CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 4 **CX/NFSDU 14/36/5**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES

Thirty-sixth Session

Bali, Indonesia
24 – 28 November 2014

PROPOSED DRAFT ADDITIONAL OR REVISED NUTRIENT REFERENCE VALUES FOR LABELLING PURPOSES IN THE GUILDELINES ON NUTRITION LABELLING (other than protein)

(Prepared by an EWG Working Group led by Australia)[1]

Governments and interested international organizations are invited to submit comments at Step 3 on **Recommendations 1-13** at Step 3 in writing by email to the Secretariat, Codex Alimentarius Commission, Joint WHO/FAO Food Standards Programme, e-mail codex@fao.org with copy to the German Secretariat of the CCNFSDU, Federal Ministry of Food, Agriculture and Consumer Protection, e-mail:ccnfsdu@bmelv.bund.de by **31 October 2014.**

1 INTRODUCTION

1.1 Consideration by CCNFSDU, 2013

At its 35th session, CCNFSDU agreed to the Nutrient Reference Value – Requirement (NRV-R) for protein (paragraph 35, REP14/NFSDU, 2013) which was adopted by the Commission in 2014.

CCNFSDU also agreed to establish an electronic Working Group (eWG), chaired by Australia and working in English (paragraph 32, REP14/NFSDU) with the following Terms of Reference (TOR):

- Recommend revised or additional NRVs-R for vitamin C, iron, zinc, selenium, manganese, molybdenum and fluoride, in accordance with the revised definition of RASB (as at 35th session) and the General Principles for establishing NRVs for the general population.
- Recommend relevant supporting information for the vitamins and minerals in TOR1.
- As appropriate, recommend amendments to the General Principles arising from consideration of TOR1.

1.2 Timeframe for Revised and Additional NRVs-R

The Committee reviewed the workplan in 2013 and extended the original completion date for NRVs-R for the general population to 2016 (paragraph 33, REP14/NFSDU). The revised timeframe allows for further consideration of NRVs-R for vitamin C and six minerals for another year to 2015 if consensus on a particular NRV-R cannot be reached at this session. However, the Committee is strongly encouraged to decide the seven NRVs-R at this session, because delaying a decision would increase the workload in 2015 which is scheduled to consider NRVs-R for the next batch of 8 vitamins and minerals.

1.3 Conduct of the Electronic Working Group

In December 2013, CCNFSDU members were invited to participate in the eWG to consider NRVs-R for vitamin C and six minerals listed in the eWG's TOR1.

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[1] **Members of the EWG :** Argentina, Brazil, Canada, Chile, Costa Rica, European Union, India, Iran, Japan, Malaysia, the Netherlands, New Zealand, Peru, Thailand, Tunisia, United States of America, Federation of European Specialty Food Ingredients Industries, FoodDrink Europe, International Alliance of Dietary/Food Supplement Associations, International Council of Beverages Associations, and National Health Federation

The eWG considered two Consultation Papers circulated in February and August 2014. Responses to the first Consultation Paper were received from 20 government and 6 international non-government members and to the second Consultation Paper from 12 government and 2 international non-government members.

1.4 Definitions

The following definitions are relevant to the consideration of NRVs-R.

a) Nutrient Reference Values

Definitions of nutrient reference values (NRVs) and NRVs-R in the Codex Guidelines on Nutrition Labelling are:

> **Nutrient Reference Values (NRVs)** are a set of numerical values that are based on scientific data for purposes of nutrition labelling and relevant claims. They comprise the following two types of NRVs:
>
> **Nutrient Reference Values – Requirements (NRVs-R)** refer to NRVs that are based on levels of nutrients associated with nutrient requirements.
>
> **Nutrient Reference Values – Non-communicable Disease (NRVs-NCD)** refer to NRVs that are based on levels of nutrients associated with reduction in the risk of diet-related non-communicable diseases not including nutrient deficiency diseases.

b) Daily Intake Reference Values, INL_{98} and UL

Definitions of daily intake reference values (DIRVs), INL_{98}, and Upper level of intake (UL) in the Annex to the Codex Guidelines on Nutrition Labelling are:

> **Daily intake reference values** as used in these Principles refer to reference nutrient intake values provided by FAO/WHO or other recognized authoritative scientific bodies that may be considered in establishing an NRV based on the principles and criteria in Section 3. These values may be expressed in different ways (e.g., as a single value or range), and are applicable to the general population or to a segment of the population (e.g., recommendations for a specified age range).
>
> **Individual Nutrient Level 98 (INL_{98})** is the daily intake reference value that is estimated to meet the nutrient requirement of 98 percent of the apparently healthy individuals in a specific life stage and sex group.
>
> **Upper Level of Intake (UL)** is the maximum level of habitual intake from all sources of a nutrient or related substance judged to be unlikely to lead to adverse health effects in humans.

c) Recognized Authoritative Scientific Body (RASB)

In 2013, the Committee made a small but significant amendment (in bold) to the working definition of RASB (paragraph 31, REP14/NFSDU):

> For the purposes of establishing Codex Nutrient Reference Values, a recognized, authoritative, scientific body other than FAO and/or WHO is an organization supported by a competent national and/or regional authority(ies) that provides independent, transparent*, scientific and authoritative advice on daily intake reference values **through primary evaluation of the scientific evidence** upon request and for which such advice is recognized through its use in the development of policies in one or more countries.
>
> * In providing transparent scientific advice, the Committee would have access to what was considered by a RASB in establishing a daily intake reference value in order to understand the derivation of the value.

1.5 General Principles for Establishing NRVs-R

The *General Principles for Establishing NRVs for the General Population* (General Principles) are given in the Annex to the Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985). General principles relevant to NRVs-R are shown as follows:

GENERAL PRINCIPLES FOR ESTABLISHING NRVs-R

3.1 Selection of Suitable Data Sources to Establish NRVs

3.1.1 Relevant daily intake reference values provided by/FAO/WHO that are based on a recent review of the science should be taken into consideration as primary sources in establishing NRVs.

3.1.2 Relevant daily intake reference values that reflect recent independent review of the science, from recognized authoritative scientific bodies other than FAO/WHO could be taken into consideration. Higher priority should be given to values in which the evidence has been evaluated through a systematic review.

3.1.3 The daily intake reference values should reflect intake recommendations for the general population.

3.2 Selection of Nutrients and Appropriate Basis for NRVs

3.2.1 Selection of Nutrients and Appropriate Basis for NRVs-R

3.2.1.1 The NRVs-R should be based on Individual Nutrient Level 98 (INL_{98}). In cases where there is an absence of an established INL_{98} for a nutrient for a specific sub-group(s), it may be appropriate to consider the use of other reference values or ranges that have been established by recognized authoritative scientific bodies. The derivation of these values should be reviewed on a case-by-case basis.

3.2.1.2 The general population NRVs-R should be determined by calculating the mean values for a chosen reference population group older than 36 months. NRVs-R derived by the Codex Alimentarius Commission are based on the widest applicable age range of each of adult males and females.

3.2.1.3 For the purpose of establishing these NRVs-R, the values for pregnant and lactating women should be excluded.

3.3 Consideration of Daily Intake Reference Values for Upper Levels

The establishment of general population NRVs should also take into account daily intake reference values for upper levels established by FAO/WHO or other recognized authoritative scientific bodies where applicable (e.g., Upper Level of Intake, Acceptable Macronutrient Distribution Range).

1.6 Application of General Principles to Selection of DIRVs from Accepted RASBs

The General Principles were applied to guide the eWG's selection of candidate DIRVs for vitamin C and the six minerals as briefly described below:

GP	APPLICATION OF GPS TO SELECTION OF DIRVS FROM ACCEPTED RASBS
3.1.1	The Committee previously considered that NRVs-R derived from WHO/FAO DIRVs for: • iron and zinc would require further consideration (paragraph 91, REP13/NFSDU) • vitamin C and selenium were *potentially* unsuitable (paragraph 86, REP13/NFSDU). Reasons to find WHO/FAO DIRVs as potentially unsuitable could include more recent evidence, or improved methodology.
3.1.2	All candidate DIRVs from accepted RASBs other than WHO/FAO were reviewed and only those determined by primary evaluation of the scientific evidence were further considered.
3.1.3	All candidate DIRVs relate to the general population.
3.2.1.1	All candidate DIRVs for vitamin C, iron, zinc, selenium were classified by the source RASBs as INL_{98}; candidate DIRVs for molybdenum were classified by the source RASBs as either INL_{98} or AI; and candidate DIRVs for manganese and fluoride were classified as AI.
3.2.1.2	The male and female candidate DIRVs for 19-50 years were averaged and rounded if necessary.
3.2.1.3	No candidate DIRVs represented recommendations for pregnant or lactating women.
3.3	The ULs set by WHO/FAO and other RASBs and aspects of their derivation were taken into account.

1.7 Stepwise Process

The 2014 eWG updated the stepwise process to reflect all General Principles and to take account of CCNFSDU's previous discussion of Recommendation 3-1, CX/NFSDU 13/35/4 which considered whether DIRVs from one or more RASBs should constitute the basis of a NRV-R. The Committee previously agreed that the decision should be made on a case-by-case basis although it anticipated that the most appropriate DIRV from one RASB would be generally selected. However DIRVs could be averaged if similarly valued DIRVs from two or more RASBs based on the same physiological endpoint were supported (paragraphs 23-25 REP14/NFSDU). Also, in recognition of WHO and FAO as primary sources of DIRVs, Step 2 refers to GP 3.1.1 as well as 3.1.2. Therefore, the stepwise process is updated to reflect last year's discussion as shown below:

STEPWISE PROCESS FOR DERIVATION OF REVISED OR ADDITIONAL NRVS-R	
Step 1	Select and accept appropriate RASBs in accordance with the working definition of RASB.
Step 2	Identify DIRVs established by WHO/FAO as suitable or unsuitable and if necessary, from RASBs for the vitamins and minerals under consideration according to GPs 3.1.1 and 3.1.2.
Step 3	For each vitamin and mineral, calculate adult candidate DIRVs from WHO/FAO and if necessary, from each accepted RASB in accordance with GPs 3.2.1, 3.2.1.1, 3.2.1.2 and 3.2.1.3.
Step 4	Compare each candidate DIRV with ULs for young children as a conservative response to GP 3.3 and set aside those DIRVs found to be unsuitable.
Step 5a	From consideration of the differences between suitable candidate DIRVs, recommend the most appropriate NRV-R
OR	
Step 5b	From consideration of the differences between highly similar and suitable candidate DIRVs, average the DIRVs to produce a representative NRV-R for recommendation to the CCNFSDU.

2 PRELIMINARY CONSIDERATIONS

2.1 Nominated RASBs

The 2014 eWG accepted the first five RASBs listed in the table below because they satisfied the working definition revised by the Committee in 2013 which added that DIRVs should be established through primary evaluation. The eWG was invited to respond to a final call for RASB nominations by submitting details of other RASBs that met the revised working definition. Although several additional scientific bodies were nominated, only the nomination of the Nordic Council of Ministers was accompanied by appropriate documentation. The Nordic Council was accepted by the eWG and therefore six RASBs and WHO/FAO are proposed as the source of DIRVs for NRVs-R. The details and supporting documentation for the recommended six RASBs are given in Attachment 1.

