An evaluation of dietary reference values for vitamins and minerals for pregnant women

No. 2021/27A/02, The Hague, 22 June 2021

Background document to:
Dietary reference values for vitamins and minerals for pregnant women
2021/27, The Hague, 22 June 2021

Health Council of the Netherlands

contents

01 introduction

This report serves as the background document for the Health Council advisory report on the micronutrient requirements of pregnant women,[1,2] prepared by the Council's Committee on Nutrition. It describes the evaluation of dietary reference values for each micronutrient. The advisory report gives recommendations based on the outcome of these evaluations. The recommendations for adult men and adult non-pregnant, non-lactating women were published in 2018.[3,4] The procedure developed to derive those recommendations was used as the basis for deriving the recommendations for pregnant women in this report. For the purpose of clarity and readability, the term 'non-pregnant women' is used when speaking of non-pregnant, non-lactating adult women of childbearing age.

There are various ways to derive a requirement for pregnant women:
1) a 'total requirement' is derived based on research in pregnant women;
2) a requirement is derived based on the requirement of non-pregnant women in combination with an 'additional requirement' of pregnant women (additive model); 3) the requirement of pregnant women is similar to the requirement of non-pregnant women.

The values for lactating women, as well as for infants and for children, will be evaluated and presented separately.

A list of abbreviations can be found in Annex A.

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

The point of departure in this evaluation of the Dutch reference values for pregnant women was to adopt EFSA's dietary reference values for pregnant women[5-34] for use in the Netherlands, unless there were major objections to these values. The Health Council of The Netherlands feels that reference values should ideally be harmonized throughout the EU. Reference values refer to populations comprising people with a broad range of characteristics, dietary habits and lifestyles. Generally, at this population level, there are no, or only small, differences in requirements between countries. A differentiation of reference values between European countries will seldom be required for physiological reasons. Furthermore, and importantly, EFSA's reports on dietary reference values provide a thorough and transparent evaluation of the scientific evidence. These reports were established by panels consisting of scientific experts from the member states, including the Netherlands. The EFSA reports on micronutrients comprised different target groups, including pregnant women. These reports were published in the period 2014-2019 and are the most recent reports on dietary reference values. Thus, these reports are assumed to be an adequate point of departure for updating the scientific background of the Dutch reference values for pregnant women. This is also why the committee did not update the literature. The committee did consider additional evidence regarding supplemental intake of with folic acid, calcium, and vitamin D, compiled for the parallel

advisory report on Dietary guidelines for pregnant women.[35-37] The available evidence on calcium and vitamin D was limited regarding dose response information. The additional evidence did not result in changes of reference values of vitamin D. Regarding calcium, the average requirement and population reference intake was changed into an adequate intake regarding the second half of the pregnancy (≥20 weeks of pregnancy; see chapter 16). Regarding folate, the available evidence only comprised periconceptional supplementation of folic acid (i.e., no meta-analyses on folate supplementation during the 2nd and 3rd trimester of pregnancy were available).

Note that reference values for larger geographical regions (e.g., for the Nordic countries, the German-speaking countries, the United States of America and Canada) were established before those of EFSA.

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

To determine whether EFSA's reference values could be adopted for pregnant women in the Netherlands, the committee identified two key questions:

1. Does a specifically Dutch context justify the non-adoption of EFSA's requirement (additional requirement) for pregnant women? The context or policy (the nutritional context or policy) in the Netherlands may differ from the European context on which EFSA's requirement (additional requirement) for pregnant women is based. This may require the use of other values in the Netherlands. Note that EFSA's values were used as the point of departure for the evaluation, because the committee anticipated that the context (nutritional context) or policy in the Netherlands would rarely give rise to the rejection of EFSA's values. For example, only three of EFSA's recommendations for micronutrients for adults were rejected due to the specific nutritional context in the Netherlands: vitamin A[a], calcium (women ≥ 50 years of age, men ≥ 70 years of age)[b], and fluoride[c].
2. Does the scientific basis used by EFSA justify the non-adoption of EFSA's requirement (additional requirement) for pregnant women? The committee evaluated the research and line of reasoning that EFSA used to establish the requirement (additional requirement) for pregnant women for each nutrient. The evaluation involved comparing EFSA's requirements (additional requirements) and their scientific basis[5-32] with the requirements (additional requirements) in five reports (sets of reports) that were considered most relevant for this purpose. The first set of reports is the compilation of values used in the Netherlands since 2014[38], based mainly on the Dutch[39-41] and Nordic[42] reports. Two reports

[a] Vitamin A is one of the few micronutrients for which the method to establish the reference values involved a proportional effect of reference weights on the reference values. The average Dutch person is taller (and, thus, has a higher body weight) than the average European on which the EFSA requirement is based.
[b] In the Netherlands these groups are advised to use vitamin D supplements. In order for the vitamin D supplements to be effective, calcium intake needs to exceed the level as advised by EFSA.
[c] Because the prevention of caries in the Netherlands involves fluoride-containing toothpaste and gels, and not fluoride intake.

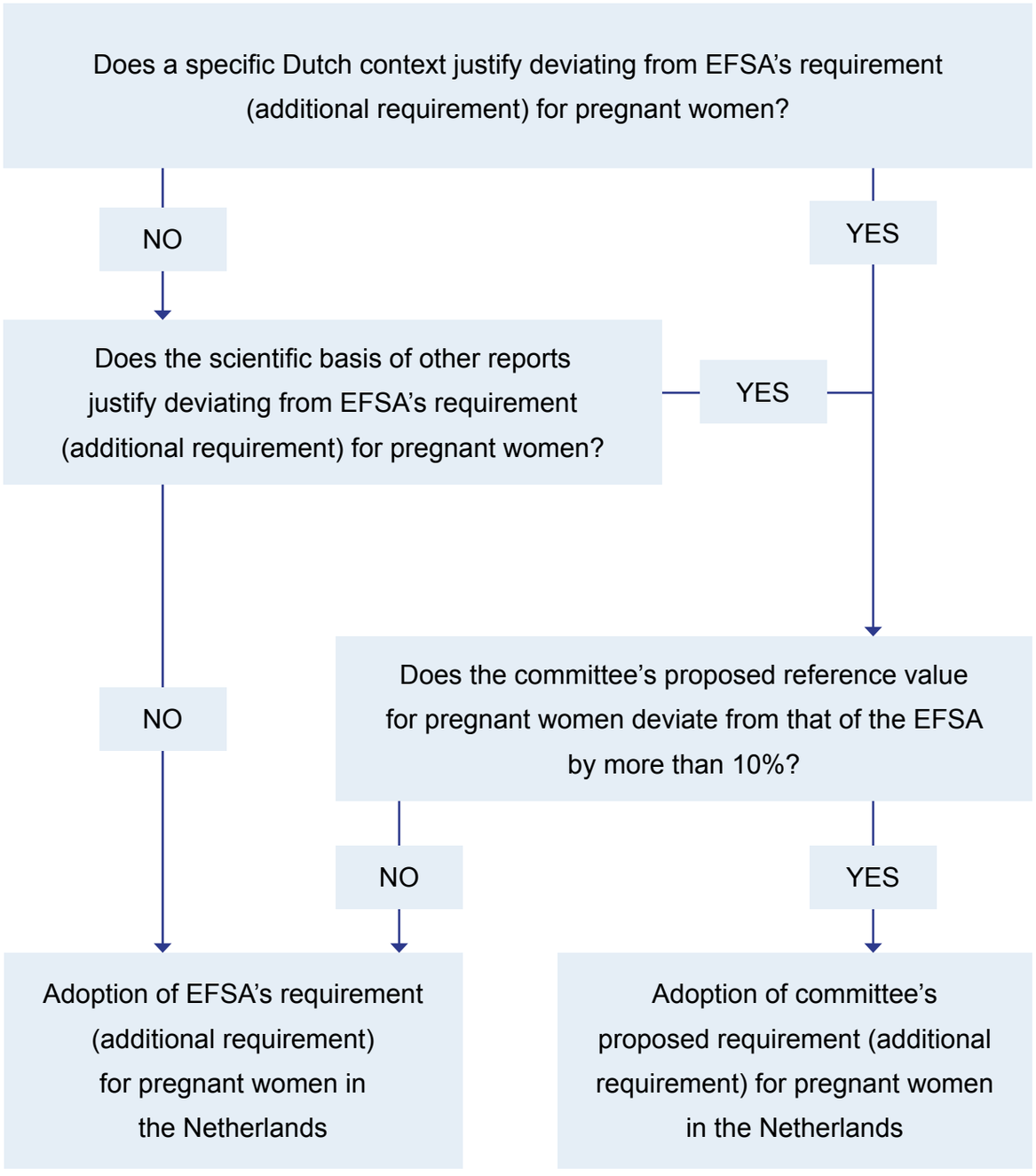
cover groups of European countries: the Nordic countries[42] and the German-speaking countries.[43] Two other reports aim to establish values for large geographical areas: the IOM reports for the United States of America and Canada[44-49] and the report by WHO/FAO[50] used in countries all over the world. The latter report is primarily intended for use in non-Western areas and, as a result the WHO/FAO reference values may deviate from the reference values for Western countries. The committee considers that rejection of EFSA's requirements (additional requirements) for pregnant women should be based on scientific evidence. This implies that if there is a lack of scientific evidence on requirements (additional requirements) for pregnant women, there is also no evidence to substantiate any objections to EFSA's requirements (additional requirements) for pregnant women or to the method used to derive them. These requirements (additional requirements) for pregnant women were then accepted for use in the Netherlands, because there is no scientific evidence available from which to derive more evidence-based requirements (additional requirements) for pregnant women than EFSA has already done.

If the answer to questions 1 or 2 was "yes", a third question was asked:

3. Does the committee's proposed reference value for pregnant women deviate from that of the EFSA by more than 10%? The committee considered it important for reference values to be harmonized throughout Europe. Therefore, if the proposed reference value (based on another report, rather than EFSA's) did not deviate by more than 10% from EFSA's reference value, then EFSA's reference value was adopted.

This line of reasoning is summarized in a flowchart presented in figure 1.1.

Figure 1.1. with line of reasoning regarding the adoption or rejection of EFSA's requirement (additional requirement) for pregnant women.



1.3 Evaluation steps taken for each nutrient

Sections 2 to 28 describe the evaluation of reference values per nutrient. Each section starts with a summary and conclusion, and the flowchart as presented in subsection 1.2. Thereafter, the evaluation and argumentation used by the committee to reach the conclusion is described in more detail, before the conclusion itself is presented. Each of these sections consists of four subsections:

Subsection 1 *"Overview and comparison of values"*	The first subsection includes two tables. The first table contains EFSA's reference values for pregnant and non-pregnant women and the values from the five (sets of) reports used for comparison. The second table contains information about the models used to derive the values for pregnant women, what the (additional) requirement is needed for, and the basis for that requirement (additional requirement). Note that the reports use different names for the different types of reference values (Annex B). The overview tables at the beginning of each section show the original terms used in the reports. In the main body of text, EFSA's terminology for the reference values is used: population reference intake (PRI), average requirement (AR), and adequate intake (AI).
Subsection 2 *"Explanation of differences between reports"*	The second subsection provides an explanation for the observed similarities and differences between the reports regarding the research and argumentation used to establish the reference values. This step provides the committee with more insight into assumptions, uncertainties, and points of discussion related to the derivation of the reference values. The original publications referred to by the reports are consulted if this was deemed necessary. For example, in case where reports deviated in their reference values or in the method used to derive these reference values. In this subsection, the committee also indicates whether organizations differentiate between trimesters in their reference values or in the argumentation they used to derive these values.

Subsection 3 *"Pregnancy-related health outcomes and deficiencies"*	The third subsection describes maternal and/or fetal deficiency symptoms associated with each nutrient. It also specifies the intake levels associated with pregnancy-related health outcomes. This information is based on EFSA's report (the original publications were not consulted. The information in this subsection generally does not form the basis for the actual reference values, but it does provide important background information for interpreting the relevance of the reference values for health. If appropriate, in this third subsection the committee also presents a text box with concise supplementation advice.
Subsection 4 *"Strength of the scientific basis and conclusions"*	In the fourth subsection, the committee interprets and evaluates the information provided in the second subsection. This subsection describes the committee's conclusion on the scientific basis for the reference values and the method used to derive these reference values. This subsection also contains a table with the reference values for pregnant women, for use in the Netherlands.

For reasons of efficiency, the committee decided to differentiate in terms of the degree of the level of detail provided. When comparison of the reports resulted in differences in approach and conclusions between the reports, the committee referred to the underlying studies as used by the reports. When a comparison of the five reports revealed few discrepancies between the reports, the committee only referred to the reports and not to the underlying studies.

For requirements that are derived from gestational weight gain (vitamin B6), or gestational weight gain in combination with the reference body weight of women before pregnancy (riboflavin and choline), the committee (re)calculated the requirements of EFSA based on data for Dutch pregnant women. The value of 64.6 kg was used for the pre-pregnancy reference weight of Dutch pregnant women (as previously applied for the 'Dietary reference values for protein'[51]). Dutch reference weights were calculated based on measured height and a healthy pre-pregnancy body mass index (BMI) of 22 kg/m^2. The value of 13.8 kg was used for gestational weight gain (in agreement with the 'Dietary recommendations for pregnant women' report).[35] In addition, the committee recalculated the dietary reference values for vitamin A for non-pregnant women,[3,4] based on the revised Dutch reference body weights, as published in 2021.[51]

1.4 Strength of the scientific basis for the method used to derive the requirement (additional requirement)

The scientific basis for the reference values for non-pregnant women (on which the reference values for pregnant women are often, but not always, based) were described in the 'Evaluation of EFSA's dietary reference values for adults'.[4] For pregnant women, an additive value is often added to the reference values for non-pregnant women. Sometimes a reference value is derived specifically for pregnant women. This subsection describes the assessment of the strength of the scientific basis for the method used to derive the requirement (additional requirement), the committee focused on the part of the reference values that specifically related to pregnancy (such as maternal or fetal tissue growth). The committee distinguished between methods of derivation with a strong, an acceptable, or a weak scientific basis (Table 1.1).

The quality of the studies largely depends on type of outcome measure, type of study, the availability of intake data, study population and population size, publication date. A plausible rationale may be based on pregnancy-

induced increased energy requirement; weight gain; physiological adjustments (like increased absorption).

Table 1.1. Scientific basis for the method used to derive the requirement (additional requirement) for pregnant women

Category	Description
Strong scientific basis	**≥ 1 systematic review or meta-analysis** of *good quality* on the requirement (additional requirement) of pregnant women.
	OR
	≥ 2 intervention studies, prospective cohort studies, or observational studies of *good quality* on the requirement (additional requirement) of pregnant women
Acceptable scientific basis	**1 intervention study, prospective cohort study, systematic review or meta-analysis** of *good quality*… AND/OR **≥ 1 intervention study, prospective cohort study, systematic review or meta-analysis** of *acceptable quality*… …on the requirement (additional requirement) of pregnant women
	OR
	≥ 2 observational studies of *acceptable quality*… OR **1 observational study** of *good quality* AND **1 observational study** of *acceptable quality*… OR **1 observational study** of *good quality*… …on the requirement (additional requirement) of pregnant women
	OR
	A plausible rationale (in the absence of studies on the requirement (additional requirement) of pregnant women)
Weak scientific basis	**1 observational study** of *acceptable quality* on the requirement (additional requirement) of pregnant women
	OR
	All types of studies of *weak quality* on the requirement (additional requirement) of pregnant women (which could not be used to derive the reference values, according to EFSA)
	OR
	The absence of studies on the requirement (additional requirement) of pregnant women

02
Vitamin A (retinol and carotenes)

Summary and conclusion

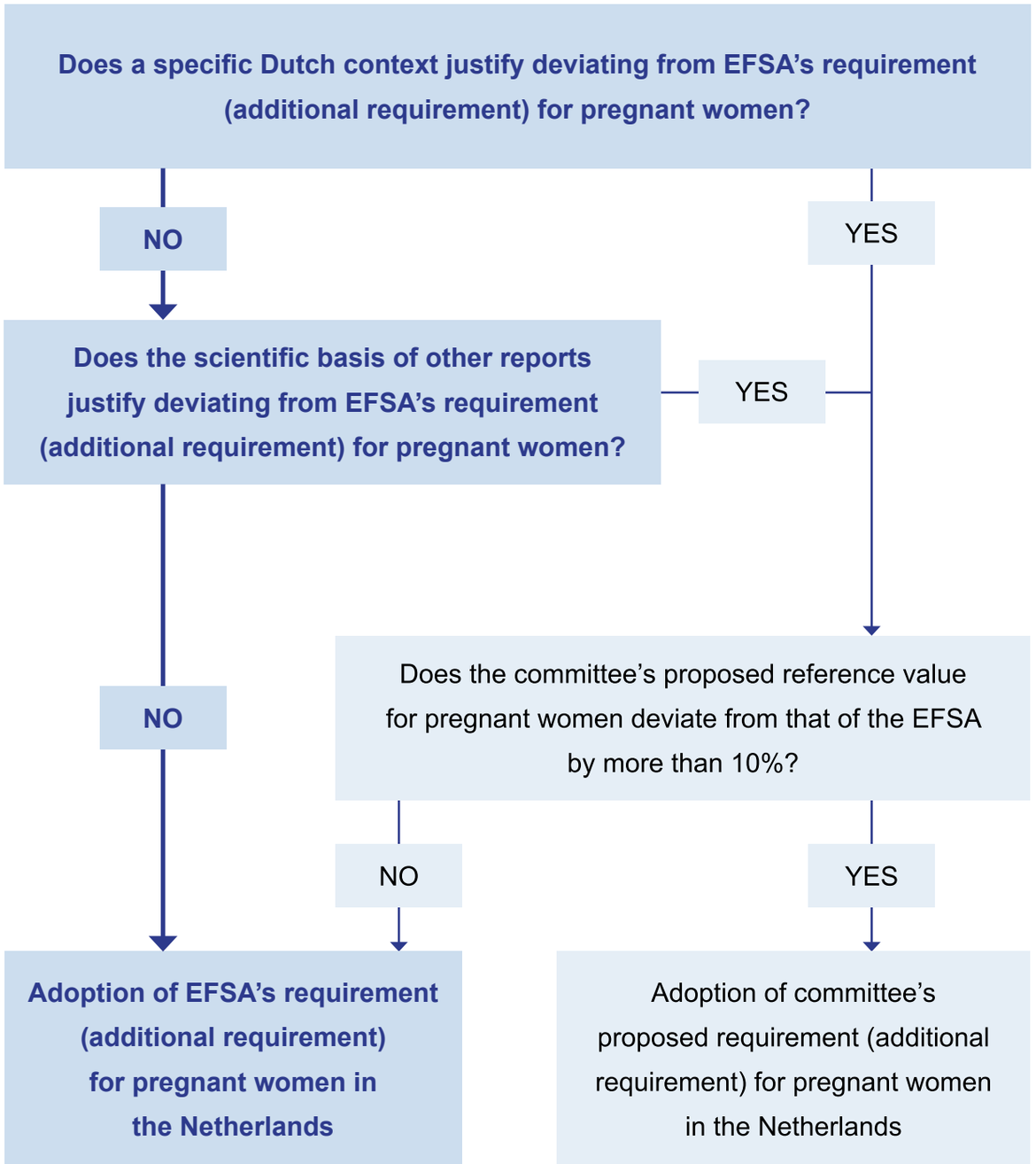
In 2018, the committee adopted EFSA's method of derivation but used the (higher) reference weights for Dutch non-pregnant women.

There appears to be a scientific consensus between the different reports concerning the use of an additive model as the method used to derive the reference values for pregnant women. The committee agrees with the choice of method used to derive the additional requirement for vitamin A during pregnancy used by EFSA. The scientific basis for the method of derivation is deemed to be acceptable.

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women and uses EFSA's CV for the calculation, resulting in the following reference values:

- AR = 580 µg RAE/d
- PR = 750 µg RAE/d

Flowchart with committee's line of reasoning for vitamin A



2.1 Overview and comparison of values

Table 2.1. Overview of the reference values for vitamin A for pregnant women and the model used to derive these values, compared with the reference values for vitamin A for non-pregnant women

Report	Type	Value pregnant women (µg RE or RAE[a]/d)	AR pregnant women (µg RE or RAE/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (µg RE or RAE[a]/d)	AR non-pregnant women (µg RE or RAE/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[5]	PRI	700	540	15	Additive	PRI	650	490	15	70-90 (preformed vitamin A) 5-65 (β-carotene)
NCM 2014[42] = HCNL 2014[38]	RI	800	550	20	Additive	RI	700	500	20	-
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	680[c]	525[c]	15	70-90 (preformed vitamin A) 5-65 (β-carotene)
DACH 2015[43]	RDA	1100	-	-	Multiplication	RDA	800	600	*(12)*	<75
IOM 2001[47]	RDA	770	550	20	Additive	RDA	700	500	20	70-90 (preformed vitamin A) 9-22 (β-carotene)
WHO/FAO 2004[50]	RI	800	370	*(58)*	Additive	RI	500	270	23	90

Abbreviations: -: Not specified, N/A: not applicable, RE: Retinol Equivalent ; RAE: Retinol Activity Equivalent

The difference is described in the HCNL 2018 report.[4] Note that the unit of expression does not influence the outcome of EFSA's factorial method, therefore, for these DRVs the RE and RAE are interchangeable. Calculations done by the committee are depicted in brackets and in italics.

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

[b] Information on the models used for each report is specified in Table 2.2.

[c] These values have been recalculated based on the revised reference body weights for the Netherlands, as published in 2021.[51] The resulting AR is 530 µg RE or RAE/d and the resulting PRI is 690 µg RE or RAE/d.

Table 2.2. Overview of the models used and the basis for the vitamin A requirements (additional requirements) for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2015[5]	Additive (**AR + 50** PRI + 50)[c]	50[d]	Vitamin A deposition due to growth in maternal and fetal tissue.	Assumptions: accumulation of retinol in the fetus over the course of pregnancy is 3600 µg and amount accumulated in maternal tissue is unknown.
NCM 2014[42] = HCNL 2014[38]	Additive (**AR + 50** RI + 100)	70	Vitamin A deposition due to growth in fetal tissue.	IOM's estimate of the additional requirement.[47]
DACH 2015[43]	Multiplication (***RDA x 1.33)***	-	Fetal lung development and maturation.	No further details.
IOM 2001[47]	Additive (**AR + 50** RDA + 70)	70	Vitamin A deposition due to growth in fetal tissue.	Assumptions: accumulation of retinol in the fetus over the course of pregnancy is 3600 µg and liver contains about half of the body's vitamin A when liver stores are low.
WHO/FAO 2004[50]	Additive (**AR + 100** RI + 300)	-	Vitamin A deposition due to growth in maternal and fetal tissue.	Assumptions: newborn infants' retinol requirement is 100 mg/d, a fetus has similar needs, and incremental maternal needs are provided from maternal reserves.

Abbreviations: -: Not specified, N/A: not applicable,. RE: Retinol Equivalent ; RAE: Retinol Activity Equivalent
The difference is described in the HCNL 2018 report.[4] Note that the unit of expression does not influence the outcome of EFSA's factorial method, therefore, for these DRVs the RE and RAE are interchangeable.
[a] If applicable: (+ additional requirement in µg RE or RAE/d).
[b] This column presents any information on absorption during pregnancy if provided by the report.
[c] Due to the CV of 15% and rounding to 1 decimal point, the additional value is equal for AR and PRI.
[d] EFSA assumes an efficiency of storage of 50% for the fetus, the efficiency of storage representing the fraction of ingested retinol which is absorbed and retained in the body (and more particularly in the liver).

2.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, on differences in reference values, and on the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report, and NCM followed IOM (2001).

Differences in the method of derivation

All reports, except DACH, used an additive model to derive the reference values for pregnant women. It is uncertain why DACH's proposed requirement is 33% higher than the rest. For this reason, no further consideration will be given to the DACH report.

EFSA and IOM used the same additional requirement of 50 µg/d for their AR values, whereas WHO/FAO used a higher additional requirement of 100 µg/d for its AR value. EFSA and IOM both based their additional requirement on the accumulation of vitamin A in the fetus' liver over the course of pregnancy, whereas WHO/FAO based its additional requirement on the newborn infants' requirement of ~100 µg/d of retinol (for growth). During the third trimester, the fetus grows rapidly and, although it is obviously smaller than full-term infants, WHO/FAO assumed that it has similar needs.

EFSA and IOM both adopted liver vitamin A concentrations of 1,800 µg, which had been derived from 10 full-term, stillborn infants of healthy mothers at 37-40 gestational weeks (these results were obtained in a 1979 Thai study).[52] IOM estimated (followed by EFSA) that a fetus accumulates 3,600 µg of vitamin A. This is based on the assumption that the liver contains about half of the body's vitamin A when liver stores are low, as in the case of newborns.

EFSA calculated the daily additional requirement for the second half of the pregnancy (i.e., 140 days), assuming a storage efficiency of 50% for the fetus, which corresponds to an adjustment factor of 2. This gives the following calculation: 3,600 µg/140 days x 2 = 51 µg/d (50 µg/d after rounding).

IOM calculated the daily additional requirement for the last trimester (i.e., 90 days), assuming a maternal vitamin-A absorption of 70%, which corresponds to an adjustment factor of 1.4. This gives the following calculation: 3,600 µg/90 days x 1.4 = 56 µg/d (50 µg/d after rounding).

Differences in the reference values

With the additive model, differences between the values given in separate reports resulted from disparities in the following three aspects.

1. The reference value for non-pregnant women:
   EFSA used a lower value for non-pregnant women than IOM and a higher value than WHO/FAO.[4]
2. The CV used:
   EFSA used a CV of 15%, whereas IOM used a CV of 20%.

3. The method used to derive the additional requirement:
   EFSA and IOM derived a lower additional requirement than WHO/FAO, as described above.

EFSA's PRI was based on the additional requirement added to the AR of non-pregnant women multiplied by twice the CV of 15%: (490 µg/d + 51 µg/d) x 1.3 = 703.3 µg/d (700 µg/d after rounding).
IOM's PRI was derived in the same way: (500 µg/d + 50 µg/d) x 1.4 = 770 µg/d.
WHO/FAO's PRI was based on twice the additional requirement[a] added to the PRI for non-pregnant women and including an additional 100 µg/d because therapeutic levels of vitamin A are generally higher than preventive levels: 500 µg/d + (2 x 100 µg/d) + 100 µg/d = 800 µg/d.

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester. The additional increment estimated by EFSA and IOM for the second half and the last trimester of the pregnancy respectively, was applied to the whole pregnancy in order to allow for the extra retinol requirement related to the growth of maternal tissues (e.g., placenta).

[a] The WHO/FAO doubled the additional requirement because a large proportion of the world's population of pregnant women live under conditions of deprivation, so this measure was needed to ensure adequacy of intake during pregnancy.

2.3 Pregnancy-related health outcomes

Deficiencies

EFSA reported that fetal 'vitamin A deficiency syndrome' is well documented in animals.[5] It comprises the following symptoms:

- Intrauterine and post-natal growth retardation.
- Large array of congenital malformations.

Intake and associated health outcomes

EFSA reported that intervention studies have investigated the effect of supplementation with retinol, often in combination with other nutrients, for the primary prevention of reproduction-related outcomes.[5] EFSA noted that the studies typically used high doses of vitamin A and that background vitamin A intake was not assessed. EFSA concluded that these data could not be used to set DRVs for vitamin A in pregnant women.

2.4 Strength of the scientific basis and conclusions

In 2018, the committee adopted EFSA's reasoning but used the reference weights for Dutch non-pregnant women (which are higher).[4]

Additive model

There appears to be a scientific consensus regarding the use of an additive model to derivate the reference values for pregnant women.

Conclusion and strength of the additive model

The committee agrees with the choice of method used by EFSA to derive the additional requirement for vitamin A during pregnancy (which is similar to IOM's and, by extension, to NCM's and HCNL 2014's as well). The higher WHO/FAO estimate is based on an extrapolation of estimates of newborn infants' requirements, which involves greater uncertainty than methods based on estimates in pregnant women/fetuses.

The evidence supporting EFSA's method of deriving the additional vitamin A requirement during pregnancy was based on a single prospective cohort study[52] of acceptable quality. The committee deems the scientific basis for this method of derivation to be acceptable.

Reference values for pregnancy

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women (Table 2.3), and uses EFSA's CV for the calculation (in accordance with the reference values for non-pregnant women).

Table 2.3. Reference values for vitamin A recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	580 µg RAE/d	*530 µg RAE/d*
Population reference intake (PRI)	750 µg RAE/d[a]	*690 µg RAE/d*

[a] PRI is calculated as ($AR_{non\text{-}pregnant}$ + additional requirement) multiplied by with twice the CV:
PRI = (525 µg RAE/d + 50 µg RAE/d) x 1.3.

03
Thiamin (vitamin B1)

Summary and conclusion

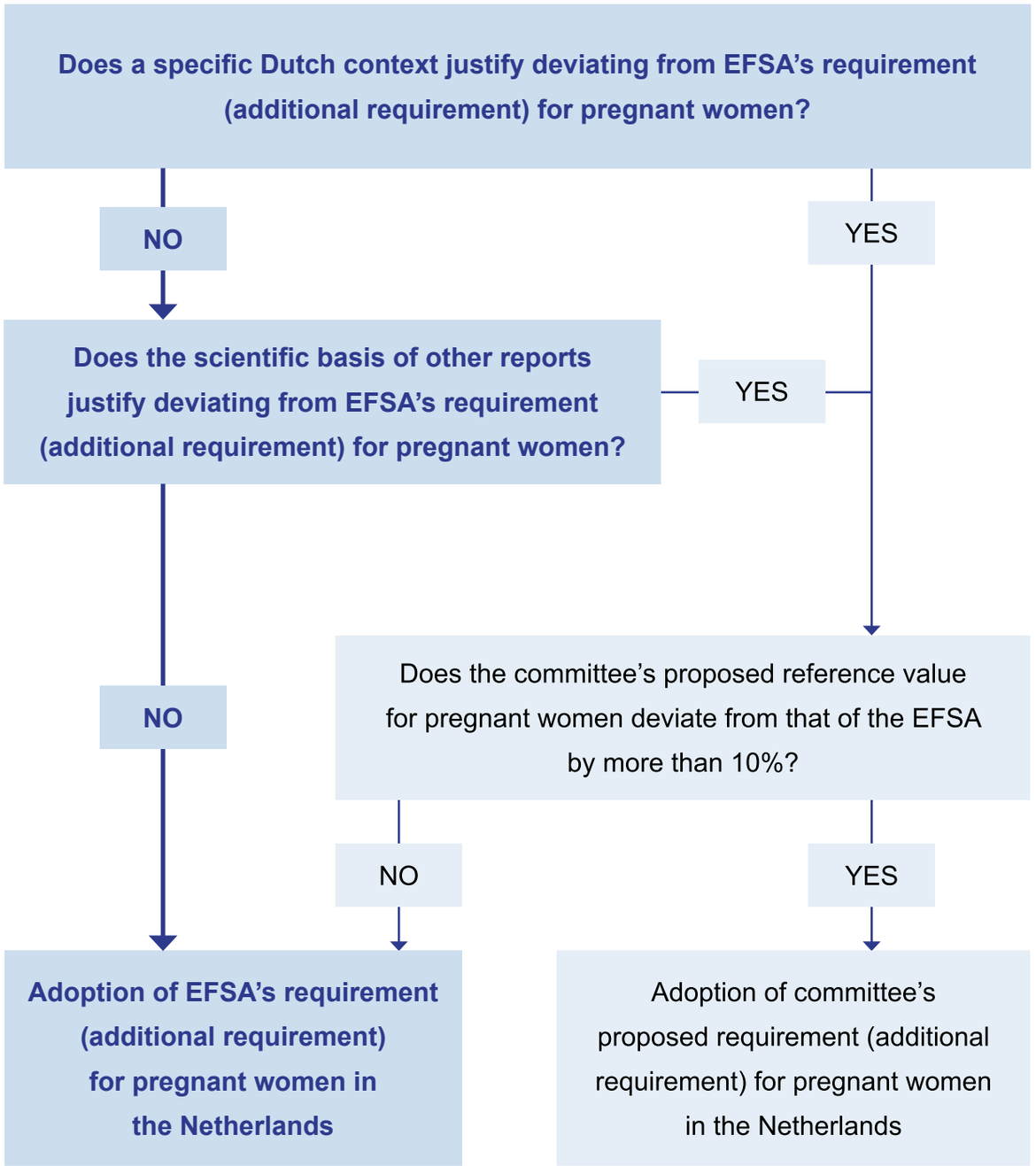
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

There appears to be a scientific consensus between the different reports regarding the use of an additive model to derive the reference values for pregnant women. The committee agrees with EFSA's choice of method for deriving the additional requirement for thiamin during pregnancy. However, it notes that the exact distribution of the different aspects of the increased energy requirement (i.e., deposition, increased energy metabolism, etc.) during pregnancy is still unclear. The scientific basis for the method of derivation is deemed to be acceptable.

The committee accepts EFSA's PRI and AR for pregnant women for use in the Netherlands. These result in the following reference values:

- AR = 0.072 mg/MJ (0.7 mg/d)
- PRI = 0.1 mg/MJ (1.0 mg/d)
- Trimester
- 1st: 0.9 mg/d
- 2nd: 1.0 mg/d
- 3rd: 1.1 mg/d

Flowchart with committee's line of reasoning for thiamin



3.1 Overview and comparison of values

Table 3.1. Overview of the reference values for thiamin in pregnant women and the model used to derive these values, compared with the reference values for thiamin in non-pregnant women

Report	Type	Value pregnant women in mg/MJ (and in mg/d)	AR pregnant women in mg/MJ (and in mg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women in mg/MJ (and in mg/d)	AR non-pregnant women in mg/MJ (and in mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2016[6]	PRI	0.1 *(1.0)*[c] *(Trimester 1st : 0.9 2nd : 1.0 3rd : 1.1)*	0.072 *(0.7)*	20	Additive	PRI	0.1 *(0.9)*	0.072 *(0.6)*	20	>95
HCNL 2000[41] = HCNL 2014[38]	RDA	*(0.13)* (1.4)	*(0.09)* (1.0)	20	Additive	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	0.1 *(0.9)*	0.072 *(0.6)*	20	>95
NCM 2014[42]	RI	0.12 (1.5[d])	0.1 (-)	10	Additive	RI	0.12 (1.1)	0.1 (0.9)	10	>95
DACH 2015[43]	RDA	*(0.13)* (1.2)[e] (Trimester 2nd : 1.2 3rd : 1.3)	0.11 (-)	10	Additive	RDA	*(0.13)* (1.0)	0.11 (-)	10	>95
IOM 1998[48]	RDA	- (1.4)	*(0.07)* (1.2)	10	Additive	RDA	- (1.1)	*(0.07)* (0.9)	10	-
WHO/FAO 2004[50]	AI	- (1.4)	- (-)	-	Additive	AI	- (1.1)	- (-)	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as follows: (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 3.2.
[c] EFSA reported the additional requirements for each trimester in Appendix K in their report. On this basis, the committee calculated the PRI for each trimester and the average PRI for pregnancy.
[d] As reported in Table 1.3 from NCM's report.[42]
[e] The committee calculated the average RDA for pregnancy, assuming an RDA for the 1st trimester equal to the RDA for non-pregnant women.

Table 3.2. Overview of the models used and the basis for the requirements (additional requirements) for thiamin in pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Basis
EFSA 2016[6]	Additive[c] **(PRI by trimester 1st: +0.0 2nd: +0.1 3rd: +0.2)**	-	Increased energy requirement.	Assumptions: thiamin requirement in mg/MJ of pregnant women does not differ from non-pregnant women, increases in average energy requirements in the 1st, 2nd, and 3rd trimesters are +0.29, +1.1, and +2.1 MJ/d respectively, and the average requirement is 0.072 mg/MJ.
HCNL 2000[41] = HCNL 2014[38]	Additive (**AR: +0.2** RDA: +0.3)[d]	-	Increased energy requirement and thiamin deposition due to growth in maternal and fetal tissue.	No further details.
NCM 2014[42]	Additive **(RI: +0.4)**[e]	-	Small increased energy requirement and thiamin deposition due to growth in maternal and fetal tissue.	IOM's estimate of the additional requirement.[48]
DACH 2015[43]	Additive **(RDA by trimester 1st: - 2nd: +0.2 3rd: +0.3)**	-	Increased energy requirement.	Assumptions: increases in average energy requirements in the 2nd and 3rd trimesters are +250 kcal/d *(+1.05 MJ/d)* and +500 kcal/d *(+2.09 MJ/d)* respectively and the average requirement is 0.45 mg/1,000 kcal *(0.11 mg/MJ)*.
IOM 1998[48]	Additive (**EAR: +0.3** RDA: +0.3)[e]	-	Small increased energy requirement and thiamin deposition due to growth in maternal and fetal tissue.	Assumptions: ~20% extra is needed for tissue growth and ~10% extra is needed for the increase in energy requirement.
WHO/FAO 2004[50]	Additive **(AI: +0.3)**[e]	-	Small increase in energy requirement and thiamin deposition, due to growth in maternal and fetal tissues.	IOM's estimate of the additional requirement.[48]

Abbreviations: -: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in mg/d).

[b] This column presents information on absorption during pregnancy if provided by the report.

[c] Estimates in mg/d are based on the reference value for thiamin (mg/MJ) and the additional energy requirement (MJ/d):

[d] AR of 0.8 and RDA of 1.1 mg/d from HCNL 2000.[41]

[e] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for AR and RDA/RI.

3.2 Explanation of differences between reports

This evaluation focuses on differences in the method of derivation, on differences in reference values, and on the use of values per trimester in the reports.

The NCM and WHO/FAO reports followed IOM (1998).

The reference values for thiamin are originally presented in mg/MJ. However, since differences in values between pregnant and non-pregnant women are not visible in units of mg/MJ, the values in this document are primarily presented in mg/d.

Differences in the method of derivation

All reports used an additive model for the reference value for pregnant women. EFSA and DACH used a lower additional requirement for pregnancy than the other reports. This was because they based their additional requirement solely on an increased energy need, whereas HCNL 2014 and IOM (followed by NCM and WHO/FAO) based their additional requirements on a small increase in energy requirement, as well as on the thiamin deposition associated with the growth of maternal and fetal tissue.

Data on thiamin requirements during pregnancy are scarce. EFSA did not derive DRVs based on the few available studies. The additional requirement was based solely on the increase in energy requirements. Both EFSA and DACH assumed that the relationship between thiamin requirement and energy requirement in pregnancy does not differ from that of other adults. Therefore, they applied the AR and PRI for non-pregnant women (expressed in mg/MJ) to pregnancy. EFSA further assumed an increase in energy requirement of 0.29, 1.1, and 2.1 MJ/d for the 1st, 2nd, and 3rd trimester respectively. This was similar to DACH's assumed increases in energy requirement of 1.05 MJ/d and 2.09 MJ/d for the 2nd and 3rd trimester respectively. EFSA's increases in energy requirements correspond to additional requirements of 0.02, 0.08, and 0.15 mg/d for the 1st, 2nd, and 3rd trimester. After multiplying by twice the CV of 20%, the additional requirements of 0.11, and 0.21 mg/d for the 2nd and 3rd trimester were similar to DACH's corresponding additional requirements of 0.11 mg/d and 0.23 mg/d for the respective trimesters.

The basis for HCNL 2014's proposed higher requirement of 0.2 mg/d higher requirement is uncertain. Nor is it clear, which proportion is attributed to increased energy need and which proportion is attributed to increased tissue growth. Therefore, no further consideration will be given to the HCNL 2014 report.

IOM attributed a proportion of ~10% to an increase in energy requirement and a proportion of ~20% to increased growth in maternal and fetal tissue. This resulted in an additional requirement for pregnancy of 0.27 mg/d (0.3 mg/d after rounding).

Differences in the reference values

With the additive model, differences between the values given in separate reports resulted from disparities in the following three factors.

1. The reference value for non-pregnant women:
   EFSA used a lower value for non-pregnant women than the other reports.[6]
2. The CV used:
   EFSA used a CV of 20%, whereas the other reports used a CV of 10%.
3. The method used to derive the additional requirement:
   EFSA and DACH derived a lower additional requirement than IOM, as described above.

EFSA's additional requirements (in mg/d) for pregnant women were estimated in Appendix K of their report for each trimester (including a CV of 20%). The committee adds these values to the PRI for non-pregnant women:

- PRI 1st trimester: 0.9 mg/d + 0.03 mg/d = 0.93 mg/d
- PRI 2nd trimester: 0.9 mg/d + 0.11 mg/d = 1.01 mg/d
- PRI 3rd trimester: 0.9 mg/d + 0.21 mg/d = 1.12 mg/d

The committee calculates an average PRI of (0.93 + 1.01 + 1.12)/3 = 1.02 mg/d (1.0 mg/d after rounding).

DACH's PRIs for pregnant women were estimated in Table A5 of their report for the 2nd and 3rd trimester by multiplying by twice the CV of 10% the AR for non-pregnant women (0.11 mg/MJ) times the daily energy requirement (including the additional increment for increased energy need): +1.05 and + 2.09 MJ/d for the 2nd and 3rd trimester respectively (9.00 MJ/d and 10.05 MJ/d):

- PRI 2nd trimester: (0.11 mg/MJ x 1.2) x 9 = 1.16 mg/d (1.2 mg/d after rounding)
- PRI 3rd trimester: (0.11 mg/MJ x 1.2) x 10.05 = 1.30 mg/d (1.3 mg/d after rounding)

The committee calculates an average PRI of (1.00 + 1.16 + 1.12)/3 = 1.15 mg/d (1.2 mg/d after rounding).

IOM estimated its PRI for pregnant women by adding the additional requirement to the AR for non-pregnant women and multiplying by twice the CV of 10%. PRI: (0.9 mg/d + 0.3 mg/d) x 1.2 = 1.44 mg/d (1.4 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

EFSA and DACH differentiated their additional requirement by trimester. EFSA reported a higher energy requirement for all trimesters, whereas DACH did not report a higher energy requirement for the 1st trimester. IOM noted that adding the additional requirement to the AR for non-pregnant women gave an AR for the 2nd and 3rd trimesters of pregnancy, yet it applied this AR to the entire pregnancy.

3.3 Pregnancy-related health outcomes

EFSA described no pregnancy-related thiamin deficiencies, nor did it cite any studies showing intake levels associated with pregnancy-related health outcomes.[6]

3.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Additive model

There appears to be a scientific consensus with regard to the derivation of the reference values for pregnant women with an additive model.

Conclusion and strength of the additive model

The committee agrees with EFSA's choice of method (which is similar to DACH's) to deriving the additional requirement for thiamin during pregnancy. The committee notes that the exact distribution is of the different aspects of the increased energy requirement (i.e., deposition, increased energy metabolism, etc.) during pregnancy is still unclear.

The evidence for EFSA's method of deriving the additional thiamin requirement was not supported by any references. Very little data is supplied on thiamin requirements during pregnancy and their results are ambiguous in this regard. The method of derivation was based on a plausible rationale. The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

The committee accepts EFSA's PRI and AR for pregnant women for use in the Netherlands (Table 3.3).

Table 3.3. Reference values for thiamin recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	0.072 mg/MJ (0.7 mg/d)	*0.072 mg/MJ (0.6 mg/d)*
Population reference intake (PRI)	0.1 mg/MJ (1.0 mg/d)[a] (Trimester 1st: 0.9 mg/d 2nd: 1.0 mg/d 3rd: 1.1 mg/d)	*0.1 mg/MJ (0.9 mg/d)*

[a] PRI is calculated as $PRI_{non\text{-}pregnant}$ + additional requirement by trimester:
PRI 1st trimester = 0.9 mg/d + 0.03 mg/d
PRI 2nd trimester = 0.9 mg/d + 0.11 mg/d
PRI 3rd trimester = 0.9 mg/d + 0.21 mg/d
The average PRI for pregnancy is calculated from these PRIs by trimester.

04
Riboflavin (vitamin B2)

Summary and conclusion

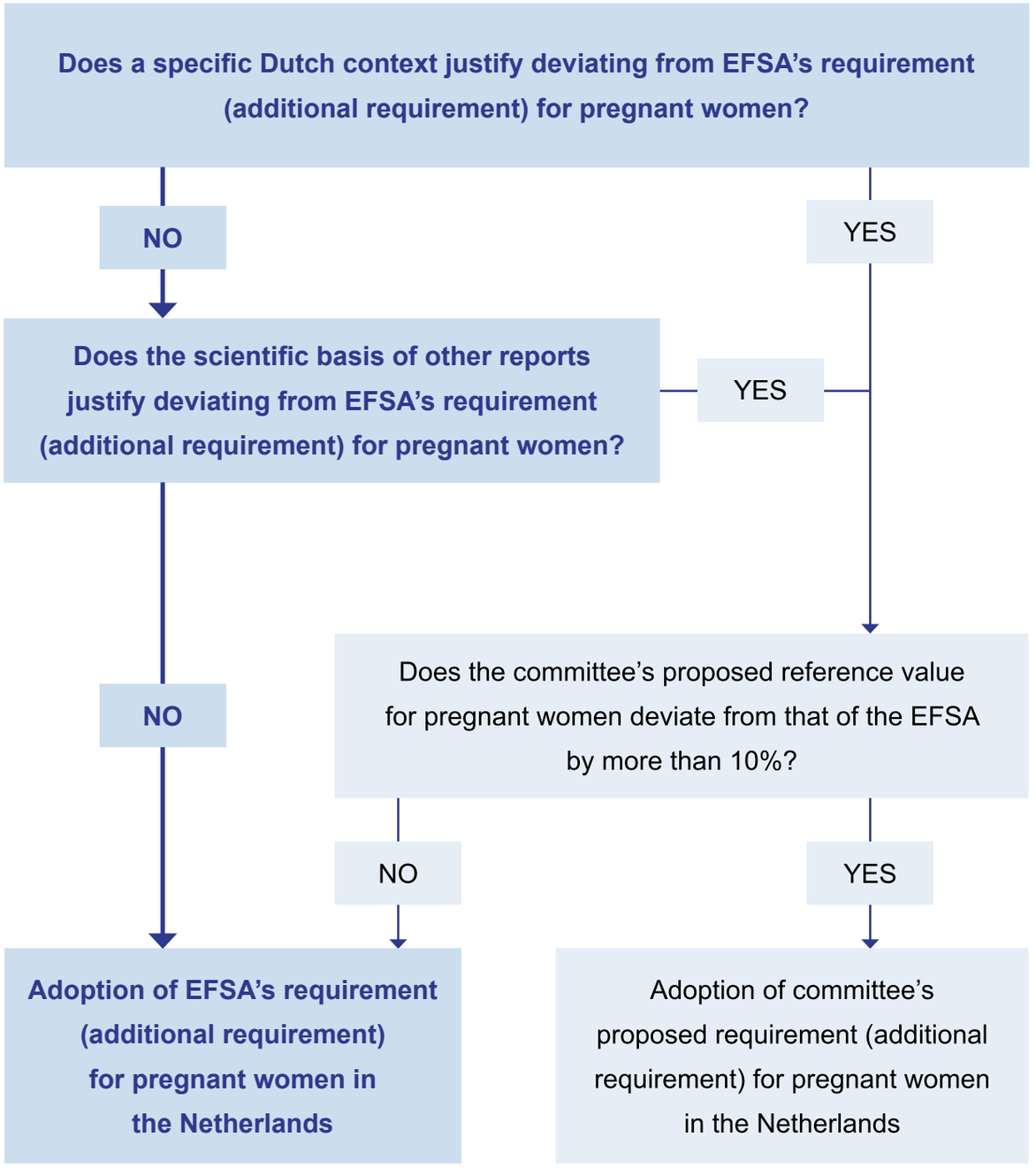
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

There appears to be a scientific consensus between the different reports with regard to the use of an additive model to derive reference values for pregnant women and to the value of this additional requirement. The scientific basis for the method of derivation is deemed to be acceptable.

The committee accepts EFSA's AR and PRI for pregnant women for use in the Netherlands, resulting in the following reference values:

- AR = 1.5 mg/d
- PRI = 1.9 mg/d

Flowchart with committee's line of reasoning for riboflavin



4.1 Overview and comparison of values

Table 4.1. Overview of the reference values for riboflavin for pregnant women and the model used to derive these values, compared with the reference values for riboflavin for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2017[7]	PRI	1.9	1.5	10	Scaling	PRI	1.6	1.3	10	95
HCNL 2000[41] = HCNL 2014[38]	RDA	1.4	1.0	*(18)*	Additive	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	1.6	1.3	10	95
NCM 2014[42]	RI	1.6[c]	-	-	Unknown	RI	Age 18-30: 1.3 Age 31-60: 1.2	1.1	-	50-60 (free riboflavin) 60-70 (whole foods)
DACH 2015[43]	RI	*(1.3)*[d] Trimester 2nd: 1.3 3rd: 1.4	-	10	Additive	RI	1.1	0.9	10	<95 (oral bolus) 60-67 (whole foods)
IOM 1998[48]	RDA	1.4	1.2	10	Additive	RDA	1.1	0.9	10	95
WHO/FAO 2004[50]	RI	1.4	-	-	Additive	RI	1.1	-	-	<95 "…but limited to ~27 mg/single meal or dose."

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 4.2.
[c] As reported in Table 1.3 in NCM's report.[42]
[d] The committee calculated the average RI for pregnancy by assuming that the RI for the 1st trimester is equal to the RI for non-pregnant women.

Table 4.2. Overview of the models used and the basis for pregnant women's riboflavin requirements (additional requirements).

Report	Model used[a]	Absorption (%)[b]	Needed for	Basis
EFSA 2017[7]	Scaling (**AR: +0.2** PRI: +0.3)	-	Riboflavin deposition due to growth in maternal and fetal tissue.	Assumptions: riboflavin requirement is related to metabolically active body mass, reference weight of non-pregnant women is 58.5 kg and the mean gestational increase in body weight during pregnancy is 12 kg.
HCNL 2000[41] = HCNL 2014[38]	Additive (AR: +0.2 **RDA: +0.3**)[c]	-	Increased energy requirement and riboflavin deposition due to tissue growth.	Assumptions: 0.1 mg/d is needed for the increase in average energy requirement and an extra 0.2 mg/d is needed for retention.
NCM 2014[42]	Additive **(RI: +0.3)**	-	-	Reference values from NNR 2004, no further details.[53]
DACH 2015[43]	Additive **(RDA by trimester 1st: - 2nd: +0.2 3rd: +0.3)**	-	Increased energy requirement.	Assumptions: increases in average energy requirement in the 2nd and 3rd trimesters are +250 kcal/*d (+1.05 MJ/d)* and +500 kcal/d *(+2.09 MJ/d)* respectively and the average requirement is 0.5 mg/1,000 kcal *(0.12 mg/MJ).*
IOM 1998[48]	Additive (AR: +0.3 **RDA: +0.3**)[d]	"Higher rate of riboflavin uptake at the maternal surface of the placenta, due to an increased level of carrier proteins."	Minor increases in energy requirement and riboflavin deposition due to growth in maternal and fetal tissues.	No further details are given concerning the assumed proportion attributed to the increased energy requirement and to the tissue growth.
WHO/FAO 2004[50]	Additive **(RI: +0.3)**	-	Riboflavin deposition due to growth in maternal and fetal tissue.	No further details.

Abbreviations: -: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in mg/d).

[b] This column presents information on absorption during pregnancy if this is provided by the report.

[c] AR of 0.8 and RDA of 1.1 mg/d from HCNL 2000.[41]

[d] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for EAR and RDA.

4.2 Explanation of differences between reports

This evaluation focuses on differences in the method of derivation, on differences in reference values, and on the use of values per trimester in the reports.

Differences in the method of derivation

EFSA used allometric scaling (described below) to establish the reference value for pregnant women, whereas all other reports used an additive model. Based on EFSA's scaling approach, the committee calculated the additional requirement for EFSA and compared it to those given in the other reports.

EFSA, HCNL 2014, NCM, IOM, and WHO/FAO all used the same additional requirement of +0.3 mg/d for their PRI values. DACH used an additional requirement of +0.2 mg/d for the 2nd trimester and +0.3 mg/d for the 3rd trimester. As stated, EFSA based their value on scaling. HCNL 2014 and IOM based their additional requirement on both the increase in energy requirement and the riboflavin deposition in newly formed maternal and fetal tissues; DACH based their additional requirement solely on the increase in energy requirement; WHO/FAO based theirs solely on the riboflavin deposition in newly formed maternal and fetal tissues. The basis for NCM's proposed 0.3 mg/d higher requirement is unclear. In NNR 2004, NCM made reference to NNR 1996, but provided no further explanation. For this reason, no further consideration will be given to the NCM report.

In the absence of sufficient data to derive DRVs for riboflavin for pregnant women, EFSA assumed that riboflavin requirement is related to metabolically active body mass. They used the reference body weight for 18-79 year old women of 58.5 kg[a] and a reference weight for pregnant women of 70.5 kg, based on a gestational increase in body weight of 12 kg[b]. Allometric scaling: $AR^{pregnant} = AR^{non\text{-}pregnant} \times (weight^{pregnant}/weight^{non\text{-}pregnant})^{0.75} = AR^{non\text{-}pregnant} \times (70.5/58.5)^{0.75} = AR^{non\text{-}pregnant} \times 1.15$.
This corresponds to an AR for pregnant women of 1.5 mg/d (i.e., an additional requirement of +0.2 mg/d).

DACH assumed an increase in energy requirement of +1.05 MJ/d and +2.09 MJ/d for the 2nd and 3rd trimester respectively. This corresponds to an additional requirement of 0.13 mg/d and 0.25 mg/d respectively.

Differences in the reference values

With the additive model, differences between the reference values given in separate reports resulted from disparities in the following three factors.

1. The reference value for non-pregnant women: EFSA used a higher value for non-pregnant women than the other reports.[7]
2. The CV used: All reports used a CV of 10% except for HCNL 2014, which used a CV of 18%.

[a] The reference body weight was based on the measured heights of 19,969 women in 13 EU Member States assuming a BMI of 22 kg/m^2.[54]

[b] Applies to women with a singleton pregnancy and a pre-pregnancy BMI of 18.5-24.9 kg/m^2.[54] The 12 kg increase in body weight applies to the end of pregnancy. The average weight gain during pregnancy is substantially smaller.

3. The method used to derive the additional requirement: All reports derived a similar additional requirement, even though their method of derivation differed slightly, as described above.

HCNL 2014's PRI was based on the additional requirement added to the PRI of non-pregnant women: 1.1 mg/d + 0.3 mg/d = 1.4 mg/d.

EFSA's PRI was based on the AR for pregnant women (as calculated above), multiplying by twice the CV of 10% resulting in a PRI (rounded) of 0.9 mg/d.

IOM's PRI for pregnant women was estimated by adding the additional requirement to the AR for non-pregnant women and multiplying by twice the CV of 10%: (0.9 mg/d + 0.3 mg/d) x 1.2 = 1.44 mg/d (1.4 mg/d after rounding).
WHO/FAO's PRI for pregnant women was estimated in the same way as IOM's PRI.

DACH's PRIs for pregnant women were estimated for the 2nd and 3rd trimester by multiplying the AR for non-pregnant women (0.12 mg/MJ) with twice the CV of 10% times the daily energy requirement (including the additional increment for the increased energy requirement) for the 2nd and 3rd trimester respectively (9.00 MJ/d and 10.05 MJ/d):

- PRI 2nd trimester: (0.12 mg/MJ x 1.2) x 9 = 1.29 mg/d
- PRI 3rd trimester: (0.12 mg/MJ x 1.2) x 10.05 = 1.44 mg/d

The committee calculates an average PRI of (1.1 + 1.29 + 1.44)/3 = 1.28 mg/d (1.3 mg/d after rounding).

Like HCNL 2014, IOM, and WHO/FAO, EFSA reported an intervention study in 12 pregnant riboflavin-deficient Filipino women (2nd or 3rd trimester).[55,56] The authors reported EGRAC values of up to ≤1.3 (indicative of an adequate riboflavin status) with a minimum riboflavin requirement of 1.36 (SD ±0.37) mg/d. This was higher than the minimum riboflavin requirement of 0.72 (SD ±0.09) mg/d needed for non-pregnant riboflavin-deficient women (n=6). The study proposed a PRI for pregnant women of 1.8 mg/d (rounded from 1.77), which involved adding a safety factor of 30% to the experimentally derived minimum riboflavin requirement to cover any individual variations. The committee notes that EFSA's PRI of 1.9 mg/d is comparable, and that the other reports' PRI of 1.4 mg/d is substantially lower than the proposed PRI from this Filipino study. EFSA concluded that this intervention study provided only supportive evidence for setting DRVs for riboflavin for pregnant women. This was due to the following limitations in the use of EGRAC: it provides only indirect information on the riboflavin status; it is considered to indicate the degree of tissue saturation with riboflavin; and the analytical methods for assessing EGRAC are not standardised.

Differences between the 1st, 2nd, and 3rd trimester

Only DACH differentiated its PRI by trimester, based on the energy requirements in each trimester. EFSA acknowledged that accretion in fetal tissue mostly occurs in the last months of pregnancy. However, in order to allow for the extra need related to the growth of maternal tissues (e.g., placenta) EFSA applied the additional requirement to the whole period of pregnancy.

4.3 Pregnancy-related health outcomes

Deficiencies

EFSA described a clinical case of a woman with riboflavin deficiency – indicated by an EGRAC of 2.81 (adequate status: ≤1.3) – that was due to a genetic defect related to a riboflavin transporter protein.[7] While the woman showed no clinical symptoms of deficiency herself, she gave birth to a child with:

- Malformations of the urinary tract.
- Clinical and biochemical signs of multiple acyl-coenzyme A dehydrogenase deficiency (MADD).

Intake and associated health outcomes

EFSA reported three studies on the association between riboflavin intake and pregnancy-related outcomes.[7] One study showed a statistically significant positive linear association of riboflavin intake at the 22nd week of gestation and birth length or birth weight. Another study showed no association between riboflavin intake (as assessed at 16 months after pregnancy as a proxy for usual intake in the preconception period) and the odds of congenital heart defects, after adjusting for folate and nicotinamide (niacin) intake. The third study showed that riboflavin intakes of <1.35 mg/d were associated with an increased risk of transverse limb deficiencies in women who were not using a folic acid-containing supplement (OR=2.94, 95% CI: 1.04-8.32) compared with unsupplemented women with riboflavin intakes of >2.57 mg/d. The committee notes that EFSA's PRI of 1.9 mg/d provides a margin above the intake level associated with transverse limb deficiencies.

EFSA concluded that these studies could not be used to derive DRVs for riboflavin in pregnancy as evidence from just a single observational study on a particular outcome is not sufficient to provide strong evidence of a relationship.

4.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Additive model

There appears to be a scientific consensus regarding the use of an additive model to derive the reference values for pregnant women.

Conclusion and strength of the additive model

The method used by EFSA to derive the additional requirement for riboflavin during pregnancy differs from the method used in the other reports. Nevertheless, it resulted in the same additional requirement of +0.3 mg/d as HCNL 2014, NCM, IOM, and WHO/FAO. There appears to be international agreement on this additional requirement.

The evidence of EFSA's method of derivation for the additional riboflavin requirement was based on allometric scaling (plausible rationale) using the mean gestational increase in body weight of 12 kg. It was also supported by the findings of a small-scale study on riboflavin requirements during pregnancy.[55,56] The committee deems the scientific basis for the method of derivation to be acceptable.

The committee used the same method of allometric scaling as used by EFSA, with an increase in body weight of 13.8 kg and a reference body weight of 64.6 kg, which resulted in the same AR and PRI values as calculated by EFSA.

Reference values for pregnancy

EFSA's reference value for non-pregnant women is higher than the corresponding values in the other reports. As a result, