An evaluation of the EFSA's dietary reference values (DRVs), Part 1

Dietary reference values for vitamins and minerals for adults

No. 2018/19A, The Hague, September 18, 2018

Background document to:

Voedingsnormen voor vitamines en mineralen voor volwassenen

No. 2018/19, The Hague, September 18, 2018

Health Council of the Netherlands

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01 introduction

This report serves as the background document for the Health Council advisory report on micronutrient requirements of adults[4], which has been prepared by the Council's Committee on Nutrition. It describes the evaluation of reference values per nutrient. The advisory report gives recommendations based on the outcome of these evaluations. The evaluations cover the reference values for healthy adults except for pregnant and lactating women. These values for pregnant women and lactating women as well as for infants and for children, will be evaluated and presented separately. This background document has been prepared by a working group of the Committee on Nutrition.

1.1 EFSA's dietary reference values are used as the point of departure

The point of departure of this evaluation of the Dutch reference values was to adopt EFSA's dietary reference values[5-32] for use in the Netherlands, unless there were major objections against these values. The Health Council considers that harmonisation of reference values across the EU is preferable. Reference values refer to populations comprising people with a broad range of characteristics, dietary habits and lifestyles, and generally, on this population level, there are no, or only small differences between countries. A differentiation of reference values between European countries will seldom be required for physiological reasons. Note that reference values for larger geographical region (e.g. for the Scandinavian countries, the German-speaking countries, the United States of America and Canada) were established earlier. Furthermore, and importantly, EFSA´s reports on dietary reference values provide a thorough and transparent evaluation of the scientific evidence, and were established by panels consisting of scientific experts from member states, including the Netherlands. The EFSA reports on micronutrients were published in the period 2014-2018 (the final report has not yet been published) and can be considered to be the most recently available, thus the use of these reports as the point of departure for updating the scientific background of the Dutch reference values was assumed to be sufficient. This is also the reason why the Committee did not carry out an update of the literature.

1.2 EFSA's reference values are accepted unless there are objections

To determine whether there were objections against the use of EFSA's reference values in the Netherlands, the Committee identified three key questions:

1. Should EFSA's reference values be rejected based on a specific nutritional context in the Netherlands that differs from (the rest of) Europe?

The nutritional context or policy in the Netherlands may differ from the European context on which EFSA's reference values are based, and this may require the use of other reference values in the Netherlands. Note

that EFSA's dietary reference values were used as the point of departure for the evaluation, because the Committee anticipated that the nutritional context or policy in the Netherlands would rarely give rise to the rejection of EFSA's dietary reference values.

2. Do (part of) EFSA's reference values differ 10% or more from the 2014 values for the Netherlands?

The Committee considered that if EFSA's reference values were close to the values currently used in the Netherlands, switching to EFSA's values would have no, or only limited implications, and this would diminish possible objections against the use of EFSA's values in the Netherlands. Note that, in these cases, the Committee still describes and evaluates the scientific basis of EFSA's reference values, so that for all nutrients the report summarizes the evidence on which the reference values are based.

3. Are there objections against the scientific basis used by EFSA for this specific nutrient?

The Committee evaluated the research and argumentation that EFSA used to establish the reference values for each nutrient; in the report, this is referred to as the evaluation of the scientific basis of EFSA's reference values for the nutrient considered. The evaluation was carried out by comparing EFSA's reference values and their scientific basis[5-32] with the reference values in five (sets of) reports which were considered most relevant for this evaluation. The first set of reports is the compilation of values which has been used in the Netherlands since 2014,[33] based mainly on the Dutch[34-36] and Scandinavian[37] reports. Two reports covered groups of European countries: the Scandinavian countries[37] and the German-speaking countries,[38] and thus required harmonisation with several European countries. Two other reports aimed to establish values for large geographical areas: the IOM reports for the United Stated of America and Canada;[2,39-43] and the report by WHO/FAO which is used in many countries all over the world.[44] The latter report is primarily used in non-Western areas and, therefore, the WHO/FAO reference values may deviate from the reference values for Western countries.

The Committee considered that objections should be based on scientific evidence. This implies that if there is a lack of scientific evidence on requirements, there is also no evidence to substantiate objections against EFSA's reference values. These reference values were then accepted for use in the Netherlands, because there is no scientific evidence available to define more evidence-based reference values than EFSA has done. The advisory report will, however, specify which of the reference values for the Netherlands are based on limited knowledge of requirements.

1.3 Evaluation steps taken for each nutrient

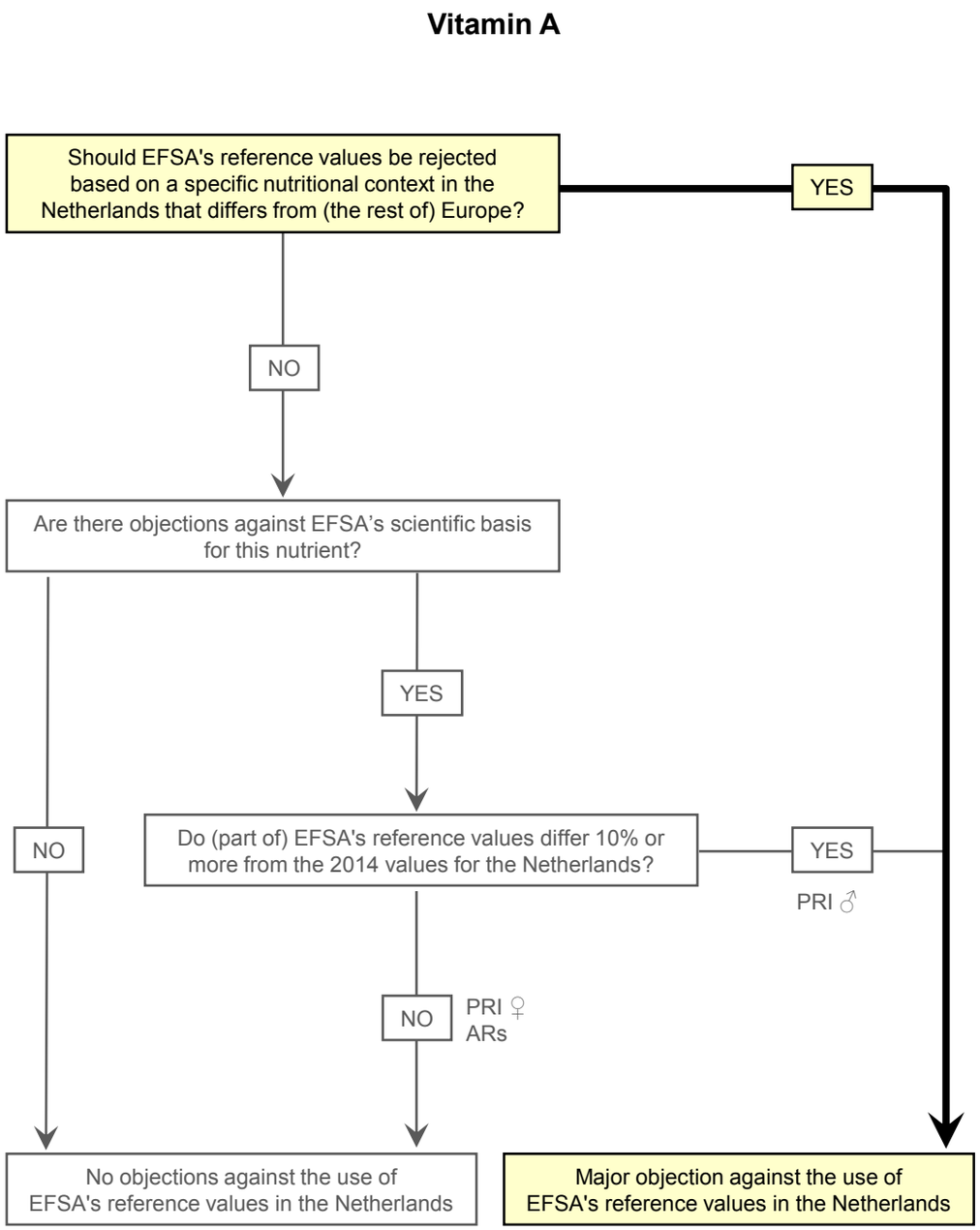
Chapters 2 to 28 describe the evaluation of reference values per nutrient. Each chapter starts with a schedule presenting the answers to the three questions described in paragraph 1.2. Thereafter, the evaluation and argumentation which the Committee used to reach the conclusion is

described in more detail, before the conclusion itself is presented. Each of these chapters consists of four paragraphs:

Paragraph 1	The first paragraph presents a table with the reference values in the EFSA report and in the five (sets of) reports which are used for comparison; the table only comprises the reports with reference values for the nutrient in question. Note that the reports use different names for the different types of reference values (Annex A). The percentual differences between EFSA's values and the values in the other five (sets of) reports are described.
Paragraph 2	The second paragraph provides an explanation for the observed differences between the reports regarding the research and argumentation used to establish the reference values. This step provided the Committee with more insight into assumptions, uncertainties and points of discussion related to the derivation of the reference values. The Committee describes the information as provided in the reports; the original publications were only consulted if considered necessary. In this second paragraph, the Committee also describes whether organisations differentiated between subgroups according to sex and/or age, and if available, the argumentation for these choices. This is relevant, because the choices regarding these subgroups are not consistent between the reports and may impact the resulting reference values. If the reports use different expression units for their reference values, this is also described in the second paragraph.
Paragraph 3	The third paragraph describes the Committee's conclusion on the scientific basis of EFSA's reference values for the nutrient considered. In this paragraph the Committee interprets and evaluates the information provided in the second paragraph, and in addition, the information from studies described by EFSA on the direct relationship between the intake of the nutrient and the occurrence, correction or prevention of clinical signs of deficiency. The latter studies generally do not form the basis of the actual reference values, but do provide relevant background information for interpreting the relevance of the reference values for health. In this third paragraph, the Committee also presents a textbox with background information on the function of the nutrient, the occurrence of deficiencies and the clinical symptoms of insufficient intakes.
Paragraph 4	The fourth and final paragraph in each chapter presents a summary of the main findings, the conclusion by the Committee and the reference values recommended for use in the Netherlands.

Population intake data for the NL were used as background information by the Committee. If EFSA's reference value(s) differ from the reference value used in the Netherlands since 2014, and are adopted by the Committee for use in the Netherlands, this has implications for the implementation and use of the reference values. For instance, on a population level, even if intake levels stay the same, the risk of insufficient intakes will appear to increase or decrease, simply as a result of a change of reference values. The National Institute for Public Health and the Environment (RIVM) described the habitual intake of Dutch adults aged 18-50 years, based on the Dutch National Food Consumption Survey 2007-2010, and compared these intakes with the Dutch reference values used from 2014, and with EFSA's reference values. The results were available for the Committee during the evaluation of the reference values and used as background information. The findings are published by the RIVM simultaneously with the present advisory report.[45] Intake data in themselves provide no information on the requirements for a nutrient and, therefore, these data were not used by the Committee as an argument for accepting or rejecting reference values.

02
vitamin A (retinol and carotenes)



2.1 Overview and comparison of values

Table 1. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI (µg RE or RAE[a]/day)			AR (µg/day)		CV[b] (%)	Main criterion
	Type	♂	♀	♂	♀		
EFSA 2015[16]	PRI	750	650	570	490	15%	Factorial approach based on the average intake needed to establish adequate liver stores of 20 µg/g liver tissue.
NCM 2014[37] = HCNL 2014[33]	RI	900	700	600	500	25/20%	Factorial approach NCM adopted IOM.
DACH 2015[38]	AI	1,000	800	600	600	33/12%[c]	Not clearly specified.
IOM 2001[41]	RDA	900	700	625	500	20%	Factorial approach based on the average intake needed to establish adequate liver stores of 20 µg/g liver tissue.
WHO/FAO 2004[44]	RI	600	19-65 yr: 500 >65 yr: 600	300	19-65 yr: 270 >65 yr: 300	50/23%	Based on values derived for prevention of (sub)clinical deficiency in late infancy, AR 4.8 and RI 9.3µg RE/kg/day (AR/RI are supported by additional data); WHO/FAO 1988 was maintained.

[a] RE = retinol equivalent; RAE = retinol activity equivalent. The difference is described and discussed in paragraph 1.2 under the header "The assumed efficiency of the conversion of carotenes to retinol, or the unit of expression of the reference values: RE versus RAE."

[b] If the coefficient of variation was not specified in the report, it was calculated as 100% x [(PRI/RI/RDA - AR) / 2] / AR.

[c] DACH assumes that the CV of women is lower than the CV of men, considering that their average plasma concentration is lower (DACH refers to Heseker et al., 1994).

Table 1 shows that NCM, IOM and especially DACH use higher values than EFSA's PRIs (+14%, +14% and +29%), whereas WHO/FAO uses a lower value (-21%).

2.2 Explanation of differences between reports

This evaluation focuses on the difference between EFSA and IOM, because:

- NCM adopted the IOM approach and values.
- The DACH approach is not clearly specified.
- The WHO/FAO-values are based on the extrapolation of estimates for infants to adults, which implies more uncertainty compared to methods based on estimates in adults.

The ARs of EFSA and IOM were estimated using a factorial method in which six estimates ("factors") are multiplied. Table 2 compares the values of all six factors and presents the evaluation of the differences by the Committee in the right column.

Differences between older and younger adults

EFSA, NCM, DACH and IOM set equal reference values for older and younger adults and WHO/FAO does so for men. WHO/FAO's value for older women (600 µg RE/d) differs from their value for younger women (500 µg RE/d), but this difference is not explained in the WHO/FAO report.

Sex differences

All reports established different values for men and women. This difference results from the difference in reference body weights between men and women (see Table 2).

The assumed efficiency of the conversion of carotenes to retinol, or the unit of expression of the reference values: RE versus RAE

The reports use different conversion factors for carotenes: EFSA and DACH express their reference values in retinol equivalents (RE) and thus assume a more efficient conversion of carotenes to retinol in comparison to HCNL, NCM, IOM, and WHO/FAO (Table 3). The EFSA Panel notes that there are large uncertainties in establishing equivalency ratios from the whole diet of large populations. In 1993, the Scientific Committee of Food used retinol equivalents (RE). The EFSA Panel considers that current evidence is insufficient to support a change.

Table 3. Differences between reports regarding the efficiency of the conversion of carotenes to retinol

	Unit of expression of dietary reference value		
	Retinol equivalents (RE)	Retinol activity equivalents (RAE)	Other conversion factors
Reports using the conversion factor	EFSA, DACH	HCNL, NCM, IOM	WHO/FAO
Amounts equivalent to 1 µg retinol :			
• β-carotene	6 µg = 1 µg RE	12 µg = 1 µg RAE	14 µg = 1 µg RAE
• Other carotenes	12 µg = 1 µg RE	24 µg = 1 µg RAE	28 µg = 1 µg RAE

Table 2. Comparison of the factorial approaches of EFSA and IOM

Factor	Wording used by EFSA for this factor	EFSA's estimate of this factor		Wording used by IOM for this factor	IOM's estimate of this factor		Evaluation of the difference
Factor 1	target liver concentration	20 µg retinol/g liver		minimum acceptable liver reserve	20 µg retinol/g liver		No difference: EFSA and IOM both use the target liver concentration suggested by Olson et al. (1987).
Factor 2	body / liver retinol stores ratio	x 1.25	(10:8)	ratio of total body: liver vitamin A reserves	x 1.1	(10:9)	EFSA notes that human data are scarce and range between 1.1 and 2.4 (40-90% of whole body retinol is in the liver). EFSA uses 1.25 (80% in the liver), IOM uses 1.11 (90% in the liver). IOM's value represents the lowest point of the range of estimates; EFSA also uses a low value, but not the lowest. As data are scarce, the Committee prefers EFSA's value.
Factor 3	liver / body weight ratio	x 0.024	(2.4%)	liver / body weight ratio	x 0.03	(1:33)	The Committee accepts EFSA's value, because it is based on an update of literature.
Factor 4	fractional catabolic rate of retinol	x 0.007	(0.7% per day)	percent of body vitamin A stores lost when ingesting a vitamin A-free diet	x 0.005	(0.5% per day)	The Committee accepts EFSA's value, because it is based on an update of literature.
Factor 5	1 / efficiency of body storage of ingested retinol	x 2 Assuming that – with adequate liver stores – 80% of body stores are found in the liver, EFSA corrects the estimate by Haskell et al. to 52%	(100%/ 50%)	1 / efficiency of storage of ingested retinol	x 2.5 Data from Bangladeshi adults with ≥20 µg retinol/g liver indicate an average efficiency of storage of ingested retinol of 42% in the liver (Haskell et al., 1997).	(100%/ 40%)	The Committee prefers EFSA's over IOM's interpretation of the publication by Haskell et al. (1997), and therefore accepts EFSA's value. EFSA corrected Haskell's estimate by for the ratio of total body over liver retinol stores, whereas IOM did not. Note that in this study, RAE-intake was almost exclusively retinol (dietary RAE intake was low: approximately 100 µg RAE/day).
	Product of factors 1-5 x 10^3	**8.4**		**Product of factors 1-5 x 10^3**	**8.25**		**Multiplication by 10^3 is needed for the conversion to microgram retinol (activity)equivalents per kilogram (instead of per gram) body weight.**
		♂	♀		♂	♀	
Factor 6	reference body weight (kg)	x 68.1	x 58.5	reference body weight (kg)	x 76	x 61	EFSA's reference body weights are relatively low for use in the Netherlands: on average, Dutch adults are taller than European adults.
	Product of factors 1-6 x 10^3	572	491	Product of factors 1-6 x 10^3	627	503	AR/EAR is calculated by multiplication of the estimates of six factors.
AR	**EFSA's AR**	**570**	**490**	**IOM's EAR**	**625**	**500**	**AR/EAR-values are rounded.**
	Coefficient of variation (CV)	15%	15%	Coefficient of variation (CV)	20%	20%	The Committee has no objections against EFSA's coefficient of variation. The coefficients of variation are based on expert judgement rather than scientific research.
	1.3 x AR	744	638	1.4 x EAR	878	704	PRI is calculated as (1 + 2xCV/100) x AR/EAR.
PRI	**EFSA's PRI**	**750**	**650**	**IOM's RDA**	**900**	**700**	**PRI/RDA-values are rounded.**

2.3 Conclusion on the scientific basis of EFSA's reference values

The Committee agrees with EFSA's estimates for five of the six factors of the factorial method (see the right column of Table 2). However, the reference body weights used by EFSA (factor 6) are relatively low for the Netherlands. On average, Dutch adults are taller than European adults. The factorial method implies that the reference values are proportional to body weight. Table 4 shows the impact on AR and PRI, using EFSA's versus HCNL's reference weights. The Committee prefers to use EFSA's method, but to replace EFSA's reference weights by the reference weights used by HCNL. The resulting values differ only slightly from HCNL 2014 (AR♂ +2.5%, AR♀ +5%, PRI♂ -11%, PRI♀ -3%).

Table 4. Effect of HCNL's higher reference weights on the average requirements and population reference intake estimates using EFSA's method

	Reference body weight (kg)		Average requirement (µg/day)		Population reference intake (µg/day)	
	♂	♀	♂	♀	♂	♀
EFSA	68.1	58.5	570	490	750	650
EFSA's method, but using HCNL's reference weights[35,36]	73.5	62.5	615	525	800	680

In this paragraph the Committee also compares these proposed ARs with intake levels associated with the occurrence, correction or prevention of deficiencies, based on studies described in the EFSA report (Table 5). In the case of vitamin A, one study is relevant in this respect: Sauberlich et al. (1974) induced visual abnormalities in 8 apparently healthy men by feeding them a low-retinol diet, and reported that these abnormalities were corrected by a retinol intake of 300 µg retinol per day and that cutaneous lesions were prevented at an intake of 600 µg/d. The Committee notes that the proposed AR for men (615 µg/day) corresponds with the intake level reported to be associated with prevention of deficiency symptoms in men, and thus appears to be relevant for health maintenance.

Table 5. Vitamin A intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation	Associated intake	Subjects	EFSA's reference
Abnormalities in adaptation to dark and in electroretinographic patterns	Up to 771 days on retinol deficient diets (0-23 µg/d)	8 adult men	Sauberlich et al. Vitamin A metabolism and requirements in the human studied with the use of labelled retinol. Vitamins and Hormones 1974; 32, 251-275.
Correction of abnormalities in adaptation to dark and in electroretinographic patterns	300 µg retinol/d 4-5 µg/kg body weight/d		
Prevention of deficiency symptoms such as electroretinographic anomalies and changes in the eyes and the skin	600 µg retinol/d		

Conclusion regarding the assumed efficiency of the conversion of carotenes to retinol, or the unit of expression of the reference values: RE versus RAE

IOM and Melse-Boonstra et al.[46] report that the results of a substantial number of studies carried out over the last decade provide support for the

use of RAE instead of RE as the unit of expression. The Committee prefers the use of RAE as the unit of expression.

Note that the unit of expression does not influence the outcome of EFSA's factorial method leading to the AR, because EFSA's factorial method estimates the retinol requirements: the estimates of factors 1, 2, 4 and 5 in Table 2 relate mainly or exclusively to retinol (not to carotenes), whereas the estimates of both remaining factors (factor 3: the liver to body weight ratio; and factor 6: reference body weight) are unrelated to retinol or carotenes. The choice regarding the efficiency of the conversion of carotenes to retinol is a separate issue, unrelated to the factorial method. Therefore, the outcome of the factorial method can be expressed in µg RAE/day.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Vitamin A is an essential nutrient as humans do not have the capability for de novo synthesis of compounds with vitamin A activity. Vitamin A is involved in the visual cycle in the retina and the systemic maintenance of growth and integrity of cells in body tissues.

Vitamin A deficiency occurs in low income countries, specifically India and Bangladesh.

Symptoms of vitamin A deficiency involve several functions, such as:

- vision (the most specific clinical consequence is xerophthalmia)
- immunity
- reproduction.

Vitamin A deficiency has also been related to:

- worsening of low iron status, resulting in vitamin A deficiency anaemia
- follicular hyperkeratosis.

2.4 Summary and conclusion

Table 6. Summary of the evaluation of EFSA's AR and PRI values for vitamin A

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL 2014's (=NCM's) ARs[a]	Slightly lower	Note that, after upward correction of EFSA's ARs using the higher reference weights of (taller) Dutch adults, the corrected ARs are slightly *higher* than HCNL 2014's (=NCM's) ARs.
EFSA's PRIs compared to HCNL's (=NCM's) RIs	Lower, especially in men	Note that, after upward correction of EFSA's PRIs using the higher reference weights of (taller) Dutch adults, the corrected PRI for men is still about 10% lower than HCNL 2014's (=NCM's) RI, whereas the corrected PRI for women is almost equal to HCNL 2014's (=NCM's) RI.
Scientific basis of EFSA's ARs	Objections	The Committee has no objections against EFSA's factorial method, based on sufficient liver stores, but considers that higher reference weights should be used for the Netherlands. Sauberlich et al. (1974) estimated that an intake of 600 µg/day is associated with the *prevention* of deficiency symptoms in men. The proposed ARs (615 µg/day) is close to this value.
EFSA's AR and PRI are expressed in retinol equivalents (RE)	The Committee prefers retinol activity equivalents (RAE)	The choice between RE and RAE does not influence the outcome of the factorial method. Therefore, the outcome of the factorial method can be expressed in µg RAE/day.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with most of the other reports evaluated. (Note that WHO/FAO does differentiate for women, but not for men).
Differentiation between men and women	Applied by EFSA	Consistent with the other reports evaluated. The differentiation is based on body weights.

[a] HCNL 2014 served as a temporary update of the Dutch reference values which had not been updated in the Netherlands since 1992. HCNL 2014 refers to a compilation of reference values from different reports that use a different terminology for the reference values (see Appendix C). The terminology used for the HCNL 2014 reference values (EAR or AR; RDA or RI or PRI; AI or RI) is determined by the report from which the HCNL 2014 reference values originate: if this is an HCNL report, the HCNL terminology is used; with values originating from other reports, such as the NCM report for vitamin A, the terminology of that report is used. For vitamin A, the terms AR and RI are used for the HCNL 2014 reference values, because these reference values originate from the NCM report.

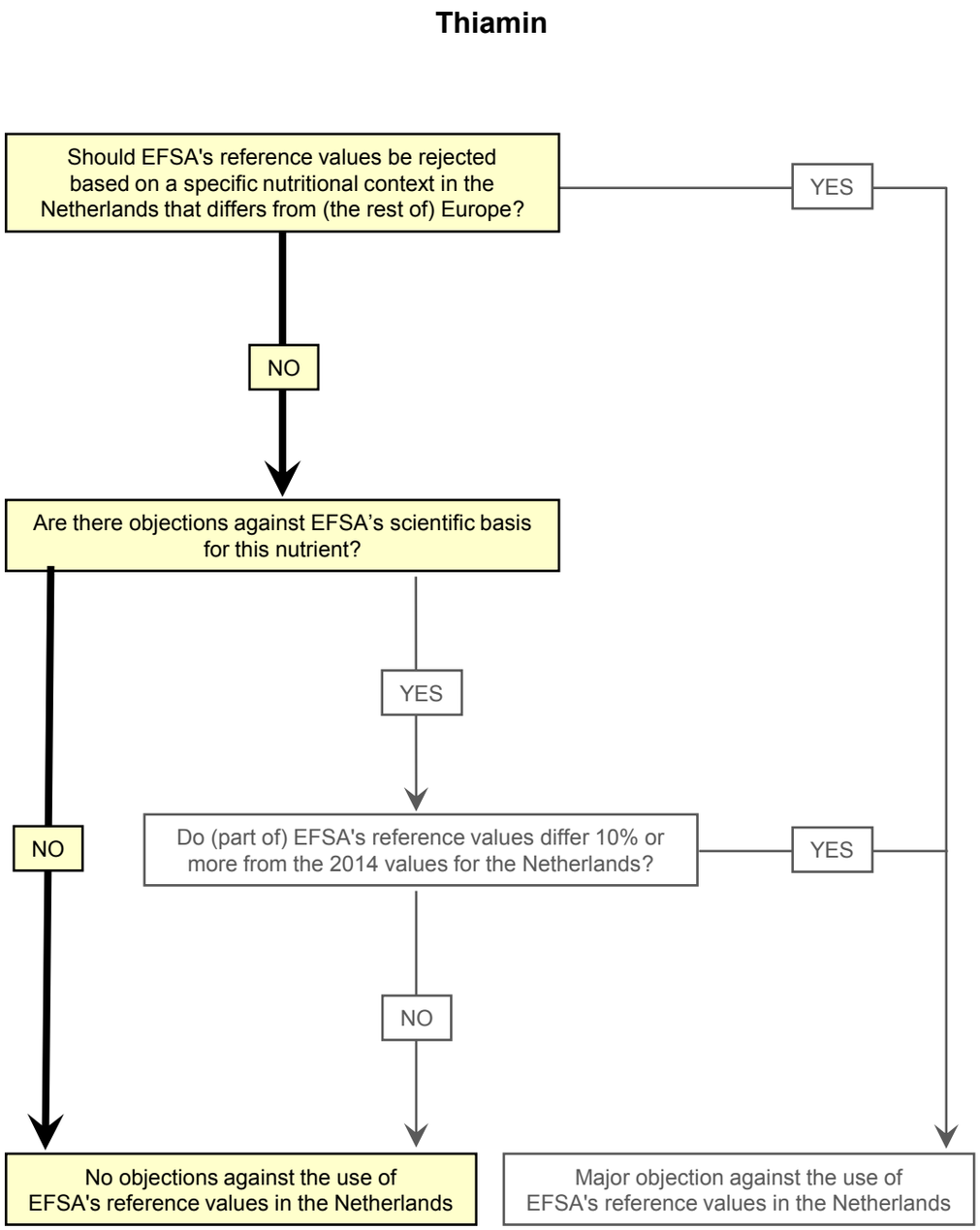
The Committee agrees largely with EFSA's factorial method of setting the reference values, but objects to one of the six factors EFSA used in the factorial method. Vitamin A is one of the few nutrients for which the method of establishing the reference values implies a proportional effect of the reference weights on the reference values. The Committee considers that higher reference weights should be used for the Netherlands, because Dutch adults are relatively tall. The resulting values are presented in Table 7.

The retinol supply to the body is established not only by the intake of retinol, but also by the intake of carotenes which are converted to retinol in the body. The Committee does not support EFSA's choice regarding the conversion factors for carotenes (EFSA expresses the reference values as retinol equivalents) but recommends expressing the reference values as retinol activity equivalents instead.

Table 7. AR and PRI for vitamin A, recommended for the Netherlands

	Men ≥18 years	Women ≥18 years
Average requirement (AR) using EFSA's factorial method but applying HCNL's reference weights	615 µg RAE/day	525 µg RAE/day
Population reference intake (PRI) using EFSA's factorial method but applying HCNL's reference weights	800 µg RAE/day	680 µg RAE/day

03
thiamin (vitamin B1)



3.1 Overview and comparison of values

Table 8 presents an overview of reference values and criteria.

EFSA and NCM express the reference values in mg/MJ, whereas HCNL, DACH, IOM and WHO/FAO express the reference values in mg/day.

NCM's RI in mg/MJ is 20% higher than EFSA's PRI; NCM's AR is 40% higher than EFSA's AR. Note that NCM uses values in mg/MJ as the starting point, but present values in mg/day in their summarising table.

A comparison of EFSA with HCNL, DACH, IOM and WHO/FAO is only possible after conversion of EFSA's values to mg/d (EFSA presents values in mg/d for four age groups and four physical activity levels in an annex[a]).

For men, the RI/RDA-values by DACH, IOM and WHO/FAO equal the average of EFSA's PRI-values converted to mg/day; HCNL's RDA is 8% lower and NCM's RI is 17% higher. For women, the RDA/RI-values by HCNL, NCM, IOM and WHO/FAO are 18% higher and the value by DACH is 10% higher than the average of EFSA's PRI-values converted to mg/day.

[a] In EFSA's appendix, values in mg/d are presented for the age groups 18-29, 30-39, 40-49 and 50-59 years for four different physical activity levels (PALs). The average of these values are used for the comparison with HCNL, IOM and WHO/FAO. At a PAL value of 1.4, the recommended intakes in the four age groups ranged between 0.9-1.0 mg/d (♂) and 0.8 mg/d (♀), at a PAL-value of 1.6 these ranges were 1.1 mg/d (♂) and 0.9 mg/d (♀), at a PAL-value of 1.8 these ranges were 1.2-1.3 mg/d (♂) and 1.0 mg/d (♀), and at a PAL-value of 2.0 these ranges were 1.3-1.4 mg/d (♂) and 1.1 mg/d (♀). The values averaged over age groups and PAL-levels were 1.2 mg/day for men and 0.9 mg/day for women.

Table 8. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RAD/AI/RI					AR			CV	Main criterion
	Type	mg/MJ	mg/day			mg/MJ	mg/d		(%)	
EFSA 2016[9]	PRI	**0.1**	*(♂ 1.2)* *(♀ 0.9)*			**0.072**	*(♂ 0.9)* *(♀ 0.6)*		20%	AR is based on data from depletion-repletion studies showing that 0.072 mg/MJ is associated with:[a] • αETK[b] <1.15 • low urinary thiamin excretion • ~0.09 mg/24h • restoration of baseline ETKA[c].
HCNL 2000[36] = HCNL 2014[33]	RDA	*(♂ 0.10-0.11)* *(♀ 0.13)*	**1.1**			*(♂ 0.07-0.08.2)* *(♀ 0.9)*	**0.8**		20%	AR is based on: • urinary thiamin excretion • αETK and ETKA.
NCM 2014[37]	RI	**0.12**	Age [d] 18-30 yr 31-60 yr >61 yr	♂ **1.4** **1.3** **1.2**	♀ **1.1** **1.1** **1.0**	**0.1**	♂[e] **1.2**	♀ **0.9**	10% [6]	Criteria are not clear. NCM refers to NCM 2004, WHO/FAO 2004, DACH 2015; IOM 1998 and Sauberlich 1979.
DACH 2015[38]	RDA	*(0.13)*	19-24 yr 25-50 yr 51-64 yr > 65 yr	**1.3** **1.2** **1.2** **1.1**	**1.0** **1.0** **1.0** **1.0**	**0.11**			10%	AR is based on adequate urinary thiamin excretion.
IOM 1998[42]	RDA		♂**1.2** ♀**1.1**			*(0.07)*	♂**1.0** ♀**0.9**		10%	AR is based on: • low urinary thiamin excretion • αETK and ETKA
WHO/FAO 2004[44]	AI		♂**1.2** ♀**1.1**							Criteria are not clear. At least partly based on Sauberlich et al., 1979.

[a] EFSA notes that, in comparison to 0.072 mg/MJ, an intake of >0.14 mg/MJ was associated with a sharp increase in urinary thiamin excretion and only slight changes in transketolase activity, indicating tissue saturation.

[b] The erythrocyte transketolase activity coefficient (αETK) is a functional marker of thiamin status. It represents the degree to which ETKA rises in response to addition of thiamin diphosphate (TDP). αETK can discriminate low ETKA due to thiamin deficiency from low ETKA due to a lack of the apoenzyme. A value of αETK <1.15 is generally considered to reflect an adequate thiamin status.

[c] The erythrocyte transketolase activity (ETKA) is a functional marker of thiamin status. It represents the basal value of the enzyme erythrocyte transketolase, without stimulation by thiamin diphosphate (TDP).

[d] NCM presents these RI-values per age group in Table 1.3 of their report, not in the summarising table at the beginning of their Chapter 19 on thiamin.

[e] NCM presents these AR-values (age group not specified) in the summarising table at the beginning of their Chapter 19 on thiamin.

[f] CV calculated as 100% x [(PRI/RI/RDA - AR) / 2] / AR.

3.2 Explanation of differences between reports

Difference in the unit of expression (mg/MJ versus mg/day)

EFSA expresses the reference values in mg/MJ instead of mg/day which is consistent with NCM. Although HCNL, DACH, IOM and WHO/FAO express the reference values in mg/day, they derive the reference values from estimates in mg/MJ. Therefore, the Committee agrees with EFSA's use of mg/MJ as the unit of expression.

Note that for the conversion of requirements in mg/MJ to mg/d, EFSA (in appendices) and DACH used average energy requirements, whereas HCNL used average energy intake. IOM does not specify whether they used energy intake or energy requirement.

The Committee concludes that the reference value in mg per MJ refers to energy intake rather than energy requirement, because the unit of expression is mainly based on the positive relationship between thiamin requirement and *energy intake* in the controlled experiment by Sauberlich et al. (1979), who studied intake levels from 0.003 to >0.14 mg/MJ.

This evaluation focuses only on EFSA, HCNL, DACH and IOM, because:

- The NCM-criteria are unclear.
- The WHO/FAO-criteria are unclear.

The reports by EFSA, HCNL, DACH and IOM are all based primarily on the depletion-repletion study by Sauberlich et al. (1979; n=7) with criteria based on achieving an adequate status (αETK and ETKA) at low levels of urinary thiamin excretion. Note that DACH uses a higher average requirement in mg/MJ because their value is based on adequate instead of low urinary excretion. EFSA also refers to the depletion-repletion study by Kraut et al. (1966; n=6) and to publications providing supporting evidence.

Note that EFSA and HCNL use a coefficient of variation of 20% to calculate PRI/RDA from AR, whereas DACH and IOM use a coefficient of variation of 10%.

Differences between older and younger adults

EFSA and NCM use one value in mg/MJ for all groups. Because of the lower energy intake/requirement of older compared to younger adults, values converted to mg/day are lower for older than for younger adults. DACH also distinguished between age groups, with lower reference values in mg/day for older compared to younger adults. The reference values set by HCNL, IOM and WHO/FAO do not differ between older and younger adults.

Sex differences

EFSA, NCM, DACH and IOM assume that the thiamin requirement in mg/MJ is equal for all groups. As a result, values converted to mg/day differ between men and women according to the differences in energy requirement. HCNL assumed that the thiamin requirement in mg/MJ is higher for women (0.09 mg/MJ) than for men (0.07-0.08 mg/MJ), with the

result that reference values expressed in mg/day are equal for women and men. The issue of whether or not to differentiate the requirement in mg/MJ between men and women is not explicitly discussed by EFSA.

3.3 Conclusion on the scientific basis of EFSA's reference values

The Committee agrees with EFSA's derivation of the AR and PRI, which is largely in line with the reports by HCNL and IOM.

Table 9 shows that clinical signs of deficiency have been induced by feeding apparently healthy subjects a low-thiamin diet with intakes up to 0.05 mg/MJ, and that in one study this intake level of 0.05 mg/MJ was associated with the correction of unspecific symptoms of deficiency. The Committee notes that EFSA's AR provides a margin above this intake level.

The Committee has no objections against the scientific basis used by EFSA to derive the AR.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

Free thiamin functions as the precursor for TDP, which acts as a coenzyme for enzymes involved in carbohydrate and branched-chain amino acid metabolism, and in energy-yielding reactions.

Thiamin deficiency occurs in populations with:

- diets low in thiamin (diets mainly consisting of milled white cereals, e.g. polished rice, white wheat flour)
- diets rich in thiaminase (thiaminase is abundant in some raw or fermented fish, ferns and insects).

In Western countries, it occurs in specific risk groups:

- alcoholism
- drug abuse
- after bariatric surgery or gastrectomy
- chronic gastrointestinal and liver disorders.

Symptoms include:

- beriberi, with mostly neurological and cardiovascular manifestations
- peripheral neuritis
- cardiac insufficiency
- tendency for oedemas

which may be accompanied by:

- extreme fatigue
- irritability
- forgetfulness, poor coordination
- gastrointestinal disturbances, constipation,
- laboured breathing
- loss of appetite and weight loss.

Thiamin deficiency also can lead to:

- Wernicke's encephalopathy (ocular abnormalities, ataxia, disturbances of consciousness)
- Korsakoff's syndrome (psychosis) resulting in amnesia, disorientation and often confabulation.

Table 9. Thiamin intake levels associated with the occurrence or correction of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/ Specific	EFSA's reference
Unspecific subjective symptoms (e.g. general malaise, headache, nausea) and physical symptoms (sinus tachycardia at rest, diminution of muscle strength and tendon reflexes)	After 30 days intake of 0.110-0.180 mg/day (0.009-0.015 mg/MJ). Symptoms disappeared after 12 days repletion with 0.540-0.610 mg/day (0.046-0.052 mg/MJ).	5 out of 8 healthy young men (age not specified)	Ziporin et al., 1965a,b
Deficiency symptoms in relation to a thiamin intake	0.05 mg/MJ (0.5 mg/day for women and 0.6 mg/day for men) for 2-8 weeks.	Not specified	Williams et al., 1942; Foltz et al., 1944; Wood et al., 1980
Anorexia and a marked impairment of mental and physical health	0.042 mg/MJ	2 healthy subjects	Williams et al., 1942
Clinical symptoms suggestive of thiamin deficiency	0.052 mg/MJ	2 healthy subjects	Williams et al., 1943
An impairment of metabolism of a glucose test dose after 30 months without specific signs of deficiency, associated with a decline in urinary excretion of thiamin down to 0.015 mg/day after 20 months	Long-term intake of 0.045 mg/MJ	Not specified	Horwitt et al., 1948; Horwitt and Kreisler, 1949

3.4 Summary and conclusion

Table 10. Summary of the evaluation of EFSA's AR and PRI values for thiamin

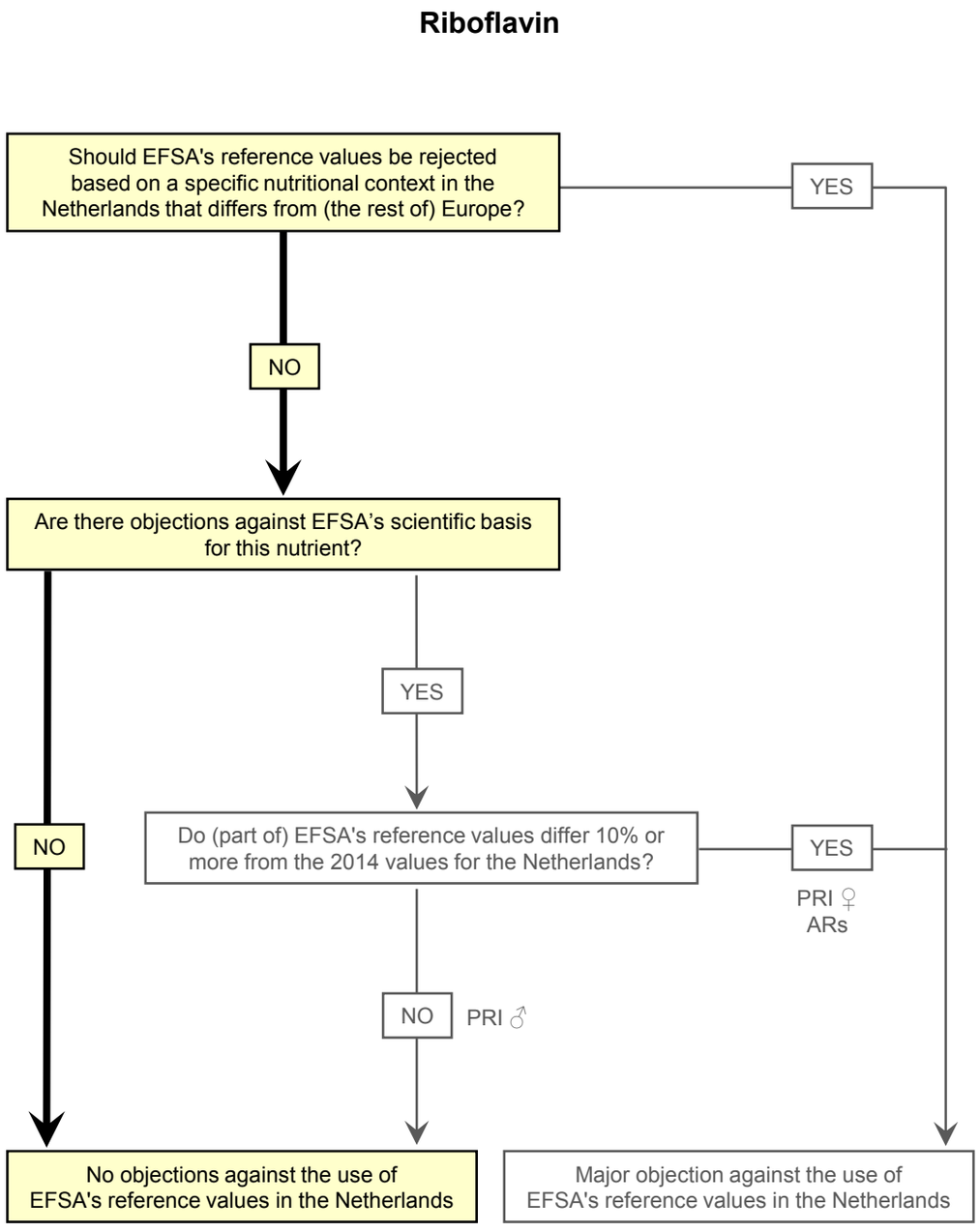
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's EARs	Not applicable, because EFSA uses a different expression unit (mg/MJ) than HCNL	Using the average of EFSA's values converted to mg/day (appendix in EFSA's report), EFSA's ARs appear to differ little from HCNL's EARs.
EFSA's PRIs compared to HCNL's RDAs	Not applicable, because EFSA uses a different expression unit (mg/MJ) than HCNL	Using the average of EFSA's values converted to mg/day (appendix in EFSA's report), EFSA's PRIs appear to differ little from HCNL's RDAs.
Scientific basis of EFSA's AR	No objections	EFSA uses the same biochemical parameters of function and status as HCNL and IOM. Clinical signs of deficiency were reported at intakes up to 0.05 mg/MJ. EFSA's AR (0.072 mg/MJ) provides a margin above this level. Although most of the other evaluated reports express the reference values in mg/day, these values are consistently based on estimates in mg/MJ.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA (but EFSA's reference value is in mg/MJ)	The values expressed in or converted to mg/d by EFSA, NCM and DACH are lower in older compared to younger adults. HCNL, IOM and WHO/FAO do not differentiate between younger and older adults.
Differentiation between men and women	Not applied by EFSA (but EFSA's reference value is in mg/MJ)	The values expressed in or converted to mg/d by EFSA, NCM, DACH, IOM and WHO/FAO are lower for women than for men. HCNL 2014 used the same value in mg/day for women and men.

The Committee has no objections against the scientific basis of EFSA's reference values, or EFSA's PRIs and ARs and recommends accepting these values (Table 11) in the Netherlands.

Table 11. AR and PRI for thiamin, recommended for the Netherlands

	Men and women ≥18 years
Average requirement (AR)	0.072 mg per MJ energy intake
Population reference intake (PRI)	0.1 mg per MJ energy intake

04
riboflavin (vitamin B2)



4.1 Overview and comparison of values

Table 12. Overview of the reference values for adults and the criteria on which these values are based.

Report	PRI/RDA/AI/RI (mg/d)				AR (mg/d)		CV (%)	Main criterion
	Type	♂		♀	♂	♀		
EFSA 2017[7,a]	PRI	1.6		1.6	1.3	1.3	10	Status and function parameters: the intake at which urinary riboflavin sharply increases (the riboflavin intake associated with the inflection point in the urinary riboflavin excretion curve); in line with EGRAC[1] <1.3.
HCNL 2000[36] = HCNL 2014[33]	RDA	1.5		1.1	1.1	0.8	18[c]	Status and function parameters: urinary riboflavin, intake at which it sharply increases, and EGRAC <1.3.
NCM 2014[37]	RI	18-30 yr 31-60 yr 61-74 yr ≥75 yr	1.6[d] 1.5 1.4 1.3	1.3 1.2 1.2 1.2	1.4[e]	1.1		The values in NCM's previous (2004) report: AR = 0.12 mg/MJ and RI = 0.14 mg/MJ (CV 10%) are maintained and applied to both children and adults. The values are based on older studies in which riboflavin status was assessed using primarily urinary excretion of riboflavin and to a lesser extent using the EGRAC (NCM mentions two ranges of cut-off values for EGRAC:1.2-1.25 and 1.3-1.4).
DACH 2015[38]	RI	19-50 yr ≥51 yr	1.4 1.3	1.1 1.0	1.1	0.9	10	AR = 0.12 mg/MJ and RI = 0.14 mg/MJ, based on EGRAC<1.2 and/or 24u urinary riboflavin excretion ≥120 µg/day. (Marginal deficiency: EGRAC 1.2-1.4 and/or 24u urinary excretion 40-119 µg/day. Deficiency: EGRAC >1.4 and/or 24u urinary excretion <40 µg/day).

Report	PRI/RDA/AI/RI (mg/d)			AR (mg/d)		CV (%)	Main criterion
	Type	♂	♀	♂	♀		
IOM 1998[42]	RDA	1.3	1.1	1.1	0.9	10	Function parameter: requirement at normal EGRAC level (normal varied between studies, with cut-off values ranging between 1.2 and 1.4).
WHO/FAO 2004[44]	RI	1.3	1.1				Status parameters: tissue saturation & urinary excretion.

[a] EFSA uses 'total riboflavin' for the sum of three dietary components (free riboflavin, and both biologically active derivates FMN and FAD). 'Free riboflavin' refers only to the first of these components.
[b] EGRAC = Erythrocyte Glutathione Reductase Activation Coefficient: the ratio of the activity of Erythrocyte Glutathione Reductase, measured in-vitro with, and without, addition of the cofactor flavin adenine dinucleotide (FAD).
[c] CV not presented by HCNL, but calculated as 100% x [(PRI/RI/RDA - AR) / 2] / AR.
[d] NCM presents these RI-values in mg/d per age group in Table 1.3 of their report.
[e] NCM presents the AR-values in mg/d in the summarising table at the start of Chapter 20 on riboflavin.

Table 12 presents an overview of reference values and criteria.

Almost all RI/RDA-values for men in the evaluated reports are between 6% and 19% lower than EFSA's PRI for men. The one exception is NCM's RI for young (18-30 years) adult men, which equals EFSA's PRI for men. All RI/RDA-values for women in the evaluated reports are between 19% and 31% lower than EFSA's PRI for women.

4.2 Explanation of differences between reports

The reports base their ARs for riboflavin on the same biochemical parameters of status (urinary riboflavin excretion) and function (EGRAC). All reports present the reference values in the unit mg/day. However, the values in the reports used for comparison are (at least partly) based on the relationship between riboflavin and energy requirements, whereas EFSA's values are not.

NCM and DACH base their reference values on requirements in mg/MJ, resulting in lower reference values for older versus younger adults and for women versus men. HCNL and IOM base the difference between their values for men and women on the relationship of riboflavin to energy requirements.

In contrast to the reports used for comparison, EFSA uses the same value (mg/day) for men and women and for younger and older adults. The EFSA Panel does note that several (but not all) studies indicate that an increase of physical activity appears to lower the riboflavin status (EGRAC increases and/or the urinary excretion of riboflavin decreases), suggesting a higher riboflavin requirement with increased energy expenditure. However, because of several limitations in these studies,[a] the EFSA Panel notes that there is a lack of experimental data showing a clear quantitative relationship between riboflavin status biomarkers (urinary excretion of riboflavin and EGRAC) and energy expenditure (or physical activity). EFSA based their AR (1.3 mg/day) on four studies estimating the mean riboflavin intakes associated with the inflection points[b] in the urinary excretion

[a] Only one of these studies reported TEE in a small number of subjects over a very wide range (8.3-19.6 MJ/day) although mean TEE did not differ during the different experimental periods in which riboflavin intake was changed. The EFSA Panel considers this a strong limitation. The Panel also notes the lack of information on the method of measurement of riboflavin intake in some of the studies, the particular aim of some of the studies (i.e. weight management studies in overweight or obese women), their short duration or small sample size, and the high variability in the characteristics of the subjects (e.g. large range of BMIs).
[b] Inflection point: the riboflavin intake level at which urinary riboflavin rises sharply.

curves. In these studies, the differences between the estimates for men and women, as well as the differences between the estimates for younger and older adults were small and there was overlap between the ranges:

- two studies in men, one in 66 men and another in 73 men (estimated inflection points were at riboflavin intakes of 1.3 mg/d, range 1.1-1.6; Horwitt et al., 1950) and 1.4 mg/d, range 1.3-1.5; Guo et al., 2016),
- one study in 4 older men and 10 older women (estimated inflection points were at riboflavin intakes of 1.1 mg/d, range 1.1-1.3; Boisvert et al.,1993), and
- one study in 14 younger women (estimated inflection points were at riboflavin intakes between 1.3 and 1.5 mg/d, range 1.3-1.6; Brewer et al., 1946).

EFSA calculated the AR for adults from the mean riboflavin intakes associated with the inflection points, weighted for the number of subjects in each study. EFSA considered that information on the variability in the requirement was absent, but the potential effect of physical activity and of MTHFR 677TT genotype on riboflavin requirement was covered by the data in the four studies. Therefore, a CV of 10% was assumed to be sufficient, resulting in a PRI of 1.6 mg/day.

Differences between older and younger adults

EFSA, HCNL, IOM and WHO/FAO use the same reference values in mg/day for younger and older adults, and appear to agree that the available research indicates that, at older age, the riboflavin requirement is not lower than at younger age. NCM and DACH set lower values for older compared to younger adults, based on the lower energy requirement of older adults (NCM and DACH base their values on a riboflavin requirement of 0.12 mg/MJ).

Sex differences

As explained earlier in this paragraph, EFSA concluded that the available evidence did not support a difference according to sex, based on the observation that estimates from two larger studies in men (Horwitt 1950, n=66, Guo 2016, n=73) were similar to the estimate from one small study in women (Brewer 1946, n=14).

The reports used for comparison have set lower reference values for women compared to men.

HCNL, NCM, DACH and IOM based the difference between their values for men and women solely on the assumed relationship between riboflavin and energy requirements.

4.3 Conclusion on the scientific basis of EFSA's reference values

The scientific basis of EFSA's reference values is described in paragraph 4.2. EFSA furthermore reports that, based on several studies, clinical signs of deficiency appear to occur at intakes up to 0.6 mg/d, whereas no deficiency has been reported at intakes within the range of 0.8-1.1 mg/day (Table 13). The Committee notes that the EFSA's AR for adults (1.3 mg/day) provides a margin above this intake level. The Committee has no objections against the scientific basis of EFSA's reference values.

Table 13. Riboflavin intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/ specific group	EFSA's reference
Signs of deficiency (not specified by EFSA)	<0.5-0.6 mg/day several months	Men and women	Sebrell et al., 1941; Williams et al., 1943; Keys et al., 1944;
Skin lesions	0.55 mg/day	3 adult men	Horwitt et al., 1950
No signs of deficiency	0.8 mg/day	Not specified	Sebrell et al., 1941; Williams et al., 1943; Keys et al., 1944; Horwitt et al., 1950; Bamji 1969
No signs of deficiency	1.0-1.1 mg/day for 6 weeks (control group)	Chinese men (18-22 yr)	Guo et al., 2016

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

Riboflavin is the integral part of the coenzymes FAD and FMN that act as the cofactors of flavoprotein enzymes involved in a variety of reactions. FAD and FMN act as proton carriers in redox reactions involved in energy metabolism, metabolic pathways and the formation of some vitamins and coenzymes. In particular, riboflavin is involved in the metabolism of niacin and vitamin B6.

Riboflavin deficiency has been reported in populations from both developed and developing countries, and is most often accompanied by other nutrient deficiencies.

Symptoms are unspecific, take several months to develop and are unreliable to assess adequacy or inadequacy. They include, e.g.:

- sore throat
- hyperaemia
- oedema of the pharyngeal and oral mucous membranes
- cheilosis
- glossitis (magenta tongue)
- seborrhoeic dermatitis, skin lesions including angular stomatitis
- normochromic normocytic anaemia characterised by erythroid hypoplasia and reticulocytopenia.

4.4 Summary and conclusion

Table 14. Summary of the evaluation of EFSA's AR and PRI values for riboflavin

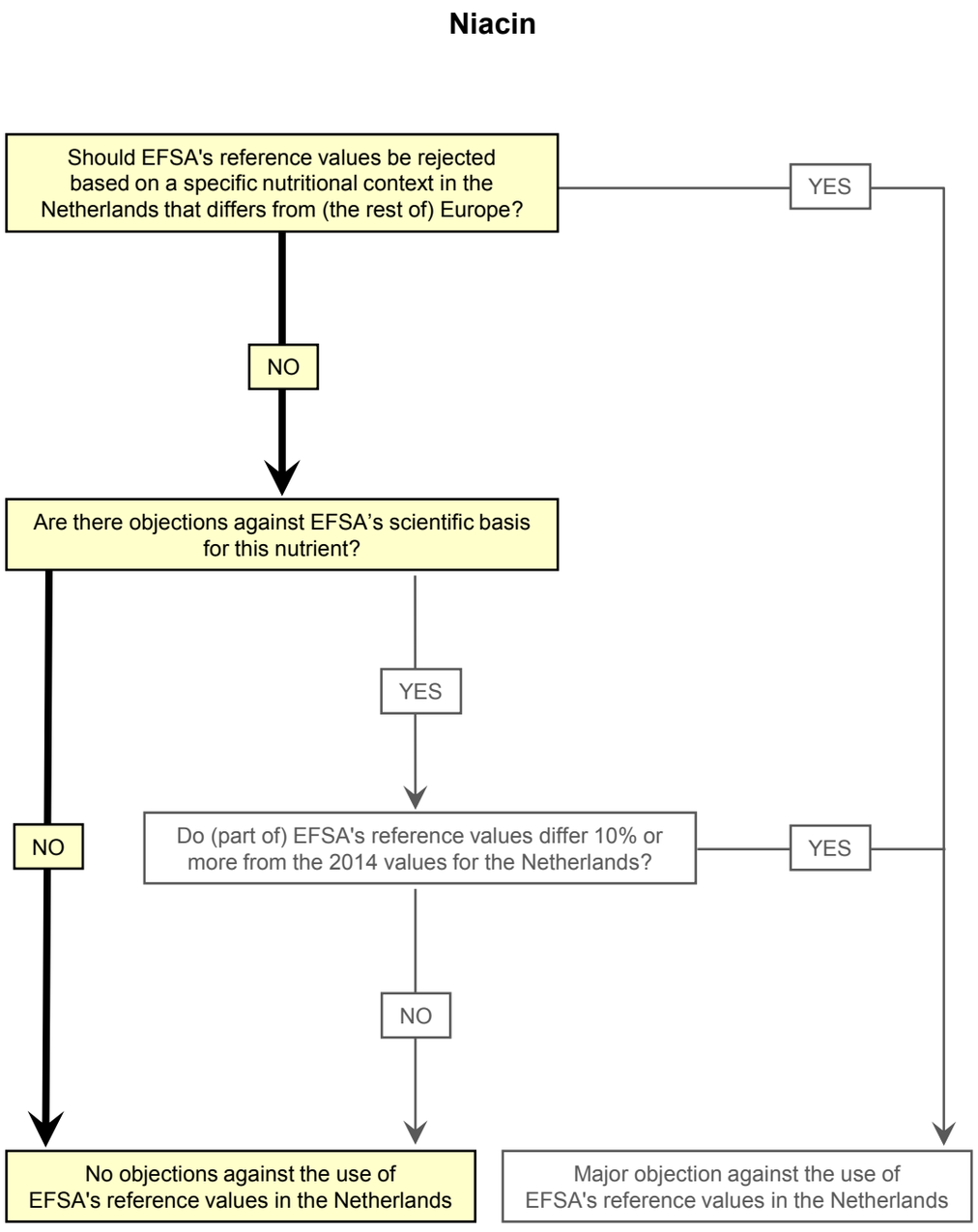
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's EARs	Higher	EFSA's AR compared to HCNL's EAR is 20% higher for men and 60% higher for women.
EFSA's PRIs compared to HCNL's RDAs	Higher, especially in women	EFSA's PRI compared to HCNL's RDA is 5% higher for men and 45% higher for women.
Scientific basis of EFSA's AR	No objections	All reports use EGRAC (cut-off values vary between 1.2 and 1.4) and/or 24-hour urinary riboflavin excretion. EFSA's AR (1.3 mg/d) provides a margin above the intake associated with deficiency (0.6 mg/day).
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with most of the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Not consistent with the reports used for comparison, which all differentiate between men and women.

The Committee has no objections against the scientific basis of EFSA's reference values, or EFSA's AR and PRI and recommends accepting these values (Table 15) in the Netherlands.

Table 15. AR and PRI for riboflavin, recommended for the Netherlands

	Men and women ≥18 years
Average requirement (AR) in mg/d	1.3 mg/d
Population reference intake (PRI) in mg/d	1.6 mg/d

05
niacin (vitamin B3)



5.1 Overview and comparison of values

Table 16 presents an overview of reference values and criteria.

EFSA, NCM and DACH express the reference values in mg NE/MJ,[a] whereas HCNL, IOM and WHO/FAO express the reference values in mg NE/day.

EFSA, NCM and DACH use the same PRI/RDA/AI/RI (1.6 mg/MJ) and the same AR (1.3 mg/MJ). NCM and DACH (but not EFSA) add that, at lower energy intakes, the PRI/RDA/AI/RI is 13 mg NE per day.

Only after conversion of EFSA's values to mg/d (which EFSA presents in an appendix), is a comparison with HCNL, IOM and WHO/FAO possible. For this comparison, the average of EFSA's converted PRI-values is used.[b] The RDAs/RIs of HCNL, IOM and WHO/FAO appear to differ little from the average of EFSA's converted PRI-values. HCNL's RDAs are 6% (♂) and 7% (♀) lower; the RDAs/RIs by IOM and WHO/FAO are 11% lower than (♂) and equal to (♀) EFSA's average value in mg/d.

[a] NCM and DACH also present reference values in milligrams per day based on one level of energy intake.

[b] In EFSA's appendix, values in mg/d are presented for different age groups and four different PAL-values. The average of these values are used for the comparison with HCNL, IOM and WHO/FAO. At a PAL value of 1.4, EFSA´s values averaged over the four age groups were 15 mg/d (♂) and 12 mg/d (♀), at a PAL-value of 1.6 the averages were 17 mg/d (♂) and 14 mg/d (♀), at a PAL-value of 1.8 the averages were 19 mg/d (♂) and 15 mg/d (♀), and at a PAL-value of 2.0 the averages were 21 mg/d (♂) and 17 mg/d (♀). The values averaged over age groups and PAL-levels were 18 mg/day for men and 14 mg/day for women.

Table 16. Overview of the reference values for adults and the criteria on which these values are based; values in bold are reference values presented in the reports, values in italics are calculated by the committee to enable a comparison to be made between reports

Report	PRI/RDA/AI/RI					AR			CV (%)	Main criterion
	Type	mg NE/MJ	mg NE/day			mg NE/MJ	mg NE/day			
			Age range	♂	♀		♂	♀		
EFSA 2014[24]	PRI	**1.6**	*(averaged 1*	*~18*	*~14)*	**1.3**			10%	Preformed niacin or tryptophan[2] required to restore "normal" urinary excretion of NMN and 2-Pyr.[3]
HCNL 2000[36] = HCNL 2014[33]	RDA			**17**	**13**		**12**	**9**	~20% [4]	Urinary excretion of NMN > 1.0 mg/d.
NCM 2014[37]	RI	**1.65**	NCM Chapter 22:	**18**	**15**	1.3	**15**	**12**	~10%[c]	Urinary excretion of niacin metabolites. In absence of new data, NCM 2004 value of 1.6 NE/MJ is maintained.
			NCM Table 1.3:							
			18-30 yr	**19**	**15**					
			31-60 yr	**18**	**14**					
			61-74 yr	**16**	**13**					
			>75 yr	**15**	**13**					
DACH 2015[38]	RDA	1.6	19-24 yr	**16**	**13**	**1.3**			10%	DACH adopted the value used by EFSA 2014, NCM 2014, UK 2009 and WHO/FAO 2004. Values in mg/d are achieved using the average energy requirements at a PAL-value of 1.4.
			25-50 yr	**15**	**12**					
			51-50 yr	**15**	**11**					
			>65 yr	**14**	**11**					
IOM 2001[41]	RDA			**16**	**14**		**12**	**11**	15%	Urinary NMN excretion > 1.0 mg/d (no pellagra signs; the metabolites are not excreted until requirement is met).
WHO/FAO 2004[44]	AI		♂ **16;** ♀ **14**							Not explicitly described.

[a] Averages for the 4 age groups between 18 and 50 years and 4 Physical Activity Levels (PAL-values) which EFSA presents in an appendix.

[b] Niacin can be synthesised in the human body from the indispensable amino acid tryptophan. Approximately 60 mg of tryptophan yields 1 mg of niacin defined as 1 mg niacin equivalent (NE).

[c] NMN = N-methylnicotinamide; 2-Pyr = N-methyl-2-pyridone-5-carboxamide.

[d] CV calculated as 100% x [(PRI/RI/RDA – AR) / 2] / AR.

[e] NCM notes that at energy intakes below 8 MJ/d the RI is 8 mg NE/day (instead of 1.6 mg NE/MJ).

5.2 Explanation of differences between reports

EFSA, HCNL, NCM and IOM base the AR on biochemical parameters of status: the intake required for "normal" urinary excretion of niacin metabolites. After conversion to mg/day, there appears to be agreement on the reference values for niacin equivalents (see 5.1). EFSA refers to three studies involving a total of 30 adults.

Difference in the unit of expression (mg/MJ versus mg/day)

EFSA, NCM and DACH express the reference values in mg/MJ, because studies of niacin requirements are presented in relation to energy intake, based on the known biochemical function of niacin in energy metabolism. HCNL, IOM and WHO/FAO express the reference values in mg/day, considering that there is insufficient experimental evidence on the effect of energy intake on niacine requirements. However, these organisations did set lower reference values for women than for men based on the function of niacin in energy metabolism. The Committee has no objections against EFSA's use of mg/MJ as the unit of expression.

Differences between older and younger adults

EFSA, NCM and DACH set one value in mg/MJ for all groups; note that NCM and DACH specified reference values both in mg/MJ and in mg/day. Their values converted to mg/day differ between younger and older adults according to the differences in energy requirements. The reference values set by HCNL, IOM and WHO/FAO are expressed in mg/d and do not differ between older and younger adults.

Sex differences

EFSA, NCM and DACH assume that the niacin requirement in mg/MJ is equal for all groups; note that NCM and DACH specified reference values both in mg/MJ and in mg/day. Their values converted to mg/day differ between men and women according to the differences in energy requirement. Values by HCNL, IOM and WHO/FAO are in mg/day, but these reference values show corresponding differences between men and women.

5.3 Conclusion on the scientific basis of EFSA's reference values

The Committee agrees with EFSA's method of setting the reference values for niacin, because EFSA and the reports for comparison use the same biochemical parameters of status. EFSA notes that signs of pellagra have been reported at intakes of up to 1 mg NE/MJ (Table 17). The Committee notes that EFSA's AR (1.3 mg/MJ) provides a margin above this intake level.

The Committee has no objections against the scientific basis of EFSA's reference values.

Table 17. Niacin intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/Specific group	EFSA's reference
3 out of 5 subjects developed pellagra after 50-60 d. 2 out of 2 subjects did not develop pellagra after 40-42 d	about 0.94 mg NE/MJ	5 women with psychoneurosis (aged 25-54 years).	Goldsmith et al. (1952)
2 out of 10 subjects developed pellagra after 80 d	0.94-0.99 mg NE/MJ	9 women and one man (aged 26-60 years, some of whom were psychiatric or neurology patients).	Goldsmith et al. (1955)
Signs of pellagra in 'some subjects'	Approx 0.9-1 mg NE/MJ	Comparison of data on niacin and tryptophan requirements (n=15 subjects, followed up to 87 weeks) with those (n=20) from two other similar publications (Frazier and Friedemann, 1946; Goldsmith et al., 1952) and an unpublished source.	Horwitt et al. (1956) mentioned this finding referring to three other studies
Subjects did not show signs of pellagra after 37 wk	1.06 mg NE/MJ (n=~15)	40 male psychiatric patients (aged ≥30 years except for one subject) followed up to 87 weeks.	Horwitt et al. (1956)

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

The function of niacin is as the precursor of the nicotinamide nucleotide coenzymes NAD and NADP, which are involved in oxidation/reduction reactions and associated with both catabolic and anabolic processes.

Niacin deficiency (pellagra) appears in populations in India and parts of China and Africa with:

- diets low in both niacin and the amino acid tryptophan (diets mainly consisting of corn or maize).

In Western countries, niacin deficiency (pellagra) occurs in specific groups with conditions or diseases interfering with niacin intake, absorption and/or metabolism, e.g.:

- chronic alcohol abuse
- anorexia nervosa
- gastrointestinal diseases characterised by malabsorption or disturbances in tryptophan metabolism.

Symptoms of pellagra:

- photosensitive dermatitis (pigmented rash that develops symmetrically in areas exposed to sunlight)
- skin lesions
- tongue and mouth soreness
- vomiting
- diarrhea
- depression
- dementia
- if untreated: death from multiorgan failure.

Early symptoms are usually non-specific and include weakness, loss of appetite, fatigue, digestive disturbances, abdominal pain, irritability.

5.4 Summary and conclusion

Table 18. Summary of the evaluation of EFSA's AR and PRI values for niacin

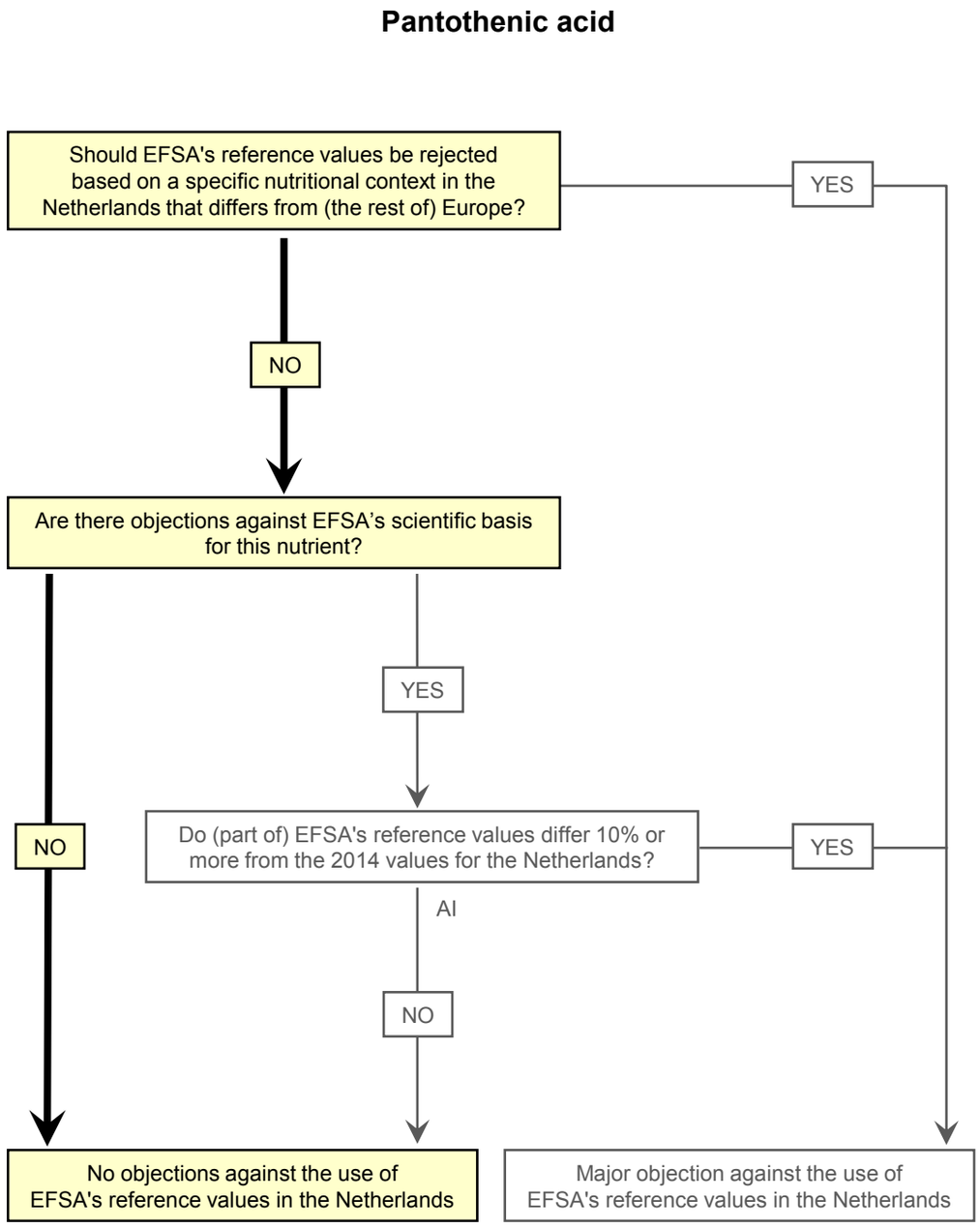
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's EARs	Not applicable, because EFSA uses a different expression unit (mg/MJ) than HCNL	Using the average of EFSA's values converted to mg/day (appendix in EFSA's report), EFSA's ARs appear to be similar to HCNL's EARs.
EFSA's PRIs compared to HCNL's RDAs	Not applicable, because EFSA uses a different expression unit (mg/MJ) than HCNL	Using the average of EFSA's values converted to mg/day (appendix in EFSA's report), EFSA's PRIs appear to be <10% higher than HCNL's RDAs.
Scientific basis of EFSA's AR	No objections	The biochemical parameters of status on which EFSA based the reference values are consistent with the reports used for comparison. Clinical signs of deficiency are reported at intakes of up to 1 mg/MJ. EFSA's AR (1.3 mg/MJ) provides a margin above this level.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA (but EFSA's reference value is in mg/MJ)	EFSA, NCM and DACH are consistent. HCNL, IOM and WHO/FAO use a different unit (mg/day) and do not differentiate between younger and older women.
Differentiation between men and women	Not applied by EFSA (but EFSA's reference value is in mg/MJ)	Consistent with all reports used for comparison.

EFSA expresses the reference values in a different unit compared to HCNL, but the differences appear to be small. The Committee has no objections against the scientific basis of EFSA's reference values, or EFSA's AR and PRI and recommends accepting these values (Table 19) in the Netherlands.

Table 19. AR and PRI for niacin, recommended for the Netherlands

	Men and women ≥18 years
Average requirement (AR)	1.3 mg NE/MJ energy intake
Population reference intake (PRI)	1.6 mg NE/MJ energy intake

06 pantothenic acid (vitamin B5)



6.1 Overview and comparison of values

Table 20. Overview of the criteria on which the PRI/RDA/RI/AI for adults are based

Report	AI (mg/d)	Main criterion
EFSA 2014[23]	5	Approximate midpoint of the observed median/mean intakes; there are no signs of insufficiencies.
HCNL 2000[36] = HCNL 2014[33]	5	Habitual intakes in populations (1-7 mg/d); there are no signs of insufficiencies. Intake balancing excretion (4 mg/d; 8 young women).
DACH 2015[38]	6	Intake in Germany (range 3.1-4.5 mg/d) and USA (♀4.1 mg/d; ♂6.2 mg/d); there are no signs of insufficiencies. At intake < 4 mg/d, blood levels are within the normal range.
IOM 1998[42]	5	The approximate midpoint of habitual intakes (4-7 mg/d); there is no evidence suggesting that this range of intake is inadequate. Intake balancing excretion (4 mg/d; 8 young women).
WHO/FAO 2004[44]	5	Observed median/mean intakes in adolescents (4-8 mg/d) and adults (4-7 mg/d). Studies in adolescents suggest that intakes of less than 4 mg/day were sufficient to maintain blood and urinary pantothenate.

Table 20 presents an overview of reference values and criteria. Note that NCM 2012 did not provide recommended intakes for pantothenic acid, due to lack of sufficient evidence.[37]

EFSA, HCNL, IOM and WHO/FAO use the same AI of 5 mg/d for all adults. DACH has set a higher AI (+20% relative to EFSA's value).

6.2 Explanation of differences between reports

The AIs in all reports are based on observed median/mean intakes, because there are no signs of insufficiencies.

IOM and HCNL additionally state that intake balances the urinary excretion at an intake of 4 mg/d. DACH mentions that intakes below 4 mg/day

appear to be sufficient to maintain blood pantothenate in adolescents. (Note that DACH does not explain why their AI for adults is set at 6 mg/d.)
The EFSA Panel considers that urinary and blood pantothenate are not suitable for deriving the AR for pantothenic acid, because their variability characteristics and their ability to discriminate between pantothenic acid insufficiency and adequacy are not well known, and no cut-off values for these biomarkers have been established.
EFSA uses European intake data to set the reference value. These data were collected between 1996 and 2010 in Austria, France, Germany, Hungary, Ireland, Poland and Portugal. EFSA mentions: "In adult men and women below about 65 years, mean/median intakes of 3.2 to 6.3 mg/day were reported. Data from France, Germany and Ireland indicated median intakes between 4.2 mg/day and 6.3 mg/day in men and between 3.3 and 5.2 mg/day in women, while data in Austria, Hungary and Portugal indicated mean intakes of 4.0 to 5.4 mg/day in men and 3.2 to 4.7 mg/day in women. In older men and women, mean/median intakes of 2.2 to 6.0 mg/day were reported. Data from France, Germany and Ireland indicated median intakes ranging from 4.2 to 6.0 mg/day in men and from 3.6 to 5.2 mg/day in women, while data in Austria, Hungary, Poland and Portugal indicated mean intakes of between 2.6 to 4.7 mg/day in men and between 2.2 and 4.4 mg/day in women."

Differences between older and younger adults and sex differences
All reports set one value for men and women aged ≥18 years.

6.3 Conclusion on the scientific basis of EFSA's reference values

EFSA's based the AI for pantothenic acid on median and mean intakes of pantothenic acid, consistent with the reports used for comparison, because pantothenic acid deficiency is rare.
EFSA provides no information on pantothenic acid intake levels associated with the occurrence, correction or prevention of deficiencies.
The Committee has no objections against the scientific basis of EFSA's reference values, but notes that median and mean intakes may substantially exceed requirements; deficiencies have not been reported in healthy subjects on normal diets.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

Pantothenic acid is a component of coenzyme A (CoA) and acyl-carrier proteins and serves in acyl-group activation and transfer, which is essential for fatty acid synthesis and oxidative degradation of fatty acids and amino acids. Humans cannot synthesise pantothenic acid and depend on its dietary intake. Pantothenic acid is ubiquitous in food.
Pantothenic acid deficiency is rare and EFSA provides no information on pantothenic acid intake levels at which deficiencies are or are not reported. Deficiency symptoms have been described in:

- subjects on a pantothenic acid antagonist
- subjects on a pantothenic acid-deficient diet.

Symptoms include:

- mood changes
- sleep disturbances
- neurological disturbances
- cardiac disturbances
- gastrointestinal disturbances.

6.4 Summary and conclusion

Table 21. Summary of the evaluation of EFSA's AI value for pantothenic acid

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AI compared to HCNL's AI 2014	Difference 0%	Consistent with HCNL
Scientific basis of EFSA's AI	No objections	EFSA's AI is based on median and mean intakes, consistent with the reports used for comparison. The Committee notes that these intakes may substantially exceed requirements.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

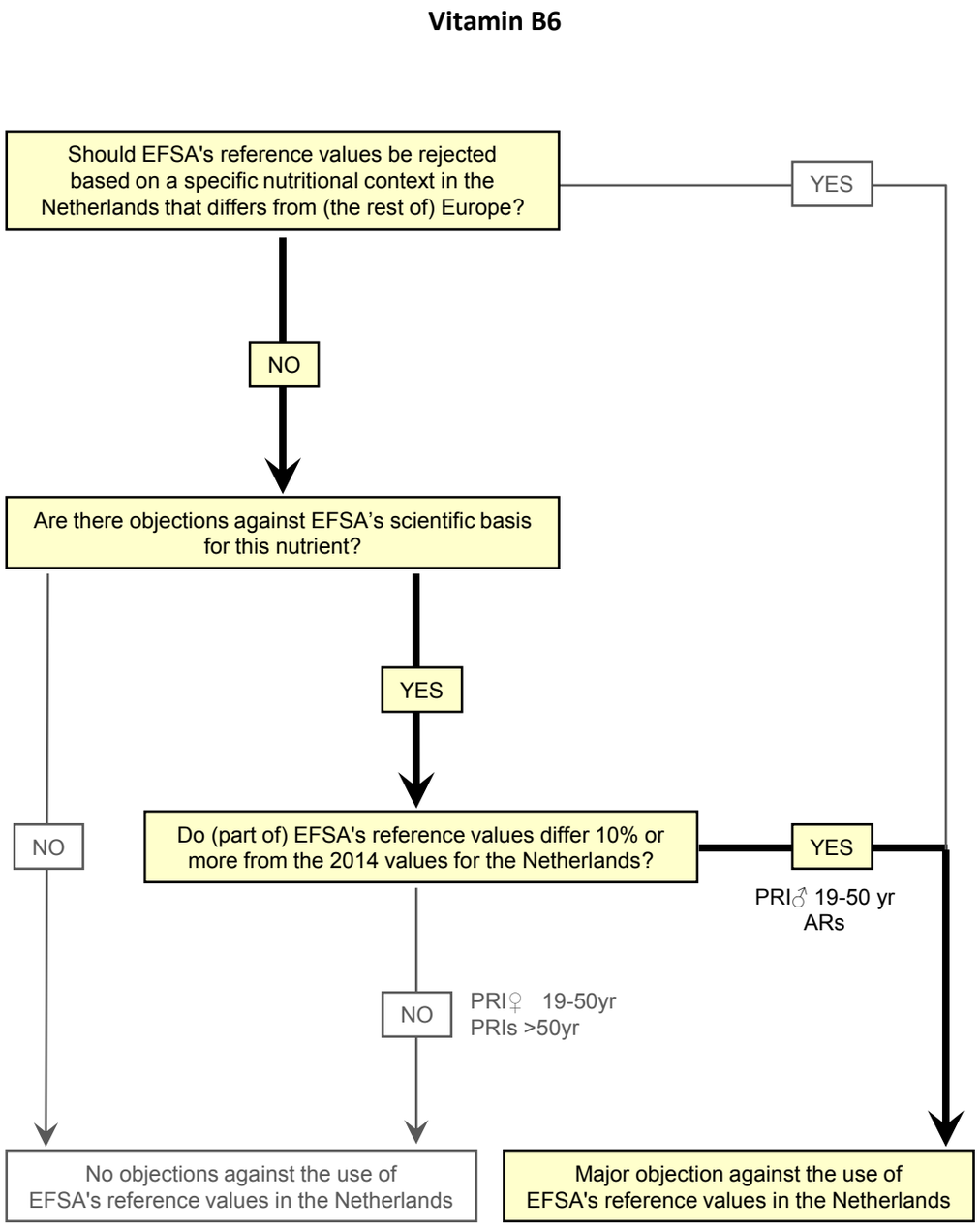
EFSA's AI for pantothenic acid equals the HCNL's AI. EFSA's AI is based on the approximate midpoint of observed median/mean intakes in European countries (other than the Netherlands), which is assumed to be adequate because no signs of deficiency are reported. Pantothenic acid deficiency is rare and has not been reported in healthy subjects on normal diets, so that the adequate intake may substantially exceed requirements. However, there is no evidence available to define a more evidence-based AI.

Therefore, the Committee has no objections against the scientific basis of EFSA's AI, or EFSA's AI for adults (Table 22).

Table 22. AI for pantothenic acid, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	5 mg/day

07
vitamin B6



7.1 Overview and comparison of values

Table 23. Overview of the reference values for adults and the criteria on which these values are based

Report	Age group	PRI/RDA/AI/RI (mg/d)			AR (mg/d)		CV (%)	Main criterion
		Type	♂	♀	♂	♀		
EFSA 2016[10]	≥18 yr	PRI	1.7	1.6	1.5	1.3	10	Status parameter: plasma pyridoxal 5'-phosphate (PLP)[a] >30 nmol/L; AR for women is based on data in women, and then extrapolated to men via allometric scaling (there are few data on men).
HCNL 2003[35] = HCNL 2014[33]	19-50 yr >50 yr	RDA RDA	1.5 1.8	1.5 1.5	1.1 1.3	1.1 1.1	20 20	Status parameter: PLP >20 nmol/L. Note: if protein intake >150 g/d, vitamin B6 requirements increase by 0.01-0.02 mg per gram of extra protein.
NCM 2014[37]	18-60 yr >60 yr	RI RI	1.5 1.5	1.2 1.3	1.3	1.0	10	The AR is based on the recommended B6 intake of 0.015 mg vitamin B6 per g protein (as 0.01 mg/g protein is associated with PLP >20 nmol/L). The value in mg/d is calculated using protein intakes of 15 energy % for younger adults and 18 energy% for older adults, and the average energy requirements.
DACH 2015[38]	19-64 yr >64 yr	AI AI	1.5 1.4	1.2 1.2	- -	- -	- -	The AI is based on the recommended B6 intake of 0.02 mg per gram protein, using the recommended protein intake.
IOM 1998[42]	19-50 yr >50 yr	RDA 2	1.3 1.7	1.3 1.5	1.1 1.4	1.1 1.3	10 10	Status parameters: excretion tryptophan catabolites (no target levels given); plasma PLP >20 nmol/L.
WHO/ FAO 2004[44]	19-50 yr >50 yr	RI RI	1.3 1.7	1.3 1.5	-	-	-	Status parameter: plasma PLP >20 nmol/l. No AR or CV mentioned.

[a] Plasma pyridoxal 5'-phosphate (PLP) is the predominant active form of vitamin B6 that functions as a coenzyme in various metabolic reactions. (The other active form is pyridoxamine 5'- phosphate or PMP.)

Table 23 shows that, in contrast to the reports used for comparison, EFSA does not set different reference values for older adults.

For younger men, the RDA/RI/AI values in all reports used for comparison are between 12% and 24% lower than EFSA's PRIs.

For older men, EFSA's PRI equals the values set by IOM and WHO/FAO, HCNL's value is 6% higher, whereas NCM's RI and DACH's AI are 12% and 18% lower.

The RDA/RI/AI values for both younger and older women in the reports used for comparison are between 6% and 25% lower than EFSA's PRIs.

Note that HCNL used a larger coefficient of variation than EFSA and IOM (20% versus 10%). Therefore the difference between the ARs are larger than the difference between the PRIs/RDAs.

7.2 Explanation of differences between reports

NCM's AR and DACH's AI are based on protein requirements, assuming that the vitamin B6 requirements linearly increase with protein intake.[a] EFSA, HCNL, IOM and WHO/FAO do not support this assumption.[b] The Committee prefers reference values based on the biochemical parameter of status, rather than on protein requirements.

The ARs by EFSA, HCNL, IOM and WHO/FAO are based on a biochemical parameter of status. The differences result from the higher cut-off value for plasma pyridoxal 5'-phosphate (PLP) used by EFSA (30 nmol/l) in comparison to HCNL, IOM and WHO/FAO (20 nmol/l).

- EFSA (2016) based the cut-off value of 30 nmol/l on one study in young adults published in 2013, indicating that mean PLP values below 30 nmol/L (mean PLP decreased from 53 to 22 nmol/L) were associated with effects on biochemical parameters: amino acid, lipid, and organic acid profiles in plasma.[c]
- IOM (1998) stated that results from a large number of studies involving various population groups (IOM provides 7 references) included substantial proportions of individuals with plasma PLP concentrations below 30 nmol/L, with no confirming clinical or other data to suggest B6 deficiency. IOM mentions that other investigators have proposed a cut-off value of 20 nmol/L for plasma PLP as an index of adequacy (IOM refers to Lui et al., J Lab Clin Med 1985; 106: 491-7) and notes that this more conservative cut-off of 20 nmol/L is not accompanied by observable health risks but allows a moderate safety margin to protect against the development of signs or symptoms of deficiency. IOM selected the cut-off value of 20 nmol/L as the basis for the EAR, but

[a] NCM uses the reference value for energy intake and the assumption that the diet provides 15 energy% protein in younger adults and 18 energy% protein in older adults. DACH uses the reference value for protein intake.

[b] EFSA considers that, within the range of observed intakes in Europe, there is insufficient evidence supporting the relationship between vitamin B6 requirement and protein intake. HCNL and IOM conclude that the relationship of vitamin B6 requirements with protein intake is not linear and – given the habitual range of protein intake - does not have to be considered in establishing vitamin B6 reference values. WHO/FAO states that, despite the involvement of PLP with many enzymes affecting amino acid metabolism, there seems to be only a slight effect of dietary proteins on vitamin B6 status.

[c] 23 young adult men and women (20-40 years) consumed a diet with <0.5 mg of vitamin B6 per day for 4 weeks and mean plasma PLP decreased from 53 to 22 nmol/L. Two publications describe the results: Gregory et al. (2013) report a variety of biochemical changes in amino acid profiles. Da Silva et al. (2013) report effects on the profiles of one-carbon and tryptophan metabolites. The Committee notes that these outcomes all are related to biochemical parameters rather than to clinical signs of deficiency.

mentions that "its use may overestimate the B6 requirement for health maintenance of more than half the group". The key references used by EFSA were not available at the publication of the IOM report.

Note that HCNL applied a higher CV (20%) than EFSA and IOM (10%) to calculate the RDA from the AR. HCNL used this higher CV because of uncertainty on the requirements.

Difference between older and younger adults

EFSA bases the AR on the intake level sufficient to maintain a plasma PLP concentration of 30 nmol/L in 50% of each group of women. For younger women, the level was estimated to be 1.2 mg of vitamin B6 per day, based on the linear regression analysis by Hansen et al. (2001).[a] This reference was published after the IOM report. For older women, the level was estimated to be 1.3 mg of vitamin B6 per day, based on other references.[b] When setting the reference values, EFSA uses the higher estimate for older women (+0.1 mg/d for older compared to younger women) for all women as a conservative approach and because the difference is small.

In the reports by HCNL, IOM and WHO/FAO a lower cut-off value for plasma PLP (20 nmol/L) is used, compared with the EFSA report (30 nmol/L). For men, this results in a lower AR for younger versus older men in all three reports. Based on the available research in each group, HCNL set the same AR for older and younger women, whereas IOM and WHO/FAO set a lower AR for younger versus older women.

Sex differences

EFSA concludes that for men, reliable data to determine the requirements are not available. Therefore, EFSA extrapolates the AR for men from the AR for women using metabolic weight, defined as $(\text{body weight})^{0.75}$, resulting in a higher value for men than for women.

IOM and HCNL base their EAR for younger men on the available studies in men, resulting in younger adults having the same AR for men and women. IOM notes that it is difficult to derive a precise EAR for younger men because most studies have identified the vitamin B6 intake that restores biomarkers to baseline values in all subjects which may be considerably higher than the intake level needed for health, and because, in most studies, the levels of vitamin B6 tested appear to have been in excess of the average requirement. HCNL also mentions that research in younger men is limited.

[a] The study by Hansen et al. (2001) is based on the combined data of 44 women (mean age about 20–30 years according to studies) participating in 6 intervention studies (5 references).

[b] EFSA based the estimate for older women on a depletion/repletion study in 2 women, an intervention study comparing 29 younger and 26 older adults, and several cross-sectional studies.

7.3 Conclusion on the scientific basis of EFSA's reference values

EFSA's cut-off value for plasma PLP is 30 nmol/L, based on one study showing biochemical effects after reducing the average plasma PLP to 22 nmol/L. The Committee notes that this cut-off value is not based on evidence regarding clinical effects, and that 22 nmol/L is closer to 20 than to 30 nmol/L. The Committee therefore considers that this study does not provide sufficient basis for the cut-off value of 30 nmol/L.
Therefore, the Committee has objections against the scientific basis of EFSA's reference values.

The Committee prefers the cut-off value for plasma PLP used by HCNL, IOM and WHO/FAO (20 nmol/L), because it is based on the absence of symptoms of deficiency.
EFSA presents some evidence on vitamin B6 intake levels associated with the occurrence, correction or prevention of deficiencies (Table 24). In eight young women, the depletion period with an intake of lower than 0.05 mg/day within 12 days resulted in abnormalities in the electroencephalograms of two women; increasing the intake to 0.5 mg/day quickly reversed these deficiency symptoms. The Committee notes that the AR-values for young women in the HCNL report (1.1 mg/day) provides a substantial margin above this intake level associated with the correction of deficiency (0.5 mg/day).
The Committee has no objections against the scientific basis of HCNL's reference values.

Table 24. Vitamin B6 intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/ Specific group	Reference
Abnormal electroencephalogram within 12 days in 2 women	Depletion diet for (maximum) 28 days: <0.05 mg B6/day	2 out of 8 young women	Kretsch et al., 1991 and 1995
The electroencephalogram was quickly normalised	Repletion with 0.5 mg B6/day		

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

The metabolically active forms PLP and PMP act as cofactors for more than 100 enzymes involved primarily in amino acid metabolism, but also in one-carbon reactions, glycogenolysis and gluconeogenesis, haem synthesis, niacin formation and other functions (lipid metabolism, neurotransmitter synthesis and hormone action).
Vitamin B6 deficiency is rare and has only been reported:

- In the USA in the early 1950s, in young infants who consumed infant formula low in vitamin B6.
- IOM 1998: "in adults … clinical symptoms of B6 deficiency have been observed only in controlled studies during depletion with very low levels of B6 and have never been seen at intakes of 0.5 mg/day or greater".

Symptoms:

- hypochromic microcytic anaemia
- neurological abnormalities (hyperirritability, convulsive seizures and abnormal electroencephalograms)
- eczema
- seborrhoeic dermatitis
- cheilosis
- glossitis
- angular stomatitis.

7.4 Summary and conclusion

Table 25. Summary of the evaluation of EFSA's AR and PRI values for vitamin B6

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's EARs	Differences >10%	For men aged 19-50 yr and all women aged >19 yr, EFSA's AR is approximately 35% and 20% higher than HCNL's EAR. For men aged >50 yr, EFSA's AR is around 15% higher than HCNL's EAR.
EFSA's PRIs compared to HCNL's RDAs	Differences partly >10%	For men aged 19-50 yr, EFSA's PRI is approximately 15%. For all adult women EFSA's PRI is 7% higher than HCNL's RDA; EFSA's PRI for men aged >50 yr is 5% lower than HCNL's RDA.
Scientific basis of EFSA's ARs	Objections	The Committee considers that there is insufficient evidence for the use of EFSA's relatively high cut-off value for plasma PLP. In young women, a correction of deficiency was reported with an intake of 0.5 mg/day, which is much lower than both EFSA's AR (1.3 mg/day) and the 2003 Dutch AR (1.1 mg/day).
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Not consistent with the reports used for comparison: all differentiate between younger and older adults for either men, or women or both.
Differentiation between men and women	Applied by EFSA	Consistent with DACH and NCM, although the basis for the differentiation differs (metabolic weight versus protein requirements). HCNL, IOM and WHO/FAO differentiate between older men and older women, but not between younger men and younger women.

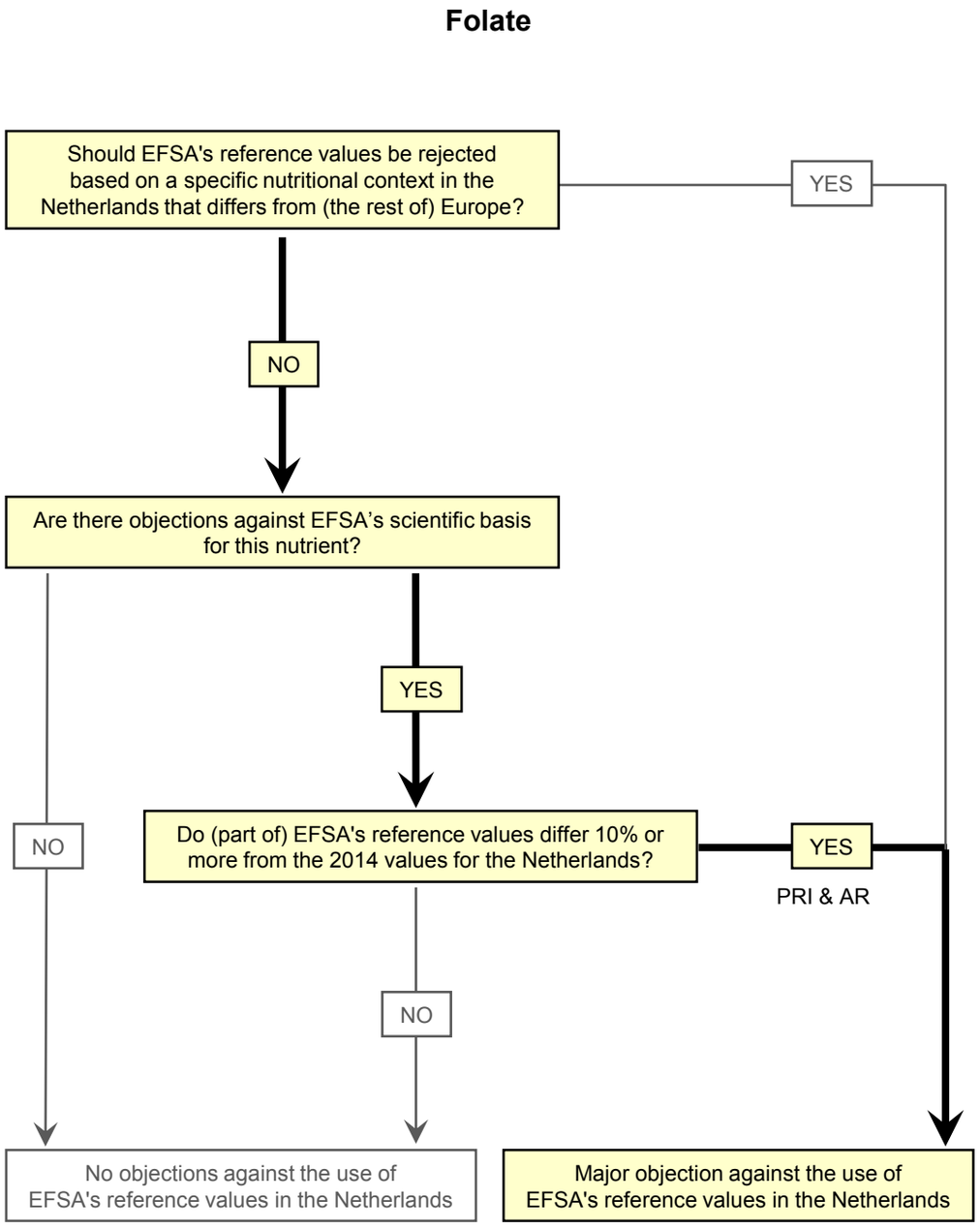
The Committee has objections against the scientific basis of EFSA's ARs, because the evidence for the use of the cut-off value for plasma PLP of 30 nmol/L is insufficient. The Committee prefers the lower cut-off value for plasma PLP used by HCNL, IOM and WHO/FAO (PLP ≥20 nmol/L), which is associated with absence of deficiency signs.

The Committee has objections against EFSA's PRI and AR for adults and recommends maintaining HCNL's reference values (Table 26).

Table 26. AR and PRI for vitamin B6, recommended for the Netherlands

	Men		Women
	18-50 years	**>50 years**	**≥18 years**
Average requirement (AR)	1.1 mg/d	1.3 mg/d	1.1 mg/d
Population reference intake (PRI)	1.5 mg/d	1.8 mg/d	1.5 mg/d

08
folate



Folate is one of the B-vitamins. Previously, folate was also called – dependent on the country – vitamin B11 or vitamin B9, but folate is internationally the preferred name. Folic acid is the synthetic form of folate, also known as pteroylmonoglutamic acid (PGA), which is used in dietary supplements and foodstuffs

8.1 Overview and comparison of values

Table 27. Overview of the PRI/RDA/RI and AR values for adults and the criteria on which these values are based, in dietary folate equivalents (DFE)[a]

Report	Age group	PRI/RDA/AI/RI Type	PRI/RDA/AI/RI (µg/d)	AR (µg/d)	CV[a] (%)	Main criterion
EFSA 2014[26]	>14 yr	PRI	330	250	15%	Serum folate (≥10 nmol/L) and erythrocyte folate (≥340 nmol/L), both cut-off values are associated with lowest plasma homocysteine.
HCNL 2003[35] = HCNL 2014[33]	>18 yr	RDA	300	200	25%	Serum folate (≥7 nmol/L); erythrocyte folate (≥300 nmol/L); plasma homocysteine (<15 µmol/L). The high CV (25%) is chosen so that the RDA also covers the higher requirement of persons with the TT-genotype for the 5,10-methylenetetra-hydrofolate reductase.
NCM 2014[37]	Reproductive age range	RI	♂ 300; ♀ 400	200	25%	Serum folate (>7 nmol/L); erythrocyte folate (>317 nmol/L); plasma homocysteine (<12 µmol/L). RI for all women in reproductive age is 100 µg/d higher than RI for men and older women, because of the possibility of unplanned pregnancies.
	Older	RI	300	200	25%	
DACH 2015[38,47]	>12 yr	RDA	300	220	15%	Serum folate (≥10 nmol/L); erythrocyte folate (≥340 nmol/L); plasma homocysteine (<12 µmol/L, secondary criterion).
IOM 1998[42]	>18 yr	RDA	400	320	10%	Serum folate (≥7 nmol/L); erythrocyte folate (≥305 nmol/L, based on the absence of hypersegmented neutrophils in the blood and on indicators chromosome damage); plasma homocysteine (<14/16 µmol/L).
WHO/ FAO 2004[44]	>18 yr	RDA	400	320	10%	WHO/FAO accepted the IOM values.

[a] If the coefficient of variation was not specified in the report, it was calculated as 100% x [(PRI/RI/RDA - AR) / 2] / AR.

Table 27 shows that HCNL's RDA, DACH's RI as well as the NCM's RI for men and older women are 9% lower than EFSA's PRI. NCM's RI for women in the reproductive age range, IOM's RDA and WHO/FAO's RI are 21% higher than EFSA's PRI.

8.2 Explanation of differences between reports

This evaluation focuses on the difference between EFSA, HCNL, NCM, DACH and IOM, because the WHO/FAO-criteria are not clear.

All reports base the ARs on the same biochemical parameters of status, but EFSA and DACH use higher cut-off values for the biomarkers than the other organisations:

- Serum folate cut-off values were 10 nmol/l (EFSA and DACH) or 7 nmol/L (HCNL, NCM and IOM).
- Erythrocyte folate cut-off values were 340 nmol/l (EFSA and DACH), 317 nmol/L (NCM) or 300/305 nmol/L (HCNL and IOM).

Although HCNL, NCM and IOM use the same cut-off values for serum and erythrocyte folate, the AR set by HCNL and NCM (200 µg/d) is substantially lower than IOM's AR (320 µg/d). The difference is the result of the publications used to set the AR. IOM gives the greatest weight to the small study by O'Keefe et al. (1995),[a] whereas HCNL and NCM do not take this publication into account because other key references indicate that lower intake levels are sufficient.[b,c] The Committee prefers the AR-value of HCNL and NCM (200 µg/d), which is based on more data than the IOM-value.