Scientific bodies nominated as RASB	**Nominating government or authority**
European Food Safety Authority (EFSA)	European Union
Institute of Medicine (IOM)	United States of America; Canada
International Zinc Nutrition Consultative Group (IZiNCG)	Thailand; UNICEF
National Health and Medical Research Council & New Zealand Ministry of Health (NHMRC/MOH)	Australia; New Zealand
National Institute of Health and Nutrition (NIHN)	Japan
Nordic Council of Ministers	The Netherlands

RECOMMENDATION 1 – RASBs

That CCNFSDU accepts the six listed scientific bodies as RASBs in accordance with GP 3.1.2:

- European Food Safety Authority (EFSA)
- United States Institute of Medicine (IOM)
- Australian National Health and Medical Research Council & New Zealand Ministry of Health (NHMRC/MOH)
- Japanese National Institute of Health and Nutrition (NIHN)
- International Zinc Nutrition Consultative Group (IZiNCG)
- Nordic Council of Ministers (Nordic countries)

2.2 Further Consideration of General Principle 3.2.1.1 (TOR 3)

Before considering the recommendations for NRVs-R, it is important to clarify General Principle 3.2.1.1 (Section 1.5) regarding the case where candidate DIRVs are a mix of INL_{98} and AI. As currently written, GP 3.2.1.1 apparently prefers an older INL_{98} to a more recent AI.

In its consideration of molybdenum, the eWG noted that some RASBs established DIRVs according to similar evidence but judged differently as to whether or not the evidence was sufficient to establish an INL_{98}. GP 3.2.1.1 does not address this situation but assumes that RASBs apply consistent criteria to the determination of an INL_{98} or AI. WHO/FAO observed in 2011 (Attachment 4, CX/NFSDU 12/34/8) in relation to the DIRVs in their report, *Review of existing daily vitamin and mineral intake reference values* (CX/NFSDU 11/33/4) that:

> "Challenges arose because of a lack of [defined] terminology among the various countries. Many countries and scientific bodies use different terms to describe the same concept. Also many countries and scientific bodies use the same term to describe different concepts. A weakness of this review is that, in order to classify and present the data, terms with varied definitions were categorized into one of three conditions. For the purposes of this review, values were categorized as either an INL_{98}, AI or unclear".

The eWG assessed several suggestions for clarifying GP 3.2.1.1. Members supported consideration of AIs providing they were more recently established than a candidate INL_{98} since the strength of evidence used to establish an INL_{98} can vary greatly among RASBs and could be similar to that used to set an AI. Most members favoured the following amendment as the recommendation as it enables a mix of older INL_{98} and more recent AIs to be considered on a case by case basis:

GP 3.2.1.1 The NRVs-R should be based on Individual Nutrient Level 98 (INL_{98}). In **certain** cases where there is an absence of**, or** an **older,** established INL_{98} for a nutrient for a specific sub-group(s), it may be **more** appropriate to consider the use of other **daily intake** reference values or ranges that have been **more recently** established by recognized authoritative scientific bodies. The derivation of these values should be reviewed on a case-by-case basis

RECOMMENDATION 2 – Clarification of GP 3.2.1.1

That CCNFSDU agrees to the following clarification of GP 3.2.1.1:

> **GP 3.2.1.1** The NRVs-R should be based on Individual Nutrient Level 98 (INL_{98}). In certain cases where there is an absence of, or an older, established INL_{98} for a nutrient for a specific sub-group(s), it may be more appropriate to consider the use of other daily intake reference values or ranges that have been more recently established by recognized authoritative scientific bodies. The derivation of these values should be reviewed on a case-by-case basis.

2.3 Upper Levels of Intake

The eWG considered the exceedance of some candidate DIRVs above an Upper Level of Intake (UL). Although General Principle 3.3 does not specify the UL age groups that should be selected, the eWG's current practice applies ULs for ages 1–6 or 1–8 years that are established by WHO (1996), IOM, EFSA and IZiNCG as shown in the following table. The individual ULs that are exceeded by at least one candidate DIRV are marked as bold- underline in the following table.

Vitamins and Minerals	UL 1-3/4-8 yrs; IOM (2006)	UL 1-3/4-6 yrs; EFSA (2006)	UL, 1-6 yrs WHO (1996)	NOAEL/UF 1.5 1-3/4-8 yrs; IZiNCG (2004)
Vitamin C (mg)	400/650	ND/ND	NA	
Iron (mg) (unknown % absorption)	40/40	ND/ND		
Zinc (mg) (unknown % absorption)	**7/12**	**7/10**	23	**8/**14
Selenium (µg)	90/150	**60**/90	ND	
Molybdenum (µg)	300/600	100/200	ND	
Manganese (mg)	**2/3**	ND/ND	ND	
Fluoride (mg)	**1.3/2.2****	**1.5/2.5****	**1.5** (3 yrs only)	

NA = Not applicable ND = not determined due to insufficient information

* NOAEL = No Observed Adverse Effect Level. UF = Uncertainty Factor

** The UL is based on 0.1 mg/kg/day and the difference between IOM and EFSA is due to selection of different reference body weights

Comparison of candidate DIRVs with ULs for children needs to be carefully considered particularly when information on requirements, absorption, metabolism and excretion of nutrients in children is extremely limited. The ULs for young children are usually extrapolated from ULs for other age groups and therefore these values reflect a higher degree of uncertainty. To assist discussion, the mean adult INL_{98} values were compared with the young child UL values *within* jurisdiction. Very similar results were found as for this project. For example, the IOM mean adult DIRV for manganese is 2.1 mg (AI) and UL 1–3 years is 2 mg. For selenium, the EFSA UL for young children, 1–3 years is 60 µg which is *below* the draft adult AI of 70 µg.

A stronger case for taking account of the UL is made when several RASBs establish a UL and that UL takes account of human evidence. For example, most candidate zinc DIRVs exceed the EFSA UL but the % dietary absorption applied to that UL is unknown. SCF/EFSA (2006) states that "the 97.5 percentile of total zinc intakes for all age groups are close to the ULs, which, in the view of the Committee, are not a matter of concern". IZiNCG (2004) refers to data from US NHANES III and comments that the dietary intake of many US children 1-3 years would have exceeded the IOM UL for that age group. Also, "given the unlikelihood that the described toxic effects of excessive zinc intakes occur in such a large proportion of children from this relatively healthy, US population, the degree of confidence in the IOM UL is relatively low".

To assist CCNFSDU's consideration of ULs, the basis for the extrapolation of the bold- underlined young age ULs in the previous table is shown below for zinc, selenium, manganese and fluoride. Taking into account the uncertainties associated with ULs for young children including from extrapolation, as well as the very conservative nature of a comparison with ULs for very young children, it is proposed that all candidate DIRVs continue to be considered.

MINERAL	RASB	UL FOR YOUNG CHILDREN
Zinc	**IOM**	No adverse effects in children could be found. UL based on a study of zinc supplemented formula for young infants (UF = 1) adjusted upwards on the basis of relative body weight. UL child = UL infant x Wt child /Wt infant.
	EFSA	There are no data on adverse effects of zinc intakes on children; there are no data to indicate that children are more susceptible to adverse effects of zinc. The UL is extrapolated from adults to children on a surface area (body weight$^{0.75}$) basis.
	WHO	Based on adverse nutrient interaction. Extrapolated from adult Zn $^{tox}_{plmax}$ using differences in basal metabolic rate.
	IZiNCG	NOAEL was set at 1 mg/kg/day based on a study of zinc supplementation of infants 6 months of age and UF of 1.5 applied. Adjusted to Reference body weight of 12 kg (1–3 yrs).
Selenium	EFSA	There are no data to support a derivation of an UL for children. The data on mottled enamel do not allow a NOAEL to be set for children. On the other hand, there are no reports indicating that children are more susceptible to adverse effects from selenium. Hence, it seems appropriate to extrapolate the UL from adults to children on a body weight basis.
Manganese	IOM	Extrapolated from adults based on high serum manganese concentrations. No reports of toxicity in children. 99th percentile intake 4–8 yrs is 4.1 mg. Adult UL adjusted downward on the basis of relative body weight and rounded down. UL child = UL adult x Wt child /Wt adult.
Fluoride	IOM	Based on LOAEL of 0.1 mg/kg/day for moderate enamel fluorosis and UF of 1.0 for up to 8 years of age applied to reference body weights.
	EFSA	The occurrence of moderate enamel fluorosis was <5% in populations at fluoride intakes of 0.1 mg/kg body weight/day. UF is 1.0 because it is derived from population studies in the susceptible group. For children up to the age of 8 years this intake level of 0.1 mg/kg body weight/day calculated on a body weight basis is proposed as the UL.
	WHO	In the absence of malnutrition, dental mottling has been reported very occasionally when the fluoride content of drinking-water exceeds 0.8 mg/L. However, it is rarely significant from the age of 4 years onwards unless fluoride intake from the diet plus drinking water exceeds 2 mg/L or the intake from water alone exceeds 1.5 mg/day. Total intakes at 1, 2 and 3 years of age should, if possible, be limited to 0.5, 1.0 and 1.5 mg/day respectively.

2.4 Reference Adult Body Weights

Based on the CCNFDSU's 2013 consideration of protein NRV-R, the reference mean adult body weight is currently 60 kg (FAO, 1988) (paragraph 26, REP14/NFSDU). The national adult body weights from CX/NFSDU 13/35/4 plus those from the Nordic Council are given in Table 2B, Attachment 2 and referenced in Attachment 3.

3 CONSIDERATION OF NRVS-R

3.1 Context for NRVs-R in Codex Guidelines

The eWG noted the two Codex Guidelines that provide the context for NRVs-R. These Guidelines and relevant provisions are:

Guidelines on Nutrition Labelling (CAC/GL 2-1985)

> 3.2.6.1: Only vitamins and minerals for which recommended intakes have been established and/or which are of nutrition importance in the country concerned should also be declared.

Guidelines for Vitamin and Mineral Food Supplements (CAC/GL 55-2005)

> 3.1.1 Vitamin and mineral food supplements should contain vitamins/provitamins and minerals whose nutritional value for human beings has been proven by scientific data and whose status as vitamins and minerals is recognised by FAO and WHO.

5.5 Information on vitamins and minerals should also be expressed as a percentage of the nutrient reference values mentioned, as the case may be, in the Guidelines on Nutrition Labelling.

The status of nutrients as vitamins and minerals is internationally recognised by WHO/FAO (2004), WHO/FAO (2006) and WHO (1996) (trace elements). The following trace elements were classified by WHO (2006) as essential: iodine, selenium, zinc, copper, molybdenum and chromium; as probably essential: manganese and four others; and as potentially toxic elements, some possibly with essential functions: fluoride and 7 others.

In assessing candidate DIRVs for molybdenum, manganese and fluoride, the eWG ranked the option to not establish a DIRV for these minerals as their second preference. Members who chose this option were concerned about the limited evidence for these DIRVs and questioned the need to establish NRVs-R for these minerals. Basing international NRVs-R on DIRVs with limited evidence might imply equivalent importance and rigour of evidence with other NRVs-R whose nutrients were of greater public health importance. If WHO/FAO had not established a DIRV, one of these members urged a pragmatic approach until further evidence was available including giving consideration to the need for international harmonisation.

3.2 Recommended NRVs-R (TOR 1)

In considering the recommendations for the NRVs-R, the eWG updated the DIRVs and supporting information previously listed in CX/NFSDU 13/35/4 in accordance with the revised working definition of RASB and information from the new RASB, the Nordic Council of Ministers. With the need for DIRVs to be established through primary evaluation, some DIRVs previously shown in 2013 were reclassified in Table 2A, Attachment 2 as NPE (not derived by primary evaluation) and omitted from further consideration.

The following Sections 3.3–3.5; 3.7–3.10 present the recommendations for NRVs-R and candidate DIRVs for vitamin C and six minerals listed in TOR 1. After two rounds of eWG consultation, the two most preferred candidate DIRVs for each nutrient were ranked according to the relative level of support for the first and second preference: Very strong majority (≥3:1); Strong majority (2:1–<3:1); Majority (1.2:1–<2:1) and Narrow majority(1:1–<1.2:1). For example, a very strong majority indicates that at least 3 times as many members preferred candidate DIRV1 than candidate DIRV2. These descriptors are used in the following Sections to indicate the eWG's level of support for the highest ranked candidate DIRV as the recommended NRV-R.

The scientific basis of all candidate DIRVs and two draft EFSA opinions are summarised in Attachment 2. All references related to candidate DIRVs, ULs and supplementary information is given in Attachment 3.

3.3 Vitamin C NRV-R

eWG preferences	**RASB**	**Candidate DIRV** (All INL_{98})
	IOM (United States & Canada)	83 mg
2.	EFSA (European Union)	103 mg
	NIHN (Japan)	100 mg
	Nordic Council of Ministers	75 mg
	WHO/FAO	45 mg
1. Majority	Average of EFSA, NIHN	100 + 103 = 101.5 rounded down to 100 mg
	Average of IOM, EFSA, NIHN	83 + 100 + 103 = 95 rounded up to 100 mg
	Current NRV-R	*60 mg*

Most of the eWG preferred candidate DIRVs in the range 80-105 mg. The eWG considered the physiological endpoint of near saturation of body stores to be the most relevant physiological endpoint as selected by EFSA as maximal neutrophil concentrations and by NIHN as optimal antioxidant activity in plasma (both 50 µg/L). These were also the two most recent reviews. According to Step 5b, these two candidate DIRVs were averaged to 101.5 mg and rounded down to 100 mg. All candidate DIRVs were below the UL.

RECOMMENDATION 3 – NRV-R for Vitamin C

That CCNFSDU agrees to revise the NRV-R for vitamin C from 60 mg to 100 mg.

3.4 Iron NRV-R

eWG preferences	RASB	**Candidate DIRV** (All INL_{98})
	IOM (United States & Canada)	13 mg (18% absorption)
	NIHN (Japan)	9 mg (15% absorption)
1. (15% & 10%) Very strong majority 2. (15% only)	WHO/FAO	14 mg (15% absorption); 22 mg (10% absorption)
	Nordic Council of Ministers	12 mg (15% absorption)
	Current NRV-R	*14 mg*

In 2012, the Committee agreed that the issues related to the NRV-R for iron (including the need for multiple NRVs-R) would require further consideration (paragraph 91, REP13/NFSDU). The 2013 eWG considered the matter of one or more NRVs-R and most members supported more than one NRV-R according to % absorption, although other members were concerned about the paucity of data for lower % absorptions and preferred a single NRV-R.

The 2014 eWG continued to strongly prefer DIRVs from WHO/FAO as they were internationally derived and consistent with single % absorption DIRVs more recently derived by other RASBs. Two of the four possible WHO/FAO % absorptions of 15% and 10% were selected because they represented likely dietary absorptions in many countries. WHO/FAO (2004) states "..for developing countries, it may be more realistic to use the figure of 5% and 10%. In populations consuming more Western-type diets, two levels would be appropriate –12% and 15%– depending mainly on meat intake". Very strong preference was expressed for these two DIRVs. All candidate DIRVs were below the UL.

RECOMMENDATION 4 – NRV-R for Iron

That CCNFSDU agrees to:

A Modify the NRV-R for iron to refer to % dietary absorption.

B Revise the NRV-R from 14 mg to 14 mg (15% dietary absorption) and 22 mg (10% dietary absorption).

3.5 Zinc NRV-R

eWG preferences	RASB	**Candidate DIRV** (All INL_{98})
	IOM (United States & Canada)	10 mg (M 41; F 48% absorption)
	NIHN (Japan)	11 mg
1. (30% & 22%) Very strong majority	IZiNCG	11 mg (30% absorption; phytate:zinc molar ratio 4-18) 14 mg (22% absorption; phytate:zinc molar ratio 19-30)
	Nordic Council of Ministers	8 mg (valid for mixed animal/vegetable diet)
	WHO/FAO	6 mg (30% absorption); 12 mg (15% absorption)
	Current NRV-R	*15 mg*
2.	Await EFSA final opinion (EU)	Draft INL_{98} 8.5 –14.5 mg; (derived) phytate: zinc molar ratio (3.5– 8.2)

In 2012, the Committee agreed that the issues relating to the NRV-R for zinc would require further consideration (paragraph 91, REP13/NFSDU). The 2013 eWG considered the matter of one or more NRVs-R and a majority of members supported more than one NRV-R according to % absorption, although some other members were concerned about the paucity of data for lower % absorptions and preferred a single NRV-R. One member preferred different values for men and women.

The 2014 eWG considered the candidate DIRVs and noted the draft EFSA opinion which may be adopted prior to this session of CCNFSDU. EFSA's draft opinion proposes four adult Population Reference Intakes (PRI) (equivalent to INL_{98}) in the range 8.5 –14.5 mg according to four levels of dietary phytate intake observed in European populations. Attachments 2 and 3 provide further details including the eWG derivation of phytate:zinc molar ratios for the PRIs.

The eWG preferred the two candidate DIRVs from IZiNCG as they were internationally derived and had updated the DIRV recommendations of IOM and WHO/FAO. IZiNCG revised the factorial contribution to endogenous zinc losses for men and women from more studies of the same methodologic type than IOM or WHO/FAO. In its assessment of % dietary absorption, IZiNCG included total diet studies only (not single meal studies as included by WHO/FAO), and excluded semi-purified formula diets likely having a very low phytate: zinc molar ratio similar to animal foods (as included by IOM), or diets containing added zinc. One eWG member noted that that IZiNCG DIRVs are easier for countries to interpret as they are based on % dietary absorption, phytate:zinc molar ratios and dietary descriptions and that national phytate intakes may not always be available. Also, no matter which candidate DIRVs are selected, the UL for young children is likely to be about the same magnitude, as discussed in Section 2.3.

RECOMMENDATION 5 – NRV-R for Zinc

That CCNFSDU agrees to:

A Modify the NRV-R for zinc to refer to % dietary absorption.

B Revise the NRV-R from 15 mg to 11 mg (30% dietary absorption) and 14 mg (22% dietary absorption).

3.6 Dietary Descriptions and Footnote for Iron and/or Zinc (TOR 2)

The 2014 eWG further considered dietary descriptions in support of NRVs-R for iron and zinc and the footnote related to these NRVs-R. Dietary descriptions from WHO/FAO (iron), and IZiNCG (zinc) were considered. The presented dietary descriptions relate to the recommended NRVs-R for iron and zinc in Sections 3.4 and 3.5 respectively.

3.6.1 Iron dietary description

The eWG considered the dietary descriptions given in Table 3.3 and the footnote to Table 7.2 of WHO/FAO (2006) that corresponded to 15% and 10% dietary absorptions as follows:

Table 3.3 (WHO/FAO (2006))	% absorption	Footnote to Table 7.2 WHO/FAO (2006))	% absorption
Diversified diet containing greater amounts of meat, fish, poultry and/or foods high in ascorbic acid	High >15	For diets rich in vitamin C and animal protein	15
Diet of cereals, roots or tubers, with some foods of animal origin (meat, fish or poultry) and/or containing some ascorbic acid (from fruits and vegetables).	Intermediate 10–15	For diets rich in cereals but including sources of vitamin C	10

The eWG considered that these dietary descriptions could be better expressed in food terms by interpreting *foods of animal origin* as *meat, fish, poultry*; and *ascorbic acid* as *fruit and vegetables;* and *greater amounts of* as *rich in* as shown:

Dietary descriptions adapted from WHO/FAO (2006)	% absorption
Diets rich in meat fish, poultry, and/or rich in fruit and vegetables	15
Diets rich in cereals, roots or tubers, with some meat, fish, poultry and/or containing some fruit and vegetables.	10

RECOMMENDATION 6 – Dietary Description for Iron

Subject to agreement to Recommendation 4, that CCNFSDU agrees to the dietary descriptions adapted from WHO/FAO (2006) that correspond to the selected NRVs-R.

3.6.2 Zinc dietary description

The IZiNCG dietary descriptions and % absorption (phytate:zinc molar ratio) corresponding to the recommended NRVs-R are as follows.

Dietary description	% absorption (phytate:zinc molar ratio)
Mixed diets, and lacto-ovo vegetarian diets that are not based on unrefined cereal grains or high extraction rate (>90%) flours	30% (4-18);
Cereal-based diets, with >50% energy intake from cereal grains or legumes and negligible intake of animal protein	22% (19-30)

RECOMMENDATION 7 – Dietary Description for Zinc

Subject to agreement to Recommendation 5, that CCNFSDU agrees to the dietary descriptions from IZiNCG that correspond to the selected NRVs-R.

3.6.3 Footnote to NRVs-R for iron and zinc

This Section is relevant only if the CCNFSDU agrees to NRVs-R of differing % absorptions for iron and/or zinc.

In 2012, the Committee agreed that the proposed deletion of the second sentence in Footnote 9 for iron and zinc in CX/NFSU 12/34/8 would require further consideration (paragraph 100, REP13/NFSDU). The 2013 eWG agreed that the second sentence referring to further guidance from WHO/FAO (2004) could be deleted because reference to particular publications could become outdated. Also, since the Committee agreed in 2013 to replace *bioavailability* with *dietary absorption*, the footnote was revised to:

> Countries should determine the appropriate NRV that best represents the dietary absorption of iron and zinc in national diets.

The 2014 eWG generally agreed to this change. However, some members considered that the text could be misinterpreted as limiting the choice of an NRV-R to either of the stated % dietary absorptions. This is not the intent of the preamble in the Annex to the Guidelines on Nutrition Labelling which states that *Governments may establish reference values for food labelling that take into account country or specific factors that affect nutrient absorption, utilization, or requirements*. The footnote was therefore further revised to reflect the intent of the Annex preamble and to replace *countries* with *national authorities* consistent with the use of that term in other footnotes to the Guidelines. As the footnote would be attached to the iron and/or zinc NRVs-R, there is no need to state iron and zinc in the footnote itself.

> **National authorities** ~~Countries~~ should determine ~~the~~ **an** appropriate NRV-R that best represents the dietary absorption ~~of iron and zinc in~~ **from** national diets.

RECOMMENDATION 8 – Footnote for Iron and/or Zinc

Subject to agreement to Recommendations 4A and 5A, that CCNFSDU agrees to the following footnote attached to the NRV(s)-R for iron and zinc.

> National authorities should determine an appropriate NRV-R that best represents the dietary absorption from national diets.

3.7 Selenium NRV-R

eWG preferences	RASB	**Candidate DIRV** (All INL_{98})
	IOM (United States & Canada)	55 µg
	NHRMC/MOH (Australia & New Zealand)	65 µg
	NIHN (Japan)	28 µg
	Nordic Council of Ministers	55 µg
1. Narrow majority	Average of IOM, NHMRC/MOH	[55 + 65] = 60
	Average of IOM, NHMRC/MOH, Nordic	[55 + 55 + 65] = 58
	WHO/FAO	30 µg
	Current NRV-R	*Value to be established*
2.	Await EFSA final opinion (EU)	Draft AI 70 µg

The 2014 eWG considered the candidate DIRVs and noted the draft EFSA opinion which may be adopted prior to this session of CCNFSDU. The preferred physiological endpoint was maximal plasma selenoprotein activity as selected by the Nordic Council of Ministers, or maximal glutathione peroxidase (GP_X) as selected by IOM and NHMRC/MOH. Most candidate DIRVs were below or equal to the lowest UL for 1–3 years (see discussion in Section 2.3).

The eWG very strongly supported the five options for candidate DIRVs in the range 55–65 µg. One member noted that the preferred candidate DIRV (60 µg) was nearly the same as averaging the two most recent DIRVs based on maximal saturation of SEPP1 selenoproteins (Nordic INL_{98}; Draft EFSA AI) or all three DIRVs (INL_{98}) based on maximal saturation of GP_X and SEPP1 selenoproteins (IOM, NHMRC/MOH, Nordic) or all four DIRVs based on maximal saturation of GP_X and SEPP1 selenoproteins (IOM, NHMRC/MOH, Nordic INL_{98}; Draft EFSA AI) which all resulted in a value close to 60 µg.

RECOMMENDATION 9 – NRV-R for Selenium

That CCNFSDU agrees to establish the NRV-R for selenium at 60 µg.

3.8 Molybdenum NRV-R

This discussion assumes that the CCNFSDU agreed to Recommendation 2 on GP 3.2.1.1. The eWG noted that candidate DIRVs for molybdenum are a mix of older INL_{98} (same study, differences in reference body weights) and a more recent AI based on observed dietary intake. All AIs based on national or regional dietary intakes are considered to be primarily evaluated.

eWG preferences	RASB	INL_{98} or AI	Candidate DIRV
1. Majority	IOM (United States & Canada)	INL_{98}	45 µg
	EFSA (European Union)	AI	65 µg
	NIHN (Japan)	INL_{98}	26 µg
2.	Do not establish NRV-R		

A majority of the eWG preferred the IOM DIRV. One member noted that the average of all three DIRVs was equal to the IOM DIRV. As mentioned in Section 3.1, some members considered that it was unnecessary to establish an NRV-R for molybdenum given the paucity of data available, or given that molybdenum deficiency in otherwise healthy humans had not been observed and there are no biomarkers for molybdenum status. All candidate DIRVs were below the UL.

RECOMMENDATION 10 – NRV-R for Molybdenum

That CCNFSDU agrees to establish the NRV-R for molybdenum at 45 µg.

3.9 Manganese NRV-R

For manganese, all RASBs consider there is insufficient evidence to establish an INL_{98} and all candidate DIRVs are AIs based on respective population dietary intake. As these AIs were based on national or regional dietary intakes, they were considered to be primarily evaluated.

eWG preferences	RASB	**Candidate DIRV** (All AI)
	IOM (United States & Canada)	2.1 mg
	EFSA (European Union)	3.0 mg
	NHMRC/MOH (Australia & New Zealand)	5.3 mg
	NIHN (Japan)	3.75 mg
1. Majority	Average of IOM, EFSA, NHMRC/MOH and NIHN and round down	= 3.5 rounded down to 3 mg
2.	Do not establish NRV-R	

A majority of eWG members preferred to average all DIRVs, given the regional representation. However, some members considered that it was unnecessary to establish an NRV-R given the paucity of scientific data available. Noting the uncertainty surrounding the UL set by only one of the two RASBs, but also noting concerns about exceedance of the UL, it is recommended that the averaged result could be rounded down to the nearest whole number.

RECOMMENDATION 11 – NRV-R for Manganese

That CCNFSDU agrees to establish an NRV-R for manganese at 3 mg.

3.10 Fluoride NRV-R

RASB	**Candidate DIRV** (All AI)
IOM (United States & Canada)	3.5 mg
EFSA (European Union)	3.2 mg

Both RASBs set AIs based on the same evidence for protection against dental caries and the AIs differ only by the application of respective reference body weights (Table 2B, Attachment 2). The eWG noted that the physiological endpoints of these candidate DIRVs did not relate to nutritional requirement but to the public health significance of fluoride in contributing to the prevention of dental caries. Internationally, WHO (2012) states that 60-90% of schoolchildren and nearly 100% of adults worldwide have dental cavities.

Nearly all eWG members considered that there was no nutritional basis for a NRV-R to be established and a majority supported suggesting to CCNFSDU that it may wish to consider a NRV-NCD for fluoride. A small number of members did not support setting any NRV if fluorosis was a public health concern.

RECOMMENDATION 12 – NRV-R for Fluoride

That CCNFSDU agrees that no NRV-R for fluoride should be established.

4 WORKING DEFINITION OF RASB (TOR 3)

After the CCNFSDU revised the working definition in 2013 to refer to *primary evaluation* (paragraphs 28-31, REP14/NFSDU), (Section 1.4c), the eWG further considered the meaning of that term. It was agreed that *primary evaluation* could mean that key components of the derivation of DIRVs were independently assessed by RASBs. Such an interpretation would not preclude different RASBs independently substantiating and concluding the same intermediate value(s), especially when the evidence base was limited. Also, AIs based on national or regional dietary intakes were considered to be primarily evaluated.

On the basis of this consideration, nearly all eWG members supported further amendment of the revised 2013 working definition by adding a second footnote to explain the intended meaning of *primary evaluation*.

Proposed second footnote to working definition of RASB

> For the purposes of establishing Codex Nutrient Reference Values, a recognized, authoritative, scientific body other than FAO and/or WHO is an organization supported by a competent national and/or regional authority(ies) that provides independent, transparent*, scientific and authoritative advice on daily intake reference values through primary evaluation** of the scientific evidence upon request and for which such advice is recognized through its use in the development of policies in one or more countries.
>
> * In providing transparent scientific advice, the Committee would have access to what was considered by a RASB in establishing a daily intake reference value in order to understand the derivation of the value.
>
> **** Primary evaluation involves a review and interpretation of the scientific evidence to develop daily intake reference values, rather than the adoption of advice from another RASB.**

RECOMMENDATION 13 – Further Amend Working Definition of RASB

That CCNFSDU agrees to add a second **footnote to the working definition of RASB in Section 1.4c to explain the term *primary evaluation*:

**** Primary evaluation involves a review and interpretation of the scientific evidence to develop daily intake reference values, rather than the adoption of advice from another RASB.**

ATTACHMENT 1

SUBSTANTIATION OF NOMINATED RASBS

Table 1A: United States & Canada; European Union

RASB	**Institute of Medicine of the National Academies of Sciences (IOM)**	**European Food Safety Authority (EFSA):**
1) Supported by one or more government(s) or competent national or regional authorities.	In 1995, the Food and Nutrition Board of the IOM, with support from the governments of Canada and the U.S., established the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRIs) to oversee the development of DRIs for nutrients. To date, this comprehensive effort has resulted in a series of DRI reports published between 1997 and 2010	The European Food Safety Authority was legally established by a European Parliament and Council Regulation No178/2002. Adopted on 28 January 2002, the Regulation laid down the basic principles and requirements of food law. It also stipulated that EFSA should be an independent scientific source of advice, information and risk communication in the areas of food and feed safety. The risk assessment and risk communication work carried out by EFSA is underpinned by strict legal criteria. EFSA has its own legal personality and while funded from the Community budget, it operates independently of the community institutions such as the European Commission and the Parliament. It is not therefore managed by the European Commission but by an Executive Director, who in turn is answerable to an independent Management Board.
2) Provides independent and transparent* authoritative scientific advice on DIRVs upon request**.** **In providing transparent scientific advice, The Committee would have access to what was considered by a RASB in establishing a daily intake reference values in order to understand the derivation of the value.*	**a) *Independent* authoritative scientific advice.** **T**he IOM is an independent, nonprofit organization established in 1970 as a branch of the National Academy of Sciences that works outside of government to provide unbiased and authoritative advice to decision makers and the public. About IOM page. Institute of Medicine Web Site. http://www.iom.edu/About-IOM.aspx The IOM applies a rigorous research process in which committee members are carefully selected to ensure the necessary expertise and to avoid conflicts of interest IOM Study Process page. Institute of Medicine Web Site. http://www.iom.edu/About-IOM/Study-Process.aspx	It provides independent and transparent authoritative scientific advice on daily intake reference values upon request. The European Food Safety Authority (EFSA) is an independent European agency funded by the EU budget that operates separately from the European Commission, European Parliament and EU Member States. In the European food safety system, risk assessment is done independently from risk management. As the risk assessor, EFSA produces scientific opinions and advice to provide a sound foundation for European policies and legislation and to support the European Commission, European Parliament and EU Member States in taking effective and timely risk management decisions. Since its creation, EFSA has established key operating principles and rules which have been adopted by its Management Board. They include a commitment to openness and transparency in all of the Authority's work. In addition the Authority is bound by European Union legislation on issues such as public access to documents. In accordance with its Founding Regulation, EFSA is legally obliged to publish on its website outcomes of its scientific work as well as main management documentation such as budgets, accounts and contracts. Most importantly, all of EFSA's activities are guided by a set of core values.

RASB	Institute of Medicine of the National Academies of Sciences (IOM)	European Food Safety Authority (EFSA):
	The committees work independently to come to consensus on questions raised, with information gathered from many sources in public meetings. The IOM study process involves checks and balances at every step to protect the integrity of its reports. **b) *Transparent* authoritative scientific advice.** The authoritative scientific advice provided by the IOM is transparent. The full content of each IOM report on Dietary Reference Intakes is available at no charge at the website below. In these reports, the Committee would have access to what was considered by the IOM in establishing daily intake reference values, and be able to understand the derivation of the values. **About reports page:** http://www.iom.edu/Reports.aspx?page=1&Series=%7b508F5CFF-EE88-4FF6-92BF-8D6CAB46F52E%7d	These are: excellence in science, independence, openness and transparency, and responsiveness. In developing its scientific opinions, EFSA follows a workflow that runs from the moment EFSA receives a request for scientific advice or initiates its own activity to the moment it publishes and communicates its scientific findings. EFSA has developed a comprehensive body of good risk assessment practices to guide its Scientific Panel and Committee experts to help ensure EFSA opinions respect the highest scientific standards. EFSA implements a quality assurance system to continually review and strengthen the quality of its scientific work. http://www.efsa.europa.eu/en/efsahow/workflow.htm http://www.efsa.europa.eu/en/efsahow/rapractice.htm With respect to dietary reference values, a process of endorsing a draft scientific opinion has been established; performing a public consultation for at least 6 weeks, considering relevant comments received and modifying the opinion accordingly, finally adoption of the opinion together with a technical report on how the comments received were dealt with. EFSA's role is to assess and communicate on all risks associated with the food chain. Since EFSA's advice serves to inform the policies and decisions of risk managers, a large part of EFSA's work is undertaken in response to specific requests for scientific advice. Requests for scientific assessments are received from the European Commission, the European Parliament and EU Member States. EFSA also undertakes scientific work on its own initiative, so-called self-tasking. EFSA's remit covers food and feed safety, nutrition, animal health and welfare, plant protection and plant health. In carrying out its work, EFSA also considers the possible impact of the food chain on the biodiversity of plant and animal habitats. The Authority performs environmental risk assessments of genetically modified crops, pesticides, feed additives, and plant pests. In all these fields, EFSA's most critical commitment is to provide objective and independent science-based advice and clear communication grounded in the most up-to-date scientific information and knowledge.

RASB	Institute of Medicine of the National Academies of Sciences (IOM)	European Food Safety Authority (EFSA):
3) Is one whose advice on DIRVs is recognised through use in policy development in one or more countries.	The IOM Dietary Reference Intakes provide the scientific basis for dietary guidelines in both the U.S. and Canada, and have been considered in the development of Codex and other international nutrition texts. In the U.S., the IOM Dietary Reference Intakes are used to develop policies in many areas including food labelling and food fortification, evaluation of food assistance programs, and food planning and procurement. http://www.iom.edu/Reports/2000/Dietary-Reference-Intakes-Applications-in-Dietary-Assessment.aspx	EFSA's independent scientific advice underpins the European food safety system. Accordingly, EFSA's advice frequently supports the risk management and policy-making processes. These may involve the process of adopting or revising European legislation on food or feed safety, deciding whether to approve regulated substances such as pesticides and food additives, or, developing new regulatory frameworks and policies for instance in the field of nutrition. EFSA is not involved in these management processes, but its independent advice gives them a solid scientific foundation. In the Regulation No178/2002, the responsibility for risk assessment is clearly separated from that of risk management. While EFSA advises on possible risk related to food safety, the responsibility for risk management lies with the EU institutions (European Commission, European Parliament and the Council, i.e. EU Member States). It is the role of the EU institutions, taking into account EFSA's advice as well as other considerations, to propose and adopt legislation as well as regulatory and control measures when and where required.

Table 1B: Japan; Nordic Countries

RASB	National Institute of Health and Nutrition (NHIN)	Nordic Council of Ministers
1) Supported by one or more government(s) or competent national or regional authorities.	The cabinet ministers affiliated with NIHN are the Ministry of Health, Labour and Welfare and the Consumer Affairs Agency, both belonging to the government of Japan. A part of research funding and administrative budget have been provided by the government of Japan.	The Nordic Council of Ministers funded the effort behind the Nordic Nutrition Recommendations 2012 (NNR). The NNR serves as the main reference point for the various national nutrition recommendations in the Nordic countries.
2) Provides independent and transparent* authoritative scientific advice on DIRVs upon request.	NIHN became Incorporated Administrative Agency in 2001 and has been collecting the basic data necessary to establish the DRIs for Japanese, which are the basic data for NRVs. The institute also conducts research to generate evidence for DRIs for Japanese, and undertakes practical research on its application.	In the production process of the NNR, more than 100 scientific experts were involved. Existing scientific evidence has been reviewed and systematic reviews were conducted by the experts. Further for each nutrient or topic peer-reviewers have been engaged to comment on the systematic reviews. A steering group with representatives from national authorities in each Nordic country has been responsible for the overall project management. All chapters of the NNR were subject to public consultations (published separately). All systematic reviews were published in Food & Nutrition Research Volume 57 (2013). Other background papers can be found on the Nordic Council of Ministers (NCM) website. Emphasis has been put on the whole diet and the current dietary practices in the Nordic countries.
3) Is one whose advice on DIRVs is recognised through use in policy development in one or more countries.	NIHN contributed to establish NRVs for Labelling purposes for nutrients in 2005. The values have been using for regulation system of nutrition labelling of foods in Japan.	The NNR are for some nutrients adopted by the Dutch Health Council. Further, the NNR serves as the main reference point for the various national nutrition recommendations in the Nordic countries.

Table 1C: Australia & New Zealand; IZiNCG

RASB	Australian National Health and Medical Research Council and New Zealand Ministry of Health (NHMRC/MOH)	International Zinc Nutrition Consultative Group (IZiNCG)
1) Supported by one or more government(s) or competent national or regional authorities.	In 2001, the Commonwealth Department of Health and Ageing asked the National Health and Medical Research Council (NHMRC) to undertake a scoping study in relation to a potential revision of the Australian/New Zealand RDIs. The New Zealand Ministry of Health funded some initial work for the review process that provided expert input into the revision of the two key nutrients iodine and selenium. The NHMRC was then commissioned in 2002 to manage the joint Australian/New Zealand revision process. http://www.nhmrc.gov.au/publications/synopses/_files/n27.pdf	The IZiNCG committee was supported by the Ministry of Public Health, Thailand, UNICEF, the United Nations University's Food and Nutrition Program for Human and Social Development (UNU/FNP) to conduct the review of zinc requirements. IZiNCG is an international group whose primary objectives are to promote and assist efforts to reduce global zinc deficiency, with particular emphasis on the most vulnerable populations of low-income countries. Acknowledgements (p S95) "This work was carried out with the aid of a grant from the Micronutrient Initiative and financial assistance from UNICEF (New York, USA), and the International Zinc Association (Brussels, Belgium). Support for the preparation of this document was also provided by the International Nutrition Foundation, the University of California, Davis, the Institute of Nutrition at Mahidol University, the Ministry of Public Health, Thailand, Padaeng Industry (Thailand), the International Union of Nutritional Sciences (IUNS), and the United Nations University's Food and Nutrition Program for Human and Social Development (UNU/FNP)." http://archive.unu.edu/unupress/food/fnb25-1s-IZiNCG.pdf
2) Provides independent and transparent* authoritative scientific advice on DIRVs upon request.	**Independent** NHMRC became an independent statutory agency within the portfolio of the Australian Government Minister for Health and Ageing, operating under the *National Health and Medical Research Council Act 1992* (NHMRC Act) on 1 July 2006. The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research; for developing health advice for the Australian community, health professionals and governments; and for providing advice on ethical behaviour in health care and in the conduct of health and medical research.	As noted above, the IZiNCG committee was requested to do this work by several parties including UNICEF and the Ministry of Public Health, Thailand. The scientific advice provided by IZiNCG was provided by an independent expert group. The IZiNCG is an independent, nonprofit organization established in 2000 and is now an affiliated body of the International Union of Nutritional Sciences. The full content of the IZiNCG assessement of zinc requirements is freely available from the United Nations University website - http://archive.unu.edu/unupress/food/fnb25-1s-IZiNCG.pdf In this report, the Committee would have access to the data used to establish the zinc daily intake reference values and be able to understand the derivation of the values, and how they differ to those set by the FAO/WHO and IOM and to evaluate their applicability to a global reference value

RASB	Australian National Health and Medical Research Council and New Zealand Ministry of Health (NHMRC/MOH)	International Zinc Nutrition Consultative Group (IZiNCG)
	http://www.nhmrc.gov.au/about/organisation-overview/nhmrcs-role **Transparent authoritative scientific advice** An expert working party was appointed to oversee the process with representation from both Australia and New Zealand. The working group were asked to complete a pro forma that asked them to assess the suitability of the IOM recommendations at the time of review and assess their suitability for use in Australia and New Zealand. The expert reviewers used the 'NHMRC Levels of Evidence' to assess the evidence used to underpin the evidence base of the IOM review, in addition to recommendations from other key countries and bodies and to assess the relevance of any new data that had been published since these reviews. All evidence tables and decision making is documented and is freely available online. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n37.pdf	The IZiNCG document was prepared by the Steering Committee (SC) of International Zinc Nutrition Consultative Group (IZiNCG) and several other experts in zinc nutrition invited by IZiNCG to assist in its preparation. The SC was appointed by the United Nations University's Food and Nutrition Program for Human and Social Development (UNU/FNP) and the International Union of Nutritional Sciences (IUNS). The document was reviewed by 10 independent experts selected by the UNU/FNP and the IUNS. The IZiNCG's response to the reviews was assessed by two additional reviewers appointed by the UNU/FNP and IUNS. Therefore, IZiNCG publication reflects the input from experts both within and outside the IZiNCG SC.
3) Is one whose advice on DIRVs is recognised through use in policy development in one or more countries**.**	The NHMRC Nutrient Reference Values are used as the scientific basis for dietary guidelines in both Australia and New Zealand, regulatory nutrient reference values for labelling purposes (although not yet updated to the most recent publication), informing public health nutrition interventions. http://www.nhmrc.gov.au/publications/synopses/_files/n27.pdf	The work of the IZiNCG was adopted Australia and New Zealand in the development of their DIRVs. Zinc DIRV established by IZiNCG and adopted by Australia and New Zealand has been used to inform public health guidelines. The advice of the IZiNCG is likely to have been recognised in other countries, but New Zealand is not currently aware of the policies in which they have been recognised. http://www.nhmrc.gov.au/publications/synopses/_files/n27.pdf

ATTACHMENT 2

SUPPORTING INFORMATION

Table 2A: Male and Female INL_{98} or AI for Vitamin C and 6 Minerals from WHO/FAO and Accepted RASBS

Vitamin or mineral (type DIRV)	19-50 yrs	United States & Canada	European Union	Australia & New Zealand	Japan	Nordic countries	(IZiNCG)	WHO/FAO
Vitamin C (mg) (INL_{98})	Male	90	110	NPE	100	75	N/A	45
	Female	75	95		100	75		45
Iron (mg) (INL_{98})	Male	8	N/A	NPE	7.3	9 (15%)	N/A	9.1 (15%) 3.7 (10%)
	Female	18			10.8**	15 (15%)		19.6 (15%) 29.4 (10%)
Zinc (mg) (INL_{98})	Male	11 (48%)	N/A	NPE	12	9 (valid for mixed animal/vegetable diet)	13 (31%) 19 (23%)	7.0 (30%) 14.0 (15%)
	Female	8 (41%)			9	7 (valid for mixed animal/vegetable diet)	8 (31%) 9 (23%)	4.9 (30%) 9.8 (15%)
Selenium (µg) (INL_{98})	Male	55	N/A	70	30	60	N/A	34
	Female	55		60	25	50		26
Manganese (mg) (AI)	Male	2.3	3	5.5	4.0	N/A	N/A	N/A
	Female	1.8	3	5.0	3.5			
Molybdenum (µg) (INL_{98}/AI*)	Male	45	65*	NPE	28	N/A	N/A	N/A
	Female	45	65*		23			
Fluoride (mg) (AI)	Male	4	3.4	NPE	N/A	N/A	N/A	N/A
	Female	3	2.9					

NPE DIRVs not derived by primary evaluation; N/A DIRV not established

xx% % dietary absorption; * indicates DIRV based on Adequate Intake; ** DIRV is for menstruating women, 19-50 yrs

Table 2B: Reference Body Weights published with DIRVS, Adults, 19-50 years

RASB (Age range (yrs))	Reference adult body weight (kg)			Basis
	Male	Female	Mean	
WHO/FAO (18+)	65	55	60	Based on (US) NCHS/CDC 1977 growth reference data (explanation given by IZiNCG)
IOM (USA & Canada) (19+)	76	61	64	Average body weights for 19-30 year olds from NHANES III corresponding to BMI (M) 24.4 (F) 22.8 kg/m^2
EFSA (European Union) (18-79)	68.1	58.5	63	Median body weight based on measured body heights and assuming BMI of 22 kg/m^2
NHMRC/MOH (Australia & New Zealand) (19+)	76	61	69	Average body weights for 19-30 year olds from Aust or NZ national health surveys: 1995, 1997, 2002
NIHN (Japan) (18-29/30-49)	63.5/68; [weighted mean 66.5]	50/52.7; [weighted mean 52.2]	59	Median body weights for 18-29/30-49 year old men and women from 2005 and 2006 National Health and Nutrition Surveys in Japan. Mean weight based on 19-50 yr age range.
NORDIC (18-30/31-60)	75.4/74.4 [weighted mean 74.8]	64.4/63.7 [weighted mean 64.0]	69	Reference weight corresponds to a body mass index (BMI) of 23 kg/m^2; data based on actual heights of populations in all Nordic countries. Mean weight based on 19-50 yr age range.

