips, and rapeseeds. The levels of glucosinolates in the modern Nordic diet are generally too low to have an impact on iodine status.

The iodine concentration in breast milk varies with the iodine intake from the diet (19). Reported levels in breast milk from Danish mothers before the introduction of salt iodisation were about 30 µg/L (20). No data is available on the iodine content of breast milk from Danish mothers after the introduction of iodised salt. Older data from Finland reported average levels of 25 µg/L in breast milk from goitrous areas compared to 53 µg/L in non-goitrous areas (19). In Sweden, breast milk samples have been reported to contain 50–90 µg/L iodine (19). Smoking is associated with lower iodine concentrations in breast milk, possibly due to impaired iodine uptake in the mammary gland (21).

The recommended indicator for measuring iodine status is the median urinary iodine concentration (UIC) in the population. Other potential indicators of iodine status and thyroid function include the thyroid volume (TV) and the concentrations of TSH, T3, T4, and serum thyroglobulin (22–25). Iodine intake is regarded as sufficient when the median UIC in the population is 100–199 µg/L (19). Iodine sufficiency during pregnancy is defined as a median UIC of 150–249 µg/L (24).

Iodine deficiency presents primarily as non-toxic goitre, i.e. an enlarged thyroid gland with normal production of thyroid hormones. Non-toxic goitre can gradually progress to toxic goitre with an increased secretion of hormones and a subsequent increase in metabolism (thyrotoxicosis). In cases of hyperthyroidism, the thyroid gland can be enlarged (toxic goitre) either in a diffuse form (Basedow's or Graves' disease) or with focal

changes (nodular goitre). In more severe cases of iodine deficiency, cretinism – which is characterised by impaired growth, mental disturbances, and disturbances in speech and acuity (deaf mutism) – can occur in infants and children, and hypothyroidism (myxoedema) can occur in adults (2, 22, 26). Although more studies are needed, mild iodine deficiency has been suggested to be associated with developmental impairment in children (15).

Requirement and recommended intake

Adults and children

The recommendations in NNR 2004 (23) for adults and children remain unchanged because there is no new data supporting changes (15). The iodine requirement to prevent goitre (increased thyroid gland size) is estimated to be 50–75 µg/d or a daily intake of approximately 1 µg/kg bodyweight (27, 28). The average requirement (AR) is estimated to be 100 µg/d for both adult women and men, and at this intake the iodine concentration in the thyroid gland reaches a plateau. The daily iodine turnover in subjects with normal thyroid function is at a similar level (29). The recommended intake is set to 150 µg/d for adults and adolescents and this includes a safety margin for any goitrogenic substances in foods. The lower limit of intake for adults is estimated at 70 µg/d.

The recommended intakes for infants and children are based on data on goitre prevalence and urinary iodine excretion in European children (30) and on extrapolations from adults based on energy and growth requirements. In iodine-sufficient populations, breast milk will cover the needs of an infant during the first months of life. For children 2–5 years old, 90 µg/d is recommended and 50–70 µg/d is estimated to be sufficient for infants and children younger than 2 years old (31).

Pregnancy and lactation

During pregnancy and lactation, an extra daily supply is needed to cover the needs of the foetus, to maintain maternal thyroid gland function, and to provide sufficient iodine in the breast milk. In NNR 2004, an extra 25 µg/d was recommended during pregnancy and an extra 50 µg/d was recommended during lactation to provide sufficient iodine in the breast milk (23).

Results from the Norwegian Mother and Child Cohort Study showed that women who used iodine-containing supplements had higher levels of urinary iodine excretion than those who did not use such supplements

and that inclusion of milk and seafood in the diet is important to secure optimal iodine nutrition (32, 33). Results from a subsample analysis in this study (n = 119) indicate that iodine intake of at least 150 µg/d would be required to get the median UIC up to the optimal range of 150–249 µg/L for pregnant and lactating women defined by the WHO (34). Because pregnant women in the Nordic countries are generally well nourished and have easy access to milk, seafood, and dietary supplements, and because there is no new data supporting changes (15), the recommendations from NNR 2004 are kept unchanged. However, there is need for better surveillance and more data on the level of iodine intake that ensures normal thyroid function in both maternal and new-born in the Nordic countries (15). Studies from Norway and Iceland show that pregnant women who do not consume, or have low intake of, dairy and/or seafood and who do not obtain iodine from supplements are at great risk of having an inadequate iodine intake (13, 34).

Reasoning behind the recommendation

The recommended daily intake for adults in NNR 2004 was based on the iodine requirement to prevent goitre and maintain normal thyroid function. The recommended intakes for infants and children were based on data on goitre prevalence and urinary iodine excretion in European children (30) and extrapolations from adults based on energy and growth requirements. The recommended daily intake for pregnant and lactating women in 2004 was based on the extra daily supply needed to cover the needs of the foetus and to provide sufficient iodine in breast milk. Iodine deficiency is known to affect thyroid function of the mother and the neonate as well as the mental development of the child (24). The reference values are kept unchanged compared to NNR 2004 (23) because there are no new scientific data to justify any major changes (15).

Upper intake levels and toxicity

An iodine intake in excess of 2 mg/d can, in rare cases, cause sensitivity reactions such as rhinitis, nasal congestion, swollen salivary glands, headache, and acne-like skin changes (35). High iodine intakes can also cause disturbances in thyroid function. Symptoms include inflammation in the thyroid gland (auto-immune thyroiditis), goitre, and hypo- or hyperthyroidism (35). High iodine intakes from drugs, certain types of seaweed, or

supplements in amounts corresponding to up to 10 mg iodine per day have resulted in increased incidence of iodine goitre along with hyperthyroidism or myxoedema in certain cases (35–39). Very high iodine excretion (up to 1,700 µg per 24 h) has been reported in subjects consuming seaweed preparations (40).

There is a substantial inter-individual variation with respect to the dose of iodine that can cause adverse effects. This complicates the assessment of an upper safe limit of intake. Persons with normal thyroid function can, in general, tolerate prolonged consumption of iodine up to 1 mg/d (35). The Scientific Committee for Food has proposed 600 µg/d of iodine as the safe upper level (UL) for adults (41). The UL is based on elevations in TSH levels after iodine intake and an enhanced response in TSH levels to thyrotropin releasing hormone (TRH) stimulation. These effects are of a biochemical nature and are not associated with any clinically adverse effects. The UL includes an uncertainty factor and is also considered acceptable for pregnant and lactating women. In children, a median UIC ≥500 µg/L was found to be associated with increasing thyroid volume in children 6–12 years old but a UIC of 300–500 µg/L was not (42). The authors of that study, however, did not rule out the possibility of adverse effects of a UIC in the range of 300–500 µg/L that were not detected in the study (42).

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36 Selenium

Selenium µg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	50	60	25	30	40
Average requirement	AR	30	35			
Lower intake level	LI	20	20			
Upper intake level	UL	300	300			

Introduction

Selenium is found in all tissues, mainly as selenomethionine, an analogue to the sulfur-containing methionine, and as selenocysteine in various selenoproteins. Selenium primarily functions as a co-factor in antioxidant activities and thyroid hormone metabolism. Severe selenium deficiency can cause cardiomyopathy, and excessive selenium intake causes toxic symptoms. Organic and inorganic selenium compounds have different metabolism and different bioavailability.

Dietary sources and intake

Foods contain a number of selenium compounds. In animal foods, there are specific selenoproteins containing selenocysteine. Foods of both animal and plant origin contain selenomethionine and possibly some selenocysteine incorporated into proteins. The inorganic forms selenite and selenate are used in dietary supplements, but they are not normally found in food.

Assessment of selenium intake from food composition databases is difficult because the selenium content varies according to the selenium concentration of the soil where crops are grown or the animals graze. Fish and other seafood, eggs, and offal are relatively rich in selenium. Cereal products and vegetables grown in the Nordic countries, with the exception of Finland after 1984, have low selenium content, whereas wheat imported

from North America has high selenium content. In general, foods from seleniferous areas of Venezuela contain much more selenium than the same foods from Scandinavia or New Zealand where the selenium levels are low (1). The selenium concentration in meat and milk depends on the amount of organic selenium in animal feeds. Fodder is generally enriched with selenite, which has a limited effect on the selenium concentration of meat and milk. In Finland, selenate has been added to agricultural fertilizers since 1984 (2). Plants convert inorganic selenate to selenomethionine. It has been assumed that selenium is not essential for plants, but evidence from Finland suggests that low levels of selenium are beneficial for plant growth through several mechanisms (3). Supplementation with fertilizers has increased both human and animal intake of organic selenium in Finland. The most important sources of selenium in the diet of Finns today are meat (which provides 40% of the selenium consumed), dairy products and eggs (25%), and cereal products (20%) (2). In Norway and Iceland, the intake of selenium has been influenced by high-selenium wheat imported from North America. In Norway, an increased use of domestically grown wheat during the last 20 years has reduced the average selenium intake of the population as measured by a reduction in blood selenium concentrations (4). In Sweden selenium has been added to animal feed since the late 1980s, thereby increasing the intake from meat and dairy products. Fish and seafood are also important dietary sources. Some animal studies have shown poor bioavailability of selenium from fish, but there were differences in bioavailability between various fish species. In humans, selenium has been shown to be readily available from Baltic herring and rainbow trout (5, 6). Other human studies have suggested reduced bioavailability of selenium from fish compared with other selenium-containing foods (7, 8). The reason for the observed differences in bioavailability is probably due to the variety of selenium species in fish, which might vary in bioavailability. Selenium reduces the availability of mercury in fish (9).

The selenium content of meat depends on the animal feed used and whether it is supplemented with inorganic or organic selenium. In muscle meat, 50%–60% of the total selenium content might be in the form of selenomethionine, and about 20%–30% of the selenium in beef and up to 50% in poultry might be selenocysteine (10).

Dairy products contain selenium mainly as selenocysteine and selenite. Supplementation could result in a wider spectrum of selenium species. Plant foods cultivated in the Nordic countries without selenium-containing fertilizers generally have low selenium concentrations. The selenium con-

centrations in meat and milk from animals fed organically grown feeds might therefore be lower than meat and milk from animals conventionally fed. The selenium intake of people who regularly consume organically grown products might thus be lower. This also applies to vegetarians and vegans because plant foods might contain very little selenium.

Approximately 80% of selenium is absorbed from food. Selenomethionine is actively transported, but knowledge to what extent other organic selenium compounds from plants are absorbed and metabolised by the body is incomplete.

According to recent dietary surveys, mean selenium intake (per 10 MJ) in the Nordic countries is 57 µg in Sweden, 47 µg in Denmark, 63 µg in Norway, 86 µg in Finland, and around 85 µg in Iceland (2, 11–16). Mean serum selenium concentrations in adults from studies during the last two decades range from 70–100 µg/L in Denmark, Norway (17, 18) and 100–120 µg/L in Finland (2, 19). Results for Swedish adolescents are comparable (20).

Physiology and metabolism

Water-soluble selenium compounds and dietary selenium (mainly organic selenium in forms such as selenomethionine and selenocysteine) are effectively absorbed, and selenates and organic selenium are absorbed somewhat better than selenites. Selenium compounds are converted to selenides before they are incorporated into specific selenoproteins. Selenomethionine is incorporated as selenide into a number of unspecific proteins. Inorganic selenium salts are retained less effectively because a major proportion is excreted in the urine. At high intakes, detoxified excretory products such as dimethyl selenide and trimethyl selenonium ions are formed. The former is exhaled via the lungs, and the latter is excreted in the urine. Dietary selenium affects the selenium concentrations in serum or plasma and red blood cells, which are useful biomarkers for all species of selenium intake in deplete individuals. Only organic selenium forms show a dose-response correlation in selenium-replete individuals (7, 21). The selenium concentration in the toenails has been recommended as the best indicator of the long-term intake of organic selenium.

Men and women tend to have similar serum selenium concentrations despite different intakes. Part of the selenium in tissues is found in functional selenoproteins. The human selenoproteome has been reported to consist of 25 selenoproteins. These include the following glutathione per-

oxidases (GSHPx): cellular (cGSHPx), extracellular (eGSHPx), phospholipid hydroperoxide (phGSHPx), and gastrointestinal (giGSHPx). Together with other metalloenzymes, these peroxidases protect tissues against oxidative damage. It is believed that the essentiality of selenium is based on the effect of GSHPx and other selenoproteins. The iodothyronine deiodinases (types I, II, and III) that produce triiodothyronine and related metabolites from thyroxine are selenoproteins. Selenium also affects the activity of the selenoprotein thioredoxin reductases, which have a number of physiological functions (22). Selenoprotein P (SePP) is synthesised mainly in the liver and is present in plasma. It has a double function as a selenium transport protein and as an antioxidative protective enzyme, and it might protect endothelial cells and low-density lipoproteins against lipid peroxidation (10, 21, 23). Other selenoproteins with unknown functions are selenoprotein W and prostatic epithelial selenoprotein (24).

Requirement and recommended intake

Three syndromes are associated with selenium deficiency. The first is a type of cardiomyopathy that particularly affects children and young women and is associated with a low intake of selenium (< 20 µg/d). This syndrome, known as Keshan disease, has occurred in people from certain parts of China (25). A similar cardiomyopathy has been observed in some isolated cases during parenteral nutrition without selenium supplementation. Keshan disease likely has a dual aetiology that involves both a nutritional deficiency of selenium as well as an infection with an enterovirus (coxsackievirus) (26). The second syndrome is an osteoarthropathy that affects children in the low-selenium areas of China. It is characterized by metaphyseal involvement with swollen joints and shortened fingers and toes and is presumably caused by selenium deficiency in combination with other pathogenic factors. In the third syndrome, the combination of low iodine and selenium intake can lead to myxoedema with development of cretinism, which has been described in the endemic goitre area of central Africa (27).

In two Finnish studies from the 1970s, low serum selenium levels (< 45 µg/L) were associated with an increased risk of cardiovascular death (13a). In Denmark, men with serum selenium concentrations below about 75 µg/L were reported to have an increased risk of myocardial infarction (28).

In a recent Cochrane meta-analysis to determine the effectiveness of selenium supplementation for the primary prevention of cardiovascular

disease (CVD) and to examine the potential adverse effect of selenium on type 2 diabetes, twelve randomised controlled trials (RCTs) met the inclusion criteria and included a total of 19,715 randomised participants (29). The two largest trials (SELECT and NPC), which were conducted in the USA, reported clinical events. There were no statistically significant effects of selenium supplementation on all-cause mortality, CVD mortality, non-fatal CVD events, or all CVD events (fatal and non-fatal). There was a small increased risk of type 2 diabetes with selenium supplementation, but this was not statistically significant. Other adverse effects reported in the SELECT trial that increased with selenium supplementation included alopecia and dermatitis grade 1 to 2. The meta-analysis concluded that the trial evidence available to date does not support the use of selenium supplements in the primary prevention of CVD. However, the baseline selenium levels in the supplemented groups were substantially higher than the threshold value (45 µg/L) reported in the earlier Finnish studies.

The cancer-preventing potential of selenium has been investigated in several large studies. A meta-analysis investigating the preventive effect of selenium supplements on cancer reported by RCTs was published in 2011 (30). Eight articles on nine RCTs were included in the analysis, and the total number of participants was 152,538, with 32,110 participants in antioxidant supplement groups and 120,428 participants in placebo groups. In a random effects meta-analysis of all nine RCTs, selenium supplementation alone was found to have an overall preventive effect on cancer incidence. Among subgroup meta-analyses, the preventive effect of selenium supplementation alone on cancer was observed in populations with a low baseline serum selenium level (< 125.6 µg/L) (RR = 0.64; 95% CI = 0.53–0.78; I^2 = 45.5%; n = 7) and in populations with a high risk for cancer (RR = 0.68; 95% CI=0.58–0.80; I^2 = 41.5%; n = 8). The meta-analysis indicated that there is possible evidence to support the use of selenium supplements alone for cancer prevention in people who have a low baseline level of serum selenium or a high risk for cancer.

The daily losses of selenium are determined by dietary intake and tissue stores and provide only limited information about requirements. The daily requirement of selenium is assumed to depend on body size. Selenium intakes of 30–40 µg/d are needed to achieve maximal GSHPx activity in serum. Intakes of 80 µg/d and 120 µg/d are needed for maximal GSHPx activity in red blood cells and platelets, respectively (31). It is not apparent, however, that maximal GSHPx activity in all tissues is necessary for optimal health.

In a 40-week supplementation study in Chinese subjects with a mean body weight of 48 kg, the plasma GSHPx activity was optimised with selenium supplements of 35 µg/d, and the SePP concentration was optimised with 49 µg/d of selenium (32). In a study of subjects with an estimated baseline selenium intake of 55 µg/d in the UK, it was found that the SePP concentration was optimised with a daily supplemenmt of 50 µg yeast selenium (33). Smaller doses were not studied, and the effects were not analysed separately for men and women. Unfortunately, only a few centres in the world are able to measure SePP. Many studies still rely on serum or plasma selenium as an endpoint for examining the response to changes in selenium intake or cross-sectional analyses to explore the association between habitual intake and selenium levels. Ballihaut et al. (34, 35) described the technical difficulties of measuring SePP. The effect of varying selenium intakes on the activity of newly discovered selenoproteins has not been studied in humans.

Information on selenium requirements for children and pregnant and lactating women is incomplete. During continued lactation, the selenium concentration of the mother's milk is reduced over time when selenium intake is less than 45–60 µg/d, but remains unchanged at intakes of 80–100 µg/d.

The selenium recommendations in different countries have been based on a Chinese study that showed maximal stimulation of plasma GSHPx activity in serum by selenium supplementation of 30 µg/d in people whose basal intake was 11 µg/d (36). In the NNR 2004, the recommendation was based on the mean + 2SD of this study and adjusted for the difference in mean body weight. The recommended intake was set to 50 µg/d for men and 40 µg/d for women.

It now appears more reasonable to base the recommendation on the optimisation of the plasma SePP concentration (32, 33), although the usefulness of this measure has been discussed for selenium-replete populations (37). In a 40-week placebo-controlled double-blind study of selenium repletion in 98 healthy Chinese subjects who had a daily dietary selenium intake of 14 µg, fourteen subjects each were assigned randomly to daily dose groups of 0 µg, 21 µg, 35 µg, 55 µg, 79 µg, 102 µg, and 125 µg of selenium as L-selenomethionine. Plasma glutathione peroxidase (GSHPX) activity, SePP1, and selenium were measured. The SePP1 concentration was optimized with the 35 µg supplement at 40 weeks, which indicated that 49 µg/d of total dietary selenium could optimize SePP concentration. GSHPX activity was optimized by the 21 µg supplement (total ingestion

of 35 µg/d). The plasma selenium concentration showed no tendency to become optimized (32).

Translating the results of the Chinese intervention study to Nordic conditions and correcting for average body size, the recommended intake in the Nordic countries should be 60 µg/d for men and 50 µg/d for women. The recommendation of the EU Scientific Committee on Food (SCF) and the US Institute of Medicine is 55 µg/d for both men and women (38, 39).

The EU SCF recommendation is 55 µg/d and 70 µg/d for pregnant and lactating women, respectively, and the recent US recommendation is 60 µg/d and 70 µg/d, respectively. The NNR 2004 recommendation was 55 µg/d for both pregnant and lactating women. Based on the considerations above, the NNR 2012 recommendation for pregnant and lactating women is increased to 60 µg/d.

The lower intake level for adults is unchanged from NNR 1996 at 20 µg/d.

The recommended intakes for children and adolescents are derived from the values for adults.

Reasoning behind the recommendation

Saturation of plasma SePP activity is now considered a better measure of adequate selenium status than the earlier used plasma GSHPx. Optimisation of SePP requires a higher intake of selenium than optimisation of GSHPx. In a recent study with Chinese participants, 50 µg/d of selenium optimised SePP (32). Correcting for body size, this would support a recommended dietary selenium intake of 50 µg/d for women and 60 µg/d for men in Western populations. The recommendation for pregnant and lactating women is increased to 60 µg/d, which accounts for the increased needs for tissue growth and lactation.

Upper intake levels and toxicity

Selenium toxicity is rare in humans but well known in animals. Acute toxicity has been observed after consumption of a large (250 mg) single dose or after multiple doses of ~30 mg. The symptoms include nausea, vomiting, and garlic-like breath odour. Other symptoms of toxicity are nail and hair deformities and, in severe cases, peripheral nerve damage and liver damage. Because of the risk of toxicity, high doses of selenium are not recommended. A no observed adverse effect level (NOAEL) for clini-

cal signs of selenium toxicity and a threshold of 850 µg/d for inhibited prothrombin synthesis were found in Chinese studies. The EU SCF derived an upper level of 300 µg/d using a factor of three to allow for uncertainties in different studies (40).

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37 Copper

Copper mg/d		Adults	Children		
			2–5 y	6–9 y	10–13 y
Recommended intake	RI	0.9	0.4	0.5	0.7
Average requirement	AR	0.7			
Lower intake level	LI	0.4			
Upper intake level	UL	5.0*			

* SCF 2003 (1).

Introduction

Copper has two oxidation states and is involved in oxidation and reduction reactions inside cells. Copper functions as a component of a number of enzymes involved in energy metabolism, the formation of connective tissues, and defence against free radicals.

Dietary sources and intake

Copper is widely distributed in food. The highest levels of copper are found in liver and other offal, while milk and milk products have a low copper content. Most grain products, meats, chocolate products, dried fruits, mushrooms, tomatoes, bananas, and potatoes contain intermediate amounts. The intake of copper in the Nordic countries varies between 1.0 mg/d and 2.0 mg/d (1).

Physiology and metabolism

Copper absorption occurs primarily in the small intestine. At normal dietary intakes (1–5 mg/d) absorption varies between 35% and 70% and is mainly regulated by the amount of copper in the diet, i.e. the percentage absorption decreases with increasing intakes. In the enterocytes of the small

intestine, copper is either bound to a copper chaperone or is chelated by metallothionein, which is a protein that is induced by zinc and sequesters copper in the mucosal cells and prevents its transfer into the circulation (2) At high zinc intakes (>50 mg/d), therefore, copper absorption is inhibited. The copper chaperones deliver the copper to copper transporting proteins for final absorption into the circulation. At high levels of dietary copper, passive diffusion also plays a role in the absorption of copper (3). After absorption from the gut, copper binds to albumin, transcuprein, low molecular weight copper histidine complexes, or a combination of these and is transported to the liver. Once absorbed into the liver, it has been suggested that copper is stored intracellularly by binding to either metallothionein or reduced glutathione. Release of copper from reduced glutathione or metallothionein makes copper available for other purposes and it is transported once again by chaperones. For example, the copper chaperone CCS1 traffics copper to superoxide dismutase (SOD) (4). Most of the copper in the plasma is transported as caeruloplasmin, which is produced in the liver. Homeostasis of copper is regulated to some extent by absorption, but also through excretion via bile, which can account for approximately 0.5 mg/d to 1.5 mg/d. Urinary excretion of copper is low.

The total body content of copper of an adult is approximately 50 mg to 120 mg, and 40% is found in muscle tissue, 15% in the liver, 10% in the brain, and approximately 6% in the plasma and erythrocytes. New-born infants have a larger amount of copper in the liver than adults, and this might act as a store of copper during the first couple months of growth. Copper deficiency in humans is rare, but it has been found in a number of circumstances. Copper deficiency has been observed in premature infants fed milk formula, in term infants recovering from malnutrition associated with chronic diarrhoea who have been fed cow's milk (5), and in patients with prolonged total parenteral nutrition without additional copper. Symptoms of copper deficiency in children are low concentrations of white blood cells, anaemia, and hair and skin depigmentation (6). Heart and skeletal abnormalities have also been observed. Most of the symptoms can be related to deficiencies in copper-containing enzymes.

There is substantial evidence from animal studies to suggest that diets low in copper reduce the activity of many of the copper-dependent metalloenzymes. The activity of some of these metalloenzymes has also been shown to decrease during human copper depletion (7, 8). There is also evidence that immune and cardiac dysfunction can occur during experimental copper deficiency and the development of such signs of deficiency

has been demonstrated in infants (7, 9). Furthermore, it has recently been demonstrated that low copper intake (<0.6 mg/d compared to a usual intake of >1.5 mg/d) might be associated with increased risk of colorectal cancer because low dietary copper increases faecal free radical production, faecal water alkaline phosphatase activity, and cytotoxicity in otherwise healthy males (10).

Serum copper and caeruloplasmin concentrations are currently used as biochemical indices of copper status and can be used to detect severe copper deficiency. The decline in serum copper and caeruloplasmin concentrations observed when healthy young men were fed a diet containing 0.38 mg/d of copper for 42 days was reversed by copper supplementation (11). In a number of other studies with higher levels of copper intake (0.66 mg/d and above) serum copper and caeruloplasmin concentrations did not decline significantly (12, 13), suggesting that this was a sufficient level of intake.

The dietary copper intake at which the serum caeruloplasmin concentration no longer increases in response to increased dietary copper might be considered the copper requirement for caeruloplasmin synthesis. Other suggested indices of copper status include SOD activity, platelet copper concentration, and cytochrome C oxidase activity because all of these have been shown to decline at low copper intakes. However, none of these indicators have been found suitable for detection of marginal copper deficiency or marginal copper toxicity (14). Instead, animal studies have suggested that copper chaperone CCS1 might be a potential biomarker for marginal copper deficiency and toxicity (14–16).

Requirement and recommended intake

Adults

The precise requirement for copper is not known. Indications of deficient copper status, using SOD activity as a marker of copper status, have been reported with intakes of 0.7 to 1 mg/d (17–19). However, other studies in young men have not found indications of changes in copper status based on SOD activity, caeruloplasmin production, or plasma copper concentrations at intakes of 0.79 mg/d for 42 days (12). In a subsequent study in young men, an intake of 0.66 mg/d for 24 days followed by an intake of 0.38 mg/d for 42 days resulted in decreasing indicators of copper status over time (11, 20). Although the levels did not fall into the deficient range, a steady state was not completely reached. Other studies have shown that intakes below 0.7 mg/d are associated with increases in biomarkers related to disease

such as faecal free radical production, faecal water alkaline phosphatase activity, and cytotoxicity (10) or deceased immune function (21). There are, therefore, limited data to establish an average copper requirement for adults, but the available data suggest that an intake of approximately 0.7–0.8 mg/d will maintain adequate copper status based on plasma copper concentrations, caeruloplasmin production, and SOD activity. The U.S. Food and Nutrition Board has based its recommended copper intake for adults on a number of indicators including plasma and platelet copper concentration, serum caeruloplasmin concentration, and erythrocyte SOD activity in controlled depletion-repletion studies (22). Data on obligatory copper losses were also used in these estimates. Based on these indicators, the average requirement was estimated to be 0.7 mg/d for adults. With a coefficient of variation of 15%, the recommended daily allowance of copper (RDA) was calculated to be 0.9 mg/d, and this recommendation has also been adopted in NNR 2012.

Children

The copper content of human breast milk is highest during early lactation and then declines over the course of lactation. The mean copper content of human breast milk during the first 6 months of lactation is approximately 0.25 mg/L (22), and there are no indications of inadequate copper status in breast-fed infants. For infants 6 to 11 months old, the requirements are based on extrapolation from adults with allowance for growth. The copper requirements for children older than one year have been calculated from estimates of adult requirements with allowance for growth (22).

Pregnancy and lactation

The requirement for extra copper during pregnancy is relatively low – approximately 0.15 mg/d in the last trimester – and this is probably met by adaptation through increased fractional absorption. The copper content of human breast milk is approximately 0.25 mg/L. With a milk production of approximately 750 mL/d and an estimated copper absorption of 50%, an extra 0.3 mg/d of copper during lactation is recommended.

Reasoning behind the recommendation

The recommendations from NNR 2004 are kept in NNR 2012 due to a lack of new data. Recommendations for children, pregnant and lactating women are also kept unchanged.

Upper intake levels and toxicity

Intake of high doses of copper leads to acute toxicity, which includes symptoms of gastric pain, nausea, vomiting, and diarrhoea, and storage of food in non-galvanised copper containers is associated with an increased risk of childhood sclerosis (26). In areas with soft water, copper can leach from copper tubes and result in high copper concentrations (more than 100 mg/L) in drinking water, and gastro-intestinal disorders have been seen with intakes of copper-contaminated water containing 3.7 mg/L (27). Infants are probably the most sensitive group, and case studies have indicated an association between high copper intake from water and symptoms of copper toxicity. Recent controlled and population-based studies found weak evidence for copper toxicity from drinking water at concentrations up to 2 mg/L (28), but it is considered prudent to recommend letting tap water run before it is used for consumption by infants, especially when used for formula.

The EU Scientific Committee on Food (SCF) has proposed that an upper limit of 5 mg/d is safe for adults (29). This is based on the absence of negative effects on liver function during copper supplementation and includes an uncertainty factor to allow for potential variability within the normal population. In addition, the SCF noted that the UL upper limit (UL) is not applicable during pregnancy and lactation due to inadequate data. The U.S. Institute of Medicine set an UL for copper of 10 mg/d largely based on the same data but used an uncertainty factor of 1.0 (22).

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38 Chromium

No recommendation given due to lack of sufficient evidence

Introduction

In ionic form, chromium exists in many valence states. Trivalent chromium (III) is the most stable form and is the principal form of chromium found in foods and dietary supplements. It is ubiquitous in nature and occurs in the air, water, soil, and biological materials. Hexavalent chromium (VI) forms chromates and dichromates that are strong oxidizers and can traverse biological membranes. Hexavalent chromium compounds occur only rarely in the environment and are almost always man-made. They are toxic, mutagenic, and environmental contaminants.

Dietary sources and intake

Analysis of chromium in foods requires special sampling procedures to avoid chromium contamination from the environment (air, stainless steel, etc.). Older analytical data on chromium contents in foods, produced before about 1980, should, therefore, be used with care. Fish, whole grain products, nuts, pulses, spices, and processed meats are good sources, but most other foods have at least low concentrations of chromium (<10 µg/100g). Foods high in simple sugars, such as soft drinks and table sugar, are not only low in chromium content but also promote chromium loss (1). Studies analysing chromium intake in the diet of the Nordic countries are scarce, but estimated intakes are in the range of 20–160 µg/d (2). Many food supplements contain chromium in doses ranging from 50–100 µg per serving unit.

Physiology and metabolism

Only 0.4–2.5% of the dietary intake of trivalent chromium is absorbed by the body (3). The element is mainly excreted via urine, and only small amounts are eliminated in sweat and bile. Organic chromium compounds are absorbed more efficiently but are rapidly excreted via bile. Simultaneous ascorbate administration increases chromium uptake both in humans and animals, and chromium absorption is also higher in both zinc- and iron-deficient animals.

The exact biological function of chromium has not yet been determined, but experimental chromium deficiency in animals results in reduced glucose tolerance in spite of normal insulin levels. Other deficiency signs in animals include impaired growth, elevated levels of serum cholesterol and triglycerides, increased incidence of aortic plaques, corneal lesions, and decreased fertility and sperm count.

Chromium is considered to be a cofactor for insulin, possibly through an influence on membrane receptors. A low molecular weight chromium-binding substance is believed to be involved in the process (4). It has also been suggested that chromium influences carbohydrate, lipid, and protein metabolism via its effect on insulin action.

Three cases have been reported of possible chromium deficiency in humans after long-term parenteral nutrition (5–7). The symptoms observed were impaired glucose tolerance and glucose utilization, weight loss, neuropathy, elevated concentrations of plasma fatty acids, depressed respiratory quotient, and abnormalities in nitrogen metabolism. The symptoms improved after chromium supplementation (200 µg/d). However, the reported concentrations of chromium in the blood and urine were above those considered normal even before the supplementation was initiated. As with foodstuffs, analytical data on chromium concentrations in biological specimens, produced before about 1980, should be regarded with caution because possible contamination in sampling and processing may have led to spuriously high levels of chromium (3). The lack of reliable biomarkers for chromium status combined with the absence of clear-cut chromium deficiency conditions are the main reasons for the current uncertainties about the biological significance of chromium as an essential trace element (3).

A number of chromium supplementation studies have been published that have investigated the effects of chromium on insulin and blood glucose levels (8) (9). In 20 randomized controlled trials (RCTs) included in a meta-analysis from 2002 (8), no effect of chromium on glucose or insulin

concentrations was seen in non-diabetic subjects. Although some studies suggested beneficial effects of chromium supplementation in individuals with type 2 diabetes (9), the results were inconclusive and further studies are needed to be able to make any claims about the benefits of chromium supplementation in this group (8–10).

Several studies have also investigated chromium supplementation in relation to body composition and lipid metabolism (10). Supplementation with 200–240 µg/d has been suggested to reduce concentrations of total and LDL cholesterol (10), but the number of studies in this area is still small and the studies that demonstrate such an effect have a high risk of being biased (10). The effects of chromium supplementation on body composition, therefore, remain inconclusive (10).

Requirements and recommended intake

As described above, the role of chromium as an essential nutrient is still unclear. If chromium is an essential trace element, it must have a specific role as an enzyme cofactor and a deficiency should produce a disease or impairment of function. Methods for evaluating chromium status are lacking, and there is still uncertainty about how chromium deficiency in humans manifests itself. Thus the requirement for chromium is not currently known.

The EU Scientific Committee for Food (SCF) (11) stated that "since data on the essentiality and metabolism of chromium are so sparse, the Committee is unable to specify any requirements". The UK Committee on Medical Aspects of Food Policy (12), however, used balance studies and regression equations to calculate a theoretical requirement for adults of 23 µg/d and stated that a safe and adequate intake level is believed to be greater than 25 µg/d for adults. The U.S. Food and Nutrition Board (13) estimated adequate intakes (AI) for chromium for different age groups based on calculations of well-balanced diets. For adults aged 19 to 50 years, the adequate intake was estimated to be 35 µg/d for men and 25 µg/d for women. Despite these estimates, the authors of a scientific report submitted to the European Food Safety Authority (EFSA) in 2012 came to the conclusion that evidence was still inadequate for setting dietary reference values for chromium (10). This conclusion was based on a systematic review including several relevant studies published between 1990 and 2011.

The Nordic Nutrition Recommendations of 2004 did not include recommendations for chromium intake. Because very few relevant human

studies have been conducted since then, it is still impossible to establish requirements and no recommendations have been set for any age group. Data are also lacking on the requirements for chromium during pregnancy, but the U.S. Food and Nutrition Board (13) suggests an increase of 5 µg/d during pregnancy over the usual chromium intake.

Within Europe, chromium concentrations in human breast milk range between 0.09 and 19.8 µg/L (10), and the chromium concentration appears to be independent of maternal chromium intake (14–16). A study on lactating Finnish mothers found an average concentration of chromium in breast milk of 0.4 µg/L (range 0.2–0.7 µg/L) (17).

Upper intake levels and toxicity

Trivalent chromium has generally low toxicity, no adverse effects were observed at intakes of 1,000–2,000 µg/d. Due to the lack of adequate data, the EU Scientific Committee for Food (11) 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 (13) and the UK Expert Group on Vitamins and Minerals (11).

The consumption of chromium picolinate, a trivalent chromium compound popular in many food supplements, is currently being debated because of possible adverse health effects. This compound might influence the central nervous system and, therefore, behaviour (18), and high doses have been associated with kidney damage (19) and potential clastogenicity has also been reported (20). It is still unclear whether these effects are due to the picolinate formulation or to a higher degree of chromium absorption. The UK Food Standards Agency (21) advises people not to take chromium picolinate and has consulted on a proposal to ban the use of this form of chromium in the manufacture of food supplements because there is a chance that it could cause cancer. A review from 2004 (22), however, evaluated one particular brand of chromium picolinate and found it to be safe.

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39 Manganese

No recommendation given due to lack of sufficient evidence

Introduction

Manganese is chemically similar to iron. It is a catalytic cofactor for arginase, pyruvate carboxylase, and mitochondrial superoxide dismutase (SOD). Manganese also functions as a specific or unspecific activator for a large number of other enzymes, some of which participate in the synthesis of proteins, mucopolysaccharides, and cholesterol.

Dietary sources and intake

Wholegrain cereals, nuts, and leafy vegetables have high manganese contents. Tea may also substantially contribute to manganese intake. Manganese intake varies from very low (<2 mg/d) to high (>8 mg/d) depending on the diet. In the Swedish market basket study in 2010 (1), the daily estimated per capita intake of manganese was 4.0 mg. A Danish study in which 100 men collected duplicate portions of their regular diets for 48 hours showed a manganese intake of 3.9 mg/d (2). The manganese intake of Finnish children 3–18 years of age was in the range of 3–7 mg/d calculated from food consumption data and food contents (2). These data indicate that manganese intake is adequate in these countries. Multivitamin-mineral and mineral supplements for adults usually provide 2–5 mg per dose.

Physiology and metabolism

The total body content of manganese is estimated to be 10–20 mg. The concentration is relatively high in bone and in organs rich in mitochondria, such as the liver, pancreas, and kidney, and concentrations are low in

muscle and plasma. Absorption from the diet is low, approximately 5%, and excretion is primarily through the bile. Animal studies have shown that iron, calcium, and phytic acid reduce the absorption of manganese (3). A negative effect of calcium has been shown in humans, but the effect of iron and phytic acid in humans does not seem to be pronounced (4). High intakes of manganese inhibit iron absorption (5), and a higher absorption of manganese has been reported in cases of iron deficiency (6, 7).

Manganese deficiency in experimental animal models results in reduced growth, skeletal abnormalities, and defects in lipid and carbohydrate metabolism (3). In humans, only a limited number of deficiency symptoms attributed to lack of manganese, have been described in experimental studies with a manganese-deficient diet (8). Dermal changes and hypercholesterolemia are possible signs of manganese deficiency, as well as diffuse bone demineralization and poor growth in children. Very little information is available concerning the relationship between manganese intake and health endpoints or disease prevention (9).

Requirement and recommended intake

Our knowledge of manganese metabolism and the consequences of low intakes are insufficient for determining requirements and recommended daily intakes for humans. Balance studies have suggested that an intake of 0.74 mg/d should be sufficient to replace daily losses of manganese (10). Intakes over 1 mg/d generally result in a positive manganese balance (9).

The U.S. Food and Nutrition Board (11) found data to be insufficient for setting an Estimated Average Requirement (EAR) for manganese but used median intakes reported from the U.S. Total Diet Study 1982–9 as a basis for setting adequate intakes (12). An Adequate Intake (AI) for adult men and women is set at 2.3 and 1.8 mg/d, respectively. In 1993, the EU Scientific Committee for Food (13) suggested 1–10 mg/d to be an acceptable intake of manganese.

The NNR 2004 (14) did not include recommendations for manganese intake. Because very few relevant human studies have been conducted since then, requirements are still difficult to determine and, therefore, recommendations are not given for any age group.

Data are also too limited to determine requirements for manganese during pregnancy and lactation, and manganese deficiency has not been observed in pregnant or lactating women. Manganese excretion from breast milk is estimated to be below 1% of the total manganese excretion, and

there is no clear correlation between dietary intake and the concentration of manganese in breast milk (9). A systematic literature review of 15 studies published from January 1990 to October 2011 reported breast milk manganese concentrations of 0.8–30 µg/L (9). The median (SD) manganese concentration of 31 Swedish milk samples was found to be 3.23 (0.27) µg/L (15).

Upper intake levels and toxicity

Manganese toxicity, which manifests as psychological and neurological changes, has been observed in workers in manganese mines (7), and the neurological symptoms are reminiscent of those seen in Parkinson's disease. Inhalation of manganese dust is the likely explanation for these effects because toxicity due to a high dietary intake is unknown. Epidemiological studies, mostly cross-sectional, indicate that manganese exposure from drinking water might have a negative effect on the nervous system of children (16, 17). The EU Scientific Committee for Food (18) found that data for setting a Tolerable Upper Intake Level (UL) of manganese were too uncertain, and the UK Foods Standards Agency (19) has also found data to be insufficient to establish a Safe Upper Level for manganese.

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40 Molybdenum

No recommendation given due to lack of sufficient evidence

Introduction

Molybdenum has a number of valences and functions in oxidation-reduction reactions in plants and lower organisms. In humans only three molybdenum-containing enzymes are known: sulphite oxidase, xanthine oxidase, and aldehyde oxidase. These enzymes are involved in catabolism of sulphur-containing amino acids and heterocyclic compounds, including purines and pyridines.

Dietary sources and intake

Molybdenum is ubiquitous in food and water as soluble molybdates, but the content of molybdenum in plants varies widely with the soil concentration of molybdenum and pH. Good food sources are grains, legumes, nuts, offal, dairy products, and eggs. Fruits, root vegetables, and muscle meat are poor sources (1). High concentrations have been found in shellfish. Molybdenum levels in drinking water are mostly low, typically less than 0.01mg/L. However, in areas near mining sites molybdenum concentrations in the water of up to 0.2 mg/L have been reported (2).

There are few published studies on the dietary intake of molybdenum in the Nordic countries. Typical intakes according to supermarket baskets or dietary surveys are in the range of 100 µg/d to 150 µg/d (3–5). In the Swedish market basket study in 2010 (6), the daily estimated per capita consumption of molybdenum was 157 µg. Many multivitamin-mineral supplements contain molybdenum and these must be taken into consideration when estimating total dietary intake.

Physiology and metabolism

Molybdenum absorption from the diet is efficient (>80%), and the body content is primarily regulated via the kidneys.

There is only one recorded case of apparent molybdenum deficiency in humans, and this occurred in a subject receiving total parenteral nutrition (50 µg/d) for 18 months due to Crohn's disease (7, 8). Unconsciousness, heart disturbances, and night blindness were observed, and the symptoms disappeared after supplementation with 160 µg/d of molybdenum.