EFSA and DACH use the same cut-off values for serum and erythrocyte folate, but the AR by DACH (220 µg/d) is somewhat lower than EFSA's AR (250 µg/d).

The coefficient of variation (CV) used to calculate the PRI from the AR varies substantially between the reports: the CV used by HCNL and NCM is the highest (25%), the CV used by EFSA and DACH is 15%, the CV used by IOM and WHO/FAO is the lowest (10%).

[a] O'Keefe et al. (1995) studied 3 groups with 5-6 subjects each. IOM's AR is the intake level in the group with the lowest supplemental level: 3 of the 5 subjects in this group had a low erythrocyte folate (<362 nmol/L) and a low serum folate (<7 nmol/L) at the end of the 70-day period on the experimental diets.

[b] HCNL based the average requirement of 200 µg/d mainly on the publications of Milne et al. (1983; n=40) and Sauberlich et al. (1987; n=10). NCM based the average requirement of 200 µg/d on the study by Sauberlich et al. (1987) and several additional studies.

[c] Note that IOM's AR (320 µg/d) is even higher than the ARs of EFSA and DACH (EFSA: 250 µg/d and DACH: 220 µg/d) which are based on higher cut-off values for serum and erythrocyte folate. EFSA bases the average requirement for adults of 250 µg folate per day on the results of the study by Kauwell et al. (2000; n=32), which is in agreement with the publications of Milne et al. (1983) and Sauberlich et al. (1987). EFSA mentions that folate intakes in the latter two studies have probably been underestimated.
DACH bases their average requirement of 220 µg/d on Milne et al. (1983), Sauberlich et al. (1987) and Herbert (1962; n=3), but adds 10% to the estimate of 200 µg/d in order to take into account a certain underestimation of the folate content of foods due to analytical limitations.

Differences between older and younger adults

EFSA, HCNL, DACH, IOM and WHO/FAO do not differentiate the reference values between younger and older adults, based on the available research.

NCM does not differentiate the reference values between younger and older men. However, for women in the reproductive age range, NCM does differentiate between women in the reproductive age and older women, based on the role of folic acid in the prevention of neural tube defects. NCM's RI for women in the reproductive age is 400 µg/d, which is 100 µg/d higher than the RI for older women (and all adult men). Note that the approach regarding the prevention of neural tube defects in infants with folic acid differs between countries; this is described and discussed below.

Sex differences

EFSA, HCNL, DACH, IOM and WHO/FAO do not differentiate the reference values between men and women, based on studies in men and studies in women.

NCM does not differentiate the reference values between older men and older women. However, NCM's RI for women in the reproductive age range is 100 µg/d higher than their RI for men in this age range. Note that the approach regarding the prevention of neural tube defects in infants with folic acid differs between countries; this is described and discussed below.

Approaches regarding the prevention of neural tube defects in infants by folic acid

The use of a supplement containing 400 micrograms of folic acid per day from at least four weeks prior to conception until eight weeks after conception (when the neural tube has closed) lowers the chance of having a child with a neural tube defect by at least 50% (estimates range 36-72%).[48,49]

Countries use different approaches to achieve this preventive effect of folic acid against neural tube defects in infants:

- In the Netherlands, women who wish to conceive are advised to use a supplement containing 400 µg/d of folic acid, starting at least four weeks prior to conception until eight weeks after conception.[49]
- Other countries such as the USA and Canada use – additionally to the advise to use a folic acid supplement – mandatory fortification of staple foodstuffs with folic acid. A disadvantage of such fortification is the resulting higher proportion of individuals with excessively high intakes of folic acid in all groups and especially in children.
- NCM set the RI for women in the reproductive age range at a 100 µg/d higher level than the RI for men in the same age range and for older men and women. NCM writes: "Women of reproductive age represent a specific challenge because there is convincing evidence that an adequate supply of folate before and up to 12 weeks after conception reduces the risk of NTD. However, far from all pregnancies are planned. Therefore, an RI of 400 µg/d for all women of reproductive

ages should provide adequate folate supply to women experiencing unplanned pregnancies."[37]

From these three approaches to achieve this preventive effect of folic acid against neural tube defects in infants, only NCM's approach involves the dietary reference values and should be considered within the context of this report. Both other approaches (supplementation, either in combination with the mandatory fortification of staple foodstuffs or not) concern implementation policies instead of dietary reference values, and therefore are beyond the scope of this report.

NCM's RI is not based on evidence regarding the folate requirement of all women in the childbearing age, but aims at a subgroup of these women: those who are going to be pregnant. The RI is set at a higher level than NCM's RI for other adults, in order to improve the folate status in women who will experience an unplanned pregnancy and in women who are not reached by information campaigns on folic acid supplementation around conception.

The Committee considers that the evaluation of implementation strategies requires a broader perspective, and prefers that dietary reference values are based on evidence regarding the requirements of the whole group.

Therefore, the Committee does not support NCM's RI.

8.3 Conclusion on the scientific basis of EFSA's reference values

The cut-off values for serum folate and erythrocyte folate used by HCNL, NCM and IOM are associated with the prevention of clinical deficiency (megaloblastic anaemia). The higher cut-off values used by EFSA and DACH are based on lowering the plasma homocysteine concentration. The Committee considers that the clinical relevance of the lowering of plasma homocysteine is unclear.

Therefore, the Committee has objections against the scientific basis of EFSA's reference values.

The Committee prefers the cut-off values for serum and erythrocyte folate used by HCNL, NCM and IOM. In paragraph 8.2, the Committee concluded that the AR-value set by HCNL and NCM (200 µg/d) are based on more data than the higher AR-value set by IOM (320 µg/d).

The Committee has no objections against the scientific basis of HCNL's reference values

EFSA did not describe publications on studies relating specific intake levels to the occurrence, correction or prevention of deficiency signs, but EFSA does mentions that NCM (2004) and the UK Department of Health (1991) associate intakes of 100 µg/day and 150-200 µg/day, respectively, with the absence of deficiency (Table 28). The Committee notes that the proposed AR (200 µg/day) corresponds with (or is higher than) intake levels associated with prevention of deficiency symptoms.

Table 28. Folate intake levels associated with the prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects	EFSA's reference
NCM 2004 set a lower level of intake of 100 µg DFE/day, based on the minimum intake needed to prevent folate deficiency anaemia (Herbert et al., 1962), daily losses from stores while on a virtually folate-free diet (Zalusky and Herbert, 1961) and the excretion in urine in well-nourished individuals (Herbert, 1987a).	100 µg DFE/day		NCM 2004
The UK COMA (DH, 1991) considered the folate concentration of autopsied liver samples, the prevalence of 8-10% of low red blood cell folate concentrations (<150 µg/mL) and the absence of overt signs of clinical and haematological folate deficiency in Canadian subjects on folate intakes of 150-200 µg/day (Hoppner et al., 1977; Hoppner and Lampi, 1980).	150-200 µg DFE/day	Canadian subjects	UK COMA (DH, 1991)

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

Folate functions as a cofactor or cosubstrate in numerous one-carbon transfer reactions that are important for the synthesis of RNA and DNA, amino acid interconversions and the process of methylation. Different folate forms are involved in specific reactions, but all of them are finally metabolised to THF.

Folate deficiency does occur in Western populations, but EFSA does not provide further information on this.

Symptoms:

- hypersegmentation of neutrophils (five to six lobes instead of two to four; this is a specific sign)
- megaloblastic anaemia (this is a sign of folate deficiency, but it can also occur as a result of vitamin B12 deficiency alone)
- lowering of granulocyte and platelet counts with the advancement of anaemia
- megaloblastosis can affect the epithelial cells of the entire gastrointestinal tract and can impair the absorption of folate and further exacerbate the deficiency state.

Folate deficiency has also been associated with (usually mild) forms of:

- irritability
- forgetfulness.

8.4 Summary and conclusion

Table 29. Summary of the evaluation of EFSA's AR and PRI values for folate equivalents

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's (=NCM's) EARs	Difference >10%	EFSA's AR is 25% higher than HCNL's EAR.
EFSA's PRIs compared to HCNL's (=NCM's) RDAs	Difference >10%	EFSA's PRI is 10% higher than HCNL's RDA.
Scientific basis of EFSA's AR	Objections	EFSA and the reports used for comparison base the AR on the intake required to maintain a cut-off value for serum and erythrocyte folate. However, EFSA uses relatively high cut-off values. The Committee prefers the cut-off values used by HCNL.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

The Committee has objections against the scientific basis of EFSA's dietary reference values, because it considers that the evidence for the use of EFSA's relatively high cut-off values for serum and erythrocyte folate is insufficient. The Committee prefers to use the lower cut-off values used by HCNL, NCM and IOM, which are associated with the prevention of clinical deficiency. The AR-value of HCNL and NCM (200 µg/d) is based on more data than the IOM's AR (320 µg/d). The Committee does not support NCM's RI for women in the reproductive age range, because this value aims specifically at the subgroup of women who are going to be pregnant. It has no objections against the scientific basis of HCNL's dietary reference values.

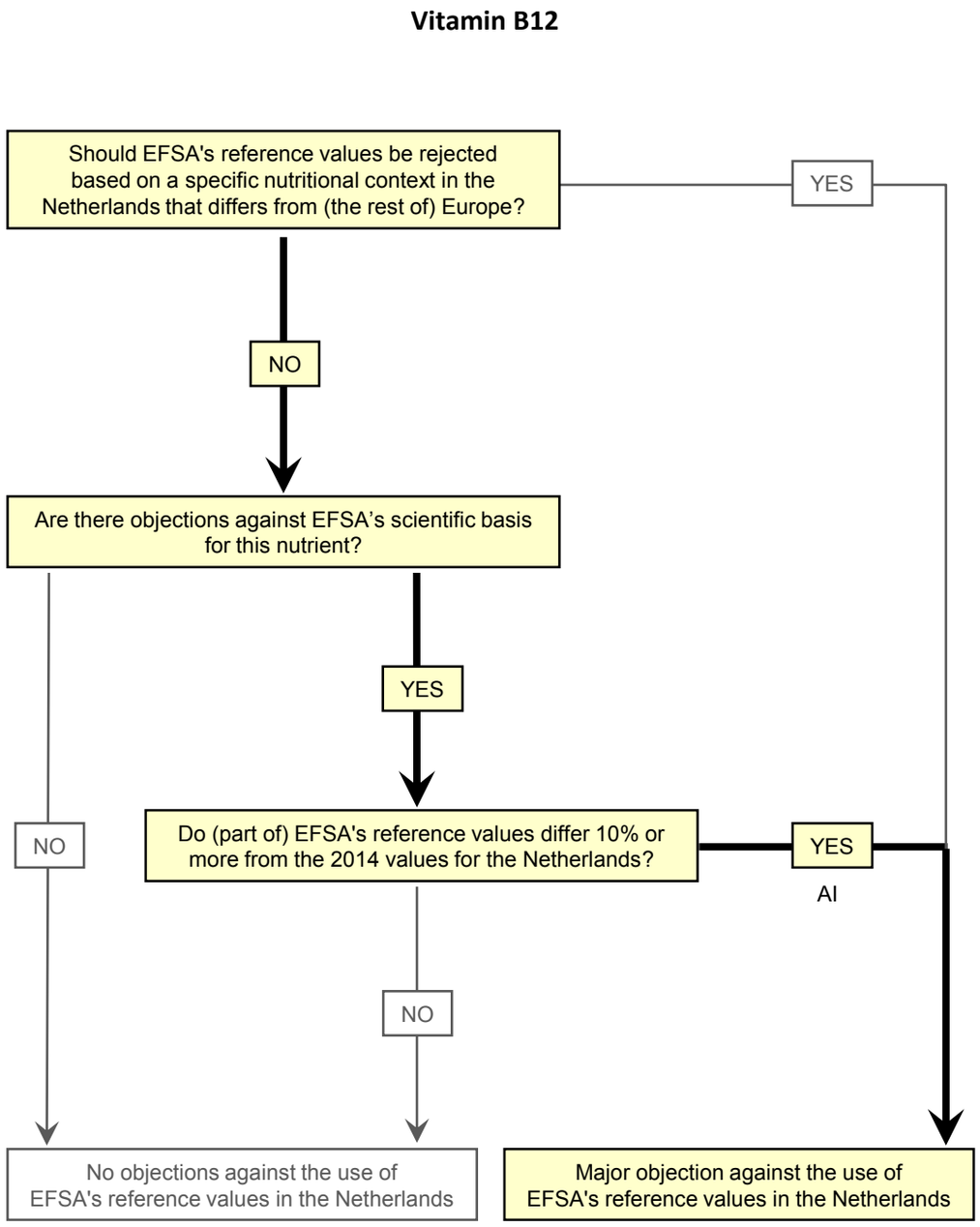
The Committee has objections against EFSA's PRI and AR for adults and recommends maintaining HCNL's reference values (Table 30).

Table 30. AR and PRI for folate equivalents recommended for the Netherlands

	Men and women[a] ≥18 years
Average requirement (AR)	200 µg/day
Population reference intake (PRI)	300 µg/day

[a] Note that women who wish to conceive are advised to use a supplement containing 400 µg/d of folic acid, starting at least four weeks prior to conception until the eighth week of pregnancy, in addition to these reference values.

09 vitamin B12 (cobalamin)



9.1 Overview and comparison of values

Table 31. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI		AR	CV	Main criterion
	Type	(µg/d)	(µg/d)	(%)	
EFSA 2015[15]	AI	4	-	-	Four status/function parameters: serum holoTC & cobalamin, MMA & tHcy and in consideration of observed intakes in several EU countries.
HCNL 2003[35] = HCNL 2014[33]	RDA	2.8	2.0	20%	Factorial method: requirement is intake needed to compensate 0.2% daily loss of body store in liver of 0.5 mg, at absorption rate 50%: AR = 2 µg/d.
NCM 2014[37]	RI	2.0	1.4	15% (20%[1])	Prevention of haematological abnormalities: In 20 patients with pernicious anaemia, an intramuscular 0.5-2.0 µg/d normalised and maintained haematological status, and 0.5-1.0 µg was sufficient for most subjects. Because these patients are unable to reabsorb B12 from bile, healthy individuals need somewhat less. In NNR 2004, AR was estimated to be 0.7 µg/d. At absorption rate of 50%, AR = 1.4 µg/d.
DACH 2015[38]	RDA	3.0	2.0	25%[a]	Prevention of haematological abnormalities and status parameter: Plasma cobalamin concentration and haematological parameters.
IOM 1998[42]	RDA	2.4	2.0	10%	Factorial method: 1) estimate intramuscular requirement for adequate hematological status (stable Hb, normal MCV & reticulocyte response): 1.5 µg/d; 2) subtract losses via bile: 0.5 µg/d; 3) correct for bioavailability: 50%. Result: EAR = 2.0 µg/d.
WHO/FAO 2004[44]	RI	2.4	2.0	10%	WHO/FAO adopted IOM 1998.

[a] CV calculated as 100% x [(PRI/RI/RDA – AR) / 2] / AR.

Table 31 presents an overview of reference values and criteria. EFSA set an AI for vitamin B12, whereas the reports used for comparison set an AR and PRI. The RDAs/RIs in these other reports are substantially lower than EFSA's AI: HCNL -30%; NCM -50%; DACH -25%; IOM and WHO/FAO -40%. The coefficients of variation used in the reports used for comparison to calculate the RDA/RI from AR ranged between 10% and 25%.

9.2 Explanation of differences between reports

This paragraph focuses on the differences between EFSA and HCNL, NCM and IOM, because DACH does not clearly describe how they arrived at the reference values, and WHO/FAO adopted the reference values of IOM. EFSA's AI is based on biochemical parameters of status and function; the ARs of HCNL and IOM are based on a factorial method, and the AR of NCM on the prevention of haematological abnormalities.

EFSA uses four biomarkers to establish the AI. This combination of biomarkers is required, because of the limitations of each individual biomarker and uncertainties with respect to the cut-off values.[a] EFSA bases the AI on two[b] studies:

- The cross-sectional study by Bor et al. (2010), providing information on biomarker levels in quintiles of estimated vitamin B12 intake (Table 32).
- The findings in the placebo-group of the intervention study by Pentieva et al. (2012), which provides information on biomarker levels at the average background vitamin B12 intake of 4 µg/day.[c]

The EFSA Panel concludes that data on the dose–response relationships between vitamin B12 intake and biochemical parameters, considered together, are limited. The available findings provide consistent evidence that a vitamin B12 intake of 4 µg/day is associated with adequate levels of all four biomarkers, indicating an adequate vitamin B12 status. EFSA added that the observed (average) intakes of adults in several EU countries range between 4.2 and 8.6 µg/day.

HCNL and IOM both established an AR of 2.0 µg/day, based on the factorial method.

EFSA did explore the factorial approach, but rejected this method, considering that – depending on the assumptions used – the estimates ranged widely (5-15 µg/day). The Committee notes that even the lowest of EFSA's factorial estimates are substantially higher than HCNL's and IOM's AR. The main reason is, that EFSA's factorial method aimed at maintaining body stores of 2 and 3 mg, which is the average body content in healthy

[a] Paragraph 2.4.6 of EFSA report: "The Panel considers that serum holoTC is the most specific and therefore the first ranked biomarker to characterise adequate cobalamin status. In addition, the Panel considers that cut-off values of reference ranges for these biomarkers have not yet been clearly defined."

[b] In paragraph 5.1.1.3 of EFSA report a third study is described: the Norwegian observational study by Vogiatzoglou et al. (2009). EFSA Panel does not use this study for setting the AI, because it provides information on biomarker-levels only for intakes ≥5 µg/day, i.e. for the mean daily vitamin B12 intakes in four groups: middle-aged men (7.3 µg/day) and women (5.5 µg/day), and older men (6.9 µg/day) and women (5.1 µg/day). In all groups, the average biomarker levels were adequate.

[c] The intervention study by Pentieva et al. (2012) provided data in 231 UK subjects with an average background vitamin B12 intake of 4 µg/day, receiving either placebo or a vitamin B12 supplement with 3.4, 12.7 or 46.1 µg/day; this study provides no information on intakes below 4 µg/day. In the placebo group (approximately 60 subjects), mean values for plasma holoTC, cobalamin, MMA and tHcy were adequate (note that mean MMA was 220 nmol/L and was thus within the range of proposed upper limits: 210 to 450 nmol/L). In all three groups using vitamin B12 supplements, the levels of all four biomarkers were adequate.

adults, whereas HCNL and IOM aimed at maintaining body stores of 0.5 mg, which is the lowest body content in individuals with no haematological symptoms of vitamin B12 deficiency.
NCM's AR of 1.4 µg/day refers to the intake associated with the maintenance of a normal haematological status.

Differences between older and younger adults and sex differences
None of the reports differentiate the reference values between younger and older adults or between men and women. There are insufficient data to differentiate between men and women.

Table 32. EFSA's information with respect to cut-off values for the four biochemical parameters used to set the AI[a]

Biochemical parameters considered by EFSA to set the AI	Information provided in the EFSA report			
	Ranges of parameter cut-off values for vitamin B12 insufficiency	Results in the reference by Bor et al., 2010[50]		
		Parameter level at observed intakes[b]		Intake above which the parameter levelled off
		Intake 2.8 µg/d	Intake 4.2 µg/d	
Serum holotrans-cobalamin (holoTC)	Range of lower limits: 11-48 pmol/L.	50 pmol/L	65 pmol/L	4 µg/d
Serum cobalamin	Range of lower limits: 134-178 pmol/L.	325 pmol/L	350 pmol/L	7 µg/d
Serum methylmalonic acid (MMA)	Range of upper limits: 210-450 nmol/L.	210 nmol/L	200 nmol/L	3-7 µg/d
Plasma total homocysteine (tHcy)	Frequently used upper limit: tHcy >15 µmol/L	8 µmol/L	7 µmol/L	4-7 µg/d

[a] The study by Bor et al. (2010) comprised 300 USA men and women. Biomarker values were reported for quintiles of B12 intake, each comprising around 60 subjects.
[b] Two intake levels are the most relevant here (quintiles 2 and 3) and are therefore reported. Quintile 2: median intake 2.8 µg/d (range 2.1-3.4 µg/d). Quintile 3: median intake 4.2 µg/d (range 3.4-5.3 µg/d).

9.3 Conclusion on the scientific basis of EFSA's reference values

The Committee notes that, in the study by Bor et al. (2010), adequate levels of all four biomarkers were reported at a vitamin B12 intake of 4.2 µg/day, but also at an intake of 2.8 µg/day (Table 32), so that these findings appear to comply with an AI of 2.8 µg/day. The study by Pentieva et al. (2012) is not suitable for assessing the adequacy of intakes below 4 µg/day, because the average background vitamin B12 intake was 4 µg/day. Although the intake of 4 µg/day is associated with adequate levels of the four biomarkers, the evidence presented indicates that a lower intake than 4 µg/day may also be adequate. EFSA does not present evidence that the AI of 4 µg/day would provide additional health benefits, in comparison to an intake of 2 µg/day. Therefore, the Committee has objections against the scientific basis of EFSA's AI.[a]

The EFSA report does not present publications relating vitamin B12 intake levels with the occurrence, correction or prevention of vitamin B12 deficiency, but EFSA does mention that intakes of 1.5-2 µg/day seem to represent a minimum requirement for maintenance of a normal haematological status, and is associated with body stores of 1-2 mg. Note that NCM associated an intake level of 1.4 µg/day with the maintenance of a normal haematological status.

[a] Note that the NCM report mentions that cross-sectional population studies have shown that biochemical indicators of vitamin B12 status are stabilised at intakes of about 4-10 µg/d among adults, but that it is unclear whether intakes in this range are associated with long-term benefits.

HCNL's AR (2 µg/day) is based on the factorial method aimed at maintaining the lowest body content in individuals with no haematological symptoms of vitamin B12 deficiency. The Committee has no objections against the scientific basis of HCNL's AR.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

In humans, two reactions are known to require cobalamin as coenzyme. One is the conversion of methylmalonyl-CoA to succinyl-CoA. The other is the transmethylation of homocysteine to methionine by methionine synthase; cobalamin and folate are both required and interact in this reaction.

In Western populations, vitamin B12 deficiency may occur in vegans, in older adults with atrophic gastritis or pernicious anemia (resulting in malabsorption of cobalamin bound to food), and in people with Imerslund-Gräsbeck syndrome.

Symptoms:

- megaloblastic anaemia (this is a sign of vitamin B12 deficiency, but it can also occur as a result of folate deficiency alone; the onset occurs later in cobalamin deficiency)
- neurological dysfunction (including myelopathy, neuropathy and neuropsychiatric abnormalities, and less often optic nerve atrophy; due to progressive demyelinating lesions of the white matter in the spinal cord and brain). Clinical cerebral features are associated with mental symptoms, such as irritability, memory disturbances, depression. In severe deficiency or advanced stages, a dementia-like illness, frank psychosis with hallucinations and paranoia may occur.

9.4 Summary and conclusion

Table 33. Summary of the evaluation of EFSA's AI values for vitamin B12

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AI compared to HCNL's RDA 2003	Differences >10%	EFSA's AR is 40-45% higher than HCNL's RDA.
Scientific basis of EFSA's AI	Objections	The evidence EFSA uses to establish their AI indicates that lower intakes may also be adequate, based on the biomarker levels used by EFSA as the scientific basis.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

The Committee has objections against the scientific basis of EFSA's AI and thus against EFSA's AI, because a lower intake may be sufficient to achieve EFSA's cut-off values for biomarkers, and EFSA presents no evidence that their relatively high AI would provide additional health benefits.

The Committee has no objections against the scientific basis of HCNL's AR. This factorial method is related to the prevention of deficiency.

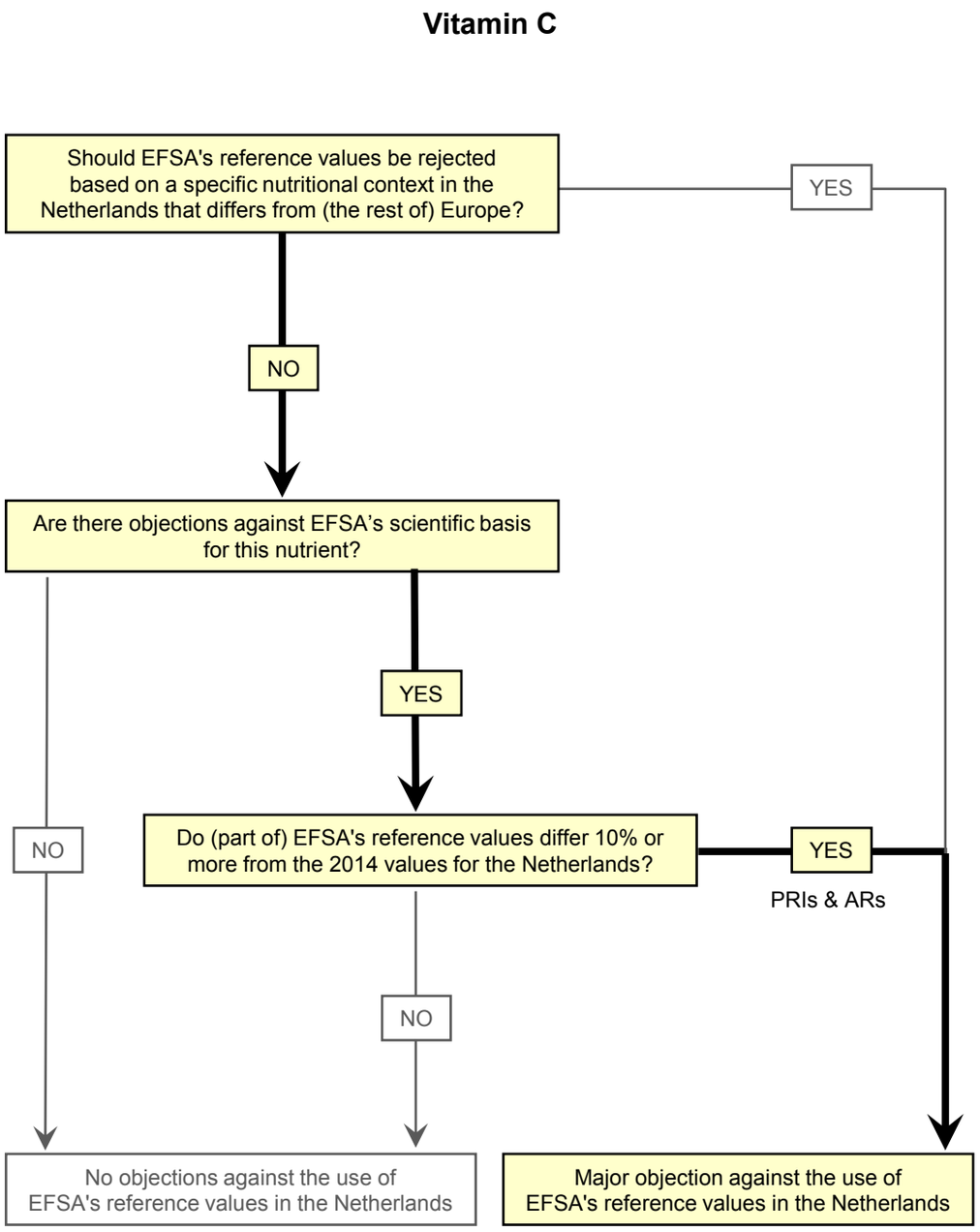
HCNL's AR is consistent with the AR in most of the reports used for comparison, although NCM set an even lower AR (1.4 µg/day).

The Committee has objections against EFSA's AI for adults, and recommends maintaining HCNL's reference values (Table 34).

Table 34. AR and PRI for vitamin B12, recommended for the Netherlands

	Men and women ≥18 years
Average requirement (AR)	2.0 µg/day
Population reference intake (PRI)	2.8 µg/day

10 vitamin C (ascorbic acid)



10.1 Overview and comparison of values

Table 35. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI (mg/d)			AR (mg/d)		CV	Main criterium
	Type	♂	♀	♂	♀		
EFSA 2013[29]	PRI	110	95	90	80	10	In healthy, non-smoking men, an intake of 90 mg/d (AR♂) balances metabolic losses at a saturated body pool of 1.5 gram (metabolic losses 50 mg/d), taking into account that urinary losses are 25% of intake and absorption is 80% of intake. The AR for women is extrapolated from the AR for men by isometric scaling (linear with body weight).
NCM 2014[37] = HCNL 2014[33]	RI	75	75	60	50	♂12,5% ♀25%	Status parameter: plasma ascorbate concentration of 32 µmol/L is associated with a lowered risk of chronic diseases. Pharmacokinetic data indicate that such concentration corresponds to a body pool of 1.0 -1.2 g, and to an intake of 60 mg/d in men and 50 mg/d in women. This is close to the intake at which vitamin C begins to be excreted in the urine. The CV for women was assumed to be double that for men, to ensure adequate non-haem iron absorption.
DACH 2015[38,51]	RDA	110	95	91	77	10	As EFSA.
IOM 2000[2]	RDA	90	75	75	60	10	Status parameter: neutrophil ascorbate concentration at near-maximal level (80%), because of its relationship with antioxidant protection.
WHO/FAO 2004[44]	RI	45	45	25-30		25-40%	Maintenance of a body content of 0.9 g vitamin C, assuming an absorption efficiency of 85%, and a catabolic rate of 2.9%. The body content of 0.9 gram is halfway between tissue saturation (1.5 g), and the point at which clinical signs of scurvy appear (0.3-0.4 g)

Table 35 shows that EFSA's PRI equals the RDA by DACH. The values by IOM, NCM and WHO/FAO are lower (-20%, -27% and -56% relative to EFSA's PRIs).

10.2 Explanation of differences between reports

The scientific basis for the reference values for vitamin C varies substantially between the reports. The ARs by EFSA, DACH and WHO/FAO are based on the metabolic losses at a certain body pool of vitamin C; EFSA and DACH aim at a saturated body pool (1.5 gram), whereas WHO/FAO aims at a body pool of 0.9 gram. NCM's reference values are based on a plasma ascorbic acid concentration of 32 µmol/L, which is associated with a body pool of 1.0-1.2 gram. IOM's ARs are based on the neutrophil ascorbate concentration. In this paragraph the methods are described in more detail.

The EFSA Panel decided to determine the AR for vitamin C in healthy adults from the vitamin C intake that balances metabolic vitamin C losses and maintains fasting plasma ascorbate concentrations at about 50 µmol/L. In healthy *non-smoking*[a] men aged 20-45 years the maximum metabolic losses of vitamin C were estimated to be about 3.0% of a saturated body pool of 1.5 gram: 40-50 mg/day, corresponding to a plasma ascorbate concentration of about 45-50 µmol/L.[b] Taking a conservative approach, and based on the fact that a complete set of data was only available in men, the EFSA Panel selected metabolic losses of 50 mg/day, an absorption of 80% and a urinary excretion of 25% of the vitamin C intake and calculated that an intake of 90 mg vitamin C per day, on average, is required to balance daily losses in men.[c]

The EFSA Panel notes that women reach the plasma concentration of 50 µmol/L with a slightly lower intake of vitamin C compared to men. No data on metabolic losses were available for women, and therefore, EFSA set the AR for women by extrapolating the AR for men, using isometric scaling (linear with the reference body weights of 68.1 for men and 58.5 for women).[d]

Assuming a CV of 10%, PRIs of 110 and 95 mg vitamin C per day are derived for men and women, respectively. EFSA notes that in almost all healthy men, the intake of 110 mg/day is associated with a plasma ascorbate concentration above 50 µmol/L.

DACH follows the same line of reasoning as EFSA, resulting in the same reference values as EFSA.

[a] EFSA notes that smokers have higher metabolic losses compared to non-smokers at similar vitamin C intakes.

[b] EFSA mentions that vitamin C intakes above 200 mg/day progressively elevate the plasma concentration to a plateau of 70-80 µmol/L or even above, at the expense of a dramatic increase in urinary excretion.

[c] AR for men (mg/d) = 50 mg/d / ((80%-25%)/100) = 50 mg/d / 0.55 = 91 mg/d, rounded to 90 mg/d.

[d] AR for women (mg/d) = 91 mg/d x (58.5/68.1) = 78 mg/d, rounded to 80 mg/d.

NCM set the AR at the vitamin C intake required to achieve a plasma ascorbate concentration of 32 µmol/L, which is associated with a body pool of 1-1.2 g. NCM notes that a concentration of 23 nmol/L and a body pool of 0.9 mg would be sufficient to prevent scurvy. NCM uses the higher cut-off value of 32 mmol/L to set the AR. This is the unweighted mean of the cut-off points in eight population studies associated with clearly lowered risk to mortality from chronic diseases, such as cancer and cardiovascular diseases. NCM's cut-off point for plasma ascorbate concentration corresponds with intakes of 60 g/d in men and 50 g/d in women.
NCM notes that women have slightly higher plasma vitamin C concentrations for a given level of intake, and therefore, NCM's AR for women is slightly lower than NCM's AR for men. However, NCM's RI-values are equal for men and women, because NCM uses a higher coefficient of variation for women than for men in order to ensure adequate non-haem iron absorption in women (25% and 12.5%, respectively).

IOM based the AR on the vitamin C intake required to achieve a neutrophil ascorbate concentration at near-maximal level (80%), which would be relevant for antioxidant protection. As no similar data were available for women, IOM assumed that women have a lower requirement due to their smaller lean body mass, total body water, and body size. IOM notes that this assumption was supported by the finding that women maintain higher plasma ascorbate concentrations than men at a given vitamin C intake. Thus, IOM extrapolated the AR for men to the AR for women, based on body weight differences.

WHO/FAO bases their reference values on the body content of 0.9 gram,[a] which is halfway between tissue saturation (1.5 g), and the point at which clinical signs of scurvy appear (0.3-0.4 g). WHO/FAO notes that the last signs of deficiency have disappeared when the body content reaches about 1.0 gram.
WHO/FAO's RI is based on the 97.5th percentile of the catabolic rate of 4.1%, which was calculated as the estimated mean catabolic rate (2.9%) plus two times the estimated standard deviation (0.6%). The 97.5th percentile of metabolic losses is then calculated to be 37 mg, which is 4.1% of the body content of 0.9 gram. Using an assumed absorption efficiency of 85%, WHO/FAO establishes the recommended intake of 45 mg per day.
WHO/FAO notes that turnover studies in women were not available. Requirements in women are expected to be lower than in men because of the smaller body size, however, in depletion-repletion studies plasma ascorbic acid concentrations fell more rapidly in women than in men. Therefore, to be prudent, WHO/FAO uses the RI for men also for women.

[a] Note that the WHO/FAO report does describe the relationship between vitamin C intake and plasma ascorbic acid, but does not use this for setting the AR and RI.

WHO/FAO calculated the AR-range of 25-30[a] mg/day by interpolation between 10 mg/day, which is the minimal intake to prevent against scurvy, and the RI of 45mg/day.

Differences between older and younger adults

None of the reports differentiate the reference values between younger and older adults.

Sex differences

All organisations consistently note that the reference values for women cannot be based on research in women, because the required studies are not available for women. EFSA, DACH and IOM differentiate between men and women based on the difference in reference weights for men and women.

Both NCM and WHO/FAO use the RI for men also for women, based on different arguments. NCM uses the same RI for men and women, to ensure adequate non-haem iron absorption in women (note that NCM's AR is lower for women than for men, based on the difference in reference body weights). WHO/FAO uses the same RI and AR for men and women, as a prudent approach, because in depletion-repletion studies plasma ascorbic acid concentrations fell more rapidly in women than in men.

The Committee notes that research in women is insufficient for an evidence-based choice between the EFSA/DACH/IOM approach and the more prudent approach of NCM and WHO/FAO.

10.3 Conclusion on the scientific basis of EFSA's reference values

The EFSA Panel considers that a saturated body pool (1.5 gram) and a plasma ascorbate concentration of 50 nmol/L is indicative of an adequate vitamin C status at which the different functions of vitamin C in the body can be fulfilled, but does not provide evidence that this provides more health benefits than the maintenance of a smaller body pool or lower plasma ascorbate concentrations.

The Committee has objections against the scientific basis of EFSA's reference values.

NCM's AR-values are based on a plasma ascorbate concentration of 32 nmol/L, which in turn is based on the cut-off points in eight population studies associated with lowered risk to mortality from chronic diseases. The vitamin C intake associated with the prevention of deficiency is 10 mg/day (Table 36).

The Committee has no objections against the scientific basis of NCM's reference values.

[a] Using the body content of 0.9 gram and the assumed average catabolic rate of 2.9%, the average metabolic losses were estimated to be 26 mg/d (2.9% of 0.9 gram). With an assumed absorption efficiency of 85%, the average requirement (after rounding) would be 30 mg per day.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Vitamin C has a number of biochemical and physiological functions in the body which are largely dependent on its ability to provide reducing equivalents in various biochemical reactions. Vitamin C is an enzyme cofactor for biochemical reactions catalysed by monooxygenases, dioxygenases and mixed function oxygenases. Vitamin C plays an important role in the biosynthesis of collagen and the synthesis of carnitine. Vitamin C is a cofactor in the conversion of dopamine to noradrenaline, is involved in the metabolism of cholesterol to bile acids, and has various other effects in the body.

The EFSA report does not provide information on the occurrence of vitamin C deficiency. The IOM report[2] notes that scurvy is rare in developed countries, but is occasionally seen in individuals who consume few fruits and vegetables, have peculiar or restricted diets, or in those who abuse alcohol or drugs.

Symptoms of vitamin C deficiency:

- Scurvy, characterised by symptoms related to connective tissue defects that result from a weakening of collagenous structures (tooth loss, joint pain, bone and connective tissue disorders, and poor wound healing).
- Depression, hypochondria and mood changes are frequently associated with scurvy and may be related to deficient dopamine hydroxylation.
- Early or prescorbutic symptoms also include fatigue, lethargy, anaemia, aching joints, and muscle weakness.

Table 36. Vitamin C intake level associated with the prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/ Specific group	EFSA's reference
No scurvy	10 mg/d	5 adult men	Baker et al., 1971; Levine, 1986; Weber et al., 1996; Burri & Jacob, 1997

10.4 Summary and conclusion

Table 37. Summary of the evaluation of EFSA's AI values for vitamin C

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's (=NCM's) ARs	Differences >10%	EFSA's AR is 50% and 60% higher than HCNL's (=NCM's) ARs for men and women, respectively.
EFSA's PRIs compared to HCNL's (=NCM's) RIs	Differences >10%	EFSA's PRI is 45% and 25% higher than HCNL's (=NCM's) RI, for men and women, respectively.
Scientific basis of EFSA's ARs	Objections	EFSA does not provide evidence that a saturated body pool (1.5 gram) and plasma ascorbate concentrations > 50 nmol/L provide more health benefits than the maintenance of a smaller body pool and lower plasma ascorbate concentrations.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Applied by EFSA	Consistent with the reports used for comparison.

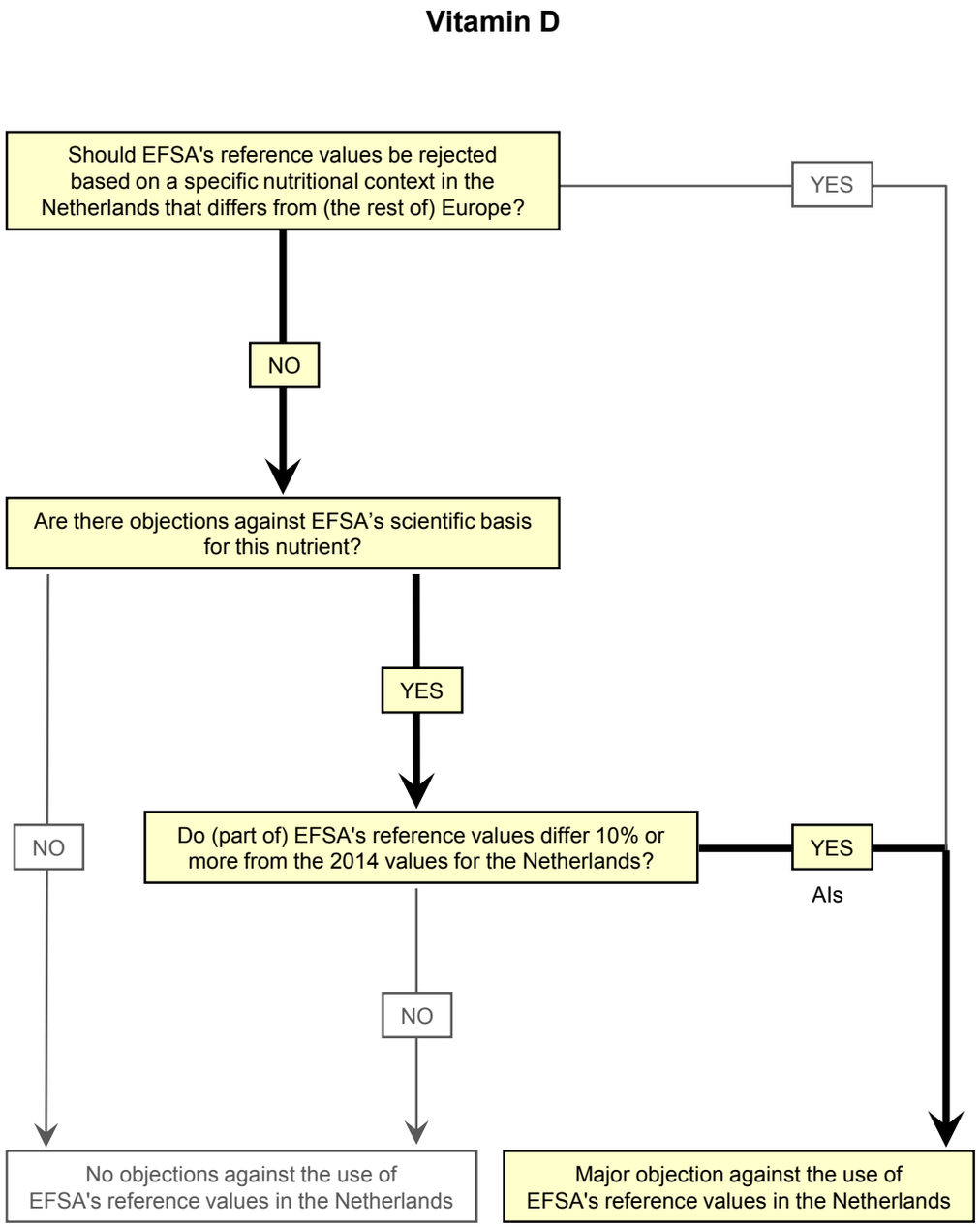
The Committee has objections against the scientific basis of EFSA's reference values. There is insufficient evidence for using a saturated body pool of vitamin C and plasma ascorbate concentrations ≥ 50 nmol/L as the basis for setting the reference values.

The Committee recommends maintaining HCNL's reference values, which are the reference values presented in the NCM report (Table 38).

Table 38. AR and PRI for vitamin C, recommended for the Netherlands.

	Men ≥18 years	Women ≥18 years
Average requirement (AR)	60 mg/d	50 mg/d
Population reference intake (PRI)	75 mg/d	75 mg/d

11 vitamin D (ergocalciferol and cholecalciferol)



11.1 Overview and comparison of values

Table 39. Overview of the reference values for adults and the criteria on which these values are based

Report	Age group	AR/RI/RDA		AR (µg/d)	CV (%)	Main criterion
		Type	(µg/d)			
EFSA 2016[8]	≥1 yr	AI	15[a]			Serum 25(OH)D[2] ≥50 nmol/L
HCNL 2012[34] = HCNL 2014[33]	0-69 yr	AI	10[a]			Serum 25(OH)D >30 nmol/L, and taking into account that (1) there are no signs that everyone in this group requires vitamin D supplementation and (2) that in Dutch people with lighter skin types, the average vitamin D production is 7 µg/day, and the average dietary intake is 3 µg/day. There is convincing evidence that daily supplementation with 10 to 20 µg vitamin D in combination with (in most studies 1 g/d) calcium reduces the risk of bone fractures.
	≥70 yr	RDA	20[a]	10		
NCM 2014[37]	1-74 yr	RI	10[c] (20[a])	7.5[c]	17%[d]	Serum 25(OH)D ≥50 nmol/L
	≥75 yr	RI	20			Serum 25(OH)D >50 nmol/L and convincing evidence on a protective effect of vitamin D on bone health, total mortality, and the risk of falling, mainly seen for combined supplementation with vitamin D and calcium.
DACH 2015[38]	≥1 yr	AI	20[a]			Serum 25(OH)D >50 nmol/L.
IOM 2011[39]	1-70 yr	RDA	15[a]	10[a]	25%[d]	AR: serum 25(OH)D >40 nmol/L RDA: serum 25(OH)D >50 nmol/L At high age there is more variability, therefore although AR is the same, RDA is higher.
	>70 yr	RDA	20[a]	10[a]	50%[d]	

Report	Age group	AR/RI/RDA		AR	CV (%)	Main criterion
		Type	(µg/d)	(µg/d)		
WHO/FAO 2004[44]	≤50 yr	AI	5[a]			Serum 25(OH)D >27 nmol/L, based on IOM 1997. Factors declining with age: skin synthesis (linear decrease as the skin thins from 20 y), rate of activation to the hormonal form of vitamin D, response of target tissues (e.g. bone).
	51-65 yr	AI	10[a]			
	>65 yr	AI	15[a]			

[a] Under conditions of minimal cutaneous vitamin D synthesis. In the presence of endogenous cutaneous vitamin D synthesis, the requirement for dietary vitamin D is lower or may even be zero.

[b] Serum 25(OH)D concentration is the main form of vitamin D in the blood circulation. It is used as a biomarker of vitamin D status in adult and children populations. It reflects the amount of vitamin D attained from both cutaneous synthesis and dietary sources.

[c] The RI set by NCM applies to conditions of normal cutaneous vitamin D synthesis. In the text NCM mentions that the recommended intake for people with little or no sun exposure is 20 µg/d.

[d] CV calculated as 100% x [(RDA/RI - AR) / 2] / AR.

Cutaneous vitamin D synthesis

In most people, the vitamin D supply is met partly by cutaneous vitamin D synthesis and partly by dietary intake. The cutaneous vitamin D synthesis depends on sunlight exposure of the skin and on skin type. In the EFSA report and in most of the reports used for comparison, the reference values for vitamin D intake refer to conditions of *minimal* cutaneous vitamin D synthesis, because:

- cutaneous vitamin D synthesis depends on the latitude and can therefore better be estimated for the country or region where the reference value is applied
- reference values are based mainly on studies carried out under conditions of minimal cutaneous vitamin D.

However, the NCM report is an exception: NCM's primary RI value refers to conditions of *normal* cutaneous vitamin D synthesis. NCM does mention that the recommended intake for people with little or no sun exposure is 20 µg/d. Note that the latter value is used for the comparison with other reports, so that the comparison of reports which is presented below, refers consistently to conditions of *minimal* cutaneous vitamin D.

Comparison of the values for conditions with minimal cutaneous vitamin D synthesis

Younger adults: Table 39 shows that, under conditions of minimal cutaneous vitamin D synthesis, EFSA's AI equals IOM's RDA, but HCNL and WHO/FAO use a lower AI/RI (-33% and -67%), whereas NCM and DACH use a higher value (both +33%).

Older adults: EFSA's AI is 25% lower than the RI/RDA values of HCNL, NCM, DACH and IOM. Note that for older adults, HCNL's RDA and NCM's RI are independent of cutaneous vitamin D synthesis, whereas the values by EFSA, DACH and IOM refer to conditions of minimal cutaneous vitamin D synthesis.

11.2 Explanation of differences between reports

The WHO/FAO-values are based on the 1997 IOM reference values. As IOM updated the reference values for vitamin D, WHO/FAO is left out of consideration in the next paragraphs.

All reports base their reference value on a biochemical parameter of status (serum 25-hydroxyvitamin D or 25(OH)D), but different cut-off values for 25(OH)D are used: EFSA, NCM, DACH and IOM use a cut-off value of 50 nmol/L, whereas HCNL uses a cut-off value of 30 nmol/L.

Furthermore, estimates of the vitamin D supply required to achieve 25(OH)D levels of at least 50 nmol/L differ between the reports: according to EFSA and IOM this cut-off level requires 15 µg/day, whereas NCM and DACH estimate that this requires 20 µg/day. Estimates depend on the type of data used in the regression analysis, which may be either the group/study averages, or data on individual subjects. The intake at which 97.5% of the population achieves a serum 25(OH)D concentration above 50 nmol per litre is estimated to be 10-12 µg/day if group/study averages are used, but 20-25 µg/day if data on individual subjects are used.[34,52] The Committee prefers regression analyses based on data of individual subjects for setting the AI, because the AI aims to cover the needs of almost all *individuals* in the population.[a]

HCNL estimated that an intake of 11-15 µg/day was required to achieve a serum 25(OH)D >30 nmol/L in almost all adults <70 years. However, the estimated total vitamin D supply in Dutch adults with light skin types was lower: 10 µg/d, based on a median intake of about 3 µg/day,[b] and an average vitamin D production in the skin of 7 µg/d over the course of the entire year.[c] Because there are no signs that all adults require vitamin D supplementation, HCNL set the AI at the value of 10 instead of 15 µg/day.[34] Based on three publications by Cashman et al., almost everyone in this group will have 25(OH)D levels >25 nmol/L with a vitamin D supply of 10 µg/day.[34] A recent publication Cashman et al. confirms this estimate.[52]

Sex differences

None of the reports differentiate the AIs between men and women.

Differences between older and younger adults

EFSA does not differentiate the AI between younger and older adults, whereas most of the reports used for comparison do. For older adults. EFSA, HCNL[d], NCM, DACH and IOM consistently aim at a serum 25(OH)D ≥50 nmol/L. For this age group, the evidence on the preventive effect of vitamin D against fractures in older adults is also considered:

- HCNL, NCM, DACH and IOM consider the results from randomised controlled trials: the intake or supplemental levels used in these trials and their effect on fracture risk.

[a] Estimates from regression analysis on group/study averages are too low, because between-person variation is not taken into account. Estimates based on individual data do take between-person variation into account.

[b] The estimated median intake of Dutch adults of Dutch descent was about 3 µg/day. The estimated mean intake of Dutch adults of Turkish or Moroccan descent was about 2 µg/day.

[c] This estimate was based on Dutch and British studies and refers to subjects with sufficient sunlight exposure of the skin. Estimates by calendar month ranged between 0 µg/d (December/January) and 13 µg/d (June/July), but these estimates were based on indirect calculations and simple models, and therefore, they should be interpreted with caution.[34]

[d] HCML considered that, based on data of individual subjects, 50% of the people aged >70 years achieve a 25(OH)D >50 nmol/L with an intake of 10 µg/d; and 97.5% achieve 25(OH)D >50 nmol/L with intakes of 20-25 µg/d.

- EFSA considers 25(OH)D levels associated with fracture risk, but considers that the results from randomised controlled trials are not useful as such for setting DRVs for vitamin D.

In HCNL's report on vitamin and mineral supplements,[53] which served as a background report for the Dutch dietary guidelines 2015, HCNL concluded that there was strong evidence from intervention studies that the use of supplements with 10-20 µg/d vitamin D per day plus 0.5-1.2 g/d calcium reduces the risk of fractures by 10% and reduces the risk of hip fractures by 15% in older adults and especially postmenopausal women.

11.3 Conclusion on the scientific basis of EFSA's reference values

Reference values for older adults

The Committee has objections to the scientific basis of EFSA's adequate intake for older adults: the Committee considers – unlike the EFSA Panel – that the reference values for adults aged ≥70 years can be based on the results from randomised controlled trials on the effect of using supplements with vitamin D and calcium on the risk of fractures.

Reference values for younger adults

EFSA, NCM, DACH and IOM use a cut-off value of 50 nmol/L, whereas HCNL uses a cut-off value of 30 nmol/L:

- For 4-69 year olds, HCNL uses a serum level of 25(OH)D >30 nmol/L, which is the target value for young children based on the risk of rickets. HCNL did not consider the findings on intermediate measures of bone health, such as bone density and calcium absorption (which could have led to a higher 25(OH)D target value), because HCNL considered that the meaning of these intermediate measures for bone health was insufficiently clear.
- EFSA provides the following scientific basis for their use of 25(OH)D ≥50 nmol/L:
  - "Some evidence" for a higher risk of increased loss of bone mass density / bone mass concentration with serum 25(OH)D <50 nmol/L. Note that HCNL considered that the meaning of these intermediate measures for bone health was insufficiently clear.[34]
  - "Limited evidence" that osteomalacia was reported at 25(OH)D <20 nmol/L and that risk appears to be small with serum 25(OH)D ≥50 nmol/L.
- IOM notes that "calcium absorption is maximal at serum 25(OH)D concentrations between 30 and 50 nmol/L with no consistent increase in calcium absorption above approximately 50 nmol/L." "For the purposes of ensuring public health in the face of uncertainty and providing a reference value for stakeholders, a prudent approach is to begin the consideration of the DRIs for these age groups with the level of 25OHD in serum that is consistent with coverage of the requirement of nearly all adults in this age range, that is, 50 nmol/L."

The Committee considers that the scientific evidence for the cut-off value of 50 nmol/L for 25(OH)D is not strong for adults <70 years; the use of this criterion appears to be a prudent approach. Furthermore, the Committee considers that the cut-off value of 50 nmol/L would require a vitamin D supply of 20 µg/day, rather than EFSA's estimate of 15 µg/day.[34,52] In the Netherlands, all Dutch adults would need to take vitamin D supplements to realise a supply of 20 µg/day. In 2012, HCNL considered that there were no signs that all Dutch adults would require vitamin D supplementation.[34] The average supply of Dutch adults with light skin types who are sufficiently exposed to sunlight is 10 µg/day, which will result in 25(OH)D levels >25 nmol/L in almost all individuals. The value of 25 nmol/L is considered to be a threshold for vitamin D insufficiency[52,54] although some organisations use a cut-off value of 30 nmol/L for this purpose. Therefore, the Committee has objections against the scientific basis of EFSA's reference values for vitamin D for adults aged <70 years.

Note that the EFSA report does not present research on the direct relationship of intake levels and the occurrence, correction or prevention of clinical deficiencies in younger adults.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, and deficiency symptoms in adults

In the body, vitamin D is converted to the main circulating form, calcidiol (25(OH)D), which can be transformed into the biologically active calcitriol (1,25(OH) $_2$D). The principal function of calcitriols is to maintain calcium and phosphorus homeostasis in the circulation, together with parathyroid hormone and fibroblast growth factor. The main target tissues of calcitriols are the intestine, the kidneys and bone.
The EFSA report does not provide information on the occurrence of vitamin D deficiency.
Symptoms in adults:

- Osteomalacia, caused by the impaired mineralisation of bone due to an inefficient absorption of dietary calcium and phosphorus.
- Clinical symptoms may include diffuse pain in muscles and bone, muscle pain and weakness, poor physical performance, increased risk of falls/falling, and a higher risk of bone fractures.
- Prolonged vitamin D insufficiency may lead to low bone mineral density (BMD) and may dispose older subjects, particularly post-menopausal women, to osteoporosis, a situation characterised by a reduction in bone mass, reduced bone quality and an increased risk of bone fracture, predominantly in the forearm, vertebrae, and hip.

11.4 Summary and conclusion

Table 40. Summary of the evaluation of EFSA's AI values for vitamin D

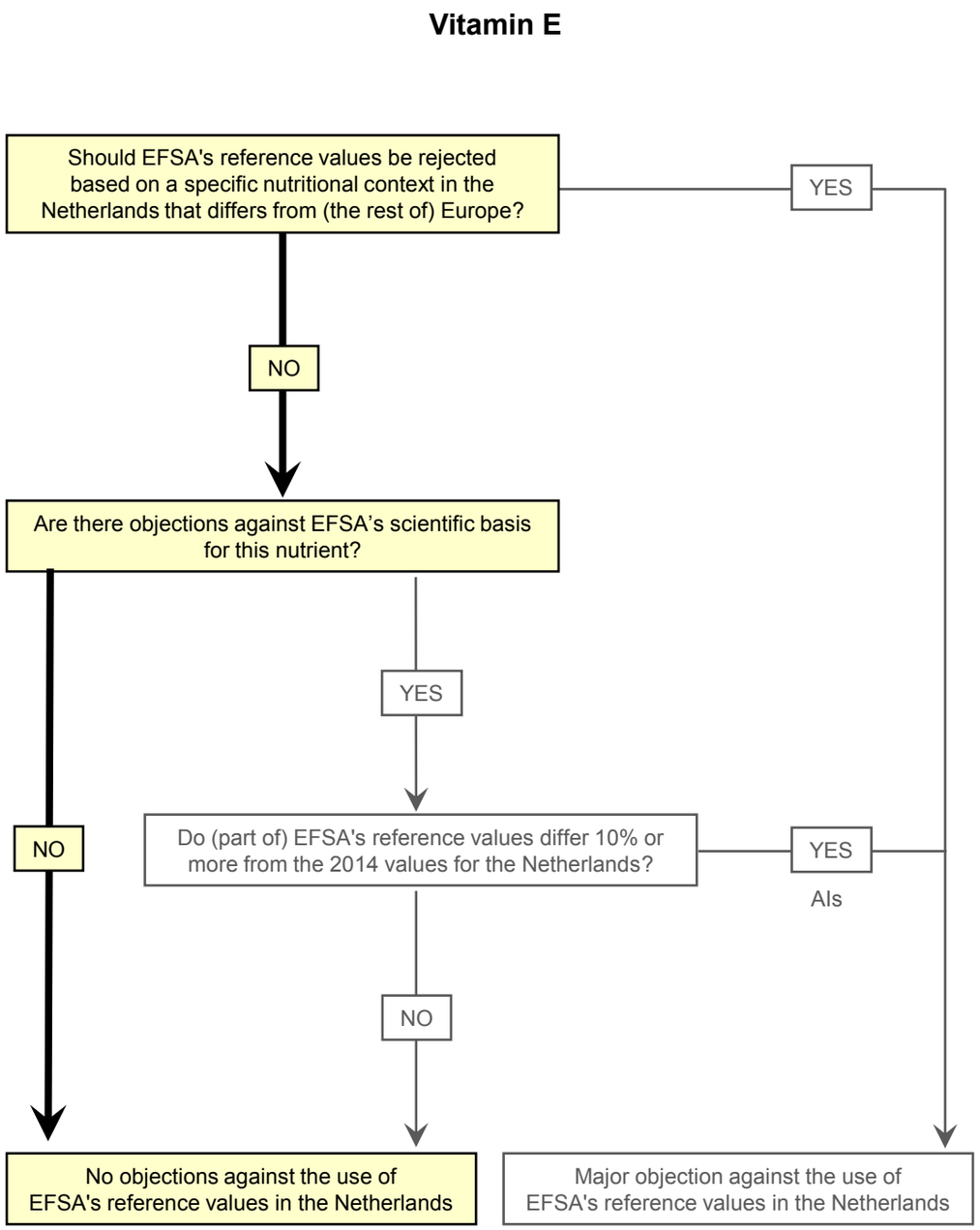
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AI compared to HCNL's RDA 2003	Differences ≥10%	EFSA's AI is 50% higher than HCNL's AI for adults <70 years, but 33% lower than HCNL's RDA for adults ≥70 years.
Scientific basis of EFSA's AI	Objections	The scientific evidence for the cut-off value of 50 nmol/L for 25(OH)D is not strong. This cut-off value of 50 nmol/L would require a vitamin D supply of 20 µg/day, rather than EFSA's estimate of 15 µg/day.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with DACH, but not with the other reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

The Committee has objections against the scientific basis of EFSA's reference values for vitamin D, and also against EFSA's AI for adults. In 2012, HCNL set reference values for vitamin D; the Committee has no objections against the scientific basis of these reference values. The Committee recommends maintaining HCNL's reference values and using these values (Table 41) in the Netherlands.

Table 41. AI, AR and PRI for vitamin D, recommended for the Netherlands

	Men and women	
	18-69 years	**≥70 years**
Adequate intake (AI) under circumstances without cutaneous vitamin D synthesis	10 µg/day	
Average requirement (AR)		10 µg/day
Population reference intake (PRI)		20 µg/day

12 vitamin E (alpha-tocopherol)



12.1 Overview and comparison of values

Table 42. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI (mg/d)			AR (mg/d)		CV (%)	Main criterion
	Type	♂	♀	♂	♀		
EFSA 2015[14]	AI ≥10 yr	13	11	-	-	-	Intake observed in EU populations with no apparent vitamin E deficiency.
NCM 2014[37] = HCNL 2014[33]	RI ≥14 yr	10	8	6	5	♂33[a] ♀30[a]	RI eventually was based on 0.4-0.6 mg α-tocopherol equivalents (α-TE) per g recommended intake of polyunsaturated fatty acids (PUFA); the origin of these values was not transparently described. Additionally, NCM considered a biochemical status parameter (plasma α-tocopherol), and the absence of signs of vitamin E deficiency at current intake levels.
DACH 2015[38]	AI 19-24 yr 25-50 yr 51-64 yr ≥65 yr	 15 14 13 12	 12 12 12 11	-	-	-	AI was determined from by PUFA intake, assuming a basic daily requirement of 4 mg TE and an additional requirement of 0.06, 0.4 and 0.6 g mg TE per gram of intake of fatty acid intake with respectively one, two or three double bonds. The origin of these values was not transparently described.
IOM 2000[2]	RDA ≥14 yr	15	15	12	12	10	Function parameter: requirement = intake sufficient for plasma alpha-tocopherol to limit peroxide-induced haemolysis to max 12%, i.e. 12 µmol/L. This requires an intake of 12 mg/d.
WHO/FAO 2004[44]	AI ≥10 yr	10	7.5	-	-	-	WHO/FAO considered the available data not sufficient to formulate recommendations for vitamin E intake except for infants.

[a] CV calculated as 100% x [(PRI/RI/RDA – AR) / 2] / AR.

Table 42 shows that lowest RIs are from NCM and WHO/FAO (-25% and -27% relative to EFSA) and the highest from IOM (+25%). DACH's value is similar to EFSA's (+6%).

α-Tocopherol versus α-tocopherol equivalents

The reference values used by EFSA, NCM[a] and IOM refer to α-tocopherol. The α-tocopherol equivalents (α-TE) used by DACH and WHO/FAO include α-, β-, γ- and δ-tocopherols and α-tocotrienols. The Committee agrees with the expression as α-tocopherol used by EFSA, NCM and IOM.

12.2 Explanation of differences between reports

EFSA's AIs are based on observed intakes, NCM's AR and DACH's AI on the relationship between vitamin E requirement and PUFA intake, and IOM's AR on a biochemical parameter of function. WHO/FAO considered that the data were not sufficient to formulate recommendations for vitamin E intake for different age groups, except for infants, and therefore did not set a reference value for vitamin E for adults.

EFSA considered that available data on biochemical markers of α-tocopherol intake, status and function, on α-tocopherol kinetics and body pools, and on the relationship between PUFA intake and α-tocopherol intake and requirement could not be used on their own, nor in combination, to derive the requirement for adults.

EFSA based the AI on vitamin E intakes observed in EU populations with no apparent vitamin E deficiency. EFSA considered intakes of α-tocopherol and/or α-tocopherol equivalents from eight dietary surveys in seven countries of the European Union (Finland, France, Ireland, Italy, the Netherlands, Sweden and the United Kingdom). The EFSA Panel considered the approximate midpoints of the range of mean intakes for α-tocopherol and α- tocopherol equivalents (Table 43) and, after rounding, set an AI for α-tocopherol at 13 mg/day for men and 11 mg/day for women. The EFSA Panel noted that these AIs are close to, or above, the intakes that are suggested from available studies on markers of α-tocopherol intake/status or on α-tocopherol kinetics and body pools.

Table 43. Average intakes of α-tocopherol and/or α-tocopherol equivalents in EU countries

Adults (age groups >18 yr)	Ranges of average intakes (midpoints of these ranges) in EU countries (mg/day)	
	α-tocopherol	α-tocopherol equivalents
Men	8.2-16 (12.1)	10.1-16.0 (13.1)
Women	7.8-12.5 (10.2)	8.9-13.5 (11.2)

IOM based the AR-value on a function parameter: the plasma α-tocopherol concentration associated with in vitro hydrogen peroxide-induced haemolysis <12%. IOM concludes: "Although the exact plasma α-tocopherol concentration that allows haemolysis to take place is

[a] In NNR 2012, vitamin E activity is confined to α-tocopherol. Vitamin E activity has previously been expressed as α-tocopherol equivalents (α-TE). Note that the tables in the NCM report mention α-TE instead of α-tocopherol as the unit of expression.

unknown, it appeared to be prudent to estimate the lowest known plasma α-tocopherol concentration as that cut-off point where haemolysis would take place in 50 percent of the population. Thus, a plasma concentration of 12 µmol/L was chosen as the concentration of plasma α-tocopherol associated with normal in vitro hydrogen peroxide-induced haemolysis. … … The data of Horwitt (1960) support an EAR of 12 mg (27.9 µmol) of α-tocopherol. The data were derived from studies in men only, and no similar data are available for women. However, there is no scientific basis for assuming different requirements for men and women, and although body weights may be greater in men, women have larger fat masses as a percent of body weight, and thus may have similar requirements."

EFSA did not use plasma/serum α-tocopherol concentration (IOM-criterion). EFSA did not consider this concentration to be a sensitive marker of dietary α-tocopherol intake, because an association between dietary α-tocopherol intake and plasma/serum α-tocopherol concentrations has not consistently been observed and, when observed, the correlation was weak. Furthermore, EFSA considered the evidence for the adequate plasma value of 12 µmol/L insufficient. There is a lack of data on the relationship between α-tocopherol concentrations in plasma/serum and those in peripheral tissues. EFSA notes that plasma/serum α-tocopherol <12 µmol/L may be indicative of α-tocopherol deficiency, but that there is a lack of data to set a precise cut-off value above which α-tocopherol status may be considered as adequate.

NCM and DACH based the AR on the PUFA-intake.

EFSA did not use the ratio of α-tocopherol intake over PUFA intake (criterion used by NCM and DACH) as the criterion to set the AI, because the required amount of α-tocopherol may differ according to the degree of saturation of the various PUFAs. EFSA considers that there is little evidence to support the ratios of 0.4 mg (criterion NCM and used as supportive evidence by IOM) or 0.6 mg of α-tocopherol per gram of dietary PUFAs, and that there were uncertainties in the intake measurements on which both ratios were based. Still, EFSA does agree that PUFA intake is probably associated with an adequate α-tocopherol intake.

Differences between older and younger adults

Note that DACH is the only organisation differentiating reference values between several age groups of adolescents/adults, which appears to result from differences in PUFA-intake. All other organisations set one value for adolescents and all adults (≥10 or ≥14 or ≥15 years old).

Sex differences

All organisations except IOM differentiate between women and men.

12.3 Conclusion on the scientific basis of EFSA's reference values

EFSA mentions that symptomatic α-tocopherol deficiency has not been reported in healthy individuals. Subjects consuming a diet with a very low vitamin E content developed signs of deficiency after more than two years

on this diet (Table 44). The Committee has no objections against EFSA's argumentation for using average intakes observed in European populations as the basis for the AI, but notes that average intakes may substantially exceed requirements.

Table 44. Vitamin E intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/Specific group	EFSA's reference
After 28 months, *in vitro* hydrogen peroxide-induced haemolysis increased from 0% to 80%	3 mg/d	19 men	Horwitt et al. 1956, Horwitt 1960, Horwitt 1962, Horwitt et al. 1963

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

α-Tocopherol is a peroxyl radical scavenger and especially protects PUFAs within membrane phospholipids and plasma lipoproteins. By protecting PUFAs within membrane phospholipids, α-tocopherol preserves intracellular and cellular membrane integrity and stability, and plays an important role in the stability of erythrocytes and in the conductivity in central and peripheral nerves.

Symptomatic α-tocopherol deficiency in individuals without any disease and who consume diets 'low' in α-tocopherol has not been reported.

Primary vitamin E deficiency, i.e. familial isolated α-tocopherol deficiency, results from a genetic defect in the α-TTP gene. Secondary vitamin E deficiency has been observed in specific patient groups (abetalipoproteinaemia, cholestatic liver diseases, severe malnutrition, fat malabsorption, and cystic fibrosis).

Symptoms of vitamin E deficiency:

- haemolytic anaemia
- neurological symptoms (ataxia, peripheral neuropathy, myopathy, pigmented retinopathy).

12.4 Summary and conclusion

Table 45. Summary of the evaluation of EFSA's AI values for vitamin E

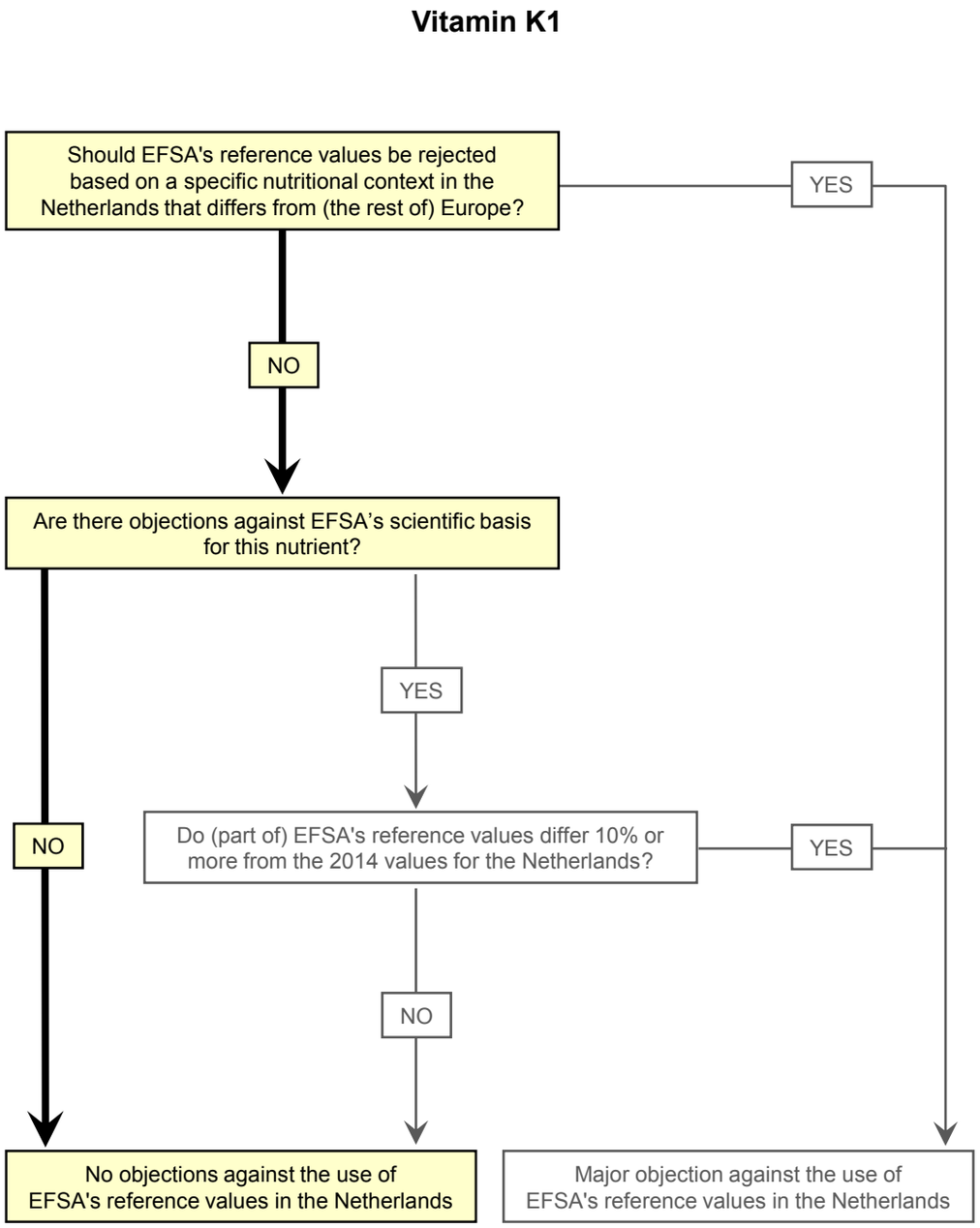
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (=NCM's) RI	Higher	EFSA's AI is 30-40% higher than HCNL's (=NCM's) RI.
Scientific basis of EFSA's AI	No objections	EFSA based their AI on average intakes, and described why they did not use the criteria used in the reports used for comparison (NCM and DACH: PUFA-intake; IOM: limitation of peroxide-induced haemolysis). Note that WHO/FAO did not set reference values for adults because of insufficient data.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with most of the reports used for comparison. Only DACH differentiates between age groups.
Differentiation between men and women	Applied by EFSA	Consistent with the reports used for comparison.
EFSA's unit of expression	α-tocopherol	Consistent with NCM and IOM, but DACH express their values in α-tocopherol equivalents.

EFSA's AI for vitamin E is based on the approximate midpoint of observed average intakes in European countries which is assumed to be adequate because no signs of deficiency have been reported in healthy individuals. Vitamin E deficiency has not been reported in healthy subjects on normal diets, so that the adequate intake may substantially exceed requirements. However, there is no evidence available to define a more evidence-based AI. Therefore, the Committee has no objections against EFSA's AI for adults (Table 46).

Table 46. AI for vitamin E (α-tocopherol), recommended for the Netherlands

	Men ≥18 years	Women ≥18 years
Adequate intake (AI)	13 mg/day	11 mg/day

13 vitamin K1 (phylloquinone)



13.1 Overview and comparison of values

Table 47. Overview of the reference values for adults and the criteria on which these values are based

Report	Vitamin K1/K2	AI			Main criterion
		Age	µg/day		
EFSA 2017[6] = HCNL 2014[33] [a]	K_1	≥18 yr	70 µg/d		The AI of 1 µg/kg/d was mainly based on the depletion/repletion study in young men (72 kg; SD 9) by Suttie et al. (1988), which showed that supplementation with 50 µg K1/day in addition to a restricted diet (median of about 32-40 µg K1/d) restored the Simplastin:Ecarin (S:E ratio, a measure of functionally active prothrombin) and urinary γ-carboxyglutamic acid (Gla) concentration to their baseline values. Considering the reference body weights, the daily phylloquinone intake would be 68.1 µg for men and 58.5 µg for women, rounded up to 70 µg/day for all adults.
NCM 2014[37]	K_1 & K_2	-			NCM evaluated vitamin K, but established no recommended intake due to lack of evidence.
DACH 2015[38]	K_1 & K_2	15-50 yr ≥51 yr	♂ 70 ♂ 80	♀ 60 ♀ 65	The AI of 1 µg/kg/d was based on the coagulation role of vitamin K.
IOM 2001[41] [a]	K_1 & K_2		♂ 120	♀ 90	Median intake, supported by data on prevention of deficiency.
WHO/FAO 2004[44]	K_1 & K_2		♂ 65	♀ 55	The AI of 1 µg/kg/d was based on the coagulation role of vitamin K and average intakes.

[a] According to HCNL 2014,[33] IOM's reference values[41] were used in the Netherlands until the publication of EFSA's AIs[6] in 2017. Once available, EFSA's reference values for vitamin K1 were used in the Netherlands. In this chapter, HCNL 2014 refers to the Dutch reference values preceding the publication of this report, i.e. EFSA's reference values.

Table 47 presents an overview of reference values and criteria. EFSA, NCM, DACH and WHO/FAO agree on the adequate intake of 1 microgram of phylloquinone per kilogram body weight, so that differences between the AIs in microgram per day between these reports result from differences in reference weights. IOM set substantially higher AI values based on median intake.

Phylloquinone (K1) and menaquinones (K2)

The vitamin K reference intakes in the EFSA report refer to phylloquinone (vitamin K_1). Although the EFSA Panel considered vitamin K as phylloquinone and menaquinones, they concluded that the available evidence on intake, absorption, function and content in the body or organs of menaquinones was insufficient, and therefore, they set AIs for phylloquinone only.

Values by NCM, DACH, IOM and WHO/FAO refer to phylloquinone and menaquinones, but the studies on which the reference value is based are mainly on phylloquinone.

13.2 Explanation of differences between reports

EFSA's AI is based on a depletion-repletion study, NCM's AI is based on the prevention of deficiency, DACH's and WHO/FAO's AI are based on biochemical parameter of function, and IOM's AI on median intake. EFSA, DACH and WHO/FAO base their adequate intakes on the value of 1 µg/kg body weight per day, and agree that this estimate is based on limited research.

EFSA states that all possible approaches to set reference values for phylloquinone (vitamin K) have considerable uncertainties.

The EFSA Panel concludes that it is not possible to use the factorial approach to derive DRVs for vitamin K due to limitations of the data on absorption and excretion of phylloquinone and menaquinones. However EFSA's attempt to use this approach results in an estimate that does not conflict with the value of 1 µg/kg body weight per day. The EFSA Panel considers that a total body pool of phylloquinone of about 0.55 µg/kg body weight in healthy adults at steady state is associated with no signs of vitamin K deficiency. Based on excretion rate estimates from a kinetic study using isotope-labelled phylloquinone (Olson et al., 2002), EFSA assumes that the losses via faeces and urine are 0.34 µg/kg body weight per day. EFSA notes that data on phylloquinone absorption in healthy adults are widely variable (range 3-80%), but that at an absorption efficiency of 35%, an intake of 1 µg/kg body weight per day would balance the losses.

The EFSA Panel considers that none of the biomarkers is suitable by itself for assessing vitamin K adequacy and notes that the results on biomarkers suggest that vitamin K intakes sufficient for an adequate prothrombine time (e.g. ≥10 µg phylloquinone/day) may not be enough for other functions controlled by vitamin K.

The EFSA Panel also reviewed data on vitamin K intakes in Europe. Mean vitamin K intakes in adults (≥18 years) ranged between 72 and 196 µg/day, but the intake estimates suffer from limitations and uncertainties of food composition data with regard to both phylloquinone and menaquinones. Two national surveys applied partially updated food composition data: the German National Nutrition Survey II estimated that median phylloquinone intake was 76 µg/day for subjects aged 15-80 years, and the Dutch National Survey estimated that the median phylloquinone plus menaquinones intake in adults of was 100-117 µg/day.[a] However, the EFSA Panel notes that the impact of the remaining uncertainty in the composition data on the results was not entirely clear. The EFSA Panel concludes that an AI established from these data cannot be sufficiently reliable.

SCF (1993) considered that an intake of phylloquinone of 1 µg/kg body weight per day was adequate, mainly based on the depletion/repletion study in young men by Suttie et al. (1988), which showed that supplementation with 50 µg phylloquinone/day in addition to a restricted diet (median of about 32-40 µg phylloquinone/day) restored the S:E ratio (a measure of functionally active prothrombin) and urinary Gla concentration to their baseline values.

The EFSA Panel concludes that the uncertainties pointed out by SCF (1993) had not been resolved, that all possible approaches investigated to set DRVs (biomarker, factorial approach, intake data) have considerable uncertainties, and there is no scientific evidence to update the previous reference value. The EFSA Panel notes that there is no indication that 1 µg/kg body weight per day of phylloquinone would be associated with a risk of deficiency in the general population and is above the intake at which an increase in prothrombine time has been observed in healthy subjects.

Based on the reference body weights used by EFSA, an intake of 1 µg/kg body weight per day corresponds to 68.1 µg/day in men and 58.5 µg/day in women. EFSA rounded these values up to establish the AI of 70 µg/day for all adults.

IOM based their AI on median intakes, taking into account that the resulting AIs are supported by data on the prevention of deficiency.

NCM gives no recommendation due to lack of sufficient evidence, but does maintain the provisional recommended intake of 1 µg/kg body weight per day in the 2004 NCM report, since no strong scientific evidence for change has emerged. Note that this value is not presented by NCM as a recommended intake.

Differences between older and younger adults

EFSA, NCM, IOM and WHO/FAO did not differentiate the AI between younger and older adults. EFSA notes that there was no evidence of

[a] Note that new RIVM estimates of the habitual vitamin K-intakes in Dutch adults aged 18-50 years also include estimates specific for phylloquinone: the median of the habitual phylloquinone intakes was 88 µg/day for men and 77 µg/day for women.[45]

different vitamin K absorption and different losses according to age in adults. DACH did differentiate: as a precaution, DACH set a higher AIs for adults ≥50 years than for adults <50 years, to take into account possible malabsorption and medication effects at a higher age.

Sex differences

In contrast to the reports used for comparison, EFSA does not propose different AI values for men and women. Based on the adequate intake per kilogram and the reference weights, the value for men was 10 µg per day higher than for women, but EFSA rounded this up to 70 µg per day for all adults, because of the large uncertainties.

13.3 Conclusion on the scientific basis of EFSA's reference values

Most reports agree that, based on limited data, 1 microgram per kilogram of body weight per day is considered adequate for the blood coagulation role of vitamin K (see paragraph 13.2). EFSA did not set separate values for men and women because of the large uncertainties. EFSA rounded the calculated values upwards (Table 48).

EFSA provides no information on vitamin K1 intake levels associated with the occurrence, correction or prevention of deficiencies.

The Committee has no objection against the scientific basis of EFSA's AI, but notes that the reference body weights used by EFSA are relatively low for the Netherlands. On average, Dutch adults are taller than European adults. However, if Dutch reference weights are applied, the AI still appears to be 70 µg/day (Table 48).

Therefore, the Committee has no objection against the use of EFSA's AI in the Netherlands.

Table 48. Effect of HCNL's higher reference weights on the average requirements and population reference intake estimates using EFSA's method

	Reference body weight (kg)		Intake estimate requirement (µg/day)		Adequate intake after rounding (µg/day)	
	♂	♀	♂	♀	Mean ♂ & ♀	Rounded
EFSA's values, based on 1 µg/kg/d, and EFSA's reference weights	68.1	58.5	68	59	64	70
Values based on 1 µg/kg/d, but using HCNL's reference weights[35,36]	73.5	62.5	74	63	68	70

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Different vitamin K-dependent Gla-proteins display calcium-mediated actions. One group of vitamin K-dependent proteins comprises blood coagulation factors. Another group includes a protein involved in bone mineralisation and other proteins which may be involved in the control of soft tissue calcification.

EFSA does not provide information on the occurrence of clinical signs of vitamin K deficiency. IOM 2001 provides the following information: "Spontaneous cases have been rare and have usually been associated with various lipid malabsorption syndromes. There are numerous case reports of bleeding episodes in antibiotic-treated patients, and these have often been ascribed to an acquired vitamin K deficiency resulting from a suppression of menaquinone-synthesizing organisms. However, these reports are complicated by the possibility of general malnutrition in this patient population and by the antiplatelet action of many of the same drugs."

In adults, vitamin K deficiency is clinically characterised by:

- a bleeding tendency in relation to a low activity of the blood coagulation factors.

13.4 Summary and conclusion

Table 49. Summary of the evaluation of EFSA's AI values for vitamin K

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AI compared to HCNL's (=EFSA's) AI	Equal	EFSA's AI has been used in the Netherlands since 2017.
Scientific basis of EFSA's AI	No objection	EFSA value of 1 µg/kg per day is used by EFSA, DACH and WHO/FAO and mentioned as a provisional recommended intake by NCM. IOM based their AIs on intake.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with IOM and WHO/FAO, but not with DACH.
Differentiation between men and women	Not applied by EFSA	Not consistent with DACH, IOM and WHO/FAO.
Unit in which the EFSA's AI is expressed	µg vitamin K1 (phyloquinone)	Not consistent with the reports used for comparison, who express the AI in µg vitamin K1+K2 (phylloquinone plus menaquinones).

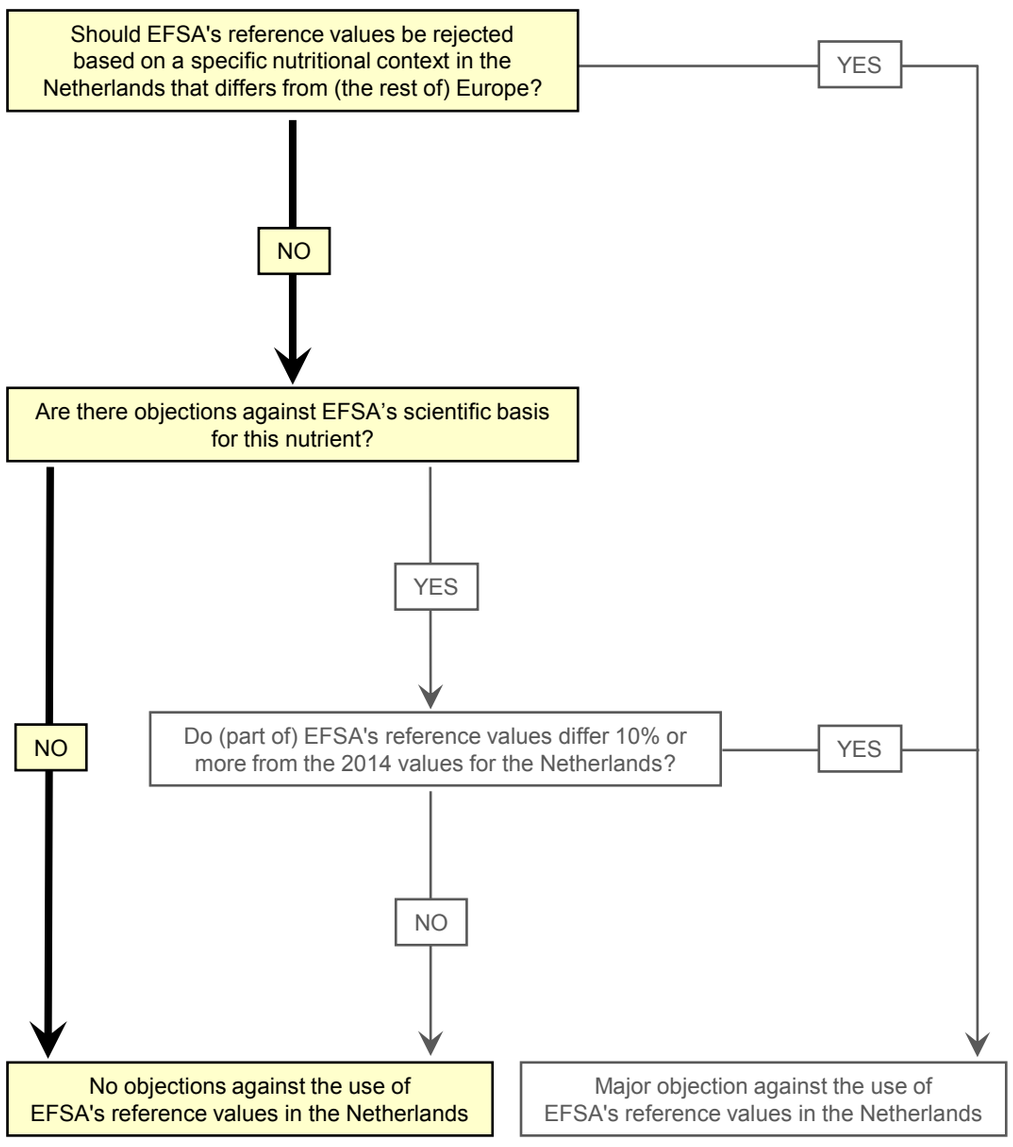
EFSA based the AI on an adequate intake of 1 µg/kg per day, but did not set different values for men and women, because of the large uncertainties. The Committee notes that vitamin K is one of the few nutrients for which the method of establishing the reference value implies a proportional effect of the reference weights on the reference values. The Committee considers that higher reference weights should be used for the Netherlands, because Dutch adults are relatively tall, but concludes that this does not result in a different AI (Table 48). The Committee has no objection against the scientific basis of EFSA's AI, or EFSA's AI, and recommends using this value (Table 50) in the Netherlands.

Table 50. AI for vitamin K1, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	70 µg/day

14 biotin

Biotin



Biotin has also been called – dependent on the country – vitamin B7, vitamin B8 or vitamin H, but biotin is the preferred name internationally.

14.1 Overview and comparison of values

Table 51. Overview of the reference values for adults and the criteria on which these values are based

Report	AI (µg/d)	Main criterion
EFSA 2014[28] = HCNL 2014[33]	40	Approximate midpoint of the observed mean/median intakes
DACH 2015[38]	30-60	Dietary intake surveys
IOM 1998[42]	30	Upward extrapolation of the AI for infants

Note that NCM and WHO/FAO did not establish reference values for biotin.

Table 51 shows that EFSA's AI is within the range set by DACH. The value used by IOM is substantially lower.

14.2 Explanation of differences between reports

Table 51 shows that EFSA's and DACH's AI's are based on intake, whereas IOM's AI is based on upward extrapolation of the AI for infants.

The EFSA Panel used the approximate midpoint of the observed mean/median intakes observed in European countries to set an AI for biotin at 40 µg/day for adults of all ages. The EFSA Panel notes that estimates of the biotin content of foods vary widely, partly as a result of natural variation, and partly depending on the analytical method used, and that this contributes to uncertainty regarding current intake estimates.

In adult men and women below about 65 years, mean/median intakes ranged from 26 to 50 µg/day, based on estimates from Germany, Ireland, Hungary, Austria and Latvia.
In older adult men and women, mean/median intakes ranged from 24 to 43 µg/day, based on estimates from Germany, Ireland, Hungary and Austria.

Differences between older and younger adults and sex differences
The reports do not differentiate the AI between younger and older adults, nor between men and women.

14.3 Conclusion on the scientific basis of EFSA's reference values

EFSA based the AI on mean/median intakes in Europe (paragraph 14.2). The Committee has no objection against the scientific basis of EFSA´s reference value.
EFSA provides no information on biotin intake levels associated with the occurrence, correction or prevention of deficiencies. There are no reports on clinical signs of deficiency resulting from insufficient dietary intake of biotine. Therefore, the adequate intake may substantially exceed requirements.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Biotin is a co-factor for several enzymes which play critical roles in the synthesis of fatty acids, the catabolism of branched-chain amino acids and gluconeogenesis. Faecal excretion of biotin has been observed to be three to six times higher than intakes, owing to the production of large amounts of biotin by the intestinal microbiota; however, the extent to which biotin is absorbed from the large intestine and contributes to biotin requirements is uncertain.
Dietary biotin deficiency is rare. Cases of biotin deficiency have been observed in:

- patients receiving long-term total parenteral nutrition without biotin supplementation
- patients with biotinidase deficiency
- people who had consumed large amounts of raw eggs (a protein in raw egg white, avidin, has a very high affinity for biotin and prevents its absorption in the small intestine).

Symptoms in adults:

- fine scaly dermatitis
- hair loss
- conjunctivitis
- ataxia.

14.4 Summary and conclusion

Table 52. Summary of the evaluation of EFSA's AI values for biotin

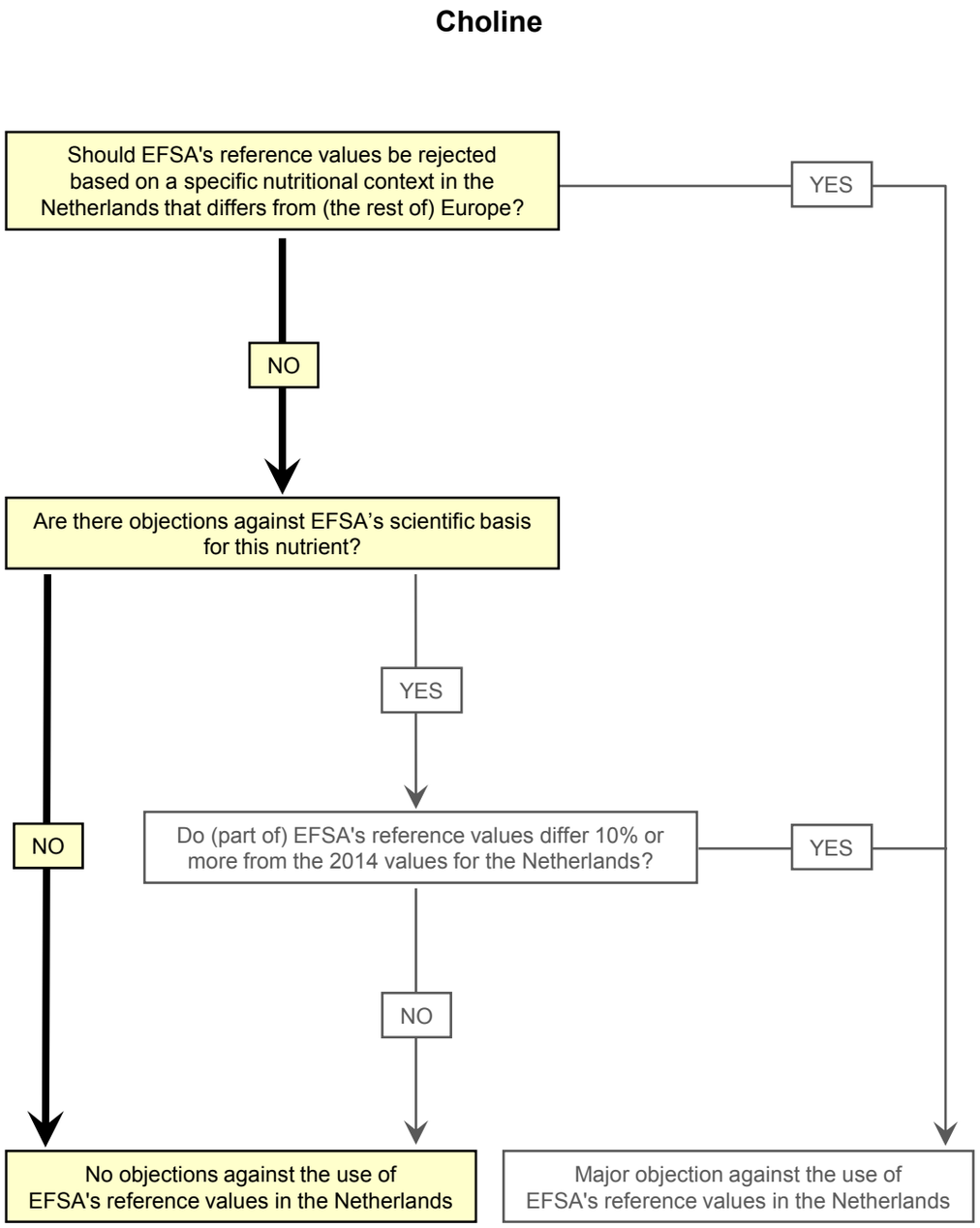
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL 2014's (=EFSA's) AI[33]	Equal	EFSA's AI has been used in the Netherlands since 2014.
Scientific basis of EFSA's reference value	No objection	EFSA and DACH based the AI on intake estimates, whereas IOM extrapolated the value for infants. NCM and WHO/FAO did not establish reference values for biotin.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

EFSA's AI for biotin is based on the approximate midpoint of observed average intakes in European countries, which is assumed to be adequate because no signs of deficiency have been reported in healthy individuals. As biotin deficiency has not been reported in healthy subjects on normal diets, the adequate intake may substantially exceed requirements. However, there is no evidence available to define a more evidence-based AI. Therefore, the Committee has no objections against EFSA's AI for adults (Table 53).

Table 53. AI for biotin, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	40 µg/day

15 choline



Choline is the preferred name for a group substances in food, including free choline and esterified forms, mainly phosphatidylcholine (PC, lecithin), phosphocholine (PChol), glycerophosphocholine (GPC) and sphingomyelin (SPM). Other esterified forms occur in minor amounts in foods. PC accounts for approximately 95% of total choline found in animal tissues. Choline, PChol and GPC are water-soluble choline compounds, whereas PC and SPM are lipid soluble.

15.1 Overview and comparison of values

Table 54. Overview of the reference values for adults and the criteria on which these values are based

Report	AI (mg/d)	Main criterion
EFSA 2016[12]	400	*Mean choline intakes* in 12 national surveys in 9 EU countries between 2000 and 2011 range from about 270 to 470 mg choline/day, with 370 mg/d as the midpoint of the range. Populations were healthy but no information on choline status was available. Supportive evidence: the amounts of choline needed to replete about 70% of depleted subjects who showed signs of organ dysfunction in one depletion/repletion study (Fischer et al., 2007).
IOM 1998[42]	♂550 ♀400	One depletion/repletion study in 16 healthy male hospitalised volunteers in which only one level of choline supplementation (500 mg choline/day) was examined and appeared to prevent alanine aminotransferase (ALT) abnormalities (Zeissel et al., 1991).

Note that NCM, DACH and WHO/FAO did not establish reference values for choline.

Table 54 shows that EFSA's AI for women equals IOM's value, whereas IOM's AI for men is 38% higher than the value used by EFSA.

15.2 Explanation of differences between reports

EFSA's AI is based mainly on intake, IOM's AI is based on a depletion/repletion study. Both base the AI on limited data.

EFSA based the AI on the mean intake level in the EU with supportive information from one depletion/repletion study.

The mean choline intakes in twelve national surveys from nine EU countries (Finland, France, Germany, Ireland, Italy, Latvia, the

Netherlands, Sweden and the United Kingdom) carried out between 2000 and 2011 were estimated by using USA food composition data on the choline content in foods (Vennemann et al. 2015).[55] Mean intakes in adults ranged between about 270 to 470 mg choline/day (midpoint 370 mg/day; 330-470 mg/day in men and 270-405 mg/day in women). EFSA mentions that these choline intake data were generally of the same magnitude as the intakes in other published studies (from Belgium, USA, New Zealand and Taiwan).

The EFSA Panel notes that choline depletion/repletion studies indicate large variability in dietary choline requirement. EFSA notes that only one depletion/repletion study[56] is informative on the choline amount needed/sufficient to reverse signs of choline deficiency.[a] Fischer et al. (2007)[56] defined choline deficiency by biochemical or clinical changes[b] between the baseline diet (550 mg choline per 70 kg per day) and the low-choline diet (<50 mg choline per 70 kg per day over ≤42 days). 57 subjects (men and women) completed the study. Six subjects (all male) showed signs of choline deficiency after the baseline diet. After 42 days with <50 mg choline per 70 kg per day, 33 subjects had become depleted, but 18 had not. Fischer et al. determined the amount of choline needed to replete the depleted subjects, using a protocol of 10-day periods with increasing choline intake levels. In 25 depleted subjects, the amount of choline needed to replete them was available. About 70% needed up to about 400 mg choline per 70 kilogram body weight for repletion. Some subjects required more than IOM's AIs for choline for repletion; some subjects became deplete quickly, whereas others took almost 7 weeks on a low-choline diet to develop organ dysfunction. Fischer et al.[56] concluded that "the requirement for choline in the diet is quite variable".

For all adults, the EFSA Panel set an AI of 400 mg/day, based on the midpoint of the range of observed mean intakes in healthy EU populations (about 370 mg/day), and in consideration of the results of the depletion/repletion study in which about 70% of the depleted subjects who had developed signs of organ dysfunction were repleted with an intake of about 400 mg/70 kg body weight per day.

IOM based their AI on one depletion/repletion study in 16 healthy male (Zeissel et al., 1991).[a] A choline intake of 500 mg/day prevented ALT abnormalities in these healthy men. IOM places the remark that "this estimate for an AI is uncertain because it is based on a single published study; it may need revision when other data become available". As only one level of choline supplementation (500 mg choline/day) was examined, EFSA rejected this study for the estimation of the choline amount needed/sufficient to reverse the signs of choline deficiency.

[a] EFSA did not use 10 other depletion/repletion studies, including Zeisel et al. (1991) which was used by IOM, as these did not provide information on the amount needed/sufficient to reverse the signs of deficiency.

[b] Fischer et al. examined the following biochemical or clinical changes: a more than 5-fold increase in serum creatine phosphokinase activity indicating muscle dysfunction; a more than 1.5-fold increase in aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, or lactate dehydrogenase, indicating liver dysfunction; or a 28% increase in liver fat (hepatic steatosis).

Differences between older and younger adults

Neither EFSA, nor IOM differentiated the AI between older and younger adults.

Sex differences

EFSA's AI applies to men and women, whereas IOM set a higher AI for men than for women. Although premenopausal women may have a lower requirement for dietary choline than postmenopausal women or men, and ranges of estimated mean total choline intake in Europe are slightly lower in women than men, the EFSA Panel considered it unnecessary to give sex-specific AIs for adults.

15.3 Conclusion on the scientific basis of EFSA's reference values

EFSA based their AI on the average intake observed in European countries, and on supportive information from a depletion/repletion study (paragraph 15.2). Choline deficiency has been reported in people on total parenteral nutrition devoid of choline. Deficiency has been induced in several studies at choline intakes of lower than 50 mg/day, but not in all subjects with this intake level. Fischer et al. (2007) reported deficiency also in some subjects at a diet with a choline content of 550 mg per 70 kilogram body weight. (Table 55). These data indicate that most individuals require a sufficient intake of choline to maintain health, and that the amount of choline required may vary substantially, but the evidence appears to originate from one research group. The Committee has no objection against the scientific basis of EFSA´s reference value.

Table 55. Choline intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/Specific group	EFSA's reference
Occurrence of biochemical signs of muscle and liver dysfunction (signs specified in paragraph 15.2)	<50 mg / 70 kg/d for up to 42 days 550 mg / 70 kg/d	33 out of 57 men and women 6 out of 57 men and women (these 6 were all men)	Fischer et al. (2007)
Muscle and liver dysfunction	< 50 mg choline	Various groups in 11 depletion-repletion studies	EFSA report, Annex D
Increased risk of non-alcoholic fatty liver disease	179 mg (the lowest quintile)	Women with a BMI >25 kg/m^2	Yu et al. (2014)

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Choline has a number of important functions: it is a precursor for the phospholipid phosphatidylcholine; it is involved in the metabolism and transport of lipids and in the folate-dependent onecarbon metabolism; and it is a precursor of acetylcholine and of betaine. EFSA notes that genetic factors, sex, menopausal state and possibly the gastrointestinal microbiome may influence the choline requirement, which appears to be highly variable. Choline intake may be essential for a large part of the population, but possibly not for all individuals.
The EFSA report does not provide information on the occurrence of choline deficiency, but IOM reported that signs of choline deficiency were reported in some individuals on total parenteral nutrition devoid of choline (but adequate for methionine and folate).
Symptoms:

- fatty liver (hepatic steatosis), which can result in non-alcoholic fatty liver disease
- liver and muscle damage as indicated by an increase in creatine phosphokinase concentration in serum
- hepatic steatosis can progress to liver damage with release of liver enzymes into the blood.

15.4 Summary and conclusion

Table 56. Summary of the evaluation of EFSA's AI values for choline

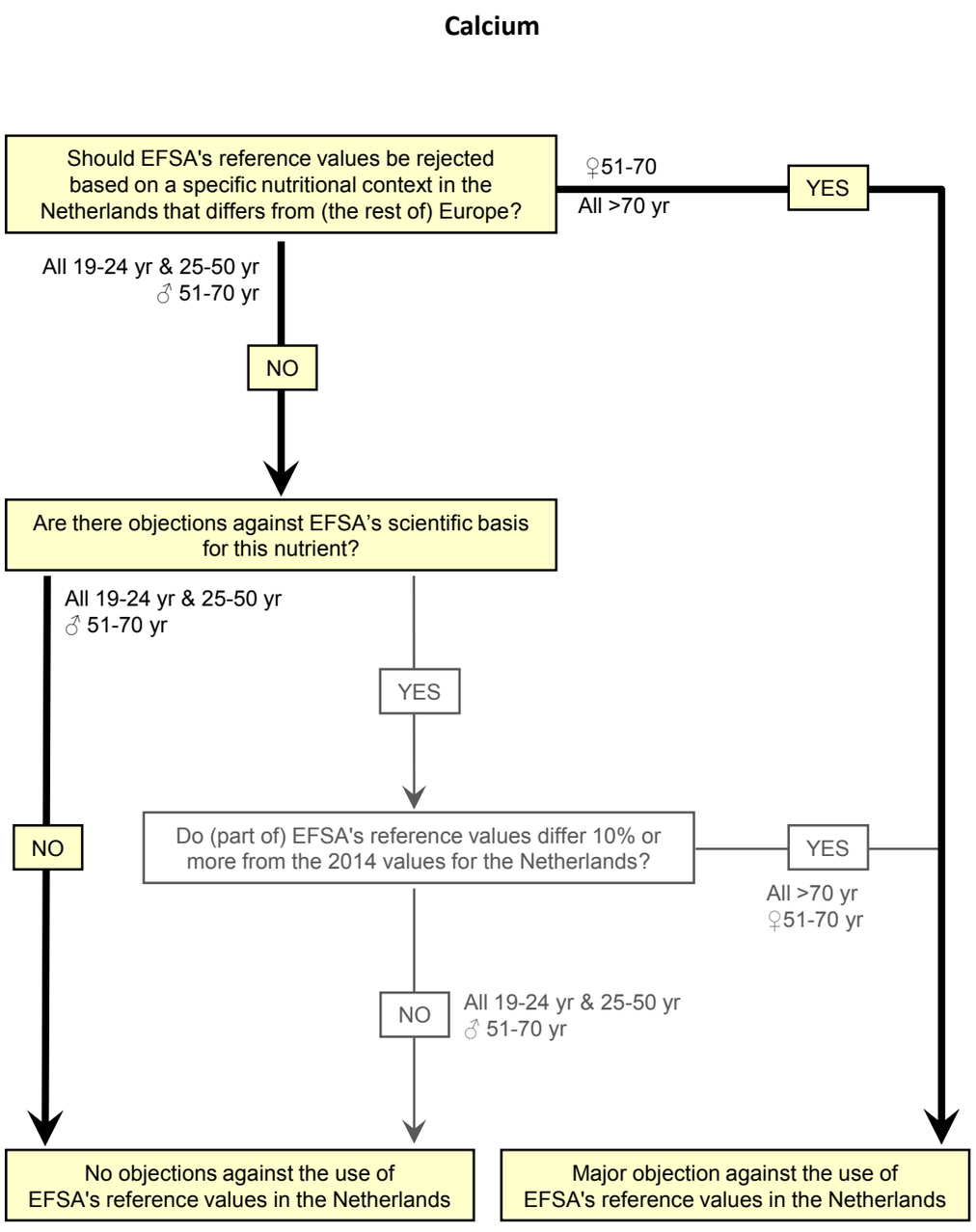
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's AI	Not applicable	HCNL has not proposed a reference value for choline intake as yet.
Scientific basis of EFSA's AI	No objection	EFSA is not consistent with IOM in using intake. IOM's AI and the supporting information used by EFSA are based on the relationship of intake with biochemical parameters of function.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with IOM.
Differentiation between men and women	Not applied by EFSA	Not consistent with IOM.

The Committee has no objection against the scientific basis of EFSA´s reference value or EFSA's AI for adults (Table 57). The Committee agrees with EFSA's note that choline depletion/repletion studies indicate large variability in dietary choline requirement.

Table 57. AI for choline, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	400 mg/day

16 calcium



16.1 Overview and comparison of values

Table 58. Overview of the reference values for adults and the criteria on which these values are based

Report	Age range	PRI/RDA/AI/RI		AR (mg/d)	CV (%)	Main criterion
		Type	(mg/d)			
EFSA 2015[19]	18-24 yr	PRI	1,000	860	10%	AR derived as the intermediate value between the AR for children aged 11-17 yr (AR 960 mg/d) and adults ≥25 years (AR 750 mg/d).
	≥25 yr	PRI	950	750		Balance data: 715 mg/d (without dermal loss) plus 40 mg/d for dermal losses. PRI is based on the upper limit of the 95% prediction interval in the balance data (904 mg/d) plus 40 mg/d for dermal losses.[a]
HCNL 2000[36] = HCNL 2014[33]	19-49 yr	AI	1,000			Factorial estimate (faecal loss: 110; urinary loss: 140; dermal loss: 30; retention 10 mg/d); assuming 30-40% absorption, leading to a value of 730-970 mg/d. Balance data supported the AI of 1,000 mg/d.
	50-69 yr	AI	1,100			The AI is in line with most observational data. Balance studies indicate that an intake of 1.2 mg/d is adequate, but this is possibly too high. Intervention studies indicate that an intake of 1.0-1.2 g/d is adequate.
	≥70 yr	AI	1,200			Intervention studies and some observational studies show that 0.9-1.0 g/d is not sufficient for this age group.

Report	Age range	PRI/RDA/AI/RI		AR (mg/d)	CV (%)	Main criterion
		Type	(mg/d)			
NCM 2014[37]	18-20 yr	RI	900			Recommendation for adolescents was extended to 18-20 year olds as some bone mass is still accreted beyond 17 years of age.
	≥21 yr	RI	800	500	30%[2]	Based on 1 long term (7 months) balance study in which 23 of 26 men aged 20-79 yr adapted gradually to maintain calcium balance at an intake of 460 mg/d (Malm, 1958). Supportive information from epidemiological studies and clinical trials.
DACH 2015[38]	≥19 yr	RI	1,000	741	15%	Pooled analysis of calcium balance studies (Hunt & Johnson 2007: 741 mg/d). There is no clear evidence that intake >1,000 mg provides additional benefit regarding the bone health of adults >65 years old.
IOM 2011[39]	♂ 19-70 yr & ♀ 19-50 yr	RDA	1,000	800		Pooled analysis of calcium balance studies (Hunt & Johnson 2007). The estimate of 741 mg/d was rounded to 800 mg/d to account for uncertainty. RDA was based on the upper limit of the 95% prediction confidence interval (1,035 rounded to 1,000 mg/d).
	♂ >70 yr & ♀ >50 yr	RDA	1,200	1,000	10%[b]	Intervention studies (meta-analysis Tang et al., 2007). Supportive evidence from a subgroup (60-79 yr) of the Women's Health Initiative trial (Jackson et al., 2006). Women aged 50-69 yr: IOM decided to provide public health protection in the face of inconsistent data.
WHO/ FAO 2004[44]	♂ 19-65 yr & ♀ preme-nopause	RI	1,000	840	10%[b]	Null balance, assumed to be equivalent to AR.
	♂>65 yr & ♀postme-nopause	RI	1,300	1,100	10%[b]	Strong evidence that Ca requirement rises during menopause. Evidence about ageing men is less convincing; the extra allowance of 300 mg/d for men >65 yr is a precaution.

[a] EFSA performed new analyses (Appendix F of EFSA-report). EFSA used the balance data from Hunt and Johnson (2007), but added data from additional studies in which calcium supplements were given (which were not included by Hunt and Johnson, 2007), and excluded individual data from younger adults (18-24 years), because of evidence that their calcium metabolism cannot be considered to be in a steady state.

[b] The coefficient of variation is not specified, but is calculated as 100% x [½ x (PRI/RI/RDA–AR)] / AR.

Table 58 shows that most reports (almost) agree on the value for adults aged 18-50 years: HCNL's AI, DACH's RI, IOM's RDA and WHO/FAO's RI (all 1000 mg/d) equal EFSA's PRI for adults aged 18 to 24 years, and are 5% higher than EFSA's PRI for adults aged ≥25 yr. However NCM's RI values are 10-20% lower than EFSA's PRIs.

For older adults, EFSA uses the same PRI (950 mg/d), whereas HCNL's AI, IOM's RDA and WHO/FAO's RI are 10-30% higher. However, NCM and DACH, like EFSA, do not differentiate the value between younger and older adults.

16.2 Explanation of differences between reports

Reference values for the youngest adults (EFSA: 18-24 yr; NCM 18-20 yr)

EFSA set higher reference values for men and women aged 18-24 years than for older adults, because calcium continues to be deposited in bones after they have ceased growing. EFSA did not base this AR and PRI on balance data, because the additional requirement for calcium in young adults is unknown. Instead, EFSA derived the AR for 18-24 yr (860 mg/d) as the intermediate value between the AR for children aged 11-17 yr (AR 960 mg/d) and adults ≥ 25 years (AR 750 mg/d). The PRI for 18-24 yr was based on a CV of 10%, and rounded down to the nearest 50; EFSA notes that the variation in requirements is unknown for this age group. As a result, EFSA's AR for adults aged 18-24 yr is substantially higher than EFSA's values for adults aged ≥25 yr (+15%), whereas the difference in EFSA's PRI-values is small (+5%).

NCM extended the recommendation for adolescents (RI 900 mg/d) to 18-20 year olds, as some bone mass is still accreted beyond 17 years of age.

The other reports do not set separate values for the youngest adults.

Reference values for adults aged between 19/21/24 years and 50/65/70 years

All reference values for adults in this age group are based on either balance data (EFSA, NCM, DACH, IOM and WHO/FAO) or a factorial approach (HCNL). Differences between reports are small for the PRI/RI/AI values, except for NCM who set a lower value based (mainly) on one Scandinavian balance study. EFSA, DACH, IOM and WHO/FAO used the pooled analysis of the available balance studies from the USA; their PRI/RDA/RI-values differ little. HCNL used a factorial method resulting in an AI-value almost equal to EFSA's PRI.

EFSA and IOM based the difference between their AR and PRI/RDA-values on the observed variation. Calcium is one of the few nutrients where data are available to account for the variation of requirements.

Reference values for adults of 50/65/70 years and older

Regarding older adults, the differences between the reports are more substantial. The discrepancy is caused by a different judgement of the evidence for the effect of a higher calcium intake on bone mass density and fracture risk in older adults.
EFSA, NCM and DACH conclude that the evidence is inconclusive and therefore cannot be used for setting the reference values.

HCNL, IOM and WHO/FAO based their higher reference values for adults older than 50, 65 or 70 years mainly on evidence from intervention studies indicating that supplementation with calcium and vitamin D (or supplementation with calcium alone) reduces fracture risk.

Sex differences

In two reports (IOM and WHO/FAO) the reference values for women increase from 50 years or after menopause, whereas the reference values for men increase at a higher age (from 70 and 65 years, respectively). None of the other reports differentiate between men and women. EFSA's AR and PRI were mainly based on the publication by Hunt et al. (2007); Hunt et al. reported that the relation between calcium output and intake, expressed as mg/d, was not sex dependent (p=.5).

16.3 Conclusion on the scientific basis of EFSA's reference values

EFSA's reference values for the youngest adults (18-24 yr)

EFSA assumes that the youngest adults (18-24 years) require more calcium than older adults, because of the continuation of calcium deposition in bones during the first years after growth has stopped (EFSA refers to Teegarden et al., 1995; Ohlsson et al., 2011; Darelid et al., 2012). The Committee has no objections against EFSA's reference values for adults aged 18-24 years.

EFSA's reference values for adults aged 24-49 years and men aged 24-69 years

All reports agree that the calcium intake of women aged 24-50 years and men aged 24-70 years should be sufficient for the maintenance of the calcium content of the body, which is estimated by calcium balance data or the factorial approach.

The Committee has no objections against EFSA's reference values for women aged 24-50 years and men aged 24-70 years.

EFSA's reference values for women aged ≥50 years and men aged ≥70 years

Since 2012, HCNL advises all Dutch persons aged 70 and over to take a daily supplement of 20 micrograms of vitamin D, and recommends all women aged between 50 and 70 years to take a daily supplement of 10 micrograms of vitamin D. This recommendation to use vitamin D supplements has consequences for the calcium requirement of older adults in the Netherlands: in order for the extra vitamin D to be effective, a sufficient calcium intake is required. Although the protective effects of the use of vitamin D supplements on bone health has primarily been reported in combination with the use of calcium supplements, HCNL concluded that there are indications that additional vitamin D without supplemental calcium also has protective effects on fracture risk if dietary calcium intake is 1,100 mg/d in women aged 50-69 years, and 1,200 mg/d in adults ≥70 years.[34]

The scientific basis of HCNL's recommendation for the combination of vitamin D supplements with an increased calcium intake in older adults, has been confirmed in the Dutch dietary guidelines 2015. HCNL concluded in the background report on vitamin and mineral supplements[53] that there was strong evidence from intervention studies that the use of supplements with 0.5-1.2 g/d calcium plus 10-20 µg/d vitamin D per day reduces the risk of fractures by 10% and reduces the risk of hip fractures by 15% in older adults and especially postmenopausal women. For calcium supplementation alone – *without* the use of a vitamin D supplement – the evidence was limited. HCNL furthermore concluded that the use of calcium supplements increases the risk of coronary heart disease (strong evidence).

The Dutch dietary guidelines 2015 conclude: "Because normal calcium intake is quite high in the Netherlands, there is generally no need for vitamin D supplementation to be combined with calcium supplementation. However, people in high-risk groups who don't eat dairy products or eat them in unusually small quantities should combine vitamin D supplementation with calcium supplementation." The Committee notes that adverse effects of higher calcium intakes have only been associated with calcium supplements, not with higher *dietary* calcium intakes.

The Committee considers that EFSA's AR and PRI for adults aged ≥25 years are not sufficient for women aged 50-69 years and adults aged ≥70 years in the Netherlands.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

Calcium is an integral component of the skeleton; approximately 99% of total body calcium is found in bones and teeth, where it is mainly present as calcium hydroxyapatite. It has a structural role, and is needed for tissue rigidity, strength and elasticity.

The remaining 1% of calcium found in the body acts as an essential intracellular messenger in cells and tissues. It has a critical role in many physiological functions involved in the regulation of metabolic processes, including vascular contraction and vasodilation, muscle contraction, enzyme activation, neural transmission, membrane transport, glandular secretion and hormone function.

A low intake of calcium often co-exists with vitamin D deficiency. Older adults with osteomalacia will have a reduced bone mass which leads to impaired bone strength. EFSA notes that genetic and environmental factors play a role in the prevention of osteopenia, osteoporosis and bone fracture.

16.4 Summary and conclusion

Table 59. Summary of the evaluation of EFSA's AR values for calcium

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's PRI compared to HCNL's AI	Equal / Lower	18-24 yr: EFSA's PRI equals HCNL's AI; 25-49 yr: EFSA's PRI is ~5% lower than HCNL's AI; 50-69 yr: EFSA's PRI is ~15% lower than HCNL's AI; ≥70 yr: EFSA's PRI is ~20% lower than HCNL's AI.
Scientific basis of EFSA's AR and PRI for women aged 18-50 years, and for men aged 18-70 years.	No objection	EFSA used balance data which, for younger adults, is consistent with NCM, DACH, IOM and WHO/FAO. HCNL used a factorial method.

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
Scientific basis of EFSA's AR and PRI for women aged ≥50 years and for men aged ≥70 years.	Objections based on a different nutritional context in the Netherlands	HCNL recommends that these groups use vitamin D supplements and, in order for the extra vitamin D to be effective, calcium intake should be higher than EFSA's PRI. Note dat EFSA considers the evidence for the preventive effect against fractures in intervention studies insufficient.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with NCM and DACH, but not with HCNL, IOM and WHO/FAO.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

For adults aged 18-24 years, for women aged 25-50 years, and for men aged 25-70 years, the Committee has no objections against the scientific basis of EFSA's reference values, or EFSA's PRIs and ARs and recommends accepting these values in the Netherlands (Table 60).

For women aged 50-69 years and for adults (men and women) aged ≥70 years, the Committee does have objections against EFSA's reference values, based on a different nutritional context in the Netherlands: HCNL recommends that all Dutch women aged ≥50 years and all men aged ≥70 years, use vitamin D supplements. As a consequence, EFSA's PRI for calcium appears to be too low for these groups. The Committee recommends maintaining the current Dutch AIs for calcium (Table 60).

Table 60. AR and PRI for calcium, recommended for the Netherlands

	18-24 years ♂ & ♀	25-49 years ♂ & ♀	50-69 years ♂	50-69 years ♀	≥70 years ♂ & ♀
Average requirement (AR)	860 mg/d	750 mg/d	750 mg/d	-	-
Population reference intake (PRI)	1,000 mg/d	950 mg/d	950 mg/d	-	-
Adequate intake (AI)	-	-	-	1,100 mg/d	1,200 mg/d

17 chromium (III)

17.1 Overview and comparison of values

Table 61. Overview of the reference values for adults and the criteria on which these values are based

Report	Age range	AI		Main criterion
		Type	(µg/d)	
DACH 2013[38]	≥19 yr	AI	30-100	Estimated need for physiological functions by WHO in 1996 (20 µg/d), with safety margin for body reserves and presumed underestimation. In the absence of satisfactory data, an AI range was derived.
IOM 2001[41]	19-50 yr	AI	35 (♂) 25 (♀)	Estimated intake: Chromium content of a mixed diet was estimated to be 3.2 µg/MJ (range 2-5.7 µg/MJ), based on chemical analysis of 22 adult diets designed by nutritionists (Anderson et al. 1992). The AI for men and women aged 19-50 yr was calculated assuming energy intake to be 11.7 and 7.8 MJ/d, respectively.
	≥51 yr	AI	30 (♂) 20 (♀)	Estimated intake: The AI for men and women aged ≥51 yr was calculated using the estimated dietary content of 3.2 µg/MJ, and assuming energy intake to be 8.8 and 6.3 MJ/d, respectively.

Note that EFSA,[27] NCM,[37] and WHO/FAO[44] did not establish reference values for trivalent chromium. HCNL[33] does not include reference values for chromium.

17.2 Explanation of differences between reports

EFSA notes that attempts to create chromium deficiency in animal models have not produced consistent results, and that there is no evidence of the essentiality of chromium (III) in animal nutrition.

EFSA furthermore notes that no symptoms have been reported in apparently healthy subjects that can be related to low chromium intake (Stearns, 2007).

EFSA describes (based on case reports) that 5 patients on total parenteral nutrition (TPN) for at least several months (up to 13 years), developed symptoms which improved after chromium supplementation.[a] These symptoms included impaired glucose tolerance, weight loss, ataxia, neuropathy, hyperaesthesia in hands and feet, postural tremor, unsteady gait and muscle weakness. EFSA notes that, in three[b] cases, the chromium concentration in the TPN solution was reported. EFSA estimated that the supply via TPN in these three cases (5-10 µg/d) is equivalent to an oral intake of 100-200 µg/day.[c] EFSA notes that the estimated median intakes in European countries are lower: 55-85 µg/day.[d] EFSA concludes that, on the basis of these case reports, it is unclear whether deficiency of chromium could be considered the only cause of glucose intolerance in these patients, whether deficiency of chromium has

[a] EFSA refers to the following publications: Jeejeebhoy et al. (1977); Freund et al. (1979); Brown et al. (1986); Verhage et al. (1996); Tsuda et al. (1998). EFSA describes one additional publication on five acute-care patients with inconclusive results: Wongseelashote et al. (2004).

[b] EFSA notes that the chromium supply via the TPN solutions was reported in three publications: Jeejeebhoy et al. (1977); Brown et al. (1986); Verhage et al. (1996).

[c] EFSA calculated the equivalent oral intake assuming an absorption efficiency of 5%, which is the upper end of the range observed for supplemental chromium. Use of a lower absorption efficiency would result in an even higher value for the oral intake equivalent.

[d] EFSA reported that chronic dietary chromium intake data were available from 17 European countries. Median dietary chromium intakes in European adults were estimated to be 57.3-83.8 µg/day (medians of lower and upper bounds).[57]

occurred in these patients and whether chromium deficiency occurs in healthy populations.

DACH used the estimation in a 1996 WHO report as the basis for its reference value, although WHO/FAO did not set a reference intake for chromium in 2004.

IOM (2001) based its reference value on the mean chromium content of 22 adult diets designed by nutritionists and assumptions on energy intake.

Differences between older and younger adults and sex differences

IOM differentiates between older and younger adults and between men and women, based on assumed energy intake. DACH did not differentiate between groups of adults.

17.3 Conclusion on the scientific basis of EFSA's reference values

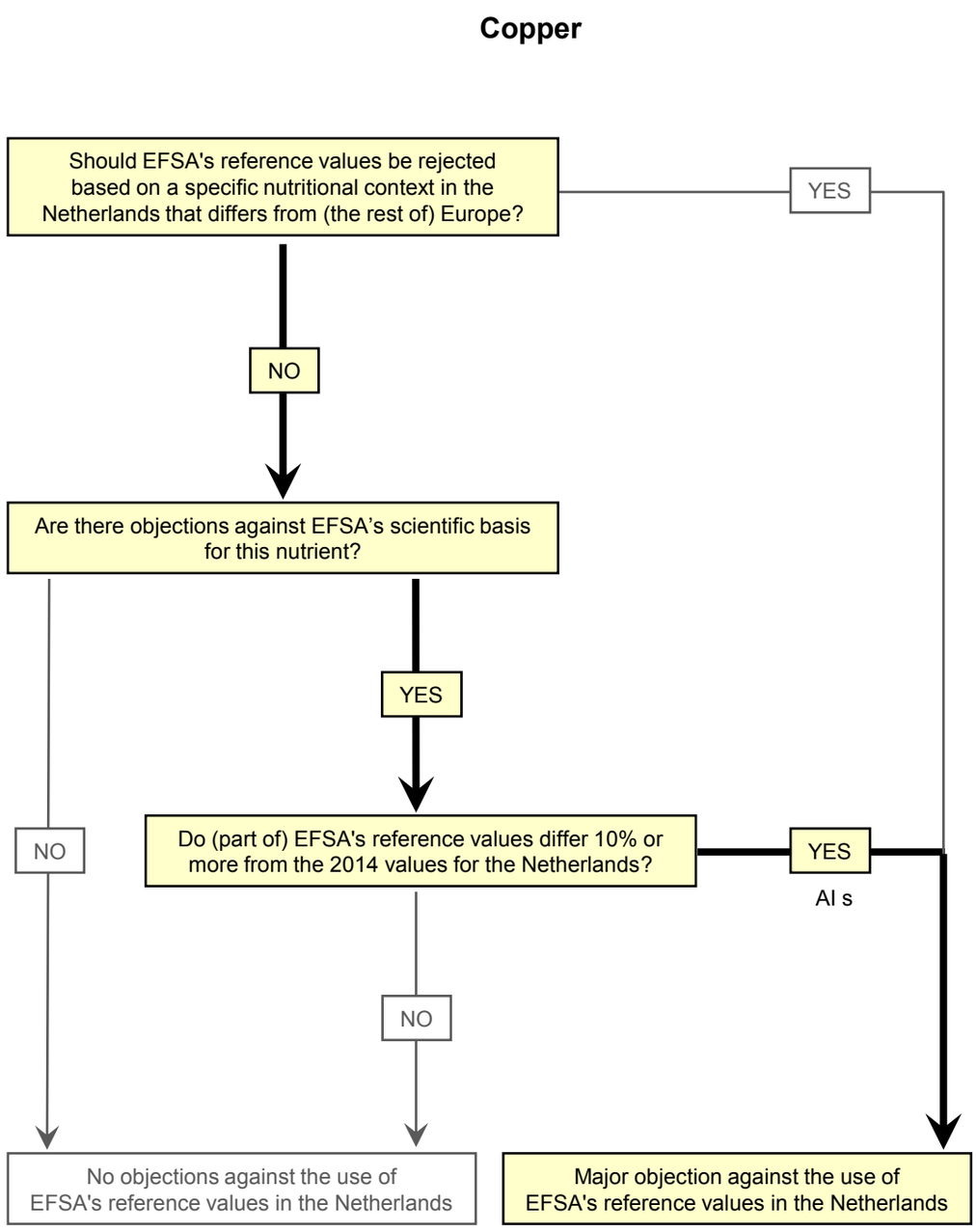
EFSA concludes that data from reported improvements associated with chromium supplementation in patients do not provide sufficient information to identify a dietary requirement for humans. The Committee has no objections against EFSA's evaluation.

17.4 Summary and conclusion

EFSA did not derive reference values for chromium, because it is not clear whether chromium is an essential trace element for healthy subjects.

The Committee agrees with EFSA's conclusion that it is not clear whether chromium is an essential trace element and with EFSA's decision to not set reference values for chromium.

18 copper



18.1 Overview and comparison of values

Table 62. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI (mg/d)			AR (mg/d)		CV (%)	Main criterion
	Type	♂	♀	♂	♀		
EFSA 2015[17]	AI	1.6	1.3	-	-	-	Observed intakes in EU for men, combined with results of balance studies.
NCM 2014[37] = HCNL 2014[33]	RI	0.9	0.9	0.7	0.7	15	NCM mentions the IOM criteria and additional criteria, and adopts the IOM values.
DACH 2015[38]	AI	1.0-1.5		-	-	-	Estimated value is based on three references without further specifications (the balance study estimate of 1.25 mg/d by Klevay et al., 1980; a WHO estimate of 1.1 µg/kg body weight dated 1996 [WHO did not set reference values for copper in 2004]; and the Scientific Committee on Food 1993 estimate of 1.1 mg/d).
IOM 2001[41]	RDA	0.9	0.9	0.7	0.7	15	IOM used a combination of two types of data: Status and function parameters: plasma and platelet copper concentration, serum caeruloplasmin concentration, and erythrocyte SOD activity in controlled depletion-repletion studies. Factorial method.

Note that WHO/FAO 2004[44] did not specify reference values for copper.

Table 62 shows that the RDA/AIs in the reports used for comparison are lower than EFSA's AIs. The differences relative to EFSA's AIs are -38% (NCM and IOM) and -14% (DACH).

18.2 Explanation of differences between reports

In 2014, HCNL advised using the NCM-value in the Netherlands. NCM adopted their values from IOM. The AI used by DACH is not further discussed in this paragraph because of insufficient information on the derivation of this value. Therefore, the Committee only explains the differences between EFSA and IOM in this paragraph.

EFSA's AI is based on intakes, IOM's AR is based on biochemical parameters of status and function and on a factorial method.

EFSA's AIs are mainly based on intakes, but for men balance data were also taken into account (balance data were not available for women). The intake data used by EFSA are from dietary surveys carried out in nine EU countries: Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the UK. Average copper intakes ranged between 1.15 and 2.07 mg/day in adults. EFSA notes some discrepancy (up to around 25%) between EFSA's estimates and the published intake estimates from the same survey and same age ranges, resulting from several sources of uncertainties: inaccuracies in mapping food consumption data according to food classifications, inaccuracies in nutrient content estimates available from the food composition tables, the use of "borrowed" copper values from other countries in the food composition database, and replacing missing copper values by values of similar foods or food groups. EFSA notes that it is not possible to conclude which of the intake estimates (i.e. the EFSA intake estimate or the published one) would be closer to the actual copper intake.

For men, EFSA also took balance data into account. The EFSA Panel describes that positive copper balance were reported at intakes of 2.49 mg/day (Turnlund et al., 1998) and 7.8 mg/day (Harvey et al., 2003), that negative balances were reported at intakes from 0.38 to 0.7 mg/day (Turnlund et al., 1998; Harvey et al., 2003), and that zero balance was reported at an intake of approximately 1.6 mg/day (Harvey et al., 2003; Turnlund et al., 2005). The EFSA Panel mentions two significant limitations to the balance studies. Firstly, underestimation of requirements appears likely, because of underestimation of copper losses: sweat and dermal losses often are not considered and were estimated to be 0.3 mg/d, on average. Secondly, in some studies, the period during which dietary intake is maintained at a fixed level before balance measurement is relatively short and may be too short for homeostatic adaptation to occur. EFSA concludes that balance studies cannot be used as the sole criterion for setting copper DRVs, but may be used together with other data.

EFSA rejects the biomarkers used by IOM. EFSA considers that these biomarkers poorly respond to copper intakes, and have limited value as biomarkers of copper status in individuals. EFSA notes that the limitation as a status parameter is especially related to copper overload: low concentrations may indicate copper depletion. EFSA describes that, at copper intakes $\geq$0.7 mg/d, no effect of copper intake on caeruloplasmin concentration was reported. Thus EFSA's objections against these

biomarkers are related to copper intake levels equal to, or higher than, IOM's EAR.

IOM's EARs and RDAs

IOM rejected the use of balance data for setting copper reference values (which were used by EFSA), because zero balance can be achieved over a broad range of dietary copper intakes and because balance studies are prone to numerous errors, and are seldom long enough to obtain valid results.

Note that IOM used the biomarkers in the lower range of copper intakes, where these levels are responsive to copper intake. IOM's derivation of the EAR of 0.7 mg/day is based on two studies in men (which taken together involved 22 men) and one study in 13 women.

The two studies in men:

- Turnlund et al., 1997: in 11 men serum copper and ceruloplasmin concentrations decreased over 42 days at an intake of 0.4 mg copper per day, and increased with copper repletion. IOM notes that the serum levels did not fall to the deficient range in this study, but were expected to have fallen to the deficient range, had the deficient diet been fed for a period longer than 42 days.
- Turnlund et al. 1990: serum copper and ceruloplasmin concentrations did not decline significantly in 11 men at intakes of 0.79 mg/day.

By application of a linear model to the data of these two studies in men, the copper requirement to maintain copper status in half of a group was estimated to be 0.55 mg/day.

One study in women:

- Milne & Nielsen, 1996: in 13 women, serum copper and ceruloplasmin concentrations did not decline significantly at intakes of 0.57 mg/day, but platelet copper concentration declined significantly in eight out of ten women, and increased with copper supplementation.

This study in women suggests that 0.6 mg/day may be a marginal intake in over half of the population. Therefore, IOM added another increment to cover half of the population: IOM's EAR is 0.7 mg/day.

IOM used a factorial method as supporting information, resulting in the estimation that an intake of 0.51 mg/day would replace the obligatory copper losses via faeces, urine, sweat and other routes.

Differences between older and younger adults

All reports set one value for the age group ≥18 years.

Sex differences

EFSA set a higher value for men than for women, whereas all reports used for comparison set one value without differentiation for sex.

18.3 Conclusion on the scientific basis of EFSA's reference values

In paragraph 18.2, the Committee described the inconsistency between EFSA and IOM in the type of data that can be used for setting the reference values.

- Both organisations note that balance data have significant limitation. Still, EFSA used the intake level associated with zero balance (1.6 mg/day) as supportive information. IOM rejected balance data, because zero balance can be achieved over a broad range of dietary copper intakes. The Committee notes that the balance data described by EFSA refer to copper intake levels that were either lower (<0.7 mg/day) or higher (>1.6 mg/day) than IOM's EAR (0.9 mg/day). EFSA does not present balance estimates for intakes larger than 0.7 mg/day and smaller than 1.6 mg/day.
- EFSA rejects the biomarkers used by IOM: EFSA considers that plasma and serum copper concentrations are of limited value as biomarkers of copper status, especially in relation to copper overload, although low concentrations may indicate copper depletion. However, IOM uses these biomarkers as indicators of a marginal status, and EFSA's objections against these biomarkers do not apply at these levels. Therefore, IOM's EAR can be considered relevant for the prevention of deficiency.

IOM notes that signs of clinical deficiency have been reported in six severely handicapped patients on prolonged enteral nutrition (age range 4-24 yr). Two patients had neutropenia, one had macrocytic, normochromic anemia, and some had bone abnormalities including reduced bone density. Copper supplementation normalised neutrophil counts and improved bone abnormalities. IOM notes that, based on extrapolation of the copper intake levels in these patients to adults, copper deficiency might be expected to develop in adults at copper intakes equal to, or lower than, about 0.4 and 0.3 mg/d in adult men and women, respectively.

EFSA presented some information on copper intake levels associated with the occurrence of deficiency, but one of these publications did not provide electrocardiogram information and, in the other, the occurrence of deficiency signs was associated with high zinc levels (Table 63).

Table 63. Copper intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/ Specific group	EFSA's reference
3 out of the 13 women: significant increase in the number of premature ventricular discharges after 21, 63 and 91 days (no electrocardiogram information provided by Milne & Nielson).	0.57 mg/d for 105 days	13 postmeno-pausal women	Milne and Nielsen, 1996
3 out of the 12 women: exhibited abnormal electrocardiographic recording (premature ventricular discharge).	1 mg/d for 90 days	12 postmeno-pausal women	Milne et al., 2001
2 women still exhibited an increased number of abnormal premature ventricular discharges after using a supplement with 3 mg/d. They were excluded from the final paper, because they both had very high zinc levels from the cement they were using for their dentures.	+3 mg/d, duration not specified		

The Committee concludes that EFSA did not provide evidence that intakes as high as EFSA's AIs are required for the prevention of deficiency symptoms.

IOM's EAR of 0.7 mg/day corresponds with the intake level reported to be associated with prevention of a marginal copper status, and provides a margin above the intake level of 0.3-0.4 mg/day which is expected to be associated with the occurrence of copper deficiency. Therefore, IOM's EAR appears to have sufficient relevance for the prevention of deficiency. IOM takes into account an assumed coefficient of variation of requirements of 15%, resulting in an RDA of 0.9 mg/day.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms in adults

Copper serves as an electron donor and acceptor in a similar chemical reaction to that for iron. In humans, cupro-enzymes are involved in many functions, including neurotransmitter synthesis, deamination, iron metabolism, superoxide dismutation, energy metabolism, dopamine to noradrenaline conversion, collagen and elastin cross-linking, and melanin synthesis.

EFSA mentions that clinical symptoms of copper deficiency are not common in humans and generally are seen as a consequence of mutations in the genes involved in copper metabolism (Menkes disease).

Symptoms of copper deficiency may include:

- normocytic and hypochromic anaemia, that is not responsive to iron supplementation
- neurological findings, most commonly due to neuromyelopathy (human swayback)
- increased risk of aneurysm as a consequence of impaired collagen and elastin synthesis
- skin and hair hypopigmentation
- leukopenia, neutropenia, hypercholesterolaemia,
- myelodysplasia
- alterations in immune function.

18.4 Summary and conclusion

Table 64. Summary of the evaluation of EFSA's AI values for copper

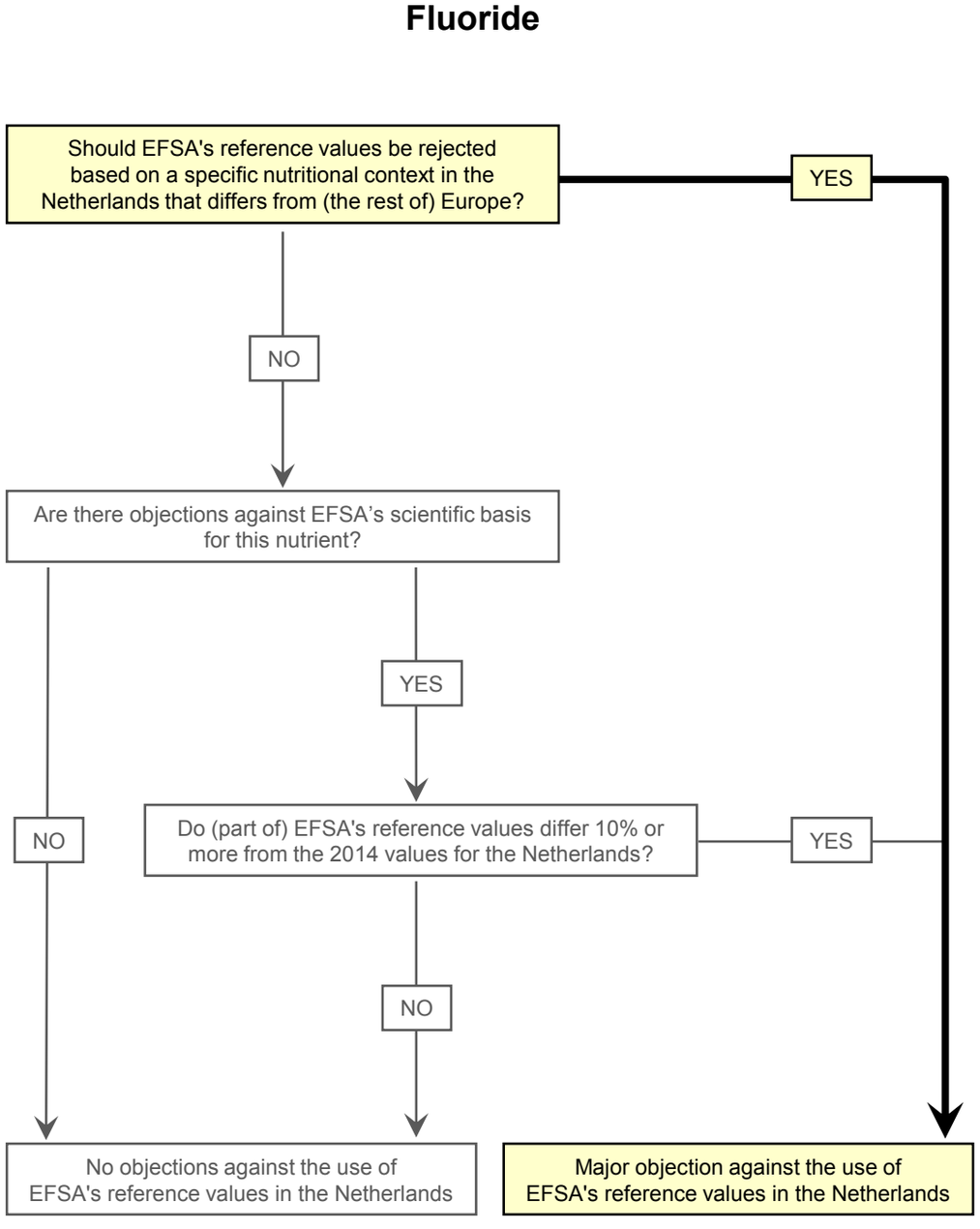
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (=NCM's) RI	Higher	EFSA's AI for men and women is about 80% and 45% higher than the current RI used in the Netherlands (NCM's RI).
Scientific basis of EFSA's AIs	Objections	EFSA is not consistent with IOM. EFSA based the AIs on intake data, and for men, additionally on balance data. EFSA did not provide evidence that intakes as high as EFSA's AIs are required for the prevention of deficiency symptoms. IOM's EAR is based on status & function parameters at low copper intake levels, with a factorial estimate as supportive information. The Committee considers that this value has sufficient clinical relevance.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Applied by EFSA	Not consistent with the reports used for comparison.

The Committee has objections against EFSA's AI for adults. EFSA did not provide evidence that the substantial increase from the current Dutch RDA to EFSA's AIs is required for the prevention of deficiency symptoms or is beneficial for health. The Committee recommends maintaining HCNL's reference values (which are the values used by IOM and NCM; Table 65), because this AR appears to have sufficient relevance for the prevention of deficiency.

Table 65. AR and PRI for copper, recommended for the Netherlands

	Men and women ≥18 years
Average requirement (AR)	0.7 mg/day
Population reference intake (PRI)	0.9 mg/day

19 fluoride



19.1 Overview and comparison of values

Table 66. Overview of the reference values for adults and the criteria on which these values are based

Report	AI (mg/d)		Main criterion
	♂	♀	
EFSA 2013[31] = HCNL 2014[33]	3.4	2.9	Data on the dose-response relationship between caries incidence and consumption of drinking water with different fluoride concentrations which were confirmed by more recent data on total fluoride intake from a study in the US. The AI of 0.05 mg per kg body weight per day is used both for children and adults. EFSA calculated values for men and women based on reference weights of 68.1 and 58.5 kg.
DACH 2015[38]	3.8	3.1	Based on IOM value of 0.05 mg per kg body weight per day as the adequate intake for caries prevention.
IOM 1997[43]	4	3	In areas with water fluoridation, the estimated intakes in children were close to 0.05 mg fluoride per kg body weight per day. Average dietary fluoride intakes of adults ranged from 0.02-0.05 mg per kg body weight per day. The value of 0.05 mg fluoride per kg body weight per day was chosen as the AI for all ages above six months, based on the extensively documented relationship between caries prevalence and fluoride concentration of water. IOM calculated values for men and women based on reference weights of 76 and 61 kg (3.8 and 3.1 mg/d) and rounded these values to achieve the AIs of 4 and 3 mg/d.

Note that NCM[37] and WHO/FAO[44] did not specify reference values for fluoride.

Table 66 shows that the differences in AIs for fluoride are limited: DACH's AIs are 11% higher (men) and 7% higher (women) than EFSA's AIs; IOM's AIs are 18% higher (men) and 3% higher (women) than EFSA's AIs.

19.2 Explanation of differences between reports

The NCM report does contain an evaluation of fluoride. NCM concludes that fluoride has a well-documented role in the prevention and treatment of dental caries, but that the mechanism is attributed to local effects on the tooth enamel surface rather than systemic effects. NCM considers that fluoride is not essential for humans.

The AIs by EFSA, DACH and IOM are based on the prevention of dental caries.

EFSA, DACH and IOM all use 0.05 mg per kg body weight per day as the adequate intake for caries prevention, largely using the same scientific basis. The differences in AIs result from different reference weights used and rounding:

- reference weights for men were 68.1 kg (EFSA) and 76 kg (DACH and IOM);
- reference weights for women were 58.5 kg (EFSA) and 61 kg (DACH and IOM);
- the difference between DACH and IOM is the result of the fact that IOM did, whereas DACH did not round the value.

EFSA notes that both the concentration of 1 mg fluoride/L in drinking water and the fluoride intake of 0.05 mg/kg body weight per day appear to be "optimal" in reducing caries prevalence and keeping dental fluorosis prevalence and severity in the population low, based on 7 studies in children in the US and Canada that were published from 1943 to 1988.

EFSA adds that the efficacy of water fluoridation in preventing caries has been confirmed in a number of predominantly observational studies, either cross-sectional or prospective and retrospective cohort studies, referring to a systematic review of studies in children and a meta-analysis of studies in adults.

However, EFSA notes: (1) that very few of the many reviewed studies provide information on the total dietary fluoride intake, (2) that the outcome measure for caries may have been affected by additional uses of non-dietary fluoride via supplements or fluoride-containing dental hygiene products, (3) that there are methodological difficulties in the measurement of the fluoride content of food and beverages, (4) that these contents appear to vary widely, and (5) that the majority of studies have not systematically addressed other factors which influence caries development (e.g. diet, dental hygiene, environment, and genetic disposition).

EFSA considers that reliable and representative data on the total fluoride intake of the European population are not available; the available data are variable and generally at or below 0.05 mg/kg body weight per day.

EFSA considers that the AI for children of 0.05 mg/kg body weight per day can also be applied to adults, including pregnant and lactating women.

Differences between older and younger adults

None of the reports differentiate the AIs between older and younger adults.

Sex differences

All reports differentiate the AIs between men and women.

19.3 Conclusion on the scientific basis of EFSA's reference values

EFSA concluded that fluoride is not an essential nutrient, but still based the AI for fluoride on the preventive effect against caries.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

No signs of fluoride deficiency have been identified in humans. One cohort study on infants from an area with a low fluoride content of drinking water described a higher rate of length and body weight gain with a fluoride supplement (0.25 mg/day from birth) than without; EFSA considers that this observation does not provide sufficient evidence to prove a causal relationship between fluoride intake and growth.
A lack of fluoride intake during development will not alter tooth development but may result in increased susceptibility of enamel to acid attacks after eruption. However, caries is not a fluoride deficiency disease and EFSA concludes that fluoride is not an essential nutrient.

In the Netherlands, the preventive effect of fluoride against caries is achieved via the use of fluoride-containing dental hygiene products and not via fluoride intake. EFSA's AIs for fluoride are rejected, based on a different nutritional situation in the Netherlands compared to the situation on which EFSA based their AIs.

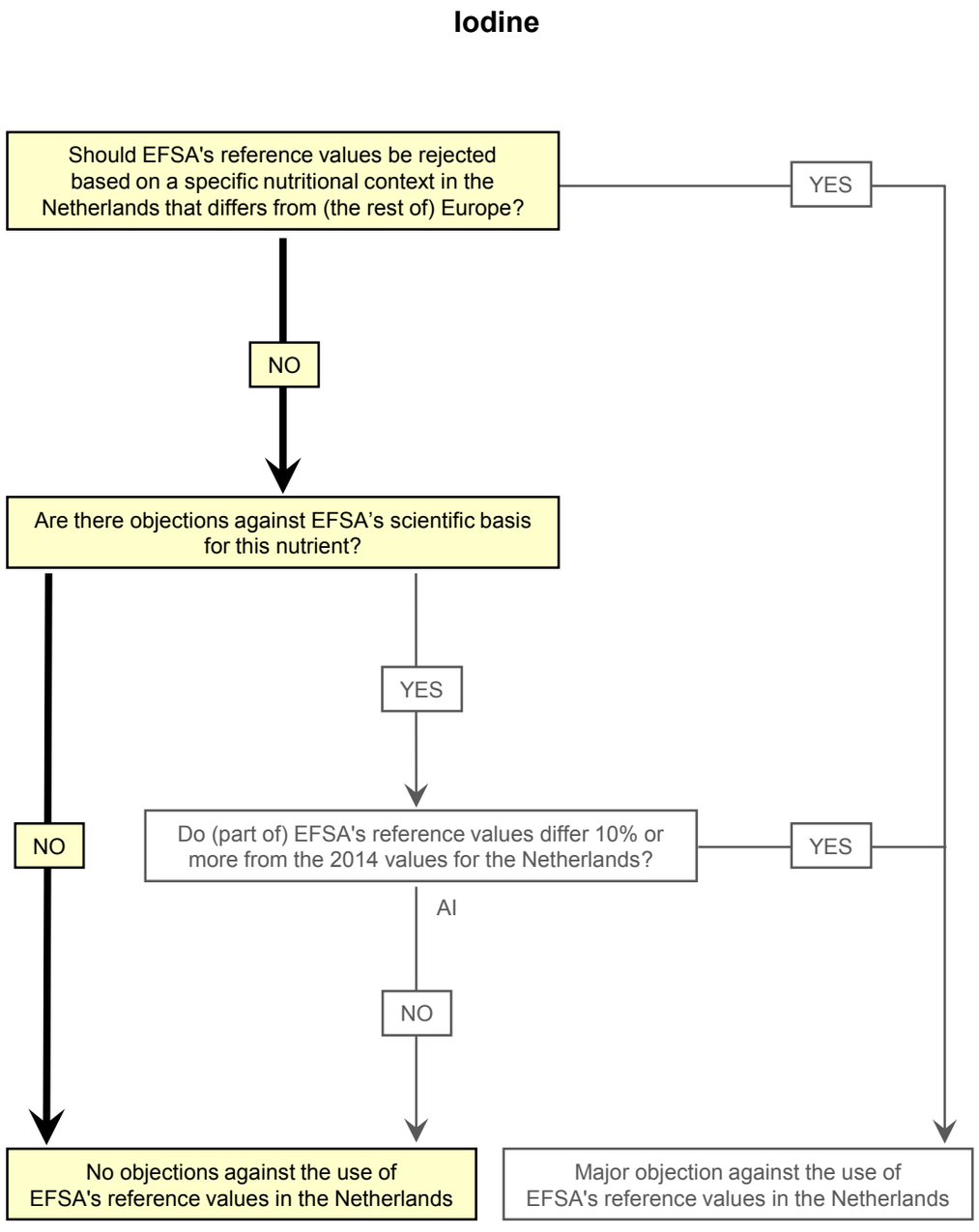
19.4 Summary and conclusion

Table 67. Summary of the evaluation of EFSA's AI values for fluoride

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to the Dutch approach	Not applicable	In the Netherlands, the preventive effect of fluoride against caries is achieved via the use of fluoride-containing dental hygiene products and not via fluoride intake.
Scientific basis of EFSA's reference value	Objections	EFSA assumes that fluoride intake is required for caries prevention, which is consistent with DACH and IOM. In the Netherlands, intake is not considered necessary; fluoride-containing dental hygiene products are used for caries prevention.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with DACH and IOM.
Differentiation between men and women	Applied by EFSA	Consistent with DACH and IOM.

The Committee rejects EFSA's AIs for fluoride, because of a different nutritional situation in the Netherlands compared to the situation on which EFSA based their AIs. In the Netherlands, fluoride-containing dental hygiene products are used for caries prevention; contrary to EFSA, fluoride intake is not considered necessary for caries prevention.

20 iodine



20.1 Overview and comparison of values

Table 68. Overview of the PRI/RDA/RI/AI values for adults and the criteria on which these values are based

Report	PRI/RDA/ AI/RI	(µg/d)	AR (µg/d)	CV (%)	Main criterion
EFSA 2014[25]	AI	150			AI is based on *urinary iodine concentration* ≥100 µg/L
NCM 2014[37] = HCNL 2014[33]	RI	150	100	25%[a]	AR is based on: • intake at which *thyroid iodine concentration* reaches a plateau • daily *iodine turnover* in subjects with normal thyroid function.
DACH 2015[38] Switzerland	AI	150			Based on *urinary iodine concentration* ≥100 µg/L and taking into account that *iodine supply* is sufficient in Switzerland as a result of the Swiss iodised salt programme.
DACH 2015[38] Germany, Austria	AI	200			Based on *urinary iodine concentration* ≥100 µg/L and taking into account that *iodine supply* is insufficient in Germany and Austria.
IOM 2001[41]	RDA	150[b]	95[b]	20%[c]	AR is based on: • the average *thyroid iodine accumulation and turnover*. With as supporting data: • *obligatory iodine excretion* is lower than AR • the approximate intake at which *iodine balance* was achieved in men; however, in women, iodine balance was estimated to be reached at a considerably higher intake. (Note: IOM uses the EFSA key reference as supporting data for the RDA in children aged 9-13 years.)
WHO/FAO 2004[44]	RI	150			RI: • corresponds to the daily *urinary iodine excretion* and to the *food iodine* content *in non-endemic areas* • necessary to maintain *plasma iodine* ≥0.10 µg/dl • necessary to maintain *thyroid iodine stores* >10 mg • corresponds to *urinary iodine concentration* ≥100 µg/L.

[a] NCM CV calculated from AR and RDA: 100% x [(150-100) / 2] / 100 = 25%.
[b] IOM rounded the RDA to the nearest 50 µg/d and the EAR to the nearest 5 µg/d.
[c] The CV presented in the IOM report is 20%, however, the CV calculated from AR and RDA is 29%.

Table 68 presents an overview of reference values and criteria. EFSA, NCM, DACH (value for Switzerland), IOM and WHO/FAO agree on an RDA/RI of 150 µg iodine per day. The DACH value for Germany and Austria is 33% higher.

20.2 Explanation of differences between reports

EFSA's AI for adult men and women (150 µg/day) is based on two estimates:

1. A urinary iodine concentration >100 µg/L was associated with the lowest prevalence of goitre in a study of 7,599 European children aged 6-15 years (DeLange et al., 1997).[a] Similar suitable data for other age groups were not available. Therefore, this threshold was also applied for adults, infants and young children.
2. EFSA assumed the average daily urinary volume to be 1.5 L, based on scientific opinion on the dietary reference values for water.[58]

Furthermore, the EFSA Panel considered that a urinary iodine excretion of 100 µg/day, estimated from late morning spot urine samples (which is supposed to be equivalent to an iodine intake of 110 µg/day) had been associated with a goitre prevalence of up to 10% in Central America in the 1960s, indicating that an iodine intake of 110 µg/day may be lower than the iodine requirements in up to 10% of the population (Ascoli and Arroyave, 1970). The EFSA Panel notes that other approaches, such as the approach based on thyroid hormone production and the factorial approach, support the AI of 150 µg/day.
EFSA did not consider the results of balance studies because these are highly variable and balances may be null at very different levels of intakes.

NCM maintained their 2004 recommendations for adults and children, based on the iodine requirement to prevent goitre and maintain normal thyroid function, because there was no new data supporting changes. NCM 2004 considered the iodine requirement to prevent goitre (increased thyroid gland size) to be 50-75 µg/d or approximately 1 µg/kg bodyweight per day, based on the 1989 *Recommended dietary allowances* for the USA and the 1992 *Nutrient and energy intakes for the European Community*. NCM estimates the average requirement to be 100 µg/d, based on the 2001 IOM report. The recommended intake of 150 µg/d for adults includes a safety margin for any goitrogenic substances in foods.

DACH based their reference values on a urinary iodine concentration ≥100 µg/L, and used data on iodine turnover and iodine supply as additional evidence. This would result in an AI of 150 µg/day. DACH considered that iodine supply is sufficient in Switzerland as a result of the Swiss iodised salt programme, and that an AI of 150 µg/day was sufficient for Switzerland. Because of an insufficient iodine supply in certain age groups and regions of Germany and Austria and considering that the

[a] This study (DeLange et al., 1997) was carried out in the Netherlands. Belgium, Luxemburg, France, Germany, Austria, Italy, Poland, the Czech and Slovak Republics, Hungary and Romania.

amount of goitrogenic substances in foods increases, DACH maintained their higher AI (200 µg/day) for Germany and Austria.

IOM refers to three studies on the thyroid iodine accumulation and turnover in 18, 274 and 4 adults, which consistently support the EAR of 95 µg/day. IOM notes that these data provide no evidence to suggest that the average iodine requirement is altered with aging, or that differences exist based on gender in adults.
IOM notes the methodological limitations of balance studies, but still mentions two balance studies as supporting evidence. In one balance study in 13 subjects, an intake of 100 µg/day resulted on average in a slightly positive balance. In a study in 4 non-pregnant (and 5 pregnant) women, balance was estimated to occur at 160 µg/day, which was used as supporting evidence for making no distinction between the EAR for men and women based on body weight.
Based on the study on thyroid iodine accumulation and turnover in 18 adults, a CV of 40% was calculated, but IOM assumed that half of this variation was due to the complexity of the experimental design and the calculations used to estimate turnover. IOM used a CV of 20% to calculate the RDA and rounded the resulting value to the nearest 50 µg.

WHO/FAO based their reference values on a urinary iodine concentration ≥100 µg/L, corresponding to an iodine intake of 150 µg/day, and on three additional types of evidence. The intake level of 150 µg/day corresponds to the iodine intake in non-endemic areas. It also provides the iodine intake necessary to maintain the plasma iodine concentration above the critical limit of 0.1 µg/dL, which is the average level likely to be associated with the onset of goitre. Moreover, this level of iodine intake is required to maintain the thyroid iodine stores above the critical threshold of 10 mg, below which an insufficient level of iodination of thyroglobulin leads to disorders in thyroid hormone synthesis.

Differences between older and younger adults and sex differences
The reports consistently do not differentiate the AIs between older and younger adults, or between men and women.

20.3 Conclusion on the scientific basis of EFSA's reference values

The Committee has no objections against the scientific basis of EFSA's AI. The value of 150 µg/day is supported by the results of other approaches to estimate the iodine requirements. Furthermore, the EFSA Panel considered that an iodine intake of 110 µg/day may be lower than the iodine requirements in up to 10% of the population (based on the Central American study by Ascoli and Arroyave, 1970, mentioned in paragraph 20.2). The AI of 150 µg/day appears to be appropriate for the prevention of iodine deficiency.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Iodine is a mandatory structural and functional element of thyroid hormones. The function of the thyroid hormones T3 and T4 encompasses the regulation of mitochondrial energy metabolism as well as cellular oxidation, thermoregulation, intermediate metabolism, carbohydrate, lipid and protein metabolism and nitrogen retention. They are particularly necessary during early growth, development and maturation of most organs. The target organs are, in particular, the developing brain, affecting the development of hearing and vision, muscles, the heart, the pituitary gland, the kidney, the reproductive system, and the bones.

According to their thyroid function, individuals are classified as euthyroid (i.e. having normal thyroid function), hypothyroid or hyperthyroid. Various mechanisms can lead to thyroid disorders, and hypo- and hyperthyroid status can be observed in cases of both insufficient and excessive iodine intakes.

In 2003, 16% of the European population had goitre. In 2011, it was estimated that 44% of the population in Europe, i.e. 393 million inhabitants, had insufficient iodine intakes as evidenced by a urinary iodine concentration <100 µg/L.

Chronic iodine deficiency may lead to:

- compensatory thyroid hypertrophy/hyperplasia with goitre. Goitre increases the risk of thyroid cancer; a large goitre may cause obstruction of the trachea and the oesophagus. Note that goitre may also result from chronic excessive iodine supply
- hypothyroidism (myxoedema), observed with severe iodine deficiency, also results from hormone deficiency and is associated with reduced metabolic rate, cold intolerance, weight gain, puffy face, oedema, hoarse voice and mental sluggishness
- cretinism, i.e. a condition of severely stunted growth and retarded physical and mental development.

IOM based the EAR on the average iodine accumulation by the thyroid obtained from the two studies of Fisher and Oddie (1969a, 1969b). The EFSA Panel notes that the average urinary iodine excretion in these studies was about 410 and 280 µg/day, respectively, which is substantially higher than found in European studies. Because both medium-term and short-term iodine accumulation in the thyroid is down-regulated with increasing intake and reaches a plateau for intakes above 80-100 µg/day, the EFSA Panel concludes that the values of 96.5 and 91.2 µg/day for mean iodine accumulation cannot be used for deriving an average requirement for the European context. The Committee agrees with EFSA's line of reasoning for not establishing an AR and PRI, but an AI.

The Health Council has previously recommended to reduce the salt consumption in the Netherlands.[62] As iodine-fortified salt is the main source of iodine for the Dutch population, a lower salt intake could lead to a greater risk of iodine deficiency and goitre. Therefore, careful monitoring of the iodine intake of the Dutch population based on 24-hour urinary iodine excretion values is crucial. For this application, carried out by the Dutch RIVM Institute, the Committee recommends to continue using the AR (100 µg/day) and RI (150 µg/day) from the NCM report, because these values enable a more detailed evaluation of the changes in iodine supply than the use of an AI value.

20.4 Summary and conclusion

Table 69. Summary of the evaluation of EFSA's AI values for iodine

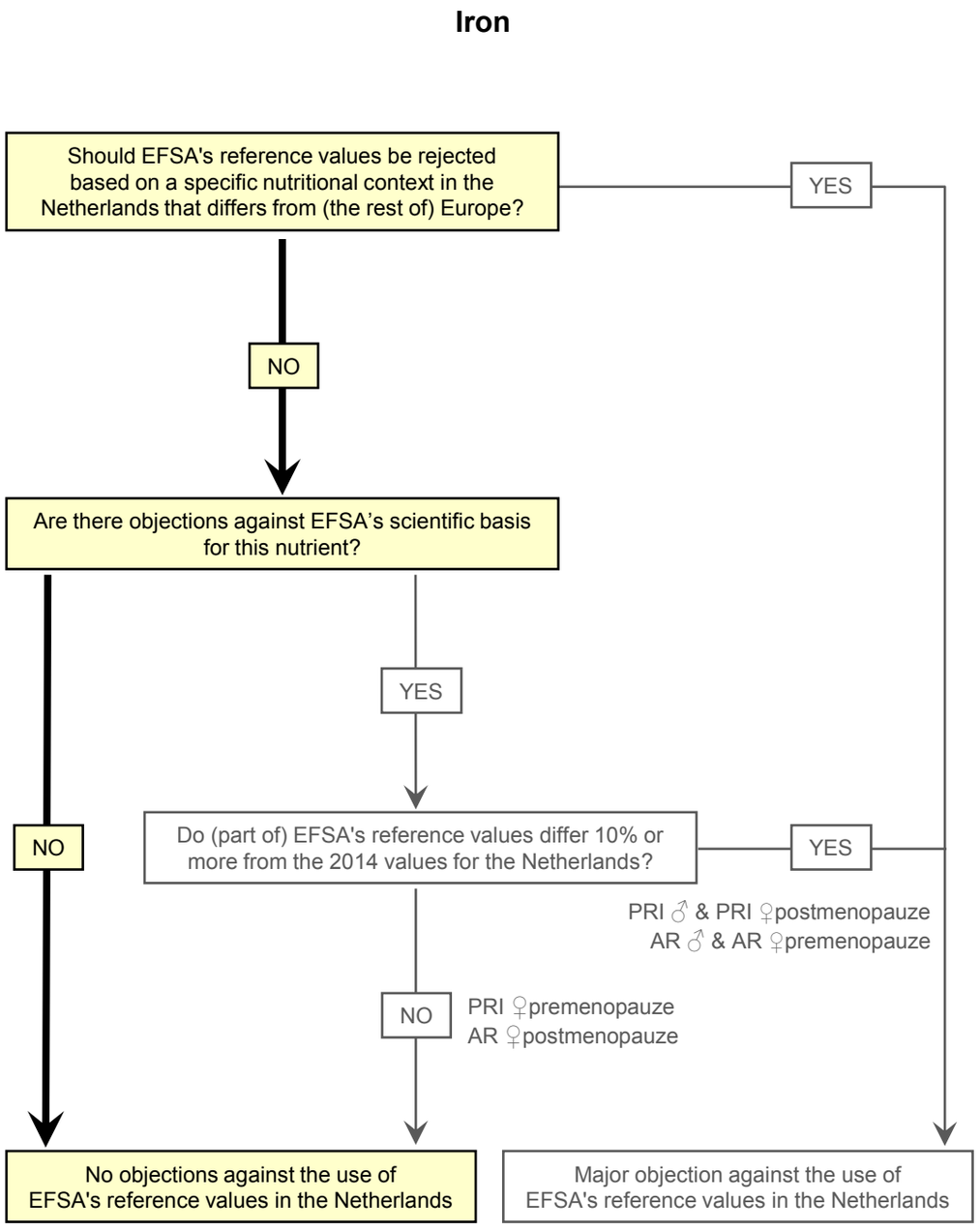
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (=NCM's) RI	Equal	EFSA's AI is equal to HCNL 2014's (=NCM's) RI which is currently used in the Netherlands.
Scientific basis of EFSA's AI	No objections	The AI appears to be directly related to the prevention of iodine deficiency, as supported by the several criteria for setting this reference value.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults in the EFSA report	No	Consistent with the reports used for comparison.
Differentiation between men and women in the EFSA report	No	Consistent with the reports used for comparison.

The Committee has no objections against the scientific basis of EFSA's AI, or EFSA's AI-value. EFSA's AI equals NCM's RI, which has been used in the Netherlands since 2014. The Committee recommends using this value (Table 70) in the Netherlands.

Table 70. AI and PRI for iodine, recommended for use in the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	150 µg/day

21
iron



21.1 Overview and comparison of values

Table 71. Overview of the reference values for adults and the criteria on which these values are based.[a]

Report	PRI/RDA/AI/RI (mg/day)				AR (mg/day)			Main criterion
	Type	♂	♀ post-meno-pause	♀ pre-meno-pause	♂	♀ post-meno-pause	♀ pre-meno-pause	
EFSA 2015[18]	PRI	11	as ♂	16	6	as ♂	7	Factorial method
NCM 2014[37] = HCNL 2014[33]	RI	9	9 (or 8[b])	15	7	6	9 (or 10[c])	Factorial method
DACH 2015[38]	AI	10	as ♂	15				Factorial method
IOM 2001[41]	RDA	8	as ♂	18	6	as ♂	8	Factorial method
WHO/FAO 2004[44]	RNI	9.1		19.6	for 15% bioavailability[d]			Factorial method
		11.4		24.5	for 12% bioavailability			
		13.7		29.4	for 10% bioavailability			
		27.4		58.8	for 5% bioavailability			

[a] No CVs presented, because the PRI/RDA are based on the 90th, 95th or 97.5th percentile of losses.

[b] NCM's RI-value for postmenopausal women is unclear: NCM specifies values of 8 and 9 mg/d (see paragraph 20.2).

[c] NCM's AR-value for premenopausal women is not clear: NCM specifies values of 9 and 10 mg/d (see paragraph 20.2).

[d] WHO/FAO present RNI values for four levels of bioavailability in the range from 5% to 15%. For the comparison of reports, WHO/FAO's RI at a bioavailability of 15% was used, because the other reports used bioavailability values in the range of 15% to 18%.

Table 71 presents an overview of reference values and criteria. Table 72 presents the underlying information used.

For men, the RDA/AI/RIs by NCM (=HCNL), DACH, IOM and WHO/FAO are -18%, -9%, -27% and -19% relative to EFSA's PRI.

Table 72. Estimated daily iron losses and absorption percentages used to set the AR and PRI/RDA/RI/AI values for adults

Report	Estimated daily iron losses (mg/d)								Absorption (%)
	♂				♀ premenopause (♀ postmenopause)				
	P50[a]	P90	P95	P97.5	P50a	P90	P95	P97.5	
EFSA 2015[18]	0.95	1.48	1.61	**1.72 used for PRI ♂**	1.34	2.44	**2.80 used for PRI ♀**	3.13	♂16% ♀18%
NCM 2014[37] = HCNL 2014[33]	1.05		**1.37 used for RI ♂**		1.35 (0.87)	**2.22 used for RI ♀ pre-meno-pause**	2.77 (1.13)[b]		15%[c]
DACH 2015[38]	Not specified								10-15%
IOM 2001[41]	1.08		1.45	**1.53 used for PRI ♂**	1.4	2.35	2.67	**3.15 used for PRI ♀**	18%
WHO/FAO 2004[44]	**1.37[d] used for RNI ♂**				**2.94[d] used for RNI ♀**				15%

[a] The P50 was used to set the AR-value.

[b] NCM values as specified in Table 34.2 of the NCM report.

[c] NCM specify explicitly that for premenopausal women they used an absorption percentage of 15%. However, the absorption percentage(s) used for men and postmenopausal women is not specified by NCM.

[d] WHO/FAO's estimated daily iron loss at a bioavailability of 15% were deduced for this table by multiplying the RNI by 0.15.

For premenopausal women, NCM and DACH use 6% lower RDA/AI/RIs than EFSA's PRI, whereas IOM's and WHO/FAO's values are 12% and 27% higher than EFSA's PRI.

For postmenopausal women, NCM, DACH and IOM have RDA/AI/RIs which are between 9% and 27% lower than EFSA's PRIs.

21.2 Explanation of differences between reports

EFSA and all the reports used for comparison base their reference values on a factorial method in which the required dietary intake is estimated from the estimated iron losses from the body and the assumed efficiency of iron absorption. The underlying thinking behind this method is that the daily losses should be replenished by dietary intake. The estimated iron losses comprise the losses via faeces, urine, sweat and skin, and for premenopausal women also via menses.

Iron is one of the few nutrients for which data are available not only on the average losses, but also on the variability of iron losses between individuals. Instead of calculating the PRI/RDA/RI's from the AR and an assumed coefficient of variation of the requirements, the PRI/RDA/RI's are based on the 90th, 95th, or 97.5th percentile of the distribution of iron losses.

All reports differentiate between premenopausal and postmenopausal women, because menses contributes substantially to the daily iron losses. In most reports, the values for adult men are also used for postmenopausal women.

Despite the relatively large knowledge on iron requirements, including the variation between subjects, the reference values vary between the reports. The use of different references or datasets may result in different estimates of (1) iron losses and (2) absorption efficiencies. The PRI/RDA/RI-values are additionally influenced by differences in the chosen (3)

percentile of the distribution of iron loss. These three types of differences either add up to larger differences, or (partly) counterbalance each other, which is elucidated on the next pages.

DACH uses the factorial method, but did not specify the components of their calculation; therefore this report is not included in the evaluation by the Committee.

Explanation of the differences between the reference values for men

ARs

NCM's AR is 17% higher than EFSA's AR for men, because the differences in two underlying estimates work in the same direction: NCM's estimate of the median iron losses is higher than EFSA's estimate, and NCM uses a slightly lower absorption percentage than EFSA (15% versus 16%).
EFSA and IOM set the same AR for men, because the differences in two underlying estimates work in opposite directions: EFSA's lower estimate of the median losses is compensated by EFSA's use of a lower absorption percentage than IOM (16% versus 18%).

PRI/RIs

For men, EFSA's PRI is higher than the values in the other reports. The differences between NCM and WHO/FAO is mainly explained by the choice regarding the percentile within the distribution of iron losses: EFSA used the 97.5th percentile, whereas NCM and WHO/FAO used the 95th percentile.
IOM and EFSA both used the 97.5th percentile of iron losses, but EFSA's estimate is higher than IOM's estimate. In addition, EFSA uses a lower absorption percentage than IOM (16% versus 18%). The differences in the two underlying estimates work in the same direction: IOM's RDA is substantially lower than EFSA's PRI.
The Committee notes that EFSA's values for men imply that the variation of the requirements for iron is relatively large (CV ~40%).[a]

Explanation of the differences between the reference values for premenopausal women

ARs

NCM's AR for premenopausal women is not clear: NCM specifies values of 9 and 10 mg/d.[b] Both NCM-values are substantially higher than EFSA's AR (7 mg/d). The difference is caused solely by NCM's use of a

[a] The coefficient of variation (CV) of iron requirements can then be deduced from EFSA's and IOM's values, as both organisations based the PRI/RDA on the 97.5th percentile of iron losses. Assuming a 'normal' distribution, the PRI, calculated as AR + [(2xCV/100) x AR], covers 97.5% of the individual requirements in the population. Therefore: CV can be calculated if the PRI is based on the 97.5th percentile of losses as:
100% * ½ * (PRI - AR) / AR. For men, the estimated CVs are ~40% (EFSA) and ~20% (IOM).

[b] NCM mentions the AR of 9 mg/d for premenopausal women in the text (page 555 of the NCM report) and in Table 34.2 (page 556) of the NCM report; this value is consistent with the underlying values presented in this table. However, NCM's AR-value for premenopausal women in the summarising Table 1.8 (page 40 of the NCM report) and in the table at the beginning of their chapter on iron (page 543 of the NCM report) is 10 mg/d.

substantially lower absorption percentage than EFSA (15% versus 18%); NCM and EFSA use the same value for the median iron losses in premenopausal women.
IOM's AR is 16% higher than EFSA's AR for premenopausal women, solely because of IOM's higher estimate of the median iron losses compared to EFSA's estimate. IOM and EFSA use the same value for the iron absorption percentage in women (18%).

PRI/RIs
For premenopausal women, NCM uses a lower RI than EFSA's PRI, whereas IOM and WHO/FAO use higher levels.
The 6% lower value of NCM relative to EFSA is the result of three differences working in opposite directions: the choice regarding the percentile of losses used (EFSA: 95th percentile; NCM: 90th percentile), and NCM's lower estimate of the 90th percentile of losses compared to EFSA, both work in the direction of a lower NCM value. This is partly compensated by the use of a substantially lower absorption percentage by NCM compared to EFSA (15% versus 18%), which works in the direction of a higher NCM value. The resulting difference between NCM's RI and EFSA's PRI is small.
The 12% higher value of IOM relative to EFSA is solely the result of the choice regarding the percentile of losses used (EFSA: 95th percentile; IOM: 97.5th percentile).
The 27% higher value of WHO/FAO relative to EFSA is the result of two differences working in the same direction: the higher estimate for the 95th percentile of losses by WHO/FAO compared to EFSA, and the substantially lower absorption percentage used by WHO/FAO relative to EFSA (15% versus 18%).

Explanation of the differences between the reference values for postmenopausal women

ARs
For postmenopausal women, EFSA, NCM and IOM set the same AR (6 mg/d). EFSA and IOM use their values for men and for postmenopausal women.

PRI/RIs
For postmenopausal women, as for men, EFSA's PRI is higher than the values in all reports used for comparison. NCM's value for postmenopausal women is unclear: NCM specifies values of 8 and 9 mg/d.[a] The other reports apply the values for men also to postmenopausal women.

[a] NCM mentions the RI of 9 mg/d for postmenopausal women in the summarising Table 1.3 (page 31 of the NCM report) and in the table at the beginning of their chapter on iron (page 543). However, in the right column of Table 34.2 (page 556) and the text (page 558) of the NCM report, NCM mentions the value of 8 mg/d for postmenopausal women.

21.3 Conclusion on the scientific basis of EFSA's reference values

The Committee has no reason to object against EFSA's estimates of iron losses, or against EFSA's assumption regarding the absorption efficiency; these estimates appear to have sufficient scientific basis.[a] The Committee also agrees with EFSA´s choices regarding the percentile of the distribution of iron losses on which the PRIs are based:

- For men and postmenopausal women, there is no reason to assume that the distribution of iron requirements would deviate from a "normal" (Gaussian) distribution.[b] Therefore, EFSA's choice to base the PRI for men on the 97.5th percentile of iron losses seems appropriate.
- For premenopausal women the distribution of the iron losses is not 'normal', but skewed as a result of the high iron losses via menses in a proportion of these women. IOM still bases the RDA for this group on the 97.5th percentile of iron losses. The skewed part of the distribution is only relevant for the subgroup of women with high iron losses via menses and, therefore, other reports base the PRI/RDA/RI for premenopausal women on the 90th percentile (NCM) or the 95th percentile (EFSA, WHO/FAO). The Committee had no objections against EFSA´s choice for the 95th percentile of iron losses.

Therefore, the Committee considers that it had no objections against the scientific basis of EFSA's reference values.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Iron is necessary for most, if not all, pathways for energy and substrate metabolism. Globin-haems are transporters of oxygen, carbon dioxide, carbon monoxide and nitric oxide, stores of oxygen and scavengers of free radicals. The cytochrome P-450 oxidase system embraces over 11,000 diverse activities including the metabolism of endogenous substrates such as organic acids, fatty acids, prostaglandins, steroids and sterols including cholesterol and vitamins A, D and K. The citric acid cycle and respiratory chain involves six different haem proteins and six iron-sulphur clusters.
Iron deficiency anaemia (a microcytic anaemia with haemoglobin concentrations below normal) is the most common nutritional deficiency disorder, being found in all countries of the world.
Women with high menstrual losses are at risk of developing iron deficiency.
Other symptoms which are not specific to iron deficiency are: spoon-shaped nails, soft nails, glossitis, cheilitis (dermatitis at the corner of the mouth), mood changes, muscle weakness and impaired immunity.
Iron deficiency is a risk factor for increased blood concentrations of cadmium.

There is international agreement on the use of the factorial method to calculate the reference values for iron. The underlying thinking, that the daily losses should be replenished, can be considered relevant for the

[a] EFSA used the dataset by Hunt et al., 2009[59], see Appendix H in EFSA report. EFSA´s estimated iron losses of premenopausal women were based on data of 19 menstruating women plus one woman aged 30 years with unknown menstrual status. EFSA´s estimated iron losses of men were based on data of 29 men. EFSA assumes that the estimates for men also apply to postmenopausal women.

[b] For nutrients with a 'normal' or 'Gaussian' distribution of the requirements of individuals, the PRI/RDA/RI value is – by definition – calculated as the AR plus twice the standard deviation of requirements, which implies that these PRI/RDA/RI-values equal the 97.5th percentile of the requirement distribution. Therefore, it seems appropriate that PRIs for groups with a 'normal' distribution of requirements (men and postmenopausal women) are based on the 97.5th percentile of iron losses.

prevention of deficiency. The Committee has no objections against the scientific basis of EFSA's reference values for iron (paragraph 21.2).

Note that the EFSA report does not provide information on intake levels associated with the occurrence or correction of deficiencies.

21.4 Summary and conclusion

Table 73. Summary of the evaluation of EFSA's AI values for iron

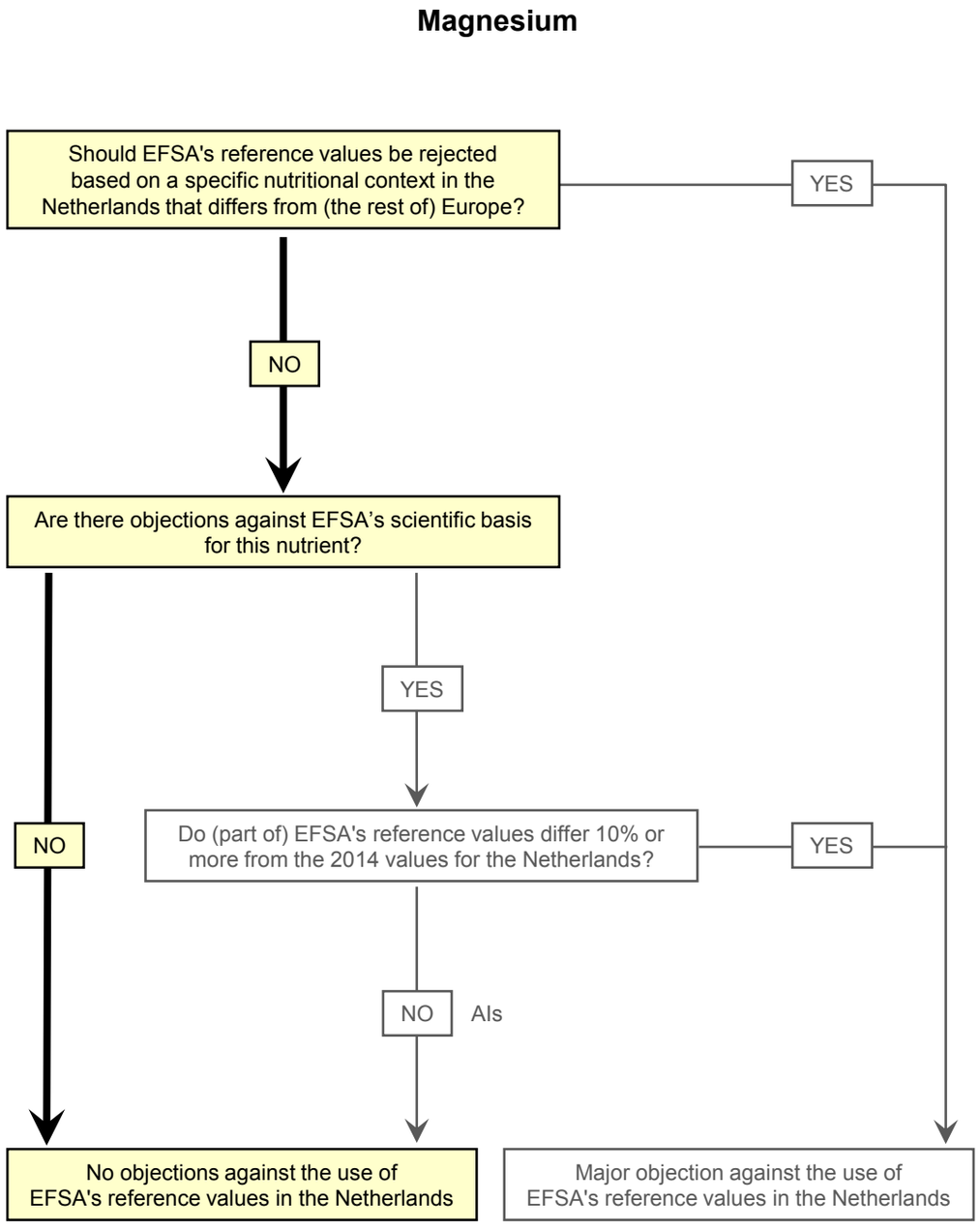
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's (=NCM's) ARs	Lower	EFSA's AR is lower than HCNL's (=NCM's) ARs for men and premenopausal women, but their AR for postmenopausal women is equal.
EFSA's PRIs compared to HCNL's (=NCM's) RIs	Higher	EFSA's PRIs are higher than HCNL's (=NCM's) RIs for all three groups (men, premenopausal and postmenopausal women).
Scientific basis of EFSA's ARs	No objections	All reports use the same methods, although the resulting values vary substantially.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Applied by EFSA	All reports differentiate between pre- and postmenopausal women, but not between younger and older men.
Differentiation between men and women	Applied by EFSA	All reports differentiate between men and pre-menopausal women; most do not differentiate between men and postmenopausal women.

The Committee has no objections against the scientific basis of EFSA's reference values, and recommends accepting EFSA's PRIs and ARs in the Netherlands (Table 74). The Committee notes that the iron requirements of women with high blood losses during menses may not be covered by the PRI for premenopausal women.

Table 74. AR and PRI for iron, recommended for the Netherlands

	Men	**Women**	
		premenopausal	**postmenopausal**
Average requirement (AR)	6	7	6
Population reference intake (PRI)	11	16	11

22 magnesium



22.1 Overview and comparison of values

Table 75. Overview of the PRI/RDA/RI/AI values for adults and the criteria on which these values are based

Report	AI/RI/RDA (mg/d)				AR (mg/d)		Main criterion
	Type	Age	♂	♀	♂	♀	
EFSA 2015[20]	AI		350	300			Mean intakes in Europe combined with the results of balance studies.
NCM 2014[37] = HCNL 2014[33]	RI		350	280			There has been no substantial new data since NCM 2004 indicating that these values should be changed.
DACH 2015[38]	AI	19-24 yr ≥25 yr	400 350	310 300			Balance studies.
IOM 1997[43]	RDA	19-30 yr 31-70 yr	400 420	310 320	330 350	255 265	Balance studies. Note that balance data were scarce for women (1 study in women aged 31-50 years, no study in women aged 51-70 years).
		≥70 yr	420	320	350	265	Balance data are not available and estimates from other methods are uncertain.
WHO/FAO 2004	RI	19-65 yr >65 yr	260 224	220 190			RIs are based on energy intake. WHO/FAO notes that their RIs must be regarded as provisional, because of the scarcity of studies.

Table 75 presents an overview of reference values and criteria.

NCM's RI for men is equal to EFSA's AI for men. NCM's AI for women is 6% lower than EFSA's value.

DACH's AI are higher than EFSA's value, especially for younger men (men 19-24 years +14% relative to EFSA's AI). DACH's value for younger

women differs little from EFSA's value (+3%). DACH's AIs for men and women aged ≥25 years equal EFSA's AIs.
IOM's RDAs are higher than EFSA's AIs, especially in men (♂ 19-30 years: +14, ♂ ≥31 years: +20% relative to EFSA). IOM's RDAs are slightly higher in women (♀ 19-30 years: +3; ♀ ≥31 years: +6% relative to EFSA).

22.2 Explanation of differences between reports

The AIs by EFSA is based on intakes. DACH and IOM base their AIs on balance data.

EFSA decided, considering all evidence available, to base the AIs on observed intakes in eight European countries (Finland, France, Ireland, Italy, Latvia, the Netherlands, Sweden, the United Kingdom). The EFSA Panel set AIs according to sex, because differences in magnesium intakes between men and women were rather large.

- For men, average intakes ranged between 264 and 439 mg/day (midpoint 352 mg/day; median 341 mg/day), and EFSA proposed an AI of 350 mg/day.
- For women, average intakes ranged between 232 and 357 mg/day (midpoint 295 mg/day; median 298 mg/day), and EFSA proposed an AI of 300 mg/day.

The EFSA Panel noted that the role of magnesium in bone structure and physiology is well established, but that there are insufficient quantitative data to use this relationship for setting AIs for magnesium. Furthermore, EFSA mentions that a pooled analysis of well-controlled balance studies (Hunt & Johnson, 2006)[a] was published after the IOM report; this study suggested that zero magnesium balance may occur at an intake as low as 165 mg/d and that homeostatic control appears to be strong over a large range of intakes (84-598 mg/d). EFSA does not use these new balance data as the primary criterion for setting the AI, because results of some large-scale and long-term prospective observational studies point to a relationship between a higher magnesium intake and a lower risk of diabetes mellitus type 2. EFSA does not base the AI on these findings from prospective observational studies, because the interpretation is complicated by the correlation between the intake levels of magnesium, fibre and potassium.[b,c]

DACH based their RIs for younger (19-24 years) and older (≥25 years) adults on balance studies. DACH refers to the IOM report, and also to two

[a] This pooled analysis (Hunt & Johnson, 2006) compiled the results of 27 balance studies conducted between 1976 and 2000 in a metabolic unit under well-controlled conditions; the minimum length of the dietary periods was 18 days. After excluding subjects with insufficient or excessive intakes of possibly interacting nutrients (calcium, copper, iron, phosphorus or zinc), the dataset comprised 150 healthy women (mean age 51 years) and 93 healthy men (mean age 28 years).

[b] EFSA mentions that some large-scale and long-term prospective observational studies indicate that higher magnesium intake (ranges of median intakes were 244-773 mg/day in the highest quintiles, and 115-270 mg/d in the lowest quintiles) were associated with a lower risk of diabetes mellitus type 2. However, this association was not found in a meta-analysis on results adjusted for dietary fibre intake (i.e. when results which were not adjusted for dietary fibre intake were excluded). Therefore, the EFSA Panel did not use this data on the association between magnesium intake and diabetes mellitus type 2 for setting reference values for magnesium.

[c] EFSA Panel also reported on meta-analyses of prospective cohort studies showing a significant inverse association between a higher magnesium intake and a lower risk of stroke. EFSA did not take this finding into account, because foods rich in magnesium are also rich in other dietary substances such as dietary fibre and potassium, so that the effect of magnesium per se cannot be unravelled.

original research publications mentioned by IOM (Lakshmanan et al., 1984; Wisker et al., 1991) and three publications not mentioned by IOM (Gullestad et al., 1994; Jones et al., 1967; Marxhall et al., 1976). DACH does not provide more information on the background of their RIs.

IOM also based their ARs and RDAs for younger (19-30 years) and older (≥31 years) adults on nine balance studies. IOM included balance studies with an adaptation period of at least 12 days, and studies determining the balance while the subjects consumed self-selected diets. The values for adult women relied heavily on the findings from one study in 18 women (and 16 men) consuming self-selected diets in a free-living environment (Lakshmanan et al., 1984).

WHO/FAO notes that the scarcity of studies from which to derive estimates of dietary allowances for magnesium has been emphasised by virtually all the agencies faced with this task.

Differences between older and younger adults

EFSA and NCM do not differentiate between older and younger adults. DACH uses slightly *higher* values for the youngest adults (19-24 years versus ≥25 years), whereas IOM uses slightly *lower* values for the youngest adults (19-30 years versus ≥31 years).

Sex differences

All reports differentiate between men and women.

22.3 Conclusion on the scientific basis of EFSA's reference values

EFSA uses the average magnesium intake as the criterion for setting the AI, because balance studies may underestimate the AI, considering research associating higher magnesium intake with lower risks of specific chronic diseases (paragraph 22.2). The Committee has no objection against this scientific basis EFSA's AIs, but notes that intake data provide little evidence on requirements.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Magnesium is a cofactor of more than 300 enzymatic reactions. It is essential in the intermediary metabolism for the synthesis of carbohydrates, lipids, nucleic acids and proteins, as well as for specific actions in various organs such as the neuromuscular or cardiovascular system. Magnesium can interfere with calcium at the membrane level or bind to membrane phospholipids, thus modulating membrane permeability and electrical characteristics. Magnesium has an impact on bone health through its role in the structure of hydroxyapatite crystals in bone.
Magnesium deficiency can have many different causes, including renal and gastrointestinal dysfunctions. Owing to the widespread involvement of magnesium in numerous physiological functions and the metabolic interactions between magnesium and other minerals, it is difficult to relate magnesium deficiency to specific symptoms such as neuromuscular irritability, muscle tremors and cramps, fasciculation, wasting and weakness, restless leg syndrome, fibromyalgia, i.e. conditions where the use of magnesium supplementation has led to inconsistent results. Magnesium deficiency can cause hypocalcaemia and hypokalaemia, leading to neurological or cardiac symptoms when it is associated with marked hypomagnesaemia (< 0.5 mmol/L).

22.4 Summary and conclusion

Table 76. Summary of the evaluation of EFSA's AI values for magnesium

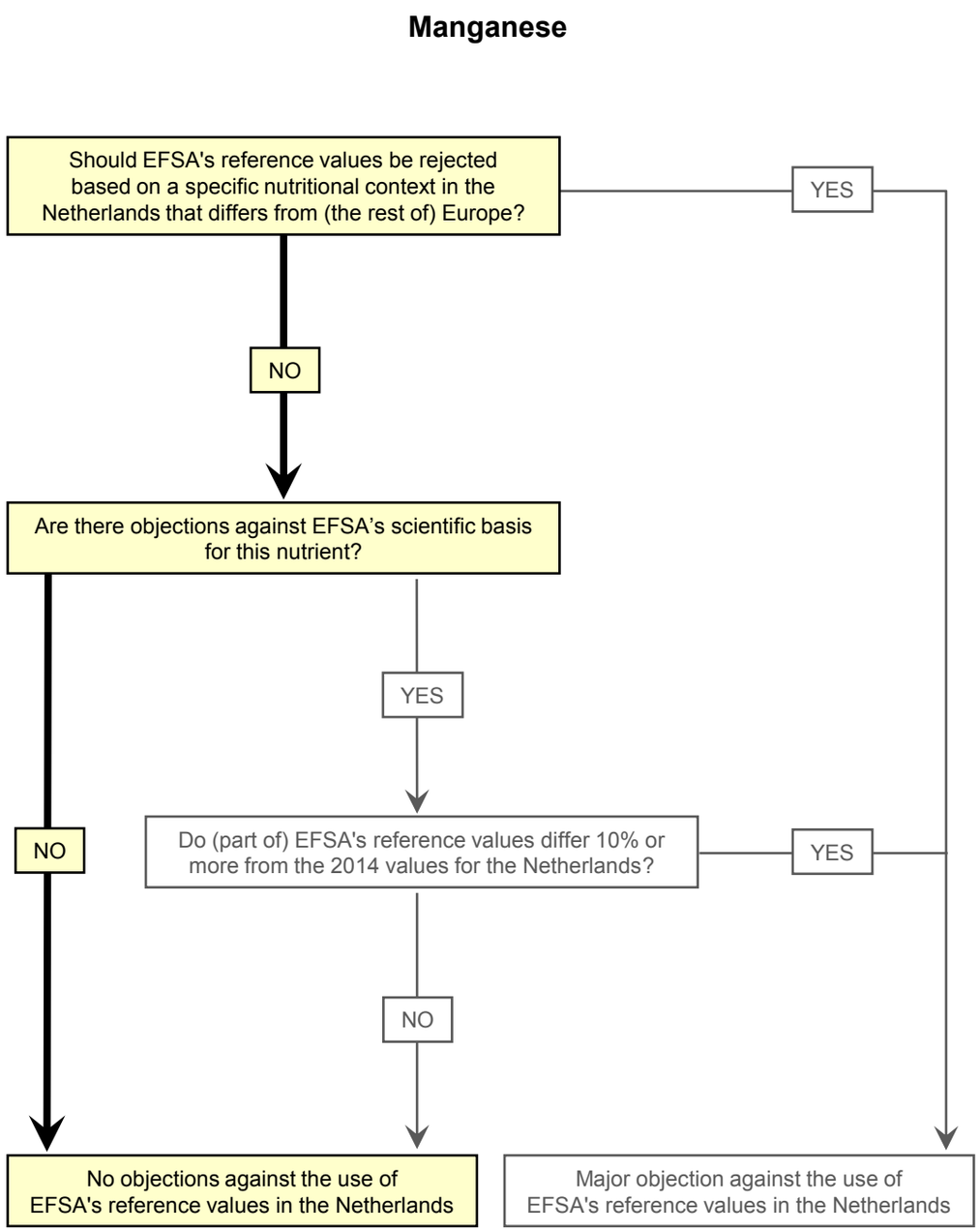
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (NCM's) RI	(Almost) equal	For men, EFSA's AI is equal to NCM's AI. For women, EFSA's AI is 7% higher than NCM's AI.
Scientific basis for EFSA's AIs	No objections	EFSA uses the average magnesium intake as the criterion to set the AI. Intake data provide little evidence on requirements.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults in the EFSA report	No	Consistent with the reports used for comparison, DACH and IOM differentiate the value for the youngest adults (up to 24 or 30 years) from older adults, but not in a consistent way.
Differentiation between men and women in the EFSA report	Yes	Consistent with the reports used for comparison.

The Committee has no objections against the scientific basis of EFSA's AIs, or EFSA's AI-values and recommends using these values (Table 77) in the Netherlands.

Table 77. AR and PRI for magnesium, recommended for use in the Netherlands

	Men ≥18 years	Women ≥18 years
Adequate intake (AI)	350	300

23 manganese



23.1 Overview and comparison of values

Table 78. Overview of the reference values for adults and the criteria on which these values are based

Report	AI (mg/d)	Main criterion
EFSA 2013[30] = HCNL 2014[33]	3.0	Mean intakes in Europe combined with the consideration that null or positive balances have consistently been observed with intakes >2.5 mg/day.
DACH 2015[38]	2-5	Intake level associated with neither deficiency nor toxicity.
IOM 2001[41]	♂2.3; ♀1.8	Median intakes in the USA.

Note that NCM and WHO/FAO did not establish reference values for manganese.

Table 78 shows that EFSA's AI is within the range used by DACH. IOM's AIs are lower than EFSA's value (-23% for men and -40% for women).

23.2 Explanation of differences between reports

EFSA and IOM base their AIs on intakes, but EFSA also considers the results from balance studies. The differences between these reports reflect the difference in intake levels between European countries and the United States.

EFSA considers that national dietary surveys from Austria, France, Germany, Hungary, Ireland, and the UK reported mean daily intake estimates for manganese ranging from 2.5 to 6.6 mg in men and from 2.0 to 5.5 mg in women, with most values around 3 mg/day.

EFSA considers that several balance studies demonstrated that the body adapts quickly to changes in manganese intake, that balance may be maintained at intakes below 2.5 mg/day, and that null or positive balances have consistently been observed with manganese intakes above 2.5 mg/day. EFSA notes that manganese balance may be influenced by the overall diet, variations in individual rates of absorption or excretion, differences in body contents and adaptation to varying dietary levels.
EFSA proposed an AI of 3 mg/day for adults, because observed mean intakes of adults in the EU are typically around 3 mg/day, and, in addition, null or positive balances have consistently been observed with intakes of manganese above 2.5 mg/day.
IOM used manganese intake estimates from the US total dietary survey 1991-1997. The median dietary manganese intake was 2.1-2.3 mg/day for men and 1.6-1.8 mg/day for women. IOM considered that dietary intake assessment methods tend to underestimate the actual daily intake of foods and, therefore, considered the highest intake value reported for the four adult age groups (19-30 years, 31-50 years, 51-70 years, 71 years and over) to set the AI for each sex. The AI was set as 2.3 mg/day for men and 1.8 mg/day for women.
IOM did not use balance data to set an EAR, because a wide range of manganese intakes can result in manganese balance. In addition, because overt symptoms of manganese deficiency are not apparent in the North American population, IOM considered that a recommended dietary allowance (RDA) based on balance data would be most likely to overestimate the requirement for most North American individuals.

Differences between older and younger adults
None of the reports differentiate between older and younger adults.

Sex differences
EFSA and DACH do not differentiate between men and women, whereas IOM does, based on median intakes.

23.3 Conclusion on the scientific basis of EFSA's reference values

EFSA based their AI on average intakes in European populations, and used results from balance studies as supportive information (see paragraph 23.2). A specific manganese deficiency syndrome has not been described in humans, but deficiency signs have been induced after 39 days on a very low manganese diet (Table 79).
The Committee has no objections against the scientific basis of EFSA's AI, but notes that mean intakes may substantially exceed requirements, as deficiencies have not been reported in healthy subjects on normal diets.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Manganese is a component of metalloenzymes such as superoxide dismutase, arginase and pyruvate carboxylase, and is involved in amino acid, lipid and carbohydrate metabolism. Evidence of manganese deficiency in humans is poor. A specific deficiency syndrome has not been described in humans. A depletion-repletion study indicated that fleeting dermatitis and miliaria crystallina are deficiency signs (Table 83).

Table 79. Manganese intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects / Specific group	EFSA's reference
Fleeting dermatitis, miliaria crystallina occurred in 5 out of the 7 men (and disappeared after repletion began)	0.11 mg manganese per day for 39 days (depletion phase)	7 men (depletion-repletion study)	Friedman et al., 1987

23.4 Summary and conclusion

Table 80. Summary of the evaluation of EFSA's AI values for manganese

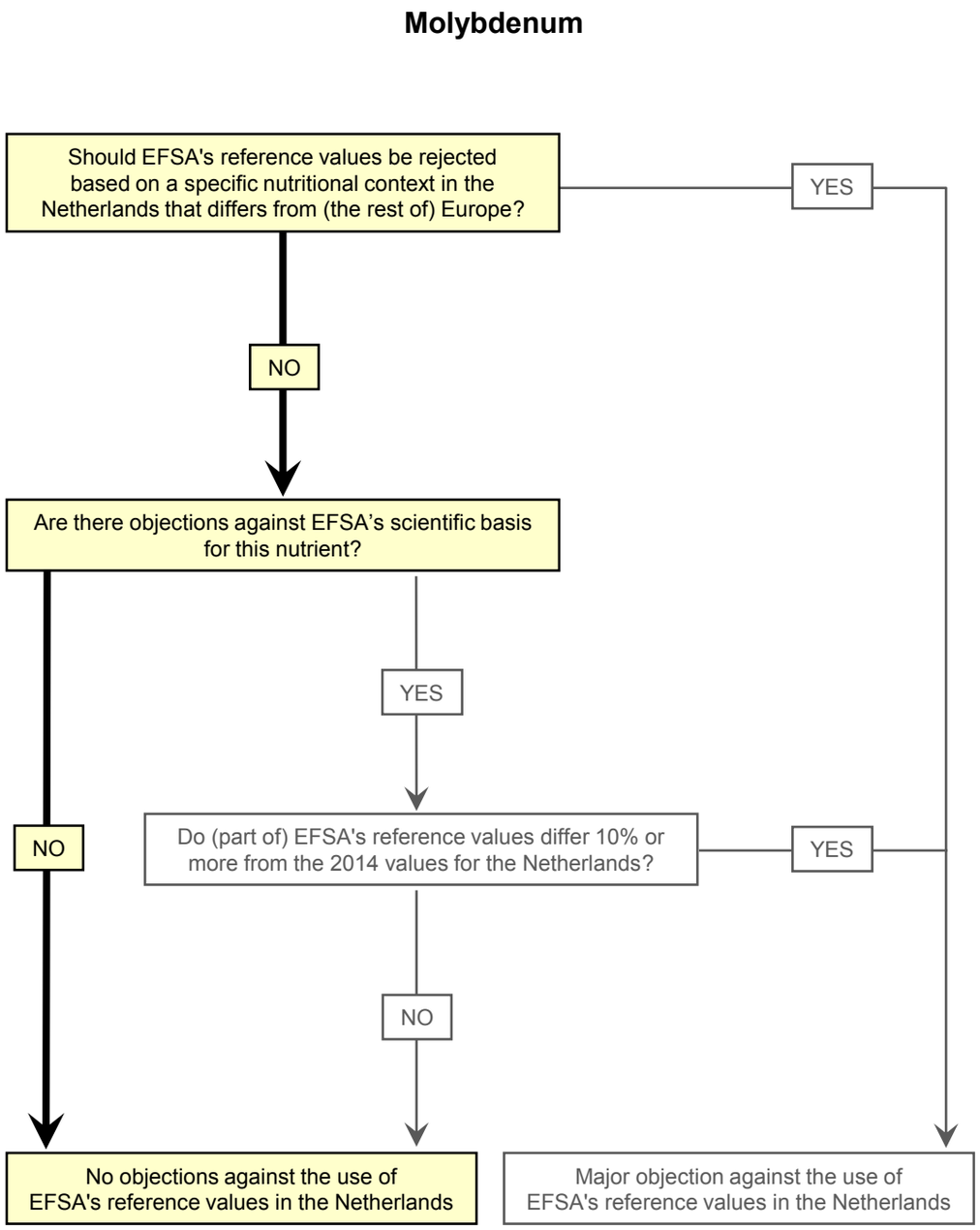
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (EFSA's) AI	Equal	EFSA's AI is already used in the Netherlands.
Scientific basis of EFSA's AIs	No objections	EFSA bases the AI on intake data, consistent with IOM. EFSA uses balance data as supportive information, unlike IOM.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Not consistent with the IOM report.

EFSA's AI for manganese is based on mean intakes and supportive information from balance studies. Mean intakes are assumed to be adequate because no signs of deficiency are reported in healthy subjects on normal diets. The average intakes may exceed requirements. Because there is no evidence available to define a more evidence-based AI, the Committee has no objections against the scientific basis of EFSA's AI for adults, or the AI-value (Table 81).

Table 81. AI for manganese, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	3.0 mg/day

24 molybdenum



24.1 Overview and comparison of values

Table 82. Overview of the reference values for adults and the criteria on which these values are based

Report	AI/RDA		EAR	CV	Main criterion
	Type	(µg/d)	(µg/d)	%	
EFSA 2013[32] = HCNL 2014[33]	AI	65			The lower end of mean intakes in European countries, supported by data of one balance study (see IOM).
DACH 2015[38]	AI	50-100			Molybdenum intakes with a mixed diet.
IOM 2001[41]	RDA	45	34	15%	Balance study in 4 young males and an assumed bioavailability of 75%.

Note that NCM and WHO/FAO did not establish reference values for molybdenum.

Table 82 shows that EFSA's AI is within the range used by DACH.

IOM's AI is 30% lower than EFSA's value.

24.2 Explanation of differences between reports

EFSA and DACH based their AIs on intakes. IOM's AR is based on a small balance study. The difference between EFSA and IOM is the result of the criterion used.

EFSA's AI was based on the lower end of the mean intakes in European countries: 74 µg/day in men and 58 µg/day in women estimated with the duplicate diet method. Based on these values, EFSA proposed an AI of 65 µg/day for all adults.

EFSA used the results from a small balance study with long duration as supportive evidence (this is the balance study on which IOM based their

EAR). In 4 adult men, balance was reported to be near zero from day 49 until day 102 of the depletion period at molybdenum intakes of 22 µg/day (Table 83).

The AR by IOM was based on the balance data in 4 young males described above. Because of the small number of subjects in this study, the value is uncertain for the group studied (young males) and the applicability to other groups (older men, younger and older women) is unknown.

Differences between older and younger adults and between men and women

None of the reports differentiate between older and younger adults, or between men and women.

24.3 Conclusion on the scientific basis of EFSA's reference values

EFSA uses the average intake observed in populations with no apparent deficiency as the criterion for setting the AI, with a small balance study of long duration as supportive evidence.

EFSA noted that, in the balance study in four men mentioned in paragraph 24.2, biochemical changes or clinical symptoms suggestive of molybdenum deficiency were not observed after consuming 22 µg/day for 102 days (Table 83); it is possible that molybdenum balance can be achieved at even lower intakes.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

In humans, molybdenum-containing enzymes (molybdoenzymes: sulphite oxidase, xanthine oxidoreductase, aldehyde oxidase and mitochondrial amidoxime reducing component) are linked with a pterin (molybdopterin) as cofactor. These enzymes are involved in the catabolism of sulphur-containing amino acids and heterocyclic compounds, including purines, pyrimidines, pteridins and pyridines, and in the metabolism of aromatic aldehydes.
Clinical signs of molybdenum deficiency in otherwise healthy humans have not been observed. A syndrome suggestive of dietary molybdenum deficiency was reported in one 24-year-old male patient with Crohn's disease and short bowel syndrome, who had used total parenteral nutrition for 12 months. Deficiency of all molybdoenzymes occurs in people with molybdenum cofactor deficiency, a rare autosomal recessive syndrome with a defective hepatic synthesis of molybdenum cofactor. This genetic defect, for which three subtypes are known according to the gene affected, has been found in a variety of ethnic groups and all over the world. It is associated with feeding difficulties and seizures starting shortly after birth, neurological and developmental abnormalities, mental retardation, encephalopathy, ectopy of the lens and usually death at an early age.

Table 83. Molybdenum intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/Specific group	EFSA's reference
Absence of biochemical changes or symptoms suggestive of molybdenum deficiency	22 µg/day for 102 days	4 adult males	Turnlund et al. (1995a)

The Committee has no objections against the scientific basis of EFSA's AI, but notes that mean intakes may substantially exceed requirements, as deficiencies have not been reported in healthy subjects on normal diets.

24.4 Summary and conclusion

Table 84. Summary of the evaluation of EFSA's AI values for molybdenum

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (EFSA's) AI	Equal	EFSA's AI is already used in the Netherlands.
Scientific basis of EFSA's AIs	No objections	EFSA bases the AI on intake data, consistent with DACH. EFSA uses a small balance study of long duration as supportive evidence. IOM based their EAR on this balance study.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

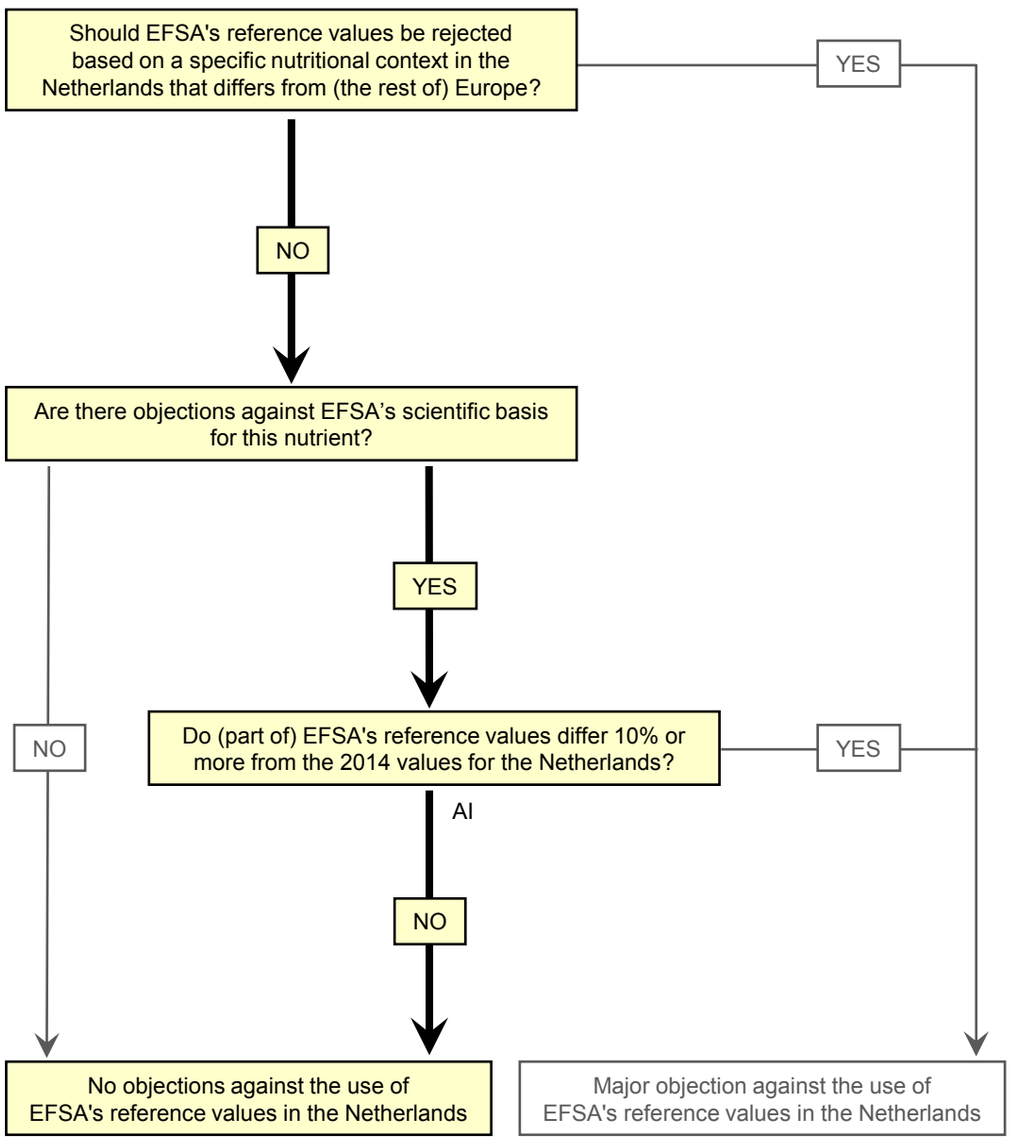
EFSA's AI for molybdenum is based on the lowest estimates of mean intakes and on supportive information from a small balance study. Mean intakes are assumed to be adequate because no signs of deficiency are reported in healthy subjects on normal diets. The mean intakes may substantially exceed requirements. However, there is no evidence available to define a more evidence-based AI.

The Committee has no objections against the scientific basis of EFSA's AI for adults, or the AI-value (Table 85).

Table 85. AI for molybdenum, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	65 µg/day

25 phosphorus



25.1 Overview and comparison of values

Table 86. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI		AR	CV	Main criterion
	Type	(mg/d)	(mg/d)	(%)	
EFSA 2015[13]	AI	550			Molar Ca:P intake ratio of 1.4:1 in combination with the PRI for calcium.
NCM 2014[37] = HCNL 2014[33]	RI	600	450	17%[a]	Intake of 400 mg/d maintains a plasma concentration of 0.8 mmol/L No substantial new data indicating that the RI should be changed. Therefore the NCM (2004) RI is maintained.
DACH 2015[38]	RI	700	580	10%	Refers to IOM (1997).
IOM 1997[43]	RDA	700	580	10%	Absorbed P needed to achieve serum P_i > 0.87 mmol/L. P-absorption efficiency = 62.5%.

[a] If the coefficient of variation was not specified in the report, it was calculated as 100% x [(PRI/RI/RDA – AR) / 2] / AR

Note that WHO/FAO did not evaluate phosphorus.

Table 86 shows that the NCM RI is 9% higher than EFSA's AI, whereas the RDAs by IOM and DACH are 27% higher than EFSA's AI.

25.2 Explanation of differences between reports

EFSA bases the AI on the intake of calcium assuming that phosphorus intake should be sufficient in relation to calcium intake. NCM, DACH and IOM base their AIs on a biochemical parameter of status.

EFSA bases the adequate intake of phosphorus on the molar ratio of calcium to phosphorus (Ca:P) in the body,[a] combined with the PRI for calcium.

EFSA assumes that the Ca:P molar ratio in the diet should be in line with the ratio in the whole body. EFSA does not take into account that the estimated average absorption is higher for phosphorus (55%-80%) compared to calcium (≤25%[19]), considering that data on phosphorus absorption are limited and vary substantially.

EFSA estimates that the Ca:P molar ratio in the body ranges from 1.4:1 to 1.9:1, based on data on whole-body Ca and P contents in Caucasian adults and on data on the Ca:P ratio in bones of healthy adults that are adjusted for the proportion of phosphorus found outside bone. As phosphorus intakes are high in Western countries, EFSA bases the AI for phosphorus on the lower end of this range: a molar Ca:P ratio of 1.4:1, corresponding to a weight ratio 1.81:1.[b] EFSA then calculates the AI for phosphorus using the PRI for calcium.[c]

IOM rejected the use of the Ca:P ratio of the diet as the basis for setting reference values, considering that this ratio has some utility under conditions of rapid growth, but no demonstrable relevance in adults. IOM notes that the ratio fails to take into account the differing absorption efficiencies for dietary calcium and phosphorus. Moreover, IOM considers that the ratio has little meaning or value, because of the relative surplus of phosphorus in the diet.[d] IOM considers that it would be inappropriate to conclude, simply on the basis of a departure from some theoretical Ca:P ratio, either that calcium intake should be elevated or, phosphorus intake reduced. IOM notes that, in balance studies in human adults, Ca:P molar ratios ranging from 0.08:1 to 2.40:1 (a 30-fold range) had no effect on either calcium balance or calcium absorption.

NCM and IOM based the AR on the intake needed to achieve a serum inorganic phosphorus concentrations (serum P_i) at the lower end of the normal range in adults.

- NCM's AR (450 mg/d) is based on the intake (400 mg/d) required to achieve a serum P_i of 0.8 mmol/L.
- IOM's AR (580 mg/d) is based on the intake (580 mg/d) required to achieve a serum P_i of 0.87 mmol/L. IOM notes that the value of serum P_i selected has a large impact on the intake estimate because, above the 'renal threshold', increases in intake result in a very gradual increase in serum P_i.[e]

[a] EFSA mentions that some observational studies in adults suggest that the Ca:P ratio in the diet may have a greater influence on bone health than the absolute intake of phosphorus, although other studies present conflicting evidence. EFSA furthermore refers to the review by Calvo and Tucker (2013) showing that in several animal models the combination of a high phosphorus intake with a low calcium intake is bad for bone health. The Committee notes that this has more relevance for an upper level for phosphorus intake than for the adequate intake.

[b] The use of the upper end of the range would have resulted in a substantially lower AI for phosphorus.

[c] The differentiation for calcium between adults aged 18-24 and >25 years (PRIs of 1000 and 950 mg calcium per day, respectively) is not applied to the AI for phosphorus which, for all adults aged 18 years or older, is set at 550 mg per day.

[d] This also applies to the habitual phosphorus intakes in Dutch adults aged 18-50 years. Estimates show that 95% of these men and women have intakes >1,200 and >900 mg phosphorus per day, respectively. Average intakes were 1,800 mg/day in men and 1.400 mg/day in women. The top 5% of these groups had intakes >2,500 mg/day (men) and >1,900 mg/day (women).[45]

[e] Note that at different places in the IOM report, 0.8-0.9 mmol/L and 0.87 mmol/L are mentioned to be the lower end of the normal adult range: the value of 0.87 mmol/L is the 2.5th percentile in adults (page 149 of the IOM report). Later in the report, IOM mentions that there is a grey zone between the empirical normal range and

EFSA rejected the use of serum P_i to derive the AI for phosphorus, considering that serum P_i is not a reliable biomarker of P intake and status: fasting serum P_i shows only minimal modifications, even in the presence of wide variations in intake,[a] serum P_i inadequately reflects body stores, and serum P_i is influenced by many factors other than phosphorus intake (age, sex, lactation, diurnal and seasonal variations, vitamin D status, apart from pathological conditions such as malabsorption syndromes and insulin-dependent diabetes mellitus).

Differences between older and younger adults and between men and women

None of the reports differentiate between older and younger adults, or between men and women.

25.3 Conclusion on the scientific basis of EFSA's reference values

The type of data used as a basis for the reference value of phosphorus is problematic: IOM rejects the use of the Ca:P ratio (which is the basis for EFSA's AI); but EFSA rejects the use of serum P_i (which is the basis of IOM's and NCM's AR).

values associated with evident deficiency disease: the lower end of the established normal range for serum P_i is 0.8 to 0.9 mmol/L, whereas clear evidence of bony or soft tissue dysfunction is not common until serum P_i levels drop below 0.3 to 0.5 mmol/L (page 159 of the IOM report).

[a] EFSA notes that, after the ingestion of a meal, serum P_i increases for a short period and then decreases again and remains within a relatively narrow range as a result of homeostatic mechanisms.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Phosphorus is involved in many physiological processes, such as in the cell's energy cycle, in regulation of the body's acid–base balance, as a component of the cell structure, in cell regulation and signalling, and in the mineralisation of bones and teeth. About 85% of the body's phosphorus is in bones and teeth, 14% is in soft tissues, including muscle, liver, heart and kidney, and only 1% is present in extracellular fluids. Phosphorus homeostasis is intricately linked to that of calcium because of the actions of calcium-regulating hormones, such as parathyroid hormone (PTH) and 1,25-dihydroxy-vitamin D (1,25(OH)2D), at the level of the bone, the gut and the kidneys.

Phosphorus deficiency presents as hypophosphataemia, i.e. serum phosphorus concentrations below 0.80 mmol/L in adults. This occurs only rarely because of inadequate dietary phosphorus intake, and is almost always due to metabolic disorders. The incidence of hypophosphataemia is high in certain subgroups of patients, such as those with sepsis, chronic alcoholism, major trauma or chronic obstructive pulmonary disease, and may also develop in kidney patients. Hypophosphataemia may also occur during the management of diabetic ketoacidosis. Mild hypophosphataemia can also occur as a common, generally asymptomatic, consequence of hyperparathyroidism.

Clinical symptoms of hypophosphataemia usually occur when serum phosphorus concentrations fall below 0.3 mmol/L, particularly when this is associated with total body phosphorus depletion. The nature and severity of the clinical symptoms depend on the extent of the phosphorus depletion and are highly variable, depending on the underlying cause and the individual patient's status. At a whole organism level, the effects of hypophosphataemia include anorexia, anaemia, muscle weakness, bone pain, rickets and osteomalacia, increased susceptibility to infection, paraesthesia, ataxia, confusion and even death.

Phosphorus deficiency is rare in healthy persons on normal diets. EFSA provides no information on phosphorus intake levels associated with the occurrence, correction or prevention of deficiencies. Almost all Dutch adults have intakes (far) above EFSA's AI.

EFSA's AI differs little from the current RDA which has been used in the Netherlands since 2014 (NCM's RI). Therefore, switching to EFSA's AI will have no implications, and the Committee has no objections against the use of EFSA's values in the Netherlands.

25.4 Summary and conclusion

Table 87. Summary of the evaluation of EFSA's AI values for phosphorus

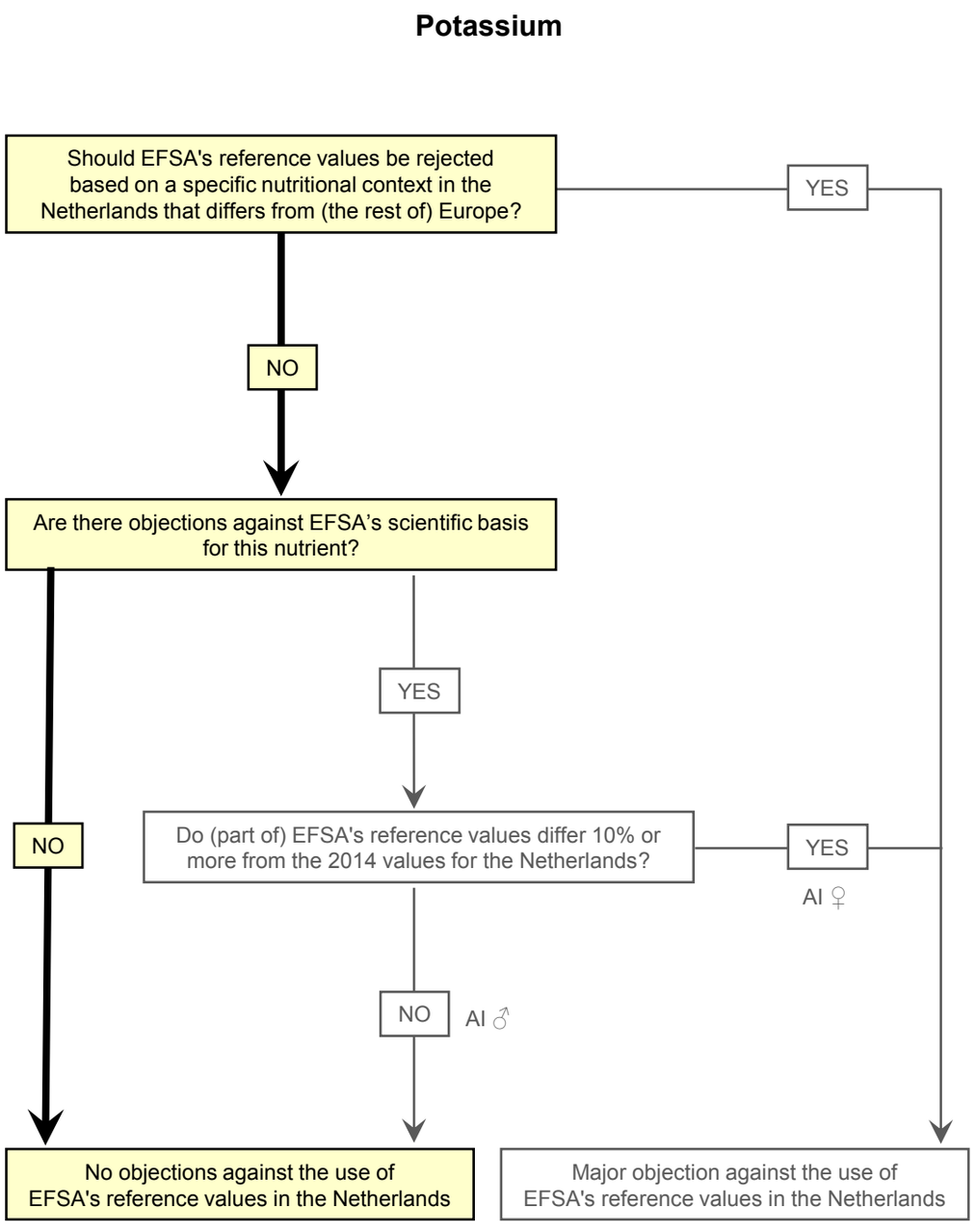
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (NCM's) RI	<10% lower	EFSA's AI is 8% lower HCNL's (=NCM's) RI.
Scientific basis of EFSA's AIs	Problematic	EFSA is not consistent with the reports used for comparison. IOM and NCM use serum inorganic phosphorus concentration.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with the reports used for comparison.

The Committee concludes that there is no consensus on the best outcome parameter to evaluate the phosphor intake and set reference values. As EFSA's AI differs little from the current RDA which has been used in the Netherlands since 2014 (NCM's RI), switching to EFSA's AI will have no implications. The Committee has no objections against the use of EFSA's values in the Netherlands and recommends using these values (Table 88).

Table 88. AR and PRI for phosphorus, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	550 mg/day

26 potassium



26.1 Overview and comparison of values

Table 89. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/RI		Main criterion
	Type	(g/d)	
EFSA 2016[11]	AI	3.5	• K-intake >3.5 g/d is beneficial for blood pressure. • K-intake <3.5 g/d is associated with a higher risk of stroke.
NCM 2014[37] = HCNL 2014[33]	RI	♂ 3.5 ♀ 3.1	A diet rich in potassium alone, or in combination with calcium and magnesium, might have a favourable effect on blood pressure and might reduce the risk of stroke and other cardiovascular endpoints. The reference values in NNR 2012 are kept unchanged compared to NNR 2004 because there are no new data to justify any major changes.
DACH 2015[38,60]	RI	2	K-intake needed for the maintenance of electrolyte homeostasis. The DACH report does not specify the origin of the value of 2 g/d.
IOM 2005[40]	AI	4.7	The AI for potassium is based on: • blunting the severe salt sensitivity prevalent in African-American men • decreasing the risk of kidney stones (a 3-year double-blind randomised controlled trial) • lowering of blood pressure in nonhypertensive individuals • decreasing bone loss The beneficial effects of potassium in these studies appears to be mainly from the forms of potassium that are found naturally in foods such as fruits and vegetables.

Note that WHO/FAO did not establish reference values for potassium. Table 89 shows that NCM's RI for men, which is the current Dutch reference value for men, equals EFSA's AI. EFSA uses the same value for men and women, whereas NCM uses an 11% lower value for women. The value used by DACH is 43% lower than EFSA's value. The IOM value is 34% higher than EFSA's value.

26.2 Explanation of differences between reports

EFSA, NCM and IOM base their AIs on the relationship with disease risk. DACH's RI is based on a factorial method.

EFSA concludes that there is evidence that a potassium intake of 3,500 mg/day has a beneficial effect on blood pressure in adults. EFSA furthermore considers that there is consistent evidence that potassium intakes below 3,500 mg/day are associated with a higher risk of stroke. EFSA derives an AI because the available data do not allow the determination of the AR and distribution of individual requirements. The AI-value is 3.5 gram per day.

NCM uses a line of reasoning which is similar to EFSA's.

IOM's AI for potassium is based on blunting the severe salt sensitivity in nonhypertensive African-American men (achieved at an intake of 4.7 g/day in a salt loading study with a total duration of 14 days) and on the association of intakes of 4.0-4.7 gram potassium per day with a lower risk of kidney stones in three prospective cohort studies (relative to intakes of 2.0, <2.9 and 3.8 g/d). Blood pressure studies in nonhypertensive individuals are supportive of this level of intake as a means to lower blood pressure. Epidemiological studies suggest that higher levels of potassium intake from foods are associated with decreased bone losses. IOM notes that the beneficial effects of potassium in these studies appear to be mainly from the forms of potassium that are found naturally in foods such as fruits and vegetables.

DACH's lower reference intake is based on the maintenance of electrolyte balance. The DACH report does not further elaborate on the origin of the value of 2000 mg/d.

Differences between older and younger adults

None of the reports differentiate between older and younger adults.

Sex differences

EFSA, DACH and IOM do not differentiate between men and women, but NCM has set a lower RI for women than for men.

26.3 Conclusion on the scientific basis of EFSA's reference values

The Committee agrees with the scientific basis of EFSA's AI (blood pressure and stroke risk), which is consistent with the conclusions on potassium in HCNL's report Dutch dietary guidelines 2015.[61]

EFSA does not explain why they did not make a difference between the AI for men and women, and the NCM do not explain why they did. The Committee considers that most randomised controlled trials and cohort studies reported conclusions only on mixed populations of men and women, and not on men and women separately. In their meta-analysis, Aburto et al. (2013) concluded that, because of this, they could not evaluate differences by sex.[62] D'Elia et al. (2011) did explore the influence of sex in their meta-analysis, based on the few studies that presented

results for men and women separately; they concluded that sex appeared to be no significant source of heterogeneity.[63] Therefore, the Committee agrees with EFSA's use of the same AI for men and women.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Potassium is the predominant osmotically active element inside cells. It plays a major role in the distribution of water inside and outside cells, assists in the regulation of the acid-base balance, and contributes to establishing a membrane potential which supports electrical activity in nerve fibres and muscle cells. Potassium has a role in cell metabolism, participating in energy transduction, hormone secretion, and the regulation of protein and glycogen synthesis. Potassium deficiency, presenting as hypokalaemia, is defined as a serum potassium concentration lower than 3.5 mmol/L. In general, deficiency may be caused by increased potassium losses via diarrhoea, vomiting, burns or excessive renal losses (owing, for example, to renal tubular acidosis, high secretion of mineralocorticoids, some diuretics) leading to low total body potassium. Hypokalaemia can also occur when total body potassium is normal in case of an intracellular shift of potassium. The most important causes of an intracellular shift include alkalosis, insulin excess, catecholamine excess and the genetic disease called familial periodic paralysis.
Hypokalaemia resulting from insufficient dietary intake is rare and may be associated with severe hypocaloric diets or occur as the result of an increased requirement needed for the synthesis of new tissue (e.g. muscle) during recovery from malnutrition.
Hypokalaemia is generally associated with increased morbidity and mortality, especially from cardiac arrhythmias or sudden cardiac death. When serum potassium concentration is <3 mmol/L, the prevalence of malignant ventricular arrhythmia has been observed to increase twofold in patients on diuretic treatment. The risk of atrial fibrillation is higher in hypokalaemic subjects compared to the general population. Other adverse consequences of hypokalaemia include polyuria, muscle weakness, decreased peristalsis possibly leading to intestinal ileus, mental depression and respiratory paralysis in severe cases.

26.4 Summary and conclusion

Table 90. Summary of the evaluation of EFSA's AI values for potassium

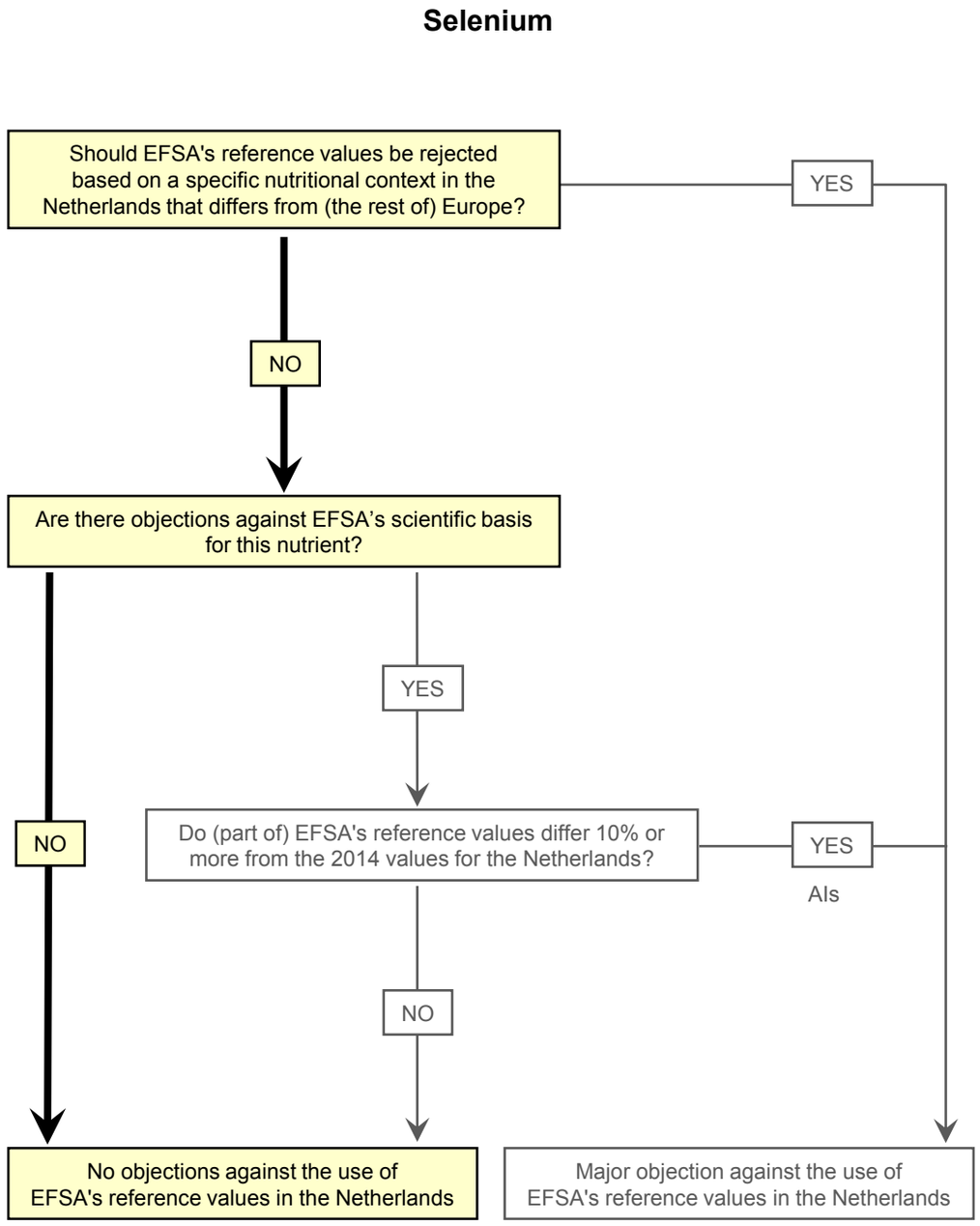
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (NCM's) RI	Equal for men, higher for women	EFSA's AI is equal to HCNL's (=NCM's) RI for men, and 11% higher than HCNL's (=NCM's) RI for women.
Scientific basis of EFSA's AIs	No objections	Consistent with NCM and HCNL; and partly consistent with IOM. DACH is not consistent with the other reports.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	Consistent with IOM and DACH, but not with NCM. NCM set a lower value for women than for men, but did not explain why.

The Committee agrees with the scientific basis of EFSA's AI and with EFSA's AI for all adults and recommends using this value in the Netherlands (Table 91).

Table 91. AI for potassium, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (mg/d)	3.5 g/d

27 selenium



27.1 Overview and comparison of values

Table 92. Overview of the reference values for adults and the criteria on which these values are based

Report	PRI/RDA/AI/ RI (µg/d)		AR (µg/d)	CV (%)	Main criterium
	Type	♂, ♀	♂, ♀	♂, ♀	
EFSA 2014[22]	AI	70			Function parameter: the selenium intake level required for plasma SEPP1 to reach a plateau value.
NCM 2014[37] = HCNL 2014[33]	RI	60, 50	35, 30	36, 33	Function parameter: optimal plasma SEPP1.
DACH 2015[38,64]	AI	70, 60			Function parameter: the selenium intake level required for plasma SePP [1] concentration to reach a plateau value. AI-values are based on 1 µg/kg/d, with body weights. ♂ 70.7 kg, ♀ 60.0 kg.
IOM 2000[2]	RDA	55	45	10	Function parameter: maximising plasma GPx activity. No difference between values for men and women, because of greater susceptibility of women to develop Keshan disease.
WHO/FAO 2004[44]					Function parameter: maximising plasma GPx activity.
19-65 yr	RI	34, 26	27, 20	12.5	♂ AR 0.42 µg/kg/d; body weight 65 kg. ♀ AR 0.37 µg/kg/d; body weight 55 kg.
≥66 yr	RI	33, 25	27, 20	12.5	♂ AR 0.41 µg/kg/d; body weight 64 kg. ♀ AR 0.37 µg/kg/d; body weight 54 kg.

[a] Note that DACH mentions SePP instead of SEPP1.

Table 92 shows that EFSA's AI is higher than the RI/AI/RDA in other reports (NCM -21%, DACH -7%, IOM -21% and WHO/FAO -57% relative to EFSA).

27.2 Explanation of differences between reports

Most reports base their reference values on biochemical parameters of function: either SEPP1 (EFSA, NCM and DACH[a]) or GPx activity (IOM and WHO/FAO).

EFSA, NCM and DACH use the same function parameter: the selenium intake level required for plasma SEPP1 to reach a plateau value.

EFSA refers to three studies: a Chinese study (Xia et al., 2010) and a study from New Zealand (Duffield et al., 1999), including both men and women, and a study from Finland, including only men (Persson-Moschos et al., 1998). The EFSA Panel noted that there were uncertainties related to the intake estimates, the extrapolation of results from Chinese individuals to the European population, and the extrapolation of findings regarding supplemental L-selenomethionine to dietary selenium. The Finnish study indicated a higher adequate selenium intake compared to the studies from China and New Zealand, explaining why EFSA's PRI is higher than the RI by NCM.

EFSA noted that measures of glutathione peroxidases (GPxs) activity can be used as a biomarker of selenium function, but that the activity of GPxs reaches a steady state with levels of selenium intake that are lower than those required for the levelling off of SEPP1 (Xia et al., 2010).[a] EFSA considered that SEPP1 is the most informative biomarker of selenium function on the basis of its role in selenium transport and metabolism and its response to different forms of ingested selenium. EFSA assumed that this levelling off is indicative of an adequate supply of selenium to all tissues, and therefore, of the fulfilment of selenium requirement. However, the EFSA Panel notes that evidence on associations between plasma SEPP1 concentration and health outcomes is insufficient; this is part of the research recommendations expressed by the EFSA Panel in the Opinion.

EFSA derived an AI instead of an AR and PRI, because of uncertainties in estimates of background dietary selenium intake, the extrapolation of results from Chinese individuals to the European population, and the extrapolation of findings on L-selenomethionine to dietary selenium.

NCM and DACH refer to only one of the three studies used by EFSA: the Chinese study (Xia et al., 2010). DACH's AI is higher than the RI by NCM, because DACH rounded the adequate selenium intake per kg body weight per day upwards.

IOM and WHO/FAO based the AR for selenium on the intake required for maximal plasma GPx activity. The values are based on the results of two intervention studies that were done in different countries but had similar designs. The Chinese study (Yang et al., 1987) suggests that a plateau of plasma GPx activity was reached with a selenium intake of 41 µg/d (this

[a] Xia et al. (2010) reports that optimisation of SEPP1 required a higher intake of selenium than maximising plasma GPx activity. The Committee notes, however, that Duffield et al. (1999) reported the opposite.

was the lowest intake at which the activity of plasma GPx activity reached a plateau after 4 months). With a weight adjustment for North American males, the selenium intake was 52 µg/d. The New Zealand study (Duffield et al., 1999) can be interpreted to suggest an EAR in the vicinity of 38 µg/d (this was the intake necessary to reach two-thirds of maximum GSHPx activity). IOM choose to use the average of those estimates, 45 µg/d, as the EAR.

IOM did not use SEPP for establishing the reference values, because an assay for SEPP was not widely available at that time and the data for selenoprotein P were insufficient to estimate a dietary requirement.

EFSA considered that measures of glutathione peroxidases (GPxs) activity can be used as a biomarker of selenium status, but noted the following limitations: (1) GPxs activity reaches a steady state with levels of selenium intake that are lower than those required for the levelling off of SEPP1,[a] (2) plasma GPx3 activity probably reflects selenium status in the kidney rather than in the whole body, (3) the relationship of intake with GPxs activity is affected by the chemical nature of the selenium, the baseline selenium status and the presence of certain diseases or polymorphisms, and (4) different expression units for GPxs activity limit comparisons between studies.

Differences between older and younger adults

EFSA, NCM, DACH and IOM do not differentiate between older and younger adults. WHO/FAO's RI-values for adults >66 years are almost the same as for adults 18-65 years.

Sex differences

EFSA and IOM did not differentiate between men and women, whereas NCM, DACH and WHO/FAO did.

One publication used by EFSA indicating that a habitual dietary selenium intake of 50-60 µg/day is not sufficient for SEPP1 concentration to level off, referred to a study in men only (Persson-Moschos et al., 1998). Both other studies used by EFSA included women and indicated that 50-60 µg/day may be sufficient (Xia et al., 2010; Duffield et al., 1999). EFSA, NCM and DACH mention an estimated requirement per kilogram body weight based on one study (Xia et al., 2010), however, this estimate appears to be calculated by dividing the estimated requirement of 49 µg/day by the average body weight of 58 kg over all 95 subjects (43 men and 52 women). The two publications that included both men and women do not present results in µg/day or in µg/kg/day for men and women separately.

It therefore appears to be appropriate to set an AI without making a sex difference.

[a] The Committee already noted on the previous page that, on this issue, Xia et al. (2010) and Duffield et al. (1999) reported the opposite.

27.3 Conclusion on the scientific basis of EFSA's reference values

EFSA considers that there is insufficient evidence on associations between plasma SEPP1 concentration and health outcomes. EFSA describes that the association between SEPP1 concentration and health outcomes has been investigated in only two nested case–control studies (Persson-Moschos et al., 2000; Epplein et al., 2014); both suggested an inverse association between plasma SEPP1 concentration and overall cancer risk, and in particular, risk of cancer of the digestive and respiratory tract. The EFSA Panel considered that these and other findings on selenium and chronic diseases cannot be used to derive DRVs, but that they are compatible with the DRVs derived based on the levelling off of plasma SEPP1.[a] Note that selenium deficiency (Keshan disease) is reported at intakes <15 µg/day (Table 93).

Table 93. Selenium intake levels associated with the occurrence, correction or prevention of deficiencies, as described by EFSA

Clinical manifestation associated with deficiency	Associated intake	Subjects/Specific group	EFSA's reference
Keshan disease	around 15 µg/day	Chinese subjects with low selenium intake from an area with endemic Keshan disease	Ge and Yang, 1993; NNR; SCF
Absence of Keshan disease	>17 µg/day	Population groups in China	Yang et al., 1987

[a] After the publication of EFSA's report, findings of the European Prospective Investigation into Cancer (EPIC) described an association between higher plasma SEPP and a lower cancer risk.[65,66]

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

A total of 25 selenoproteins have been identified in humans. These have a variety of functions, including antioxidant effects, T-cell immunity, thyroid hormone metabolism, selenium homeostasis and transport, and skeletal and cardiac muscle metabolism. Selenoprotein P (SEPP1) plays a central role in selenium supply to tissues and participates in the regulation of selenium metabolism in the organism.

Selenium deficiency affects the expression and function of selenoproteins. Clinical manifestations of selenium deficiency are poorly defined. Symptoms observed in patients receiving selenium-free total parenteral nutrition (TPN) include skeletal myopathy and muscle weakness. Several cases of cardiomyopathy were reported, although selenium deficiency appeared to be only one of the aetiological factors in these subjects. Pseudoalbinism and red blood cell macrocytosis were also observed in children receiving selenium-free TPN.

There are concerns that combined low intake of iodine and selenium contributes to the risk of myxoedematous cretinism, described in the endemic goitre area of central Africa.

Selenium deficiency is also involved in the degeneration of organs and tissues leading to the manifestation of Keshan and Kashin-Beck diseases.

Keshan disease is an endemic cardiomyopathy occurring mainly in children and young women. It is apparent in population groups in China with particularly low selenium intake (around 15 µg/day). Keshan disease is not yet fully understood, but there is some evidence for a dual aetiology, including both selenium deficiency and infection with an enterovirus.

Kashin-Beck disease is a chronic degenerative osteochondropathy occurring in pre-adolescence or adolescence in selenium-deficient areas. It is endemic in some areas in China, but also in Mongolia, Siberia and North Korea. The aetiology of the disease is largely unknown. Possible risk factors seem to include mycotoxins in food, humic and fulvic acids in drinking water and selenium and iodine deficiency.

The Committee has no objections against the scientific basis of EFSA's AI. The Committee agrees with EFSA that there is insufficient evidence on associations between the levelling off of plasma SEPP1 concentration and

health outcomes, although limited results from observational studies indicate that the concentration of plasma SEPP1 may be inversely associated with cancer risk. The Committee notes that other reports established lower AI-values based on the levelling off of plasma SEPP1 concentration. The Committee has no major objections against EFSA's AI, but notes that the evidence that EFSA's relatively high AI for selenium will result in health gain compared to the lower values in some other reports, is limited.

27.4 Summary and conclusion

Table 94. Summary of the evaluation of EFSA's AI values for selenium

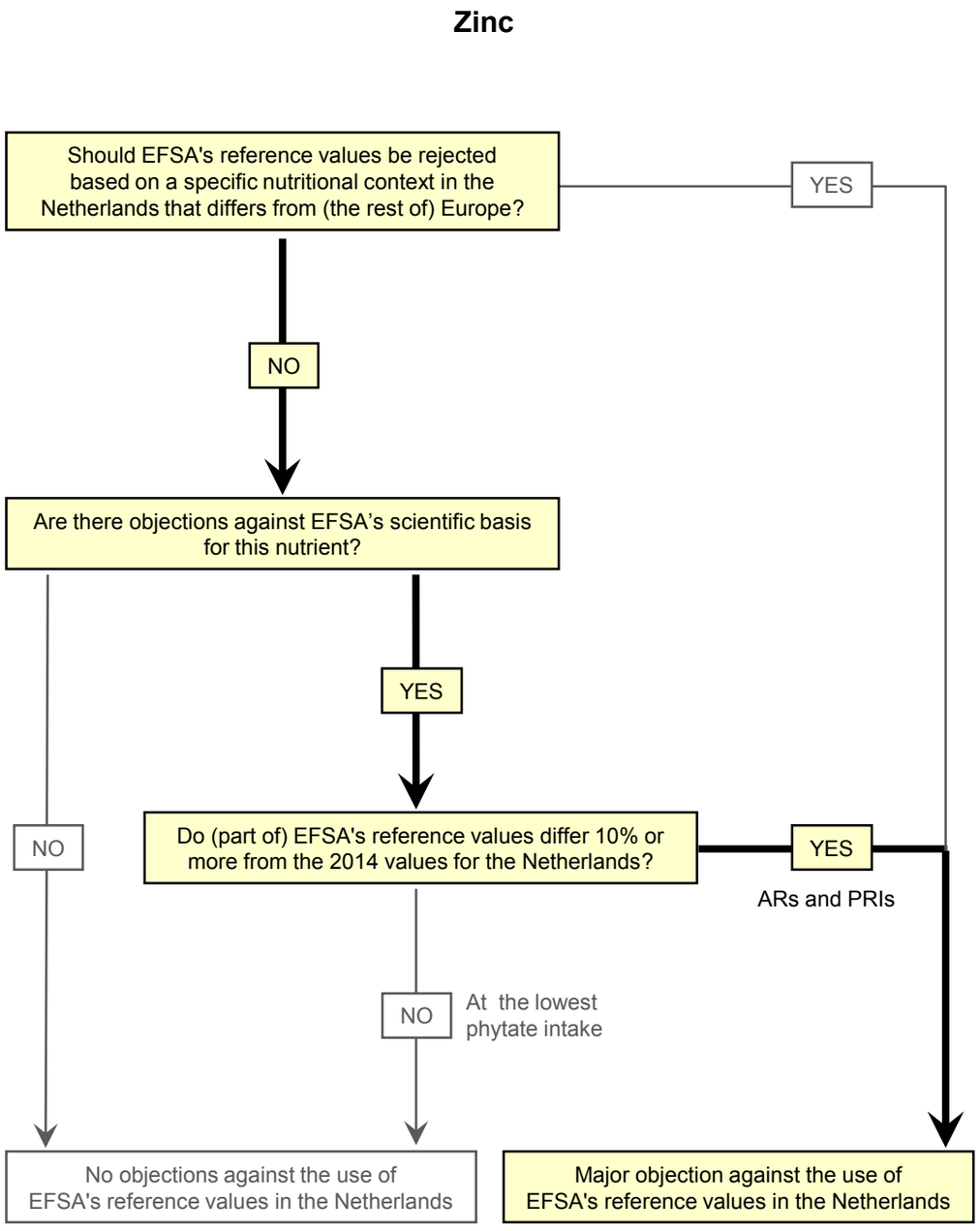
Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's AIs compared to HCNL's (=NCM's) RI	Higher	EFSA's AI is 17% higher than HCNL's (=NCM's) RI for men and 40% higher than HCNL's (=NCM's) RI for men.
Scientific basis of EFSA's AIs	No objections	EFSA, NCM and DACH use SEPP1, whereas IOM and WHO/FAO use maximal plasma GPx activity.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Not applied by EFSA	EFSA and IOM do not differentiate between men and women, whereas NCM, DACH and WHO/FAO do.

The Committee has no objections against the scientific basis of EFSA's AI, or EFSA's AI-value, and recommends using EFSA's AI in the Netherlands (Table 95). The Committee notes that the evidence on which EFSA based their relatively high AI-value, is limited.

Table 95. AI for selenium, recommended for the Netherlands

	Men and women ≥18 years
Adequate intake (AI)	70 µg/day

28 zinc



28.1 Overview and comparison of values

Table 96. Overview of the reference values for adults and the criteria on which these values are based.

Report	PRI/RDA/RI (mg/d)			AR (mg/d)		CV (%)	Main criterion	Physiological requirement (mg/d)		Absorption (%)
	Type	♂	♀	♂	♀			♂	♀	
EFSA 2014[21] Phytate intake: 300 mg/day 600 mg/day 900 mg/day 1,200 mg/day	 PRI PRI PRI PRI	 9.4 11.7 14.0 16.3	 7.5 9.3 11.0 12.7	 7.5 9.3 11.0 12.7	 6.2 7.6 8.9 10.2	[a]	Factorial approach using regression analysis on data of individuals to estimate: 1) physiological requirement for absorbed Zn; 2) zinc intake needed to meet this physiological requirement, estimated for 4 phytate intake levels. PRI is based on the 97.5th percentile of reference weight.	3.2	2.9	Using regression analysis
(Averages: [b]		*12.9*	*10.1*	*10.1*	*8.2)*					
NCM 2014[37] = HCNL 2014[33]	RI	9	7	6.4	5.7	15	Factorial method. Estimates for endogenous Zn losses (sweat, urine, sperm, menses,) adopted from IOM: ♂ 1.27 mg/d; ♀ 1.0 mg/d, but intestinal losses estimated to be 1.4 mg/d (♂ & ♀).	2.27	2.0	40%

Report	PRI/RDA/RI (mg/d)			AR (mg/d)		CV (%)	Main criterion	Physio-logical require-ment (mg/d)		Absorp-tion (%)
	Type	♂	♀	♂	♀			♂	♀	
DACH 2015[38]	RI	10.0	7.0	7.5	5.5	15	Factorial method.	2.2	1.6	30%
IOM 2001[41]	RDA	11	8	9.4	6.8	10	Factorial method. Physiological requirement for absorbed zinc is the point at which absorbed Zn equals the endogenous losses (sweat, urine, sperm, menses: ♂ 1.27 mg/d; ♀ 1.00 mg/d). The EAR is estimated by regression analysis on group mean values.	3.84	3.3	Using regres-sion analysis
WHO/FAO 2004[44] Bioavailability:							Physiological requirement for absorbed zinc was	1.4	1.0	
High	RI	4.2	3.0	2.8	2.0	25	defined as losses			High
Moderate	RI	7.0	4.9	4.7	3.2	25	during the early			Moderate
Low	RI	14.0	9.8	9.4	6.5	25	phase of Zn depletion before reductions in excretion take place.			Low
	(Averages:[b]	*8.4*	*5.9)*							

[a] EFSA estimated PRI directly based on the 97.5th percentile of reference body weights (thus did not estimate PRI as AR + 2xCV).

[b] These averages were not presented in the report, but calculated by the Committee for the comparison with other reports.

Table 96 shows that, in comparison to the average of PRI-values for four levels of phytates intake presented by EFSA, the RIs in other reports are substantially lower (NCM -30%; DACH -26%; IOM -17%; WHO/FAO -48%). Values by IOM and values for males by DACH are within the range presented by EFSA, whereas values by NCM and WHO/FAO and the values for females by DACH are lower than this range.

28.2 Explanation of differences between reports

All reports use factorial methods based on estimates of physiological requirements (the requirements for absorbed zinc) and absorption (the zinc intake needed to meet this physiological requirement). EFSA performed regression analyses on data at the level of the individual and based the PRI on the 97.5th percentile of reference weight. IOM performed regression analyses which were similar in nature, but IOM used group mean values. Other reports based their estimates on the factorial method, using average values.

Differentiation based on phytate intake[a]

EFSA does not set one, but four PRIs/ARs for zinc per sex, because of the large variation in requirement related to different phytate intakes. When phytate intake is high, the requirement is estimated to be about 70% higher than when phytate intake is low.

EFSA reports that the range of dietary phytate intake in the few European countries for which English-language data are available varies widely.

[a] Phytate can also decrease the absorption of other minerals, such as iron and calcium.

EFSA notes that ranges of phytate intakes by adults have been estimated for a mixed diet (300 to 800 mg/day), mixed diets with a high proportion of unrefined cereal grain products and legumes (700 to 1,400 mg/day), and vegetarian diets (1,600 to 2,500 mg/day). The wide variation in phytate intake can partially be explained by differences in dietary patterns within and between countries, and partially by methodological problems associated with phytate intake assessment.

