

**Codex Committee on Nutrition and Foods for Special Dietary Uses**

**Electronic Working Group**

**DRAFT REVISED AND ADDITIONAL NUTRIENT REFERENCE VALUES FOR VITAMINS,  
MINERALS**

(Chaired by Australia)

**THIRD CONSULTATION PAPER, JULY 2015**

Please respond by completing the **RESPONSE FORM** at Attachment 3

return to **janine.lewis@foodstandards.gov.au**

**by Friday 21 August 2015**

**A INTRODUCTION**

In 2014, the 36<sup>th</sup> session of the CCNFSDU deferred a decision on the NRV-R for iron so it could be considered in light of EFSA's forthcoming scientific opinion on iron requirements. The European Food Safety Authority (EFSA) released its draft scientific opinion on iron requirements in May 2015 for public consultation until 19 July 2015.

This year's Consultation Paper 2 (CP2) foreshadowed a third Consultation Paper (CP3) to consider *the NRVs-R for iron and possibly other vitamins and minerals in this batch that are expected soon and for which EFSA has not yet issued a draft scientific opinion*. EFSA released a draft scientific opinion on copper requirements in June which closes on 6 August 2015. EFSA has not yet released opinions on vitamin D or chloride. Therefore CP3 considers the NRV(s)-R for only iron and copper, as well as iron dietary descriptions and it notes the applicability to iron NRV-R of the footnote agreed for zinc by CCNFSDU in 2014 and the Commission in 2015. Unfortunately the eWG and CCNFSDU timeframes are now such that the eWG will not be able to take further releases of EFSA draft scientific opinions in 2015 into account before the 37<sup>th</sup> session of CCNFSDU.

Please refer to Section A of the previous eWG consultation paper, May 2015 (CP2) for general information on the General Principles for Establishing NRVs-R and their application to selection of DIRVs from accepted RASBs, relevant definitions and the stepwise process for derivation of new or revised NRVs-R. The response time is limited to 4 weeks because only two minerals are under consideration in CP3.

**DIRVs and ULs updated with EFSA's draft scientific opinions for iron and copper**

Candidate DIRVs for iron in Table 2 CP2, 2014 were considered by the 2014 eWG, and were considered for copper by 2015 eWG in Section 1.6 CP2, 2015. These DIRVs have now been updated to include the draft EFSA DIRVs including the comparison with ULs for young children in accordance with GP 3.3 in Table 1.

From Table 1, no candidate DIRVs for iron exceeded all quantified ULs so all candidate DIRVs for this mineral can be further considered. However, the DIRVs for copper from Europe (draft) and Australia New Zealand are AIs and both exceed the US/Canada and EU ULs for young children aged 1-3 years but not the ULs for children in the next bracket aged 4-6/4-8 years, or the 1996 WHO/FAO value.

This situation previously occurred in 2014 for the candidate DIRVs (all AIs) for manganese such that all were higher than the ULs for the younger age group, but they were either lower than, equal to or higher than the ULs for the older age group. The CCNFSDU took account of these results in accordance with GP 3.3 and accepted an NRV-R for manganese that exceeded the UL for 1-3 years and was equal to the UL for 4-8 years since the general population was described as from 4 years. The Chair notes this precedent.

**Table 1: Average adult DIRVs from RASBs; comparator UL young children**

| Vitamin or Mineral (INL <sub>98</sub> unless indicated by AI) | US & Canada | EU                | Aust & NZ   | Japan   | Nordic countries | WHO/FAO                  | UL 1-3/4-8 yrs; US & Canada | UL 1-3/4-6 yrs; EU | UL (1-6) WHO (1996) |
|---|-------------|-------------------|-------------|---------|------------------|--------------------------|-----------------------------|--------------------|---------------------|
| Iron (mg) (% absorption)                                      | 13 (18%)    | Draft 13.5 (17%)  | NPE         | 9 (15%) | 12 (15%)         | 14.4 (15%)<br>21.6 (10%) | 40/40                       | ND/ND              | --                  |
| Copper (µg)   | 900         | Draft 1,450<br>AI | 1,450<br>AI | 800     | NPE              | —                        | 1,000/3,000                 | 1,000/2,000        | 1,500               |