Scaling (extrapolation) used to adjust DIRVs to reference body weights

RASBs sometimes applied scaling to convert male DIRVs to female DIRVs, or to adjust the results obtained from subjects of a certain body weight in experimental studies to reference body weights. Two scaling methods were used:

USA & Canada; European Union; Australia & New Zealand

Linear scaling: EAR (F) = EAR (M) x (Ref B wt F/Ref B wt M)

Japan

Because the efficiency of energy metabolism is highly correlated with body surface area, a formula estimating body surface from body height and/or body weight has been widely used to determine energy metabolism. Among the formulae developed to estimate body surface area from body height and/or weight, a formula developed in 1947 using the weight ratio to the 0.75^{th} power was used in determining the [Japanese] DRIs such that

$X = Xo * (W/Wo)^{0.75}$

where X is EAR or AI; Xo is reference value of EAR or A; W is reference body weight of the specific age group; Wo is the median or mean of body weight of group that provided EAR or AI reference value

Table 2C: Supplementary Information: Vitamin C, Fe, Zn, Se

	Physiological endpoint for EAR	Reason for choice of endpoint(s)	Relevant parameters in calculation of EAR/AI	EAR; Coefficient variation Calculation EAR	Yr(s) evaluated (latest Yr)
1 Vitamin C					
United States & Canada	80% maximal neutrophil concentration. Animal studies show that concentration of ascorbate in leukocytes more accurately reflects liver and body pool ascorbate than plasma concentration.	Estimates of body pool or tissue levels that are adequate to provide antioxidant protection with little or no urinary loss. Endpoint is halfway between neutrophil level at which there is no urinary excretion and maximum neutrophil level at which 25% urinary excretion occurs.	Dose response curve neutrophil ascorbic acid as a function of vitamin C intake.	EAR M 75 mg; F 60 mg; 10% CV EAR (M) equates to dietary intake that maintains 80% maximal neutrophil concentrations (1 mmol/L). EAR (F) = EAR (M) x ref B wt(F)/ref B wt(M)	1998–2000 (1996)
European Union	Maintenance of fasting plasma ascorbate concentrations at around 50 µmol/L. Plasma and leukocyte ascorbate concentrations considered appropriate biomarkers of status. Plasma ascorbate concentration selected over leukocyte ascorbate because of larger data set.	Fasting plasma ascorbate concentrations at 45-50 µmol/L correspond to near saturation of body pools (adequate status) with minimal urinary excretion that allows the fulfilment of vitamin C functions. Plasma ascorbate concentrations > 10 µmol/L but < 50 µmol/L are indicative of a suboptimal status with a risk of insufficiency.	Metabolic loss: 50 mg Urinary excretion: 25% intake Dietary absorption: 80% intake	EAR M 90 mg; F 80 mg; 10% CV EAR (M) = 50 mg metabolic loss/(absorption - excretion) rounded down. EAR (F) = EAR (M) x ref B wt(F)/ref B wt(M)	?–2013 (2013)
Japan	Maintenance of fasting plasma ascorbate concentrations at around 50 µmol/L.	Optimal plasma antioxidant activity helping to prevent cardiovascular disease is achieved by a plasma ascorbic acid concentration of 50 µmol/L.	Dose response curve plasma ascorbate as a function of vitamin C intake.	EAR M 85 mg; F 85 mg 10% CV	2008–2009 (2006)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
Nordic countries	Intake needed to achieve plasma concentration of 32 mmol/L using pharmacokinetic data from Levine	Unweighted mean of 8 studies with mortality as outcome. Role of ascorbic acid in preventing morbidity and mortality from chronic disease like cancer and cardiovascular diseases.	Pharmacokinetic data from Levine et al shows that concentration of ascorbic acid in plasma of 32 mmol/L corresponds with an approximate intake of 60 mg/d in men and 50 mg in women	EAR M 60 mg, F 50 mg 25% allowance for inter-individual variation	?-2012 (2012)
WHO/FAO	Amount required to half saturate body tissues with vitamin C in 97.5% population.	Assumed this is best indicator of adequacy currently available.	Body content 900 mg (Replete content 20 mg/kg x 75 kg (M)); Average catabolic rate 2.9% No urinary excretion Dietary absorption 85%	EAR (back calculated from RNI) M 37 mg; F 37 mg 10% CV EAR (M) = Male body content x catabolic rate x absorption. EAR (F) = EAR (M) because prudent to retain as female plasma concentrations fall more rapidly.	1998–2004 (1998)
2 Iron					
United States & Canada	Factorial modelling of factors: basal loss, menstrual loss, dietary absorption. Because distribution of iron requirement is skewed i.e. not normally distributed, the simple addition of requirement components is inappropriate. Monte Carlo simulation generated a large theoretical population for each factor.	Total need for absorbed iron can be estimated	Basal loss (median) (M) 1.08 mg (F) 0.896 mg; Menstrual loss (median) (F) 0.51 mg Dietary absorption (upper value) 18%	EAR M 6 mg; F 8.1 mg %CV not applied (RDA derived as 97.5th percentile distribution of iron requirements) EAR (M) = basal loss/absorption (F) = (basal loss + menstrual loss)/absorption	1998–2000 (2000)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
	Median and 97.5th percentiles of each distribution used in calculation of EAR and RDA respectively.				
Japan	Factorial calculation of factors: Basal loss (mostly faecal), menstrual loss, iron storage, dietary absorption.	Total need for absorbed iron can be estimated	Basal loss 0.96 mg/day for 68.6 kg extrapolated to B wt each sex using 0.75th power of a B wt ratio. Menstrual loss 0.55 mg Dietary absorption 15%	EAR M 6.3 mg; F 8.8 mg (menstruation 19-50 yrs) 10% CV --- Basal loss (M) = 0.96 x [B wt (M)/68.6)]$^{0.75}$ Basal loss (F) = 0.96 x [B wt (F)/68.6)]$^{0.75}$ EAR (M) = basal loss (M)/absorption EAR (F) = (basal loss (F) + menstrual loss)/absorption	2008–2009 (2003)
Nordic countries	Amounts needed to cover basic losses and growth for approximately 95% for the individuals. For women of childbearing age, amounts that meets the needs of approximately 90% or menstruating women	Iron needs for growth, basal losses, menstrual losses	Iron absorption of 15%	EAR M 7 mg; F 9 mg %CV not presented --- EAR=((need for growth+ median basal loss + median menstrual loss)/15)*100	?-2013 (2013)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
WHO/FAO	Because distribution of iron requirement is skewed for menstruating women i.e. not normally distributed, the simple addition of requirement components is inappropriate. Median and 95th percentiles of each distribution for losses used in calculation.	The RNIs are based on the 95th percentile of the absorbed iron requirements/dietary absorption.	Basal loss: (M) 1.05 mg (median); 1.37 mg (95th percentile) (F) 0.87 mg (median) + menstrual loss 0.48 mg (median); or 1.90 mg (95th percentile) Total absolute requirements: (M) 1.05 mg (median); 1.37 mg (95th percentile) (F) 1.46 mg (median); 2.94 mg (95th percentile) Selected dietary absorption 15% & 10%	EAR (Back calculated from RNI, males only) M 7.2 mg (15%); 10.8 (10%) 15% CV EARs cannot be calculated from RNIs for adult females 19-50 years because of the skewed distribution of requirements.	1998–2004 (1998)
3 Zinc					
United States & Canada	Factorial analysis to determine the minimal quantity of absorbed zinc that is adequate to replace endogenous losses.	Sufficient number of metabolic studies on zinc homeostasis to estimate zinc dietary requirements	Linear regression of intestinal excretion of endogenous zinc vs absorbed zinc plus other loss (urine; integument and sweat; semen/menstruation). Other Loss: (M) 1.27 mg; (F) 1.0 mg	EAR M 9.4 mg; F 6.8 mg % dietary absorption (M) 41%; (F) 48% 10% CV	1998–2000 (1997)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
			Intercept of line of perfect agreement of endogenous loss vs absorbed zinc with line of total endogenous loss vs absorbed zinc for men and women = average total minimal quantity absorbed zinc (M) 3.84 mg; (F) 3.3 mg	EAR is the amount of ingested zinc that matches total endogenous losses from the relationship of absorbed vs ingested zinc. From asymptotic regression of absorbed zinc on zinc intake.	
Japan	Factorial modelling method to determine the minimal intake necessary to maintain zinc balance.	Total need for absorbed zinc can be estimated	Average endogenous loss (urine + integument and sweat + semen/menstruation) (M) 1.27 mg; (F) 1.0 mg Linear equation of total endogenous excretion vs absorbed zinc (M) = 0.628 (qty zinc absorbed + 0.2784+1.27); (F) = 0.628 (qty zinc absorbed + 0.2784 + 1.0) x [ratio B wt (76(M)/61(F))$^{0.75}$]. Where total endog excretion = zinc absorption (M) = 4.16 mg (F) = 3.92 mg	EAR M 10 mg; F 7.7 mg 10% CV Relationship zinc intake vs zinc absorption for 76 kg = 1.113 x zinc intake$^{0.5462}$ (M) 11.18 mg; (F) 10.03 mg, then adjusted down by (Jap M or F B wt/76)$^{0.75}$	2008–2009 (2001)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
IZiNCG	Factorial analysis to determine the minimal quantity of absorbed zinc that is adequate to replace endogenous losses.	Comprehensive review and update of recommendations of US&Canada, and WHO/FAO. Generally supported US/Canada conceptual approach. Used the lower WHO/FAO reference body weights than US&Canada. More studies (also included women, no geographic limitations) than US&/Canada in linear regression. Only total diet studies included (same as US&Canada); single meal studies excluded (WHO/FAO used single meal and total diet studies). Excluded semi-purified formula or zinc-fortified diets from total diet studies (US&Canada; WHO/FAO included).	Average endogenous loss (urine + surface + semen) (M) 1.15 mg; (F) 0.8 mg (menstrual loss, negligible). Linear regression of faecal loss versus absorbed zinc. Intercept of total endogenous loss versus absorbed zinc and line of equality of absorbed zinc represents minimal quantity of absorbed zinc required to replace total endogenous losses: (M) 2.69 mg; (F) 1.86 mg	EAR M 10 mg; F 6 mg (mixed diet) M 15 mg; F 7 mg (unrefined diet 12.5% CV EAR = mean physiologic requirement of absorbed zinc/estimated average absorption. Derived from relationship between total zinc intake and absorbed zinc (from logit regression) for 2 diet categories of phytate:zinc molar ratios representing a mixed/refined vegetarian diet, or an unrefined, cereal-based diet. % Absorption: Mixed/refined vegetarian diet M 26%} Mean M + F 31% F 34% } Unrefined cereal-based diet (1 study) M 18%} Mean M + F 23% F 25% }	Unknown years evaluated; published 2004 (2003)
Nordic countries	Factorial method, estimates of the daily losses and the corresponding amount of zinc to be ingested to replace the losses and additional zinc for periods of tissue growth	Info available on total endogenous zinc losses	Food and Nutrition Board Figures have been used to estimated endogenous losses and routes other than intestine	EAR M 6.4 mg, F 5.7 mg %CV =15% EAR = ((Endogenous intestinal losses + endogenous other losses)/40)*100	?-2012 (2012)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
European Union (DRAFT)	Factorial analysis to determine 1) minimal quantity of absorbed zinc adequate to replace endogenous losses i.e. the physiological requirement and 2) the amount of dietary zinc needed to meet physiological requirement taking into account the inhibitory effect of dietary phytate on zinc absorption.	Sufficient number of whole-day studies of true zinc absorption in healthy subjects; for stage 1): these studies needed to provide information on endogenous faecal zinc and total absorbed zinc, with availability of individual data points from the pertinent studies; for stage 2): the studies needed to provide (mean) estimates on total dietary zinc, total absorbed zinc and total dietary phytate.	1) Multiple regression analysis of intestinal excretion of endogenous zinc vs absorbed zinc plus other losses (urine; integument, sweat, semen, menstrual loss). 2) Saturation response modelling to characterise the relationship of the quantity of zinc absorbed to the quantity ingested.	EAR M 7.5–12.7 mg; F 6.2–10.2 mg (phytate intakes 300-1200 mg/day) CV% N/A. PRIs derived from zinc requirement of individuals with a body weight at 97.5th percentile for reference weights for M&F. EAR = calculation of physiological requirement for median reference body weights of M and F in the EU (2.9 mg/day for 58.5 kg, 3.2 mg/day for 68.1) then derivation of zinc intake needed to match the physiological requirement for phytate intakes of 300, 600, 900, 1200 mg/day, which cover the range of mean/median phytate intake observed in the EU.	2014 (2013)
WHO/FAO	Factorial analysis to determine the minimal quantity of absorbed zinc that is adequate to replace endogenous losses.	Total need for absorbed zinc can be estimated	Absorbed zinc corresponding to obligatory loss during the early phase of zinc depletion before adaptive reductions in excretion take place (M) 1.4 mg; (F) 1.0 mg. Algorithms developed and applied to requirement estimates for absorbed zinc.	EAR (back calculated from RNI) M 3.5 mg; F 2.5 mg (50% abs'n); M 5.8 mg; F 4.1 mg (30% abs'n) M 11.7 mg; F 8.2 mg (15% abs'n) 10% CV	1998–2004 (1998)