Stable isotopes have been used to investigate molybdenum metabolism in healthy men aged 22–33 years (9–12). Molybdenum absorption was efficient (about 90%) when subjects ingested diets containing five levels of the metal (ranging from 22 µg/d to 1,490 µg/d) for 24 days each. Excess molybdenum was rapidly excreted in urine, but whole-body retention was increased when the dietary level was low. Molybdenum status is difficult to determine because low plasma levels are tightly maintained by up-regulated urinary excretion in response to increased intakes (8).

Requirement and recommended intake

Adult men fed a diet with only 22 µg/d molybdenum for 102 days did not develop any symptoms of molybdenum deficiency leading Turnlund and co-workers (11) to suggest that the minimum daily requirement for this trace element is about 25 µg.

Based on these findings, the U.S. Food and Nutrition Board (13) set a Recommended Dietary Allowance (RDA) for adult men and women at 45 µg/d. The average dietary intake of molybdenum in U.S. men and women is more than twice this level.

The NNR 2004 (14) did not include recommendations for molybdenum intake. The evidence regarding molybdenum in relation to setting dietary reference values is still limited (8) and is not considered sufficient to establish requirements. Accordingly, recommendations are not given for any age group.

Upper intake levels and toxicity

The absence of toxicity symptoms in men with a daily intake of 1,490 µg molybdenum for 24 days (10) provides a working upper boundary for further studies. The U.S. Food and Nutrition Board (13) set a Tolerable

Upper Intake Level (UL) of 2 mg/d based on impaired reproduction and growth in animals. A British expert group concluded that there are insufficient data from animal and human studies to establish a Safe Upper Level for molybdenum (15). The Scientific Committee on Food (SCF) set the UL at 0.6 mg/d for adults and between 0.1 mg/d and 0.5 mg/d for children aged 1–17 years (16).

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41 Fluoride

No recommendation given due to lack of sufficient evidence

Introduction

Fluoride is found in food and drinking water either in an ionic form or bound in complexes. Fluoride has a well-documented role in the prevention and treatment of dental caries, but the mechanism is attributed to local effects on the tooth enamel surface rather than systemic effects. Fluoride is not considered essential for humans.

Dietary sources and intake

Fluoride levels in foods (except water) are generally low with a few exceptions. Fish eaten with the bones, such as canned sardines, some teas and mineral waters, and drinking water in some areas have the highest content. Little data on fluoride intake from food is available, but according to the EFSA (1) fluoride intakes from food (except for fruit juice, mineral water, and tea) for young children, older children, and adults are reported to be 0.04, 0.11, and 0.12 mg/d, respectively. Fruit juice, mineral water, and tea are estimated to contribute with 0.01 mg, 0.06 mg, and 0.26 mg fluoride, respectively. Tap water and other water sources such as mineral waters can contribute various amounts of fluoride depending on the concentration in the water. In the EFSA report, the contribution of fluoride from tap water in adults was reported to be around 0.06 mg/d at a concentration of 0.13 mg/L and about 0.5 mg/d at a concentration of 1.0 mg/L (1). Toothpaste can also contribute to the ingested fluoride, especially in small children. It is estimated that in adults <10% of the toothpaste is ingested because the spitting reflex is well developed, but the intake in children has been reported to be as high as 48% in 2 to 3 year olds, 42% in 4 year

olds, 34% in 5 year olds, and 25% in 6 year olds. In children aged 8 to 12 years, the ingestion is reported to be ~10% (2).

Physiology and metabolism

Fluoride in drinking water is effectively absorbed (>90%), but complex-bound fluoride in foods is less well absorbed. Approximately 50% of the absorbed fluoride is excreted via the kidneys, and the rest is incorporated into the bones and, in childhood, into the teeth. Thus, the main proportion of fluoride in the body is complex-bound to calcium in the skeleton and tooth tissues. These fluoride complexes can replace the hydroxyl ions in hydroxyapatite crystals – making the crystals less acid-soluble – and this was previously believed to be the basis for fluoride's ability to prevent dental caries. However, the presence of fluoride in the mouth and subsequent deposition of CaF_2 onto the tooth biofilm acts as a fluoride reservoir that can influence the balance between enamel demineralisation and remineralisation, and this is now recognized as the basis for the cariostatic effect of fluoride (3). Aside from this local effect, the biological functions of fluoride in humans remain uncertain.

Requirement and recommended intake

No recommendation for daily fluoride intake is given because it is not considered an essential trace element. This agrees with the EC Scientific Committee for Foods, which also did not set any recommended intake (4). The U.S. Institute of Medicine was unable to establish an RDA but has set an adequate intake for fluoride that is based on the observed estimated intake judged to reduce the incidence of dental caries in a group of healthy adults (5). For adults, this level was set to 3 mg/d and 4 mg/d for women and men, respectively (5).

Upper intake levels and toxicity

An intake of 2.2 g/kg bodyweight is lethal in adults. In children, 15 mg/kg bodyweight is lethal and 5 mg/kg bodyweight causes acute symptoms such as nausea, stomach pain, and vomiting. Chronic high intakes can affect skeletal mineralisation and kidney function (6). The most common side effect of high fluoride intake is enamel fluorosis or "mottled teeth". Fluorosed enamel is composed of hypomineralized sub-surface enamel

covered by well-mineralized enamel, but the exact mechanisms of dental fluorosis development have not been fully elucidated (7). High fluoride intake/exposure has been associated with effects on thyroid metabolism. However, the exposures necessary for caries prevention provided from toothpaste or drinking water have not been shown to affect thyroid function (1, 8, 9).

The EFSA (1) considered that a daily intake of up to 0.1 mg of fluoride per kg bodyweight in children up to 8 years old leads to no significant occurrence of "moderate" forms of fluorosis in permanent teeth. Based on this, a UL was set to 1.5 mg/d for children 1–3 years old, 2.5 mg/d for children 4–8 years old, 5 mg/d for children 9–14 years old, and 7 mg/d for older children and adults.

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