ND Not determined due to insufficient data;

NPE DIRV not derived by primary evaluation

### **Adoption of revised NRV-R for zinc by Codex Commission**

Previous eWGs recommended that NRVs-R for iron and zinc refer to the same type of information. In July this year, the 38<sup>th</sup> session of the Codex Alimentarius Commission revised the NRV-R for zinc by adopting CCNFSDU's recommendation for two NRVs-R and associated dietary descriptions according to % dietary absorption, and a footnote indicating national or regional discretion in selection an appropriate NRV-R (Appendix IV, REP 15/NFSDU) as shown below.

|        |   |
|--------|---|
| Zinc** | 11 (30% dietary absorption; Mixed diets, and lacto-ovo vegetarian diets that are not based on unrefined cereals grains or high extraction rate (>90%) flours)<br>14 (22% dietary absorption; Cereal-based diets, with >50% energy intake from cereal grains or legumes and negligible intake of animal protein) |
|--------|---|

\*\* Competent national or regional authorities should determine an appropriate NRV-R that best represents the dietary absorption from relevant diets.

The Chair proposes that the eWG consider the same range of elements for the iron NRV-R as those adopted for the zinc NRVs-R.

## **B CONSIDERATION OF ISSUES**

### **1 Previous consideration of candidate DIRVs for iron as the basis of the NRV-R**

The 2013 eWG considered the matter of one or more NRVs-R for iron [and zinc], 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 considered CP2 which provided 4 candidate DIRVs:

| <b>RASB</b>                  | <b>Candidate DIRV (All INL<sub>98</sub>)</b>   |
|------------------------------|--|
| IOM (United States & Canada) | 13 mg (18% absorption)                         |
| NIHN (Japan)                 | 9 mg (15% absorption)                          |
| Nordic Council of Ministers  | 12 mg (15% absorption)                         |
|                              |  |
| WHO/FAO (2004)               | 14 mg (15% absorption); 22 mg (10% absorption) |
| <i>Current NRV-R</i>         | 14 mg  |

NPE Australia New Zealand sourced from IOM

The 2014 eWG continued to strongly prefer DIRVs from WHO/FAO (CX/NFSDU 14/36/5) 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”.

| <b>2014 eWG preferences</b>     | <b>RASB</b>                  | <b>Candidate DIRV (All INL<sub>98</sub>)</b>      |
|---------------------------------|------------------------------|---|
|                                 | IOM (United States & Canada) | 13 mg (18% absorption)                            |
|                                 | NIHN (Japan)                 | 9 mg (15% absorption)                             |
| 1. (15% & 10%)<br>2. (15% only) | WHO/FAO                      | 14 mg (15% absorption);<br>22 mg (10% absorption) |
|                                 | Nordic Council of Ministers  | 12 mg (15% absorption)                            |
|                                 | <i>Current NRV-R</i>         | 14 mg   |

### **EFSA draft scientific opinion for iron (2015)**

EFSA issued a draft scientific opinion on iron requirements in May 2015 and submissions closed on 19 July 2015. The opinion has not been formally adopted and may be subject to change following public consultation however it is expected that the final scientific opinion will be adopted before the next session of CCNFSDU.

Key information from Section 6 in EFSA's draft opinion is provided below; further details are provided in Attachments 1 and 2.

The Panel set DRVs for adult men and premenopausal women using modelled obligatory losses; such losses at the 97.5<sup>th</sup> percentile were used as a basis for calculation of INL<sub>98</sub> for men. The skewed distribution of basal losses of iron likely arising from menstrual losses necessitated some careful evaluation of the upper cut-off level for losses and requirements and the derivation of a INL<sub>95</sub> for premenopausal women in general.

The Panel has, in the light of absorptive and homeostatic adaptation in the acquisition and systemic distribution of iron depots, tried to be pragmatic in its use of percentage absorption figures to calculate DRVs from the physiological requirements. It is assumed that the diets and iron status of the EU population are largely similar to those in the nationally representative survey in the UK and that the distribution of serum ferritin concentration and associated percentage absorption of iron would also be similar and therefore, appropriate for converting physiological requirements to DRVs for iron for the EU population.

The Panel notes that iron requirements are very different before and after menopause due to the presence or absence of menstrual iron losses and considers that the occurrence of menopause, rather than age, should define DRVs for women. The Panel

also considers that DRVs do not need to be derived for vegetarians as a separate population group because the bioavailability of iron from European vegetarian diets is not substantially different from diets containing meat.

In relation to men, the 97.5<sup>th</sup> percentile of the model-based distribution of obligatory losses is 1.72 mg/day. A representative serum ferritin concentration at the lower end of observed distributions and reference ranges was taken as 30 µg/L. This is associated with a percentage dietary iron absorption of 16%. Using this figure to convert the physiological requirement into the dietary requirement results in a INL<sub>98</sub> of 10.8 mg/day rounded to 11 mg/day.

In relation to premenopausal women, the 95<sup>th</sup> percentile of the model-based distribution of obligatory losses of 2.80 mg/day was selected since the data are skewed due to large menstrual losses of some women. The Panel assumes the same representative serum ferritin concentration as 30 µg/L which corresponds to a percentage dietary iron absorption of 18%. Intakes meeting the dietary iron requirement of ~95% of premenopausal women are calculated as 15.6 mg/day, which converts to 16 mg/day after rounding. The Panel considers that the INL<sub>95</sub> meets the dietary requirement of 95% of women in their reproductive years and is derived from a group of premenopausal women some of whom use oral contraceptives, as is the case in the EU.

The 2015 eWG is asked to review the candidate DIRVs for iron including EFSA's draft scientific opinion. The Chair has followed EFSA's draft recommendations for Population Reference Intakes for premenopausal women as INL<sub>95</sub>, rather than using the INL<sub>97.5</sub> which corresponds to 17.4 mg/day, and results in an average adult INL<sub>98</sub> of  $[10.8 + 17.4 = 28.2]/2 = 14.1$  mg/day.

| RASB                         | Candidate DIRV<br>(All INL <sub>98</sub> except INL <sub>95</sub> for premenopausal women (EFSA)) |
|------------------------------|---|
| IOM (United States & Canada) | 13 mg (18% absorption)  |
| EFSA (EU)                    | 13.5 mg (17% absorption)  |
| NIHN (Japan)                 | 9 mg (15% absorption)   |
| Nordic Council of Ministers  | 12 mg (15% absorption)  |
| WHO/FAO (2004)               | 14 mg (15% absorption); 22 mg (10% absorption)  |
| <i>Current NRV-R</i>         | 14 mg   |

If more than one % absorption is preferred, the current footnote applicable to the NRVs-R for zinc also will be applied to NRVs-R for iron.

**Q1** After reviewing CCNFSDU's previous decisions on NRVs-R for zinc, and considering the candidate DIRVs for iron including from the EU, which candidate DIRV(s) including % absorptions for iron do you prefer (amount, two values, single value)?

### Dietary descriptions related to iron NRV-R

Following the strong preference for WHO/FAO as the basis of the NRV-R, the 2014 eWG considered the dietary descriptions in Table 3.3 and 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 2014 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           |

As indicated above, EFSA's draft scientific opinion commented that: *DRVs do not need to be derived for vegetarians as a separate population group because the bioavailability of iron from European vegetarian diets is not substantially different from diets containing meat.*

EFSA describes *bioavailability* as a measure of the absorption and utilisation (haemoglobin incorporation) of dietary iron and is expressed either as a percentage or fraction of the total iron intake.

**Q2a** Should dietary description(s) corresponding to % iron absorption(s) be included so as to be consistent with the NRVs-R for zinc?

**Q2b** If a candidate DIRV of a single % iron absorption from a RASB other than WHO/FAO were to be preferred by the eWG, could the dietary description proposed for 15% iron absorption be applied to a % absorption higher than 15% i.e. up to 18%?

## 2 Previous consideration of candidate DIRVs for copper as the basis of the NRV-R

The 2015 eWG considered CP1 which provided 4 candidate DIRVs for copper:

| RASB                                | INL <sub>98</sub> or AI | Candidate DIRV (µg)     |
|-------------------------------------|-------------------------|-------------------------|
| IOM (United States & Canada)        | INL <sub>98</sub>       | 900                     |
| NHMRC/MOH (Australia & New Zealand) | AI                      | 1450                    |
| NIHN (Japan)                        | INL <sub>98</sub>       | 800                     |
| WHO (1996)                          | Normative requirement   | 750                     |
| Current NRV-R                       |                         | Value to be established |

NPE Nordic countries sourced from IOM

The next table summarises members' preferences in response to CP1 and CP2 for the leading candidate DIRVs for copper including a suggestion for averaging the two DIRVs that are INL<sub>98</sub>. The majority of members selected the DIRV recommended by or equivalent to the IOM of 900 µg/day; this support strengthened in response to CP2.

| No. (CP1) | No (CP2) | Candidate DIRV (µg)         | Compiled comments  |
|-----------|----------|-----------------------------|--|
| 9         | 11       | 900 (IOM)                   | <p>It is an INL<sub>98</sub> based on the physiological endpoint of a combination of indicators in controlled depletions/repletion studies using specific amounts of copper in men and women.</p> <p>Average of IOM and NIHIN INL<sub>98</sub> but rounding the average of 850 µg to 900 µg since the IOM rounded their DIRVs to the nearest 100 µg. Level is sufficient to avoid deficiency and is the average of the values of all RASBs.</p> <p>Value based on experimental data and is INL<sub>98</sub>.</p> <p>This is the middle of the range of proposals and based on experimental data and a INL<sub>98</sub>.</p> <p>This is based on primary evaluation of the experimental data.</p> |
| 6         | 3        | Average of IOM, NIHIN = 850 | <p>INL<sub>98</sub> should be selected in accordance with GP3.2.1.1 and supports averaging candidate DIRVs from IOM and NIHIN because these two organisations seem to take the same calculation approach.</p> <p>Unrounded average of the IOM and NIHIN DIRVs of 850 as they are based on the same physiological endpoint, depletion/repletion studies.</p>  |

#### **EFSA draft scientific opinion for copper (2015)**

EFSA issued a draft scientific opinion on copper requirements in June 2015. The opinion has not been formally adopted and may be subject to change following public consultation however it is uncertain whether the final scientific opinion will be adopted before the next session of CCNFSDU.

Key information from Section 6 in EFSA's draft opinion is provided below; further details are provided in Attachments 1 and 2.

The Panel considers that there are no biomarkers of copper status which are sufficiently robust to be used to derive requirements for copper. The Panel also considers that there are significant limitations to copper balance studies but that they may be used in conjunction with intake data to inform the setting of DRVs for copper for adults. The Panel proposes to set an AI using both observed intakes and the results from balance studies despite their limitations.

The range of average copper intake in eight EU countries for people aged 18–65 years is 1.47–1.67 mg/day for men and 1.19–1.44 mg/day for women, excluding one national survey of pregnant women. The Panel notes that midpoints of ranges for intake estimates in these and older adult age and sex groups are in good agreement with medians, for the respective sex and age groups, of the average intakes estimated per survey.

The Panel notes that there is at present insufficient evidence for considering different DRVs according to age in adults, and decided to merge the ranges for all men aged 18 years and older for which the midpoint is 1.47 mg/day. Similarly, for women, the merged range for all women aged 18 years and older is at the midpoint of 1.30 mg/day. The median of average intakes of adult women (≥ 18 years) is 1.29 mg/day and the median of average intakes of adult men (≥ 18 years) is 1.52 mg/day

Given these difference in intake, the Panel proposes to set AIs for men and women separately. For men, based on observed intake and taking into account that zero copper balance was reported at a copper intake of approximately 1.6 mg/day in men,

the Panel proposes an AI of 1.6 mg/day. For women, based on observed intakes, the Panel proposes an AI of 1.3 mg/day.