	Physiological endpoint for EAR	Reason for choice of endpoint(s)	Relevant parameters in calculation of EAR/AI	EAR; Coefficient variation Calculation EAR	Yr(s) evaluated (latest Yr)
4 Selenium					
United States & Canada	Maximum plasma glutathione peroxidase (GP_X) activity	(GP_X) activity can serve as an index of selenium status and has been measured in individuals consuming varying amounts of selenium.	Average of 2 intervention studies (China, (1987) (B wt corrected); New Zealand (1999)) of relationship between selenium intake (including by supplementation) and GPx activity adjusted to B wt (M). Based on plateau occurring at supplemental level of +10 µg.	EAR M 45 µg; F 45 µg 10% CV EAR (F) same as for (M) because women more susceptible to deficiency disease.	2005 (2005)
European union (DRAFT)	Plateau of plasma selenoproteins (SEPP1). SEPP) is the most informative biomarker of selenium status given their role in selenium transport and metabolism and its response to different forms of selenium intake.	Indicative of an adequate supply of selenium to all tissues and to reflect saturation of the functional body pool ensuring that all physiological functions involving selenium are covered.	Habitual Se intakes of 50-60 µg/day were not sufficient for SEPP1 concentrations to reach a plateau in Finnish individuals whereas Se intakes above 100 µg/day consistently did so in population groups from Finland, United Kingdom, and USA.	AI due to uncertainties in the small evidence base of suitable intervention studies Adults 70 µg	2014 (2011)
Australia & New Zealand	Maximum plasma glutathione peroxidase (GP_X) activity	(GP_X) activity can serve as an index of selenium status and has been measured in individuals consuming varying amounts of selenium.	Average of 2 intervention studies (China, (2005) B wt corrected); New Zealand (1999)) of relationship between Se intake (including by supplementation) and GPx activity adjusted to B wts (M&F)	EAR M 60 µg; F 50 µg 10% CV	2005 (2005)

	Physiological endpoint for EAR	**Reason for choice of endpoint(s)**	**Relevant parameters in calculation of EAR/AI**	**EAR; Coefficient variation** **Calculation EAR**	**Yr(s) evaluated (latest Yr)**
			Based on plateau occurring at supplemental level +25 µg.		
Japan	Maintain 2/3 maximum plasma glutathione peroxidase (GPx) activity.	Relationship between selenium intake and GP_X activity has been particularly well established.	Based on one Chinese study (1988). Se intake to maintain 2/3 maximum plasma glutathione peroxidase (GPx) activity is 24.2 µg for 60 kg adult.	EAR M 25 µg; F 20 µg EAR extrapolated using 0.75th power of a weight ratio of B wts	2008–2009 (1988)
Nordic countries	Saturation of plasma SePP activity	Saturation of plasma SePP1 activity is now considered as better measure of adequate selenium status than the earlier used plasma GPx.	Results of Chinese intervention study (2010) translated to Nordic conditions and correcting for average body size, Recommended intake estimated	EAR M 35 µg; F 30 µg ?%CV	?-2012 (2012)
WHO/FAO	Maintenance of 2/3 of plasma GPx which is indicative of adequate selenium reserves.	Balance techniques are inappropriate. GP_X activity can serve as an index of selenium status and has been measured in individuals consuming varying amounts of selenium.	Based on one study of adult males (unreferenced), of relationship between selenium intake (including by supplementation) and GPx activity adjusted to ref B wts	EAR (back calculated from RNI) M 28 µg; F 22 µg 10% CV	

EFSA Draft Scientific Opinion for Zinc – Additional Information

EFSA estimations of adult PRIs for zinc are based on reference body weights for a BMI of 22 kg/m^2. The adult PRI was estimated as the zinc requirement for individuals with a body weight at the 97.5th percentile for reference body weights for men and women, respectively, as body weight is a strong determinant for the requirements for zinc and as this approach is considered to have less uncertainty than the mathematical application of a CV of between 10% and 20%. As dietary zinc requirement depends on body weight and dietary phytate intake, EFSA considers it appropriate to estimate PRIs for the range of mean/median dietary phytate intakes observed in Europe thus reflecting the variety of European dietary patterns.

PRI mg/day (male ≥ 18 yrs) [@ b wt 79.4 kg]	PRI mg/day (female ≥ 18 yrs [@ b wt 68.1 kg]	PRI (ave F&M) mg/day	Level of phytate intake (mg/day)	eWG derived phytate:zinc molar ratio
9.4	7.5	8.5	300	3.5
11.7	9.3	10.5	600	5.7
14.0	11.0	12.5	900	7.1
16.3	12.7	14.5	1200	8.2

The eWG derived the phytate;zinc molar ratio of the EFSA PRIs according to the equation from IZiNCG (2007).

$$\frac{\text{mg phytate per day/ 660}}{\text{mg zinc per day/ 65.4}}$$

EFSA estimated that European adults ingest 300-800 mg/day of phytate with a mixed diet and that the phytate increases to 700-1400 mg/day for mixed diets with a high proportion of unrefined cereal grain products and legumes, whereas dietary phytate intake may be as high as 1600-2500 mg/day in adults on vegetarian diets.

Table 2D: Supplementary Information: Mn, Mb, F
Assume all % values divided by 100 in calculations

	Physiological endpoint for EAR/ Choice of AI*	**Reason for choice of EAR endpoint(s)/choice of AI***	**Relevant parameters in calculation of EAR/AI**	**EAR/AI; Coefficient variation (EAR only)** **Calculation EAR/AI**	**Year(s) when evaluated (Year of latest literature)**
5 Molybdenum					
United States & Canada	Balance in controlled studies with specific amounts of Mb consumed (M).	Plasma or urinary Mb does not reflect Mb status	1 balance study (1995) (4 M). Average balance (102 days) with intake of 22 ug. Lack of evidence of deficiency. Plus estimate of 3 µg for miscellaneous losses. Estimate 75% absorption.	EAR M 34 µg; F 34 µg 15% CV EAR = (Intake at balance + miscellaneous loss)/absorption. No evidence to suggest F requirements differ from M.	1998–2000 (1998)
European Union	Data on the relationship between Mb intakes and health outcomes were unavailable for the setting of DIRVs.	Based on observed Mb intakes with a mixed diet at the lower end of observed EU intakes and the apparent absence of signs of deficiency in Europe.	Lower end of observed EU intakes noted to be higher than a (1995) balance study in men on zero molybdenum balance showing absence of biochemical changes or symptoms indicative of molybdenum deficiency at intakes as low as 22 µg for three months.	AI Insufficient evidence to derive an EAR M 74 µg; F 58 µg	2005–2013 (2013)

	Physiological endpoint for EAR/ Choice of AI*	**Reason for choice of EAR endpoint(s)/choice of AI***	**Relevant parameters in calculation of EAR/AI**	**EAR/AI; Coefficient variation (EAR only)** **Calculation EAR/AI**	**Year(s) when evaluated (Year of latest literature)**
Japan	Balance in controlled study with specific amounts of Mb consumed (M).		1 balance study (1995) (4 M). Average balance (102 days) with intake of 22 ug (76.4 kg). Plus estimate of 3 ug for integumental and sweat losses.	EAR M 23 µg; F 20 µg EAR = (Intake at balance + integumental and sweat loss) EAR extrapolated using 0.75^{th} power of a weight ratio of B wts	2008–2009 (2001)
6 Manganese					
United States & Canada	There were insufficient data to set an EAR, therefore an AI was set. Balance studies are problematic because of the rapid excretion of Mn into bile and because Mn balances during short- and moderate-term studies do not appear to be proportional to Mn intakes. A number of studies have achieved balance over a wide range of Mn intakes.	Based on median intakes from FDA Total Diet Study from Food, 1991-97 and apparent absence of overt symptoms of deficiency.	Approach supported by several balance studies that concluded that balance could be achieved at around 2.1 – 2.5 mg.	AI M 2.3 mg; F 1.8 mg Highest median intake value reported for adult male and female age groups. Highest median intake selected to account for dietary underestimation.	1998–2000 (1999)