NCM and DACH acknowledge the differences in bioavailability, but set their reference values based on an average bioavailability value.

WHO sets reference values for three levels of bioavailability (high, moderate and low).

Differences between older and younger adults

None of the reports differentiate the ARs and PRI/RI/RDAs between younger and older adults

Sex differences

All reports differentiate the ARs and PRI/RI/RDAs between men and women.

28.3 Conclusion on the scientific basis of EFSA's reference values

The Committee considers that EFSA may over-emphasise the role of phytate intake in zinc absorption, because the inhibitory effect of phytate on mineral bioavailability is dependent of many factors, such as pH, content of minerals and phytate, solubility of phytates and concentration of enhancers or inhibitors.[67,a] The Committee notes that phytate intake cannot be estimated in the Netherlands yet, because phytate is not included in the Dutch food composition table.

Furthermore, EFSA estimates the PRIs for adults as the zinc requirement of individuals with a body weight at the 97.5th percentile for reference body weights for men and women, i.e. 79.4 kg for men and 68.1 kg for women. EFSA considers that body weight is a strong determinant of the requirement for zinc, and therefore, this approach would have less uncertainty than the mathematical application of a CV of between 10 and 20%. The Committee notes that the concept of a percentile of *reference* body weights is unclear and not further explained by EFSA; body weights in the adult populations differ much more than indicated by this 97.5th percentile.

The Committee considers that the average of EFSA's values is high relative to the reports used for comparison, including the NCM values which are now used in the Netherlands, which is undesirable because of the narrow margin between the PRI and the upper level (25 g/day).

EFSA provides no information on zinc intake levels associated with the occurrence, correction or prevention of deficiencies. Based on these three arguments, the Committee has objections against the scientific basis of EFSA's reference values.

[a] Schlemmer et al. (2009) conclude that prediction of the bioavailability of minerals from diets just based on the phytate content in foods is not reliable, as all other factors involved in the phytic acid–mineral interaction have to be taken into consideration.

Background information – a summary of the information provided by the EFSA report – on the function of the nutrient, the occurrence of clinical deficiency and deficiency symptoms

Zinc has a wide array of vital physiological functions and is ubiquitous within every cell in the body. Three general functional classes (structural, regulatory, and catalytic) define zinc's role in biology. There is protection against deficiency by homeostatic mechanisms at both a whole body and a tissue level.
It is the abundance that is thought to be the reason why it has proved so challenging to link zinc deficiency with specific symptoms (infants with acrodermatitis enteropathica are the exception: for this group, specific symptoms of severe zinc deficiency have been observed).
Clinical features of zinc deficiency are non-specific. Mild to moderate dietary zinc depletion is a cause of several non-specific features including growth retardation, depressed immune function with susceptibility to infections, delayed wound healing, loss of appetite and loss of cognitive function. Severe restriction of dietary zinc is a cause of other clinical features including skin rashes.
Acute acquired zinc deficiency states have been extensively documented, primarily in patients dependent on intravenous nutrition lacking zinc. From the IOM report it can be added that individuals with malabsorption syndromes including sprue, Crohn's disease, and short bowel syndrome are at risk of zinc deficiency due to malabsorption of zinc and increased urinary zinc losses.

28.4 Summary and conclusion

Table 97. Summary of the evaluation of EFSA's AR and PRI values for zinc

Main findings, used for the conclusion		
Aspect	**Conclusion**	**Comment**
EFSA's ARs compared to HCNL's (=NCM's) AR	Higher	EFSA's ARs are 15-100% higher than HCNL's (NCM's) ARs for men and 10-80% higher than HCNL's (NCM's) ARs for women, dependent on the phytate level considered.
EFSA's PRIs compared to HCNL's (=NCM's) RIs	Higher	EFSA's PRIs are 5-80% higher than HCNL's (NCM's) RIs for men and women, dependent on the phytate level considered.
Scientific basis of EFSA's ARs	Objections	The Committee considers that EFSA may over-emphasise the role of phytate intake in zinc absorption. The Committee considers that EFSA's use of the 97.5th percentile of reference body weights for setting the PRIs, is unclear and not explained by EFSA.
Other findings		
Aspect	**Conclusion**	**Comment**
Differentiation between younger and older adults	Not applied by EFSA	Consistent with the reports used for comparison.
Differentiation between men and women	Applied by EFSA	Consistent with the reports used for comparison.

The Committee recommends maintaining HCNL's (NCM's) ARs and RDAs (Table 98).

Table 98. AR and PRI for zinc, recommended for the Netherlands

	Men ≥18 years	Women ≥18 years
Average requirement (AR)	6.4 mg/d	5.7 mg/d
Population reference intake (PRI)	9 mg/d	7 mg/d

29 summary

29.1 The 2018 reference values for the Netherlands

As described in the introduction to this background document (paragraph 1.1), the point of departure of this evaluation of the Dutch reference values was to adopt EFSA's dietary reference values for use in the Netherlands, unless there were major objections against these values. The Committee considered three key questions: (1) Should EFSA's reference values be rejected based on a specific nutritional context in the Netherlands that differs from (the rest of) Europe? (2) Do (some of) EFSA's reference values differ 10% or more from the 2014 values for the Netherlands? (3) Are there objections against the scientific basis for EFSA's reference value(s) for this nutrient?

For most nutrients, the evaluations in this report resulted in the recommendation to adopt EFSA's reference values for use in the Netherlands (Table 99, for more information see Annex C).

- The Committee adopts EFSA's reference values for 16 micronutrients: thiamin, riboflavin, niacin, pantothenic acid, vitamin E, vitamin K1, biotin, choline, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium and selenium.
- Regarding trivalent chromium, the Committee adopts EFSA's conclusion to set no reference value.

For two nutrients, the conclusions by EFSA were accepted partially.

- For calcium, the Committee adopts EFSA's reference values for calcium for adults aged between 18 and 50 years, and for men aged 51 to 70 years. However, for women aged 51 to 70 year and for adults older than 70 years, the Committee maintains the reference values which have been used since 2000. In the Netherlands, it is recommended that these groups of older adults use vitamin D supplements. A calcium intake higher than EFSA's PRI is required for these vitamin D supplements to be effective in reducing the risk of bone fractures.
- For vitamin A, the Committee does adopt EFSA's method for estimating the average requirement, but uses the higher Dutch reference weights instead of EFSA's reference weights. Therefore, the reference values proposed for vitamin A also differ from EFSA's values. Furthermore, the Committee does not support EFSA's choice regarding the conversion factors for carotenes (EFSA expresses the reference values as retinol equivalents), but recommends expressing the reference values as retinol activity equivalents instead.

The Committee does not adopt EFSA's values for 8 nutrients:

- For 7 micronutrients, the Committee maintains the reference values that have been used in the Netherlands since 2014: vitamin B6, folate, vitamin B12, vitamin C, vitamin D, copper, and zinc, based on objections against the scientific basis of EFSA's reference values.

- For fluoride, the Committee also does not accept EFSA's reference value. Based on a nutritional context in the Netherlands that differs from (the rest of) Europe: in the Netherlands, fluoride intake is not considered necessary for caries prevention because of the use of fluoride-containing dental-hygiene products (in adults: toothpaste). Therefore, the Committee does not consider it appropriate to apply a dietary reference intake in the Netherlands.

Table 99. Overview of the old and new reference values for the Netherlands[a]

Nutrient	The 2018 Dutch reference values			2018 versus 2014 Dutch values	The 2014 Dutch reference values		
	Reference value		Origin		Reference value		Origin
Vitamin A as retinol activity equivalents (RAEs)	AR♂ AR♀ PRI♂ PRI♀	615 µg RAE/d 525 800 680	This report	Changed	AR♂ AR♀ PRI♂ PRI♀	600 µg RAE/d 500 900 700	NCM 2014
Thiamin	AR PRI	0.072 mg/MJ 0.1	EFSA 2016	Changed	AR PRI	0.8 mg/d 1.1	HCNL 2000
Riboflavin	AR PRI	1.3 mg/d 1.6	EFSA 2017	Changed	AR♂ AR♀ PRI♂ PRI♀	1.1 mg/d 0.8 1.5 1.1	HCNL 2000
Niacin	AR PRI	1.3 mg/MJ 1.6	EFSA 2014	Changed	AR♂ AR♀ PRI♂ PRI♀	12 mg/d 9 17 13	HCNL 2000
Pantothenic acid	AI	5 mg/d	EFSA 2014	Unchanged	AI	5 mg/d	HCNL 2000
Vitamin B6	**19-50 years:**				**19-50 years:**		
	AR PRI	1.1 mg/d 1.5	HCNL 2003	Unchanged	AR PRI	1.1 mg/d 1.5	HCNL 2003
	>50 years:				**>50 years:**		
	AR♂ AR♀ PRI♂ PRI♀	1.3 mg/d 1.1 1.8 1.5	HCNL 2003	Unchanged	AR♂ AR♀ PRI♂ PRI♀	1.3 mg/d 1.1 1.8 1.5	HCNL 2003
Folate[b]	AR PRI	200 µg/d 300	HCNL 2003	Unchanged	AR PRI	200 µg/d 300	HCNL 2003

Nutrient	The 2018 Dutch reference values			2018 versus 2014 Dutch values	The 2014 Dutch reference values		
	Reference value		Origin		Reference value		Origin
Vitamin B12[c]	AR PRI	2.0 µg/d 2.8	HCNL 2003	Unchanged	AR PRI	2.0 µg/d 2.8	HCNL 2003
Vitamin C	AR♂ AR♀ PRI	60 mg/d 50 75 (♂&♀)	NCM 2014	Unchanged	AR♂ AR♀ PRI	60 mg/d 50 75 (♂&♀)	NCM 2014
Vitamin D[d]	**18-69 years:**[e]				**18-69 years:**		
	AI	10 µg/d	HCNL 2012	Unchanged	AI	10 µg/d	HCNL 2012
	≥70 years:[f]				**≥70 years:**		
	AR PRI	10 µg/d 20	HCNL 2012	Unchanged	AR PRI	10 µg/d 20	HCNL 2012
Vitamin E as α-tocopherol	AI♂ AI♀	13 mg/d 11	EFSA 2015	Changed	AR♂ AR♀ PRI♂ PRI♀	6 mg/d 5 10 8	NCM 2014
Vitamin K1 (phylloquinone)	AI	70 µg/d	EFSA 2017	Unchanged	AI	70 µg/d	EFSA 2017
Biotin	AI	40 µg/d	EFSA 2014	Unchanged	AI	40 µg/d	EFSA 2014
Choline	AI	400 mg/d	EFSA 2016	Changed	No reference value		
Calcium	**18-24 years:**				**19-49 years (♂&♀):**		
	AR PRI	860 mg/d 1,000	EFSA 2015	Changed	AI	1,000 mg/d	HCNL 2000
	25-49 years (♂&♀) and men 50-69 years:						
	AR PRI	750 mg/d 950	EFSA 2015	Changed			
	Women 50-69 years:				**50-69 years (♂&♀):**		
	AI	1,100 mg/d	HCNL 2000	Unchanged	AI	1,100 mg/d	HCNL 2000
	≥70 years (♂&♀):				**≥70 years (♂&♀) :**		
	AI	1,200 mg/d	HCNL 2000	Unchanged	AI	1,200 mg/d	HCNL 2000
Chromium III	No reference value		EFSA 2014	Unchanged	No reference value		
Copper	AR PRI	0.7 mg/d 0.9	NCM 2014	Unchanged	AR PRI	0.7 mg/d 0.9	NCM 2014
Fluoride	No reference value		This report	Changed	AI♂ AI♀	3.4 mg/d 2.9	EFSA 2013
Iodine	AI	150 µg/d	EFSA 2014	Changed	PRI AR	150 µg/d 100	NCM 2014

Nutrient	The 2018 Dutch reference values			2018 versus 2014 Dutch values	The 2014 Dutch reference values		
	Reference value		Origin		Reference value		Origin
Iron	**Men**				**Men**		
	AR	6 mg/d	EFSA 2015	Changed	AR	7 mg/d	NCM 2014
	PRI	11			PRI	9	
	Women premenopause				**Women premenopause**		
	AR	7 mg/d	EFSA 2015	Changed	AR	9 (10?[g]) mg/d	NCM 2014
	PRI	16			PRI	15	
	Women postmenopause				**Women postmenopause**		
	AR	6 mg/d	EFSA 2015	Unchanged	AR	6 mg/d	NCM 2014
	PRI	11		Changed	PRI	9 (8?[a])	
Magnesium	AI♂	350 mg/d	EFSA 2015	Changed	AI♂	350 mg/d	NCM 2014
	AI♀	300			AI♀	280	
Manganese	AI	3.0 mg/d	EFSA 2013	Unchanged	AI	3.0 mg/d	EFSA 2013
Molybdenum	AI	65 µg/d	EFSA 2013	Unchanged	AI	65 µg/d	EFSA 2013
Phosphorus	AI	550 mg/d	EFSA 2015	Changed	AR	450 mg/d	NCM 2014
					PRI	600	
Potassium	AI	3.5 g/d	EFSA 2016	Changed	AI♂	3.5 g/d	NCM 2014
					AI♀	3.1	
Selenium	AI	70 µg/d	EFSA 2014	Changed	AR♂	35 µg/d	NCM 2014
					AR♀	30	
					PRI♂	60	
					PRI♀	50	
Zinc	AR♂	6.4 mg/d	NCM 2014	Unchanged	AR♂	6.4 mg/d	NCM 2014
	AR♀	5.7			AR♀	5.7	
	PRI♂	9			PRI♂	9	
	PRI♀	7			PRI♀	7	

[a] All abbreviations in the table are explained in the glossary (Annex B).
[b] Note that women who wish to conceive are advised to use a supplement containing 400 µg/d of folic acid, starting at least four weeks prior to conception until the eighth week of pregnancy, in addition to these reference values.
[c] In the Netherland, it is recommended that adults on a vegan diet use supplemental vitamin B12 to achieve an adequate supply of this vitamin.[53]
[d] In most people, vitamin D supply is met partly by cutaneous vitamin D synthesis and partly by dietary intake. The reference values for vitamin D intake refer to conditions of *minimal* cutaneous vitamin D synthesis.[34]
[e] In the Netherlands, it is recommended that adults with dark skin or who do not spend enough time outdoors, women who wear a veil, and all women aged 50-70 years use a daily supplement with 10 µg vitamin D to ensure an adequate vitamin D supply.[34]
[f] In the Netherlands, it is recommended that adults over 70 years use a daily supplement with 20 µg vitamin D to ensure an adequate vitamin D supply.[34]
[g] For iron, NCM's AR for premenopausal women and NCM's RI for postmenopausal women are not clear. This is described in footnotes in paragraph 21.2, where the differences between the ARs for premenopausal women and the PRIs for postmenopausal women are explained.

29.2 Scientific basis for the 2018 Dutch reference values

The scientific basis for the different reference values varies (Table 100). For some nutrients, the reference values are based on the intake required to achieve a certain cut-off value for a biomarker of status or function. Other reference values are based on a factorial method in which the estimated averages for specific underlying aspects ('factors') are combined to calculate the reference value; the estimates for the factors generally originate from different studies. A third approach is the balance method, which follows a similar line of reasoning as the factorial method; these studies often use isotopes and produce estimates at the level of the individual. As a fourth approach, reference values can be based on the clinical effects of different intake levels in intervention studies. For some nutrients none of these four methods are available or can be used to establish the reference value. In such cases, the reference values are based on intake data alone, often based on intake levels of healthy individuals on normal diets with no signs of deficiency.

Biomarkers of status or function

The type of data that is predominantly used as the basis for the reference values, especially for vitamins, are biomarkers of status or function, or both. Reference values for 11 micronutrients are based on this type of data.

Table 100. Scientific basis of the 2018 Dutch reference values for specific nutrients[a]

Nutrient	Biomarker		Factorial method or balance data		Intervention studies (clinical effect)	Intake data	
	Status	Function	Stores	Losses		Midpoint	Lower end
Thiamin	**+**	**+**	-	-	-	-	-
Riboflavin	**+**	**+**	-	-	-	-	-
Niacin	**+**	-	-	-	-	-	-
Vitamin B6	**+**	-	-	-	-	-	-
Folate	**+**	-	-	-	-	-	-
Vitamin C	**+**	-	-	-	-	-	-
Vitamin D, younger adults	**+**	-	-	-	-	-	-
Vitamin K1	-	**+**	-	-	-	-	-
Copper	**+**	**+**	-	-	-	-	-
Iodine	**+**	-	-	-	-	-	-
Selenium	**+**	-	-	-	-	-	-
Vitamin A	-	-	**+**	-	-	-	-
Vitamin B12	-	-	**+**	-	-	-	-
Calcium, younger adults	-	-	-	**+**	-	-	-
Iron	-	-	-	**+**	-	-	-
Zinc	-	-	-	**+**	-	-	-
Vitamin D, older adults	-	-	-	-	**+** fracture risk	-	-
Calcium, older adults	-	-	-	-	**+** fracture risk	-	-
Potassium	-	-	-	-	**+** blood pressure, stroke	-	-
Pantothenic acid	-	-	-	-	-	**+**	-
Vitamin E	-	-	-	-	-	**+**	-
Biotin	-	-	-	-	-	**+**	-
Choline	-	-	-	-	*(+ depletion & repletion)*	**+**	-
Magnesium	-	-	-	-	-	**+**	-
Manganese	-	-	-	*(+)*	-	**+**	-
Molybdenum	-	-	-	*(+)*	-	-	**+**

[a] The primary criteria are indicated in bold, supportive criteria in italics and between brackets.

A factorial method or balance data

The reference values for 5 nutrients are based on a factorial method or balance data. The method appears to aim at a different goal when it is applied to vitamins compared to when it is applied to minerals. For the two vitamins for which this method was used, the method assesses the intake needed to maintain body stores associated with prevention of deficiency. For the three minerals, the method assesses the intake needed to replace daily losses of the nutrient from the body.

Intervention studies relating intake to clinical effects

The reference values for three micronutrients are based on intervention studies relating intake to clinical effects.

Intake data

The reference values for most of the remaining nutrients are based on intake data, which is the case for 4 vitamins and 3 minerals. For two minerals, EFSA used intake data in combination with the available information from balance studies.

29.3 The type of reference value

This report is the background document for the advisory report on the 2018 micronutrient dietary reference values for Dutch adults.[4] In the advisory report, the Committee summarises how the average requirements (ARs), population reference intakes (PRIs) and adequate intakes (AIs) can be applied. There are differences in application possibilities between nutrients for which an AR and PRI is established, compared to those with an AI. This information is not repeated here, but Table 101 summarises which type of reference value is available in the 2018 Dutch reference values, and whether this implies a change compared to the 2014 guidelines.

Table 101. Type of reference value in 2018 and 2014

		2014 Dutch reference value type	
		AR & PRI	AI
2018 Dutch reference value type	AR & PRI	vitamin A thiamin riboflavin niacin vitamin B6 folate vitamin B12 vitamin C vitamin D ♂& ♀ ≥70 years copper iron zinc	calcium ♂& ♀ 18-49 yr and ♂ 50-69 yr
	AI[a]	vitamin E iodine phosphorus selenium	pantothenic acid vitamin D ♂& ♀ 18-69 yr vitamin K1 biotin calcium ♀ 50-69 yr and ♂& ♀ ≥70 yr magnesium manganese molybdenum potassium

[a] The 2018 Dutch reference value for choline is an AI as well, but choline was not part of the 2014 Dutch reference values.

Average requirements (ARs) and population reference intakes (PRIs)

In the 2018 Dutch reference values, ARs and PRIs are available for 8 vitamins (vitamin A, thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, vitamin C) and, for the subgroup of older adults (≥70 years), also for vitamin D.

This type of reference values (ARs and PRIs) is available for 3 minerals (copper, iron, zinc) and, for the subgroup of younger adults and middle-aged men, also for calcium.

This implies a change from AI values to AR and PRI values for calcium only.

Adequate intakes (AIs)

The 2018 Dutch reference values, comprise AIs for 5 vitamins (pantothenic acid, vitamin E, vitamin K1, biotin, choline) and, for the subgroup of younger adults (18-69 years), also for vitamin D.

This type of reference values (AIs) are available for 7 minerals (iodine, magnesium, manganese, molybdenum, phosphorus, potassium, selenium) and, for the subgroup of older adults and middle-aged women, also for calcium.

This implies a change from AR and PRI values to AI values for vitamin E, iodine, phosphorus and selenium.

29.4 Differentiation between subgroups of adults

The evaluations per nutrient in Chapters 2-28 of this background report include a description of whether or not reference values differ between subgroups of adults: (men versus women; younger versus older age groups), and information on the argumentation for these choices, if available from the reports. The Committee concludes that a scientific basis for either differentiating between subgroups or not, is not available for many nutrients, but is available more frequently for the differentiation between men and women, than for the differentiation between age groups.

Differentiation of the reference values between men and women

The 2018 reference values differ between men and women for 8 nutrients: vitamin A, vitamin B6 for adults aged >50 years, vitamin C, vitamin E, calcium for adults aged 50-69 years, iron for younger adults, magnesium and zinc. The arguments for differentiating between men and women are listed in Table 102.

The reference values for thiamin and niacin are expressed in grams per megajoule, without differentiation between men and women. However, this implies that the values in milligrams per day – on average – are higher for men than for women, based on the differences in energy intake.

Table 102. Differentiation of reference values between adult men and women

Nutrient	Argument for differentiation between men and women	Origin
Vitamin A	Requirements are assumed to be proportional with the reference body weight, which is higher in men than in women.	EFSA & IOM
Vitamin B6[8]	In the age group >50 yr, the reference values for men are higher than for women, based on the available evidence on each group.	HCNL
Vitamin C	The AR is higher for men than for women, because in men the adequate biomarker level (plasma ascorbate ≥32 μmol/L) requires a higher vitamin C intake than in women. The PRI is equal for men and women, because of the higher PRI for iron in premenopausal women (vitamin C improves iron absorption).	NCM
Vitamin E	Vitamin E intake is higher in men than in women.	EFSA
Calcium[a]	In this age group 51-70 yr, it is recommended that women (but not men) use supplemental vitamin D, and in order for this vitamin D supplement to be effective, their calcium requirement is higher than in men of this age group.	HCNL
Iron[a]	Estimated iron losses are higher in premenopausal women than in men (whereas iron losses in postmenopausal women are assumed to be equal to those in men).	EFSA
Magnesium	Magnesium intake is higher in men than in women.	EFSA
Zinc	Estimated zinc losses are higher in men than in women.	NCM

[a] Differentiation between the reference values for men and women only in subgroups of adults.

For most nutrients, the 2018 reference values are equal for men and women. In eight nutrients this has a scientific basis: the available estimates for men (almost) equal the available estimates for women, or the male versus female sex did not significantly contribute to the variation in requirements between individuals. This applies to riboflavin, vitamin B6 (younger adults), folate, vitamin B12, vitamin D, calcium, iodine, copper and potassium, and to vitamin B6 (age groups 18-50 years), and calcium (age groups 18-49 and ≥70 years).

However, for nine nutrients, no scientific evidence is presented for applying the same reference value to men and women. This applies to pantothenic acid, vitamin B12, vitamin K1, biotin, choline, manganese, molybdenum, phosphorus and selenium.

The Committee notes that the reference values for five of these are based on intake data, which seems to be inconsistent with magnesium and vitamin E (Table 100). However, the intake data for pantothenic acid, biotin, choline, manganese and molybdenum have larger uncertainties than those for magnesium and vitamin E. Pantothenic acid, biotin, choline, manganese and molybdenum are not included in the Dutch Food Composition Database, contrary to vitamin E and magnesium. Iodine intake is preferably estimated from the urinary excretion over a 24-hour period, and therefore the availability of valid intake data is limited compared to other nutrients. The larger uncertainties explain why a different choice is made for these five nutrients.

The reference values for vitamin K1 and phosphorus also have substantial uncertainty. Note that the vitamin K1 requirement is assumed to be proportional to body weight, but still, EFSA does not differentiate between men and women because of these uncertainties. For iodine and selenium, there are no data or insufficient data for men and women separately.

Differentiation of the reference values between adult age groups

For four nutrients, the reference values differ between age groups: vitamin B6, vitamin D, calcium and iron. The arguments for differentiating between age groups, are listed in Table 103.

The reference values for thiamin and niacin are expressed in grams per megajoule, without differentiation between age groups. However, this implies that the values in milligrams per day – on average – are higher for younger adults than for older adults, based on the differences in energy intake.

For riboflavin, vitamin B6 (women) and folate, the report from which the 2018 Dutch reference value is adopted, explicitly notes that there are no indications that the requirements are influenced by age. (Note that the reference values refer to the healthy population, so that, e.g. for vitamin B12, they do not apply to older people with vitamin B12 absorption problems).

For 16 nutrients, the requirement of older versus younger adults is not addressed in the report from which the 2018 Dutch reference value is adopted. This applies to: vitamin A, pantothenic acid, vitamin C, vitamin E, biotin, choline, copper, iodine, iron (men), magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc.

Table 103. Differentiation of reference values between age groups

Nutrient	Argument for differentiation between men and women	Origin
Vitamin B6	The available research indicates that the requirement is higher for older versus younger men.	HCNL
Vitamin D	Evidence from randomised controlled trials in older adults indicated that the use of supplements with 10 to 20 µg/d of vitamin D in combination with calcium may reduce the risk of bone fractures.	HCNL
Calcium	In the Netherlands, it is recommended that older women (≥50 years) and older men (≥70 years) use vitamin D supplements. A higher calcium intake is required in order for the extra vitamin D to be effective in reducing the risk of fractures.	HCNL
Iron	Iron losses are higher in premenopausal women than in postmenopausal women because of menses.	EFSA

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annexes

A types of reference values and their definitions

EFSA defines the reference values as follows[1]:

- Average Requirement (AR):
  the level of (nutrient) intake that is adequate for half of the people in a population group, given a normal distribution of requirement.
- Population Reference Intakes (PRI):
  the level of (nutrient) intake that is adequate for virtually all people in a population group.
- Adequate Intake (AI):
  the value estimated when a Population Reference Intake cannot be established because an average requirement cannot be determined. An Adequate Intake is the average observed daily level of intake by a population group (or groups) of apparently healthy people that is assumed to be adequate.

Note that the tolerable upper intake levels are not evaluated in this background document, but will be described and evaluated in a separate report. EFSA defined the tolerable upper intake level as follows[3]:

- Tolerable upper intake level (UL)
  The maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

This background document evaluates the average requirements (ARs), population reference intakes (PRIs), and adequate intakes (AIs) for micronutrients for adults.

- The AR describes the level of intake which is required by half of the subjects in the population group.

The AR is the average value of the assessed requirements of individuals.

- Both PRIs and AIs describe the levels of intake which are sufficient for almost all the individuals in the population group considered.

A PRI is established only if an AR is available. The PRI is calculated as the AR plus twice the assessed or assumed standard deviation of the requirements of individuals. When an AR cannot be established, the PRI cannot be calculated, and an AI is established instead. The AI is the intake level associated with adequate (markers of) health in (almost) all individuals.

Note that the reports use different names for these three types of reference values, see Table 104. The Committee adopted EFSA's terminology.

- ULs describe the highest intake levels which are considered to be safe; at intakes higher than the UL, the risk of undesirable effects of overconsumption increases. The ULs are not evaluated in this report.

Figure 1 illustrates these reference values. It shows that AR- and PRI-values both correspond to a specific point in the distribution of individual requirements: they are considered to represent the intake level sufficient for 50% and 97.5% of the population group, respectively. If an AI is established, there is some uncertainty – by definition – regarding the place of this intake level on the distribution of individual requirements. This also applies to the UL.

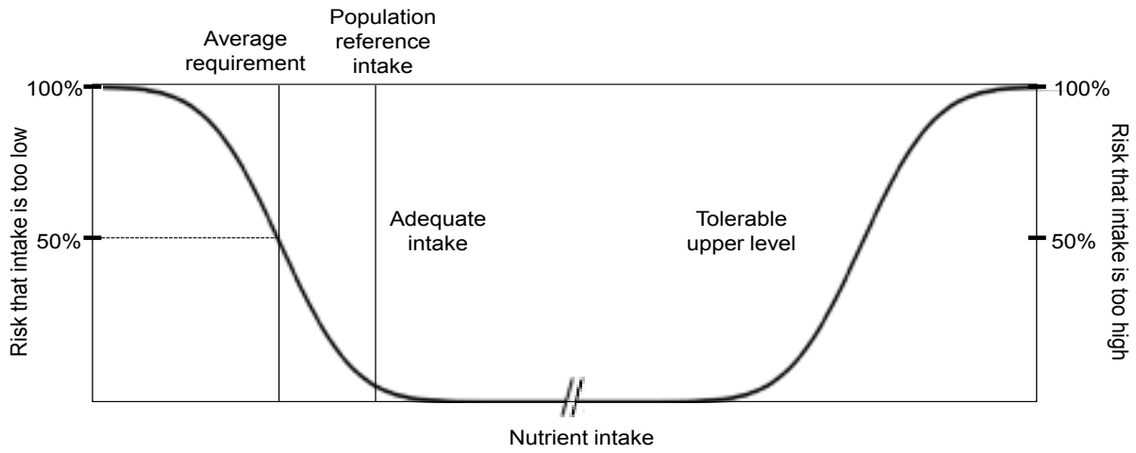

Figure 1. Types of dietary reference values in relation to the intake of the nutrient (x-axis) and the risk that intake is to low or too high (left and right y-axis, respectively)

Table 104. Terms used for the reference values in the six (sets of) reports

European Food Safety Authority (EFSA)	Dietary Reference Values	Average Requirement (AR)	Population Reference Intake (PRI)	Adequate Intake (AI)
Health Council of the Netherlands (HCNL)	Dietary Reference Intakes (in Dutch: voedingsnormen)	Estimated Average Requirement (EAR) (in Dutch: gemiddelde behoefte)	Recommended Daily Allowance (RDA) (in Dutch: aanbevolen hoeveelheid)	Adequate Intake (AI) (In Dutch: adequate inname)
Nordic Council of Ministers (NCM)	Dietary Reference Values	Average Requirement (AR)	Recommended Intake (RI)	Recommended Intake (RI)
Germany, Austria and Switzerland (DACH)	Reference values for nutrient intake	Average Requirement	Recommended Intake	Estimated value for nutrient intake
Institute of Medicine (IOM)	Dietary Reference Intakes	Estimated Average Requirement (EAR)	Recommended Daily Allowance (RDA)	Adequate Intake (AI)
World Health Organization (WHO) / Food and Agri-cultural Organization (FAO)	-	Estimated Average Requirement (EAR)	Recommended Nutrient Intake (RNI)	Recommended Nutrient Intake (RNI)

B list of abbreviations

Abbreviation	Meaning	Short explanation (of relevance), mainly based on the EFSA reports on dietary reference values
AI	Adequate Intake	The AI is the level of (nutrient) intake that is adequate for virtually all in an apparently healthy people in a population group; the AI is established when the AR (and thus the PRI/RDA) cannot be determined.
ALT	Alanine aminotransferase	ALT is an enzyme found mostly in liver and kidney cells. ALT is released into the blood when the liver is damaged.
AR	Average Requirement	The AI is the level of (nutrient) intake that is adequate for half of the people in an apparently healthy population group, given a normal distribution of requirement.
BMR	Basal Metabolic Rate	BMR is the energy expenditure in a both physically and psychologically undisturbed state (but not asleep), post-absorptive, in a thermally neutral environment.
CV	Coefficient of Variation	In this report, CV is generally used as the coefficient of variation of the nutrient requirement, expressed as a percentage. If the nutrient requirement is normally distributed, the PRI/RDA/RI is calculated as (1 + [2xCV/100]) times the average requirement.
DACH	Deutschland (Germany), Austria, and Confoederatio Helvetica (Switzerland)	DACH (or D-A-CH) are the German-speaking countries which establish dietary reference values together.
DRV / DRI	Dietary Reference Value / Dietary Reference Intake	A DRV / DRI is a quantitative reference value (such as AR, PRI, AI, UL) for nutrient intakes for healthy individuals and populations which may be used for assessment and planning of diets.
EAR	Estimated Average Requirement	The EAR is IOM's and HCNL's reference value equivalent to EFSA's AR.
EGRAC	Erythrocyte Glutathione Reductase Activation Coefficient	EGRAC is the ratio of the activity of Erythrocyte Glutathione Reductase, measured in-vitro with, and without, addition of the cofactor flavin adenine dinucleotide (FAD).
EFSA	European Food Safety Authority	EFSA is the agency of the European Union (EU) that provides independent scientific advice and communicates on existing and emerging risks associated with the food chain, including the establishment of dietary reference values.
ETKA	Erythrocyte TransKetolase Activity	ETKA is a functional marker of thiamin status. It represents the basal value of the enzyme erythrocyte transketolase, without stimulation by thiamin diphosphate (TDP).
αETK	Erythrocyte TransKetolase Activity Coefficient	αETK is a functional marker of thiamin status. It represents the degree to which ETKA rises in response to addition of thiamin diphosphate (TDP). αETK can discriminate low ETKA due to thiamin deficiency from low ETKA due to a lack of the apoenzyme. A value of αETK < 1.15 is generally considered to reflect an adequate thiamin status.
GPx	Glutathione Peroxidase	GPx activity is a biomarker of selenium function.
HCNL	Health Council of the Netherlands	HCNL is an independent Dutch scientific advisory body with the task of advising the government and parliament about matters in the areas of public health and medical research, including dietary reference intakes.
HoloTC	Holotranscobalamin	Serum holoTC is the physiologically active form of cobalamin that delivers the vitamin to cells. It is considered an earlier biomarker for changes in cobalamin status than serum cobalamin concentration. EFSA notes that lower limits of reference intervals for serum holoTC range between 11 and 48 pmol/L in adults, depending on the reference population used.

Abbreviation	Meaning	Short explanation (of relevance), mainly based on the EFSA reports on dietary reference values
IOM	Institute of Medicine	IOM is the institute which established the DRIs for the USA and Canada. IOM is the former name of the Health and Medical Devision programme of the National Academy of Medicine (NAM). The NAM is the American nonprofit, non-governmental organisation, which provides national advice on issues relating to biomedical science, medicine, and health, and serves as an adviser to the nation to improve health. The NAM is a part of the National Academies of Sciences, Engineering, and Medicine, along with the National Academy of Sciences (NAS), National Academy of Engineering (NAE), and the National Research Council (NRC).
MCV	Mean Corpuscular Volume of erythrocytes	MCV is a measure of the average volume of a red blood cell, attained by multiplying a volume of blood by the proportion of blood that is cellular (the hematocrit), and dividing that product by the number of erythrocytes (red blood cells) in that volume.
NCM	Nordic Council of Ministers	NCM is a geo-political inter-parliamentary forum for co-operation between the Nordic countries Denmark, Finland, Iceland, Norway and Sweden as well as the autonomous areas of the Faroe Islands, Greenland and the Åland Islands. NCM develops the Nordic Nutrition Recommendations (NNR).
NMN	N-methylnicotinamide	The excretion of niacin metabolites is mainly as NMN and 2-Pyr. NMN is formed by methylation of niacin in the liver.
NE	Niacin Equivalent	1 mg NE = 1 mg niacin (nicotinic acid and nicotinamide) = 60 mg tryptophan.
25(OH)D	25-hydroxyvitamin D	Serum 25(OH)D concentration is used as a biomarker of vitamin D status in adult and children populations. It reflects the amount of vitamin D attained from both cutaneous synthesis and dietary sources.
P_i	Inorganic phosphorus	Serum inorganic phosphorus is the most commonly used indicator of phosphorus status.
P50, P97.5	50th and 97.5th percentiles of a distribution	A percentile (or a centile) is a measure used in statistics indicating the value below which a given percentage of observations in a group of observations fall. The dietary reference values AR and PRI/RDA are set respectively at the P50 and P97.5 of the distribution of requirements.
PAL	Physical Activity Level	The PAL is a person's energy expenditure over a 24-hour period, divided by his or her basal metabolic rate (BMR).
PLP	Pyridoxal 5'-Phosphate	PLP is one of the six substances with vitamin B6 activity present in food. PLP and pyridoxamine 5'-phosphate (PMP) are metabolically active (the other four substances with vitamin B6 activity are converted in the body into PLP or PMP). Plasma PLP is considered to be the most suitable biomarker for deriving reference values for vitamin B6, because it reflects the tissue stores (biomarker of status) and has a defined cut-off value for an adequate vitamin B6 status.
PRI	Population Reference Intake	The PRI is EFSA's reference value for the level of (nutrient) intake that is adequate for virtually all apparently healthy people in a population group, on condition that this value is established based on the average requirement (AR).
PUFA	Poly-Unsaturated Fatty Acids	PUFA are fatty acids with at least two double bonds in their chemical structure.
2-Pyr	N-methyl-2-pyridone-5-carboxamide	The excretion of niacin metabolites is mainly as NMN and 2-Pyr. 2-Pyr is formed by oxidation of NMN. (2-Pyr) and N-methyl-4-pyridone-carboxamide (4-Pyr).
RE / RAE	Retinol Equivalent / Retinol Activity Equivalent	The biological value of substances with vitamin A activity is expressed RE or RAE. The conversion factors for the conversion of carotenes to vitamin A (retinol) differ between RE and RAE. EFSA uses RE, with 1 µg RE equalling 1 µg of retinol, 6 µg of β-carotene and 12 µg of other provitamin A carotenoids. IOM, NCM and DACH use RAE, with 1 µg RAE equalling 1 µg of retinol, 12 µg of β-carotene and 24 µg of other provitamin A carotenoids.
RDA	Recommended Daily Allowance	The RDA is IOM's and HCNL's reference value equivalent to EFSA's PRI.
RI	Recommended Intake	The RI is NCM's, DACH's and WHO/FAO's reference value equivalent to EFSA's PRI.
RIVM	Rijksinstituut voor Volksgezondheid en Milieu	RIVM is the Dutch National Institute for Public Health and the Environment.

Abbreviation	Meaning	Short explanation (of relevance), mainly based on the EFSA reports on dietary reference values
SEPP1	Selenoprotein P	SEPP1 is considered the most informative biomarker of selenium function on the basis of its role in selenium transport and metabolism and its response to different forms of selenium intake. Intervention studies using different levels of selenium intake showed that plasma SEPP1 concentration levels off in response to increasing doses of selenium. The levelling off of plasma SEPP1 was considered to be indicative of an adequate supply of selenium to all tissues and to reflect saturation of the functional selenium body pool, ensuring that selenium requirement is met.
tHcy	Total homocysteine	Plasma tHcy is a marker of cobalamin status. Plasma tHcy is not a specific marker, because it is also affected by other dietary factors (e.g. selected B vitamins, choline and betaine), as well as renal insufficiency and some lifestyle factors.
SOD	SuperOxide Dismutase	Erythrocyte SOD activity is used by IOM as a biomarker of copper status. EFSA considers that erythrocyte SOD is not a suitable biomarker of copper status.
α-TE	alpha-Tocopherol Equivalent	α-TE is a generic term for compounds with vitamin E activity: α-, β-, γ- and δ-tocopherols and α-, β-, γ- and δ-tocotrienols.
UL	tolerable Upper intake Level	The UL is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.
WHO/FAO	World Health Organisation / Food and Agriculture Organisation	WHO and FAO are specialised agencies of the United Nations. WHO is specialised in international public health; FAO in food and agriculture.

C overview of the 2018 and 2014 reference values for the Netherlands[a]

Nutrient	The 2018 Dutch reference values				2018 versus 2014	The 2014 Dutch reference values			
	Reference values		Origin	Type of data on which the values are based		Reference values		Origin	Type of data on which the values are based
Vitamin A	AR♂ AR♀ PRI♂ PRI♀	615 µg RAE/d 525 800 680	This report	EFSA's factorial method estima-ting the intake needed to maintain body stores associated with absence of deficiency, but using HCNL's reference weights	Changed	AR♂ AR♀ PRI♂ PRI♀	600 µg RAE/d 500 900 700	NCM 2014	Factorial approach as IOM 1998
Thiamin	AR PRI	0.072 mg/MJ 0.1	EFSA 2016	Biomarkers of status (urinary excretion) and function (αETK, ETKA)	Changed	AR PRI	0.8 mg/d 1.1	HCNL 2000	Biomarkers of status (urinary excretion) and function (αETK, ETKA)
Riboflavin	AR PRI	1.3 mg/d 1.6	EFSA 2017	Biomarkers of status (intake at which urinary excretion sharply increases) and function (EGRAC)	Changed	AR♂ AR♀ PRI♂ PRI♀	1.1 mg/d 0.8 1.5 1.1	HCNL 2000	Biomarkers of status (intake at which urinary excretion sharply increases) and function (EGRAC)
Niacin	AR PRI	1.3 mg/MJ 1.6	EFSA 2014	Biomarkers of status (urinary excretion of metabolite)	Changed	AR♂ AR♀ PRI♂ PRI♀	12 mg/d 9 17 13	HCNL 2000	Biomarkers of status (urinary excretion of metabolite)
Pantothenic acid	AI	5 mg/d	EFSA 2014	Midpoint of observed median / mean intakes in Europe	Unchanged	AI	5 mg/d	HCNL 2000	Habitual population intakes
Vitamin B6	**19-50 years:**					**19-50 years:**			
	AR PRI	1.1 mg/d 1.5	HCNL 2003	Biomarker of status (plasma PLP)	Unchanged	AR PRI	1.1 mg/d 1.5	HCNL 2003	Biomarker of status (plasma PLP)
	>50 years:					**>50 years:**			
	AR♂ AR♀ PRI♂ PRI♀	1.3 mg/d 1.1 1.8 1.5	HCNL 2003		Unchanged	AR♂ AR♀ PRI♂ PRI♀	1.3 mg/d 1.1 1.8 1.5	HCNL 2003	
Folate[a]	AR PRI	200 µg/d 300	HCNL 2003	Biomarkers of status (serum folate, erythrocyte folate, plasma homocysteine)	Unchanged	AR PRI	200 µg/d 300	HCNL 2003	Biomarkers of status (serum folate, erythrocyte folate, plasma homocysteine)
Vitamin B12[b]	AR PRI	2.0 µg/d 2.8	HCNL 2003	Factorial method estimating intake needed to maintain the smallest body stores associated with absence / prevention of deficiency	Unchanged	AR PRI	2.0 µg/d 2.8	HCNL 2003	Factorial method estimating intake needed to maintain the smallest body stores associated with absence / prevention of deficiency
Vitamin C	AR♂ AR♀ PRI	60 mg/d 50 75 (♂&♀)	NCM 2014	Biomarkers of status (plasma ascorbate)	Unchanged	AR♂ AR♀ PRI	60 mg/d 50 75 (♂&♀)	NCM 2014	Biomarkers of status (plasma ascorbate)

[a] All abbreviations in the table are explained in the glossary (Annex B).

Nutrient	The 2018 Dutch reference values				2018 versus 2014	The 2014 Dutch reference values			
	Reference values		Origin	Type of data on which the values are based		Reference values		Origin	Type of data on which the values are based
Vitamin D[c]	**18-69 years:**					**18-69 years:**			
	AI	10 µg/d	HCNL 2012	Biomarker of status (25(OH)D) randomised controlled trials on the effect of using supplements with vitamin D and calcium on fracture risk	Unchanged	AI	10 µg/d	HCNL 2012	Biomarker of status (25(OH)D) randomised controlled trials on the effect of using supplements with vitamin D and calcium on fracture risk
	≥70 years:					**≥70 years:**			
	AR	10 µg/d	HCNL 2012		Unchanged	AR	10 µg/d	HCNL 2012	
	PRI	20				PRI	20		
Vitamin E as α-tocopherol	AI♂	13 mg/d	EFSA 2015	Midpoint of range of mean intakes in Europe	Changed	AR♂	6 mg/d	NCM 2014	RI of polyunsaturated fatty acids (PUFA), assuming that the average requirement is 1 mg vitamin E per gram PUFA
	AI♀	11				AR♀	5		
						PRI♂	10		
						PRI♀	8		
Vitamin K1	AI	70 µg/d	EFSA 2017	Biomarkers of function (simplastin:ecarin ratio; urinary Gla concentration)	Unchanged	AI	70 µg/d	EFSA 2017	Biomarkers of function (simplastin:ecarin ratio; urinary Gla concentration)
Biotin	AI	40 µg/d	EFSA 2014	Midpoint of range of mean intakes in Europe	Unchanged	AI	40 µg/d	EFSA 2014	Midpoint of range of mean intakes in Europe
Choline	AI	400 mg/d	EFSA 2016	Midpoint of mean choline intakes in Europe, rounded upwards, with supportive evidence from a depletion-repletion study	Changed	No reference value			Choline was not mentioned in HCNL 2014
Calcium	**18-24 years:**					**18-50 years:**			Factorial method based on the replacement of daily calcium losses and balance data
	AR	860 mg/d	EFSA 2015	Intermediate between value 11-17 and >25 years	Changed	AI	1,000 mg/d	HCNL 2000	
	PRI	1,000							
	25-50 years (♂&♀) and Men 51-70 years:								
	AR	750 mg/d	EFSA 2015	Balance data based on the replacement of daily calcium losses	Changed				
	PRI	950							
	Women 51-70 years:			Randomised controlled trials on the effect of using supplements with vitamin D and calcium on fracture risk, considering that HCNL advises these groups to take a vitamin D supplement		**51-70 years (♂&♀) :**			Randomised controlled trials on the effect of using supplements with calcium and vitamin D on fracture risk for older adults
	AI	1,100 mg/d	HCNL 2000		Unchanged	AI	1,100	HCNL 2000	
	>70 years (♂&♀):					**>70 years (♂&♀) :**			
	AI	1,200 mg/d	HCNL 2000		Unchanged	AI	1,200	HCNL 2000	
Chromium III				HCNL adopted EFSA's conclusion in 2014 (no reference values)					HCNL adopted EFSA's conclusion in 2014 (no reference values)
Copper	AR	0.7 mg/d	NCM 2014	Biomarkers of status (plasma & platelet copper concentration, serum caeruloplasmin concentra-tion), biomarkers of function (erythrocyte SOD activity) and a factorial method	Unchanged	AR	0.7 mg/d	NCM 2014	Biomarkers of status (plasma & platelet copper concentration, serum caeruloplasmin concentra-tion), biomarkers of function (erythrocyte SOD activity) and a factorial method
	PRI	0.9				PRI	0.9		
Fluoride				No reference value	Changed	AI♂	3.4 mg/d	EFSA 2013	Relationship between caries incidence and fluoride intake from drinking water
						AI♀	2.9		

Nutrient	The 2018 Dutch reference values				2018 versus 2014	The 2014 Dutch reference values			
	Reference values		Origin	Type of data on which the values are based		Reference values		Origin	Type of data on which the values are based
Iodine	AI	150 µg/d	EFSA 2014	Biomarker of status (urinary iodine concentration)	Changed	PRI AR	150 µg/d 100	NCM 2014	Biomarker of status (thyroid iodine concentration), and the intake required to prevent goitre and maintain a normal thyroid function
Iron	**Men**					**Men**			
	AR PRI	6 mg/d 11	EFSA 2015	Factorial method based on the replacement of	Changed	AR PRI	7 mg/d 9	NCM 2014	Factorial method based on the replacement of daily iron losses
	Women premenopause					**Women premenopause**			
	AR PRI	7 mg/d 16	EFSA 2015		Changed	AR PRI	9 (10?) mg/d[d] 15	NCM 2014	
	Women postmenopause					**Women postmenopause**			
	AR PRI	6 mg/d 11	EFSA 2015		Unchanged Changed	AR PRI	6 mg/d[d] 9 (8?)	NCM 2014	
Magnesium	AI♂ AI♀	350 mg/d 300	EFSA 2015	Mean intakes in Europe combined with the results of balance studies	Changed	AI♂ AI♀	350 mg/d 280	NCM 2014	There are no substantial new data since NCM 2004 indicating that these values should be changed
Manganese	AI	3.0 mg/d	EFSA 2013	Mean intakes in Europe combined with findings in balance studies	Unchanged	AI	3.0 mg/d	EFSA 2013	Mean intakes in Europe combined with findings in balance studies
Molybdenum	AI	65 µg/d	EFSA 2013	Mean intakes in Europe combined with findings in balance studies	Unchanged	AI	65 µg/d	EFSA 2013	Mean intakes in Europe combined with findings in balance studies
Phosphorus	AI	550 mg/d	EFSA 2015	Recommended calcium intake, assuming that the adequate intake is 1 mol phosphorus per 1.4 mol calcium	Changed	AR PRI	450 mg/d 600	NCM 2014	Biomarker of status (plasma concentration)
Potassium	AI	3.5 g/d	EFSA 2016	Effects on blood pressure and stroke risk	Changed	AI♂ AI♀	3.5 g/d 3.1	NCM 2014	Effects on blood pressure and stroke risk
Selenium	AI	70 µg/d	EFSA 2014	Biomarker of status (plasma SEPP1)	Changed	AR♂ AR♀ PRI♂ PRI♀	35 µg/d 30 60 50	NCM 2014	Biomarker of status (plasma SEPP1)
Zinc	AR♂ AR♀ PRI♂ PRI♀	6.4 mg/d 5.7 9 7	NCM 2014	Factorial method based on the replacement of daily zinc losses	Unchanged	AR♂ AR♀ PRI♂ PRI♀	6.4 mg/d 5.7 9 7	NCM 2014	Factorial method based on the replacement of daily zinc losses

[a] Note that women who wish to conceive are advised to use a supplement containing 400 µg/d of folic acid, starting at least four weeks prior to conception until the eighth week of pregnancy, in addition to these reference values.

[b] In the Netherlands, it is recommended that adults on a vegan diet use supplemental vitamin B12 to achieve an adequate supply of this vitamin.[53]

[c] In most people, the vitamin D supply is met partly by cutaneous vitamin D synthesis and partly by dietary intake. The reference values for vitamin D intake refer to conditions of minimal cutaneous vitamin D synthesis. In the Netherlands, it is recommended that adults with dark skin or who do not spend enough time outdoors, women who wear a veil, and all women aged 50-70 years use a daily supplement with 10 µg vitamin D to ensure an adequate vitamin D supply. In the Netherlands, it is recommended that adults over 70 years use a daily supplement with 20 µg vitamin D to ensure an adequate vitamin D supply.[34]

[d] For iron, NCM's AR for premenopausal women and NCM's RI for postmenopausal women are not clear. This is described in footnotes in paragraph 21.2, where the differences between the ARs for premenopausal women and the PRIs for postmenopausal women are explained.

Committee and working group

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