The 2015 eWG is asked to review the candidate DIRVs for copper including EFSA's draft scientific opinion. The finally recommended NRV-R for copper will be expressed according to the convention:  $mg \geq 1$  mg and  $\mu g < 1$  mg, consistent with all NRVs-R reviewed to date.

| <b>RASB</b>                         | <b>INL<sub>98</sub> or AI</b> | <b>Candidate DIRV (<math>\mu</math>g)</b> |
|-------------------------------------|-------------------------------|---|
| IOM (United States & Canada)        | INL <sub>98</sub>             | 900                                       |
| EFSA (European Union)               | AI                            | 1,450                                     |
| NHMRC/MOH (Australia & New Zealand) | AI                            | 1,450                                     |
| NIHN (Japan)                        | INL <sub>98</sub>             | 800                                       |
| Average of IOM and NIHN             | INL <sub>98</sub>             | 850                                       |
| <i>Current NRV-R</i>                |                               | <i>Value to be established</i>            |

**Q3** After considering the 2015 eWG's responses and the candidate DIRVs for copper including from the EU, which candidate DIRV do you prefer?

ATTACHMENT 1

**Table 1: Male and Female INL<sub>98</sub> or AI for iron and copper from WHO/FAO and Accepted RASBs**

| Vitamin or mineral<br>(type DIRV)                                      | 19-50 yrs | United<br>States &<br>Canada | European<br>Union | Australia &<br>New Zealand | Japan | Nordic<br>countries              | WHO/FAO                  |
|--|-----------|------------------------------|-------------------|----------------------------|-------|----------------------------------|--------------------------|
| Iron (mg) (%<br>absorption)<br>(INL <sub>98</sub> unless<br>indicated) | Male      | 8 (18%)                      | 11 (16%)          | NPE                        | 7.3   | 9 (15%)                          | 9.1 (15%)<br>3.7 (10%)   |
|  | Female    | 18 (18%)                     | 16* (18%)         |                            | 10.8* | 15 (15%)<br>(INL <sub>95</sub> ) | 19.6 (15%)<br>29.4 (10%) |
| Copper (μg) (INL <sub>98</sub><br>or AI)                               | Male      | 900                          | 1,600 (AI)        | 1,700 (AI)                 | 900   | NPE                              | –                        |
|  | Female    | 900                          | 1,300 (AI)        | 1,200 (AI)                 | 700   |                                  | –                        |

\* DIRV for menstruating/pre-menopausal women

**Table 2: Supplementary Information: Iron and copper**

Assume all % values divided by 100 in calculations

|                        | <b>Physiological endpoint for EAR or choice of AI</b>   | <b>Reason for choice of endpoint(s)</b>   | <b>Relevant parameters in calculation of EAR/AI</b>  | <b>EAR and Coefficient variation; or AI</b>   | <b>Year(s) evaluated (Year latest literature)</b> |
|------------------------|---|---|--|---|---|
|                        |   |   |  | <b>Calculation EAR/AI</b>   |   |
| <b>1 Iron</b>          |   |   |  |   |   |
| United States & Canada | Factorial modelling of factors: basal loss, menstrual loss, dietary absorption.<br><br>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. Median and 97.5 <sup>th</sup> percentiles of each distribution used in calculation of EAR and RDA respectively. | Total need for absorbed iron can be estimated   | Basal loss (median)<br>(M) 1.08 mg<br>(F) 0.896 mg;<br><br>Menstrual loss (median) (F) 0.51 mg<br><br>Dietary absorption (upper value) 18%   | EAR<br><br>M 6 mg; F 8.1 mg<br><br>%CV not applied (RDA derived as 97.5 <sup>th</sup> percentile distribution of iron requirements)<br><br>EAR<br>(M) = basal loss/absorption<br>(F) = (basal loss + menstrual loss)/absorption | 1998–2000 (2000)                                  |
| European Union         | Estimate of physiological iron requirement using whole body iron loss data derived from isotope studies (2009) in 29 men and 19 menstruating women.   | This considered more accurate than combining all losses from the different routes and magnifying the uncertainty of estimate. | (M) 50 <sup>th</sup> and 97.5 <sup>th</sup> percentile model-based distribution of iron turnover and daily losses ~ 0.95 and 1.72 mg/day.<br>Assumed serum ferritin 30 ug/L and associated with dietary absorption of 16%.<br>(F) 50 <sup>th</sup> and 95 <sup>th</sup> percentile model-based distribution of iron losses ~ 1.34 and 2.80 mg/day. Assumed serum | EAR<br><br>M 6 mg; F 7 mg   | ? (2014)  |

|                  |   |  |   |   |                  |
|------------------|---|--|---|---|------------------|
|                  |   |  | ferritin 30 ug/L and associated with dietary absorption of 18%.   |   |                  |
| Japan            | Factorial calculation of factors: Basal loss (mostly faecal), menstrual loss, iron storage, dietary absorption.   | Total need for absorbed iron can be estimated                              | <p>Basal loss 0.96 mg/day for 68.6 kg extrapolated to B wt each sex using 0.75<sup>th</sup> power of a B wt ratio.</p> <p>Menstrual loss 0.55 mg</p> <p>Dietary absorption 15%</p>  | <p>EAR</p> <p>M 6.3 mg; F 8.8 mg (menstruation 19-50 yrs)<br/>10% CV</p> <hr/> <p>Basal loss (M) = <math>0.96 \times [B \text{ wt (M)}/68.6]^{0.75}</math></p> <p>Basal loss (F) = <math>0.96 \times [B \text{ wt (F)}/68.6]^{0.75}</math></p> <p>EAR (M) = basal loss (M)/absorption</p> <p>EAR (F) = (basal loss (F) + menstrual loss)/absorption</p> | 2008–2009 (2003) |
| Nordic countries | <p>Factorial modelling of factors: basal loss, menstrual loss, dietary absorption.</p> <p>Amounts needed to cover basic losses and growth for approximately 95% individuals except for women of childbearing age, amounts that meet the needs of approximately 90% of menstruating women.</p> | Iron needs for growth, basal losses, menstrual losses                      | <p>Basal loss:</p> <p>(M) 1.05 mg (median); 1.37 mg (95<sup>th</sup> percentile)</p> <p>(F) 0.87 mg (median) + menstrual loss 0.48 mg (median); or 1.90 mg (95<sup>th</sup> percentile)</p> <p>Total absolute requirements:</p> <p>(M) 1.05 mg (median); 1.37 mg (95<sup>th</sup> percentile)</p> <p>(F) 1.35 mg (median); 2.22 mg (90<sup>th</sup> percentile)</p> <p>Iron absorption of 15%</p> | <p>EAR</p> <p>M 7 mg; F 9 mg</p> <p>%CV not presented</p> <hr/> <p>EAR=((need for growth+ median basal loss + median menstrual loss)/15)*100</p>  | ?-2013 (2013)    |
| WHO/FAO          | Because distribution of iron requirement is skewed for menstruating women i.e. not normally distributed, the simple   | The RNIs are based on the 95 <sup>th</sup> percentile of the absorbed iron | Basal loss:   | EAR (Back calculated from RNI, males only)  | 1998–2004 (1998) |

|   |   |   |   |  |
|---|---|---|---|--|
| <p>addition of requirement components is inappropriate. Median and 95<sup>th</sup> percentiles of each distribution for losses used in calculation.</p> | <p>requirements/dietary absorption.</p> | <p>(F) 0.87 mg (median)<br/>+ menstrual loss<br/>0.48 mg (median); or 1.90 mg (95<sup>th</sup> percentile)</p> <p>Total absolute requirements:<br/>(M) 1.05 mg (median);<br/>1.37 mg (95<sup>th</sup> percentile)<br/>(F) 1.46 mg (median); 2.94 mg (95<sup>th</sup> percentile)</p> <p>Selected dietary absorption<br/>15% &amp; 10%</p> | <p>M 7.2 mg (15%); 10.8 (10%)<br/>15% CV</p> <hr/> <p>EARs cannot be calculated from RNIs for adult females 19-50 years because of the skewed distribution of requirements.</p> |  |
|---|---|---|---|--|

|                         | <b>Physiological endpoint for EAR or choice of AI</b>   | <b>Reason for choice of endpoint(s)</b>   | <b>Relevant parameters in calculation of EAR/AI</b>   | <b>EAR and Coefficient variation; or AI</b> | <b>Year(s) evaluated (Year latest literature)</b> |
|-------------------------|---|---|---|---|---|
|                         |   |   |   | <b>Calculation EAR/AI</b>                   |   |
| <b>2 Copper</b>         |   |   |   |   |   |
| United States & Canada  | Combination of indicators in controlled depletion/repletion studies using specific amounts of copper in men or women.   | If significant decreases in serum Cu, ceruloplasmin, superoxide, dismutase (SOD) on experimental diet and reversed with added copper, then diet was deficient and insufficient to maintain status.<br>A lack of change in copper status indicates that the level of copper in the experimental diet is adequate to maintain status. | 3 studies, M or F. Indicators included plasma and platelet Cu, ceruloplasmin, superoxide, dismutase (SOD).  | EAR<br>M; 900 µg; F 900 µg<br>15% CV.       | 1999–2001 (2000)                                  |
| European Union          | No biomarkers of copper status are sufficiently robust to be used to derive requirements for copper. Significant limitations to copper balance studies such as possibly reflecting only adaptive changes before reaching a new steady state, or conditions for maintenance of nutrient stores for a given diet. | Although significant limitations to copper balance studies, they may be used together with observed dietary intakes to set DRVs.  | Average copper intakes from 8 EU countries for M and non-pregnant F aged 18+ years, rounded up, and M consistent with finding of zero copper balance at 1.6 mg/day. | AI  | ? 2015  |
| Australia & New Zealand | Small data sets were insufficient to set EAR  |   | Based on highest mean adult intake from 1995 and 1997 national dietary surveys in Australia and New Zealand.  | AI  | ?–2005 (1999)                                     |

|       |   |  |  |                                     |                     |
|-------|---|--|--|-------------------------------------|---------------------|
| Japan | Saturation of biomarkers of copper status: plasma Cu, urinary Cu and salivary Cu and plasma CuSOD activity. |  | Minimal intake to achieve saturation of selected biomarkers as 0.72 mg/day (for males) and extrapolated by body weight (see Table 3) for females | EAR<br>M 700 µg; F 600 µg<br>15% CV | 2008–2009<br>(1998) |
|-------|---|--|--|-------------------------------------|---------------------|

ATTACHMENT 2

REFERENCES

References for DIRVs, ULs for Iron and Copper and Iron Dietary Descriptions

| Nutrient<br>(information)  | Name of publication  | Year<br>Publication | Bibliographic Reference   | Official Weblink  |
|--|--|---------------------|---|---|
| <b>INTERNATIONAL: WHO/FAO or WHO or WHO/FAO/IAEA;</b>            |  |                     |   |   |
| Iron<br>(DIRV)   | Vitamin and Mineral Requirements in Human Nutrition  | 2004                | World Health Organization and Food and Agricultural Organization (2004) <i>Vitamin and Mineral Requirements in Human Nutrition</i> , 2 <sup>nd</sup> edition. WHO, Geneva   | <a href="http://www.who.int/nutrition/publications/micronutrients/9241546123/en/">http://www.who.int/nutrition/publications/micronutrients/9241546123/en/</a> |
| Iron<br>(Back calculated EAR)<br><br>(Iron dietary descriptions) | Guidelines on Food Fortification with Micronutrients   | 2006                | World Health Organization and Food and Agricultural Organization (2006) <i>Guidelines on Food Fortification with Micronutrients</i> . WHO, Geneva   | <a href="http://www.who.int/nutrition/publications/micronutrients/9241594012/en/">http://www.who.int/nutrition/publications/micronutrients/9241594012/en/</a> |
| Copper<br>(UL)   | Trace elements in human nutrition and health   | 1996                | World Health Organization (1996) <i>Trace elements in human nutrition and health</i> , WHO, Geneva  | <a href="http://www.who.int/nutrition/publications/micronutrients/9241561734/en/">http://www.who.int/nutrition/publications/micronutrients/9241561734/en/</a> |
| <b>USA &amp; CANADA</b>  |  |                     |   |   |
| Iron, copper<br>(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. <i>Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc</i> . Washington, DC: The National Academy Press. | <a href="http://www.nap.edu/catalog.php?record_id=10026">http://www.nap.edu/catalog.php?record_id=10026</a>   |

| <b>Nutrient<br/>(information)</b>  | <b>Name of publication</b>  | <b>Year<br/>Publication</b> | <b>Bibliographic Reference</b>  | <b>Official Weblink</b>   |
|------------------------------------|---|-----------------------------|---|---|
| <b>EUROPEAN UNION</b>              |   |                             |   |   |
| Iron (draft DIRV)                  | Draft Scientific Opinion on Dietary Reference Values for Iron                     | 2015                        | EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. <i>Draft Scientific Opinion on Dietary Reference Values for Iron</i> . Doi: 10.2903/j.efsa20YY. NNNN   | <a href="http://www.efsa.europa.eu/en/consultations/call/150526.htm">http://www.efsa.europa.eu/en/consultations/call/150526.htm</a>             |
| Copper (draft DIRV)                | Draft Scientific Opinion on Dietary Reference Values for Copper                   | 2015                        | EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. <i>Draft Scientific Opinion on Dietary Reference Values for Copper</i> . Doi: 10.2903/j.efsa20YY. NNNN   | <a href="http://www.efsa.europa.eu/en/consultations/call/150629a.htm">http://www.efsa.europa.eu/en/consultations/call/150629a.htm</a>           |
| Iron, copper (UL)                  | Tolerable Upper Intake Levels for Vitamins and Minerals                           | 2006                        | Scientific Committee on Food and European Food Safety Authority. 2006. <i>Tolerable Upper Intake Levels for Vitamins and Minerals</i> . EFSA, Parma   | <a href="http://www.efsa.europa.eu/en/ndatopics/docs/ndatolerableuil.pdf">http://www.efsa.europa.eu/en/ndatopics/docs/ndatolerableuil.pdf</a>   |
| <b>AUSTRALIA &amp; NEW ZEALAND</b> |   |                             |   |   |
| Copper (DIRV)                      | Nutrient Reference Values for Australia and New Zealand                           | 2006                        | <i>Nutrient Reference Values for Australia and New Zealand; 2006</i> ; Australian Government Department of Health and Ageing, National Health and Medical Research Council; and New Zealand Ministry of Health; Canberra, Australia | <a href="https://www.nhmrc.gov.au/guidelines-publications/n35-n36-n37">https://www.nhmrc.gov.au/guidelines-publications/n35-n36-n37</a>         |
| <b>JAPAN</b>                       |   |                             |   |   |
| Iron, copper (DIRV)                | Dietary Reference Intakes for Japanese, 2010                                      | 2013                        | <i>Dietary Reference Intakes for Japanese, 2010</i> ; 2013; Journal of Nutritional Science and Vitaminology vol. 59, supplement ISSN 0301-4800  | <a href="https://www.jstage.jst.go.jp/browse/jnsv/59/Supplement/_contents">https://www.jstage.jst.go.jp/browse/jnsv/59/Supplement/_contents</a> |
| <b>NORDIC COUNTRIES</b>            |   |                             |   |   |
| Iron (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<br><br>All systematic reviews were published in Food & Nutrition Research Volume 57 (2013). Other                        | <a href="http://www.norden.org/en/publications/publikationer/2014-002">http://www.norden.org/en/publications/publikationer/2014-002</a>         |

| <b>Nutrient<br/>(information)</b> | <b>Name of publication</b> | <b>Year<br/>Publication</b> | <b>Bibliographic Reference</b>   | <b>Official Weblink</b> |
|-----------------------------------|----------------------------|-----------------------------|--|-------------------------|
|                                   |                            |                             | background papers can be found on the Nordic Council of Ministers (NCM) website. |                         |

[INSERT SUBMITTER NAME HERE]

**SUBMITTER RESPONSE FORM, EWG NRV-R JULY 2015**

| <b>Q. No.</b> | <b>Question</b>   | <b>Response including the reasons for your answer:</b> |
|---------------|---|--|
| 1             | After reviewing CCNFSDU's previous decisions on NRVs-R for zinc, and considering the candidate DIRVs for iron including from the EU, which candidate DIRV(s) including % absorptions for iron do you prefer (amount, two values, single value)? |  |
| 2a            | Should dietary description(s) corresponding to % iron absorption(s) be included so as to be consistent with the NRVs-R for zinc?  |  |
| 2b            | If a candidate DIRV of a single % iron absorption from a RASB other than WHO/FAO were to be preferred by the eWG, could the dietary description proposed for 15% iron absorption be applied to a % absorption higher than 15% i.e. up to 18%?   |  |
| 3             | After considering the 2015 eWG's responses and the candidate DIRVs for copper including from the EU, which candidate DIRV do you prefer?  |  |