	Physiological endpoint for EAR/ Choice of AI*	**Reason for choice of EAR endpoint(s)/choice of AI***	**Relevant parameters in calculation of EAR/AI**	**EAR/AI; Coefficient variation (EAR only)** **Calculation EAR/AI**	**Year(s) when evaluated (Year of latest literature)**
European Union	The available data are insufficient to derive EAR, therefore, an AI set.	Based on observed Mn intakes with a mixed diet and the apparent absence of signs of deficiency in Europe.	Supported by null or positive balances consistently observed with intakes of Mn above 2.5 mg, in balance studies lasting 11–60 days.	AI M 3 mg; F 3 mg Mean intakes of adult men and women range from 2 to 6 mg/day in the EU, with a majority of values around 3 mg/day.	2005–2013 (2013)
Australia & New Zealand	There were insufficient data to set an EAR, therefore an AI was set.	Based on median intakes from reanalysis of New Zealand (1997, 2002) and Australian (1995) nutrition surveys and using Mn content of US foods.	–	AI M 5.5 mg; F 5.0 mg Highest median intake value reported for adult male and female age groups. Highest median intake selected to account for dietary underestimation.	2005 (2003)
Japan	There is insufficient information to set an EAR, therefore an AI was set.	Based on estimates of average Mn intakes in Japan. The possibility of dietary Mn deficiency is nearly 0% because plant foods, including cereals and beans, contain high levels of Mn.	-	AI M 4.0 mg; F 3.5 mg Average adult intake 3.7 mg adjusted up for males and down for females based on differences in energy intake.	2008–2009 (2005)

	Physiological endpoint for EAR/ Choice of AI*	**Reason for choice of EAR endpoint(s)/choice of AI***	**Relevant parameters in calculation of EAR/AI**	**EAR/AI; Coefficient variation (EAR only)** **Calculation EAR/AI**	**Year(s) when evaluated (Year of latest literature)**
7 Fluoride					
United States & Canada	Data are not available to determine EAR, therefore an AI was set.	AI based on estimated intakes that have been shown to reduce the occurrence of dental caries maximally in a population without causing unwarranted side effects including moderate dental fluorosis.	AI set at 0.05 mg/kg based on extensively documented relationships between caries experience and both water fluoride concentration and fluoride intake. This intake confers a high level of protection against dental caries and is associated with no known unwanted health effects.	AI M 4 mg; F 3 mg 0.05 mg/kg x B wts for M and F.	<1997 (1992)
European Union	Fluoride is not an essential nutrient. Therefore, no EAR for the performance of essential physiological functions can be defined. Nevertheless, the setting of an AI is appropriate because of the beneficial effects of dietary fluoride on prevention of dental caries. Reliable and representative data on the total fluoride intake of the European population are not available.	The AI is based on epidemiological studies (performed before the 1970s) showing an inverse relationship between the fluoride concentration of water and caries prevalence. As the basis for defining the AI, except for one confirmatory longitudinal study in US children, more recent studies were not taken into account as they did not provide information on total dietary fluoride intake, were potentially confounded by the use of fluoride-containing dental hygiene products, and did not permit a conclusion to be drawn on a dose-response relationship between fluoride intake and caries risk.	Estimates of mean fluoride intakes of children via diet and drinking water with fluoride concentrations at which the caries preventive effect approached its maximum whilst the risk of dental fluorosis approached its minimum.	AI M 3.4 mg; F 2.9 mg 0.05 mg/ kg x B wts for M and F.	2005–2013 (2013)

ATTACHMENT 3

REFERENCES

Table 3A: References for DIRVs, ULs and Dietary Descriptions

Nutrient (information)	Name of publication	Year Publication	Bibliographic Reference	Official Weblink
INTERNATIONAL: WHO/FAO or WHO or WHO/FAO/IAEA; IZiNCG				
Vit C, iron, zinc, selenium (DIRV)	Vitamin and Mineral Requirements in Human Nutrition	2004	World Health Organization and Food and Agricultural Organization (2004) *Vitamin and Mineral Requirements in Human Nutrition,* 2nd edition. WHO, Geneva	whqlibdoc.who.int/publications/2004/9241546123.pdf
Vit C, iron, zinc, selenium (Back calculated EAR) (iron & zinc dietary descriptions)	Guidelines on Food Fortification with Micronutrients	2006	World Health Organization and Food and Agricultural Organization (2006) *Guidelines on Food Fortification with Micronutrients*. WHO, Geneva	www.who.int/nutrition/.../guide_food_fortification_micronutrients,pdf
Zinc, fluoride (UL)	Trace Elements in Human Nutrition and Health	1996	World Health Organization and Food and Agricultural Organization and International Atomic Energy Association (1996) *Trace Elements in Human Nutrition and Health*. WHO, Geneva	whqlibdoc.who.int/publications/1996/9241561734_eng_fulltext.pdf
Zinc (DIRV and dietary descriptions)	Assessment of the risk of zinc deficiency in populations and options for its control 1st IZiNCG technical document	2004	International Zinc Nutrition Consultative Group (2004). *Assessment of the risk of zinc deficiency in populations and options for its control. Food and Nutrition Bulletin (25(1):S99-129 (Supplement 2).*	http://archive.unu.edu/unupress//food/fnb25-1s-IZiNCG.pdf

Nutrient (information)	Name of publication	Year Publication	Bibliographic Reference	Official Weblink
USA & CANADA				
Iron, Zinc, Molybdenum, Manganese (DIRV, UL)	Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc.	2001	IOM (Institute of Medicine). 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc.* Washington, DC: The National Academy Press.	http://www.nap.edu/catalog.php?record_id=10026
Vitamin C, Selenium (DIRV, UL)	Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.	2000	IOM (Institute of Medicine). 2000. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.* Washington DC: National Academy Press.	http://www.nap.edu/catalog.php?record_id=9810
Fluoride (DIRV, UL)	Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride.	1997	IOM (Institute of Medicine). 1997. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride.* National Academy Press.	http://www.nap.edu/catalog.php?record_id=5776
EUROPEAN UNION				
Vitamin C (DIRV)	Scientific Opinion on Dietary Reference Values for Vitamin C	2013	EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013. *Scientific Opinion on Dietary Reference Values for vitamin C*. EFSA Journal 2013;11(11):3418, 68 pp	http://www.efsa.europa.eu/en/efsajournal/pub/3418.htm
Molybdenum (DIRV)	Scientific Opinion on Dietary Reference Values for Molybdenum	2013	EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013. *Scientific Opinion on Dietary Reference Values for molybdenum*. EFSA Journal 2013;11(8):3333, 35 pp	http://www.efsa.europa.eu/en/efsajournal/pub/3333.htm
Manganese (DIRV)	Scientific Opinion on Dietary Reference Values for Manganese	2013	EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013. *Scientific Opinion on Dietary Reference Values for manganese*. EFSA Journal 2013;11(11):3419, 44 pp	http://www.efsa.europa.eu/en/efsajournal/pub/3419.htm

Nutrient (information)	Name of publication	Year Publication	Bibliographic Reference	Official Weblink
Fluoride (DIRV)	Scientific Opinion on Dietary Reference Values for fluoride	2013	EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013. *Scientific opinion on Dietary Reference Values for fluoride*. EFSA Journal 2013;11(8):3332, 46 pp.	http://www.efsa.europa.eu/en/efsajournal/pub/3332.htm
Selenium DRAFT (DIRV)	DRAFT Scientific Opinion on Dietary Reference Values for selenium	2014	EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition, and Allergies), 2014. *Scientific opinion on Dietary Reference Values for Selenium*. EFSA Journal 2014;volume(issue):NNNN, 67 pp. doi:10.2903/j.efsa.2014.NNNN	http://www.efsa.europa.eu/F49E9D4D-0AB0-4AE2-9891-0A445DC6E5AA/FinalDownload/DownloadId-D48B0FD65896524EF690A9A0A7D7D36D/F49E9D4D-0AB0-4AE2-9891-0A445DC6E5AA/en/consultationsclosed/call/140715.pdf
Zinc DRAFT (DIRV)	DRAFT Scientific Opinion on Dietary Reference Values for zinc	2014	EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. *Draft Scientific opinion on Dietary Reference Values for Zinc*. EFSA Journal 2014;11(8):NNNN, 74 pp. doi: 10.2903/j.efsa2014.NNNN	http://www.efsa.europa.eu/F49E9D4D-0AB0-4AE2-9891-0A445DC6E5AA/FinalDownload/DownloadId-E57BD83F10C828446648B84A9DB3358F/F49E9D4D-0AB0-4AE2-9891-0A445DC6E5AA/en/consultationsclosed/call/140514.pdf
All 7 nutrients (UL)	Tolerable Upper Intake Levels for Vitamins and Minerals	2006	Scientific Committee on Food and European Food Safety Authority. 2006. *Tolerable Upper Intake Levels for Vitamins and Minerals*. EFSA, Parma	http://www.efsa.europa.eu/en/ndatopics/docs/ndatolerableuil.pdf
AUSTRALIA & NEW ZEALAND				
Selenium, manganese (DIRV)	Nutrient reference values for Australia and New Zealand	2006	*Nutrient Reference Values for Australia and New Zealand*; 2006; Australian Government Department of Health and Ageing, National Health and Medical Research Council; and New Zealand Ministry of Health; Canberra, Australia	http://www.nhmrc.gov.au/publications/synopses/_files/n27.pdf Evidence appendix - http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n37.pdf

Nutrient (information)	Name of publication	Year Publication	Bibliographic Reference	Official Weblink
JAPAN				
Vitamin C, iron, zinc, selenium, molybdenum, manganese (DIRV)	Dietary Reference Intakes for Japanese, 2010	2013	*Dietary Reference Intakes for Japanese, 2010*; 2013; Journal of Nutritional Science and Vitaminology vol. 59, supplement ISSN 0301-4800	https://www.jstage.jst.go.jp/browse/jnsv/59/Supplement/_contents
NORDIC COUNTRIES				
Vitamin C, iron, zinc, selenium (DIRV)	Nordic Nutrition Recommendations 2012 Integrating nutrition and physical activity	2013	Nordic Nutrition Recommendations 2012. Integrating nutrition and physical activity. ISBN 978-92-893-2670-4 All systematic reviews were published in Food & Nutrition Research Volume 57 (2013). Other background papers can be found on the Nordic Council of Ministers (NCM) website.	http://www.norden.org/en/publications/publikationer/2014-002

Table 3B: Additional References

Information	Name of publication	Year Publication	Bibliographic Reference	Official Weblink
Reference body weights	*Requirements of Vitamins A, Iron, Folate, and Vitamin B_{12}*	1988	Food and Agriculture Organization (1988) *Requirements of Vitamins A, Iron, Folate, and Vitamin $B_{12.}$* Report of Joint FAO/WHO Expert Consultation. FAO, Rome	Not available
Reference body weights	*Scientific Opinion on Dietary Reference Values for Energy*	2013	EFSA Panel on Dietetic Products, Nutrition and Allergies (2013) Scientific Opinion on Dietary Reference Values for Energy. EFSA Journal, 11(1):3005, 112 pp	http://www.efsa.europa.eu/en/efsajournal/doc/3005.pdf
Fluoride – public health significance	*Oral Fact Sheet No. 318*	2012	WHO (2012) Oral Health Fact Sheet No. 318. WHO, Geneva	http://www.who.int/mediacentre/factsheets/fs318/en/
Phytate: zinc molar ratio calculation	*Determining the risk of zinc deficiency: Assessment of dietary zinc intake*	2007	International Zinc Nutrition Consultative Group (2007). Technical Brief No. 3.	http://www.izincg.org/files/english-brief3.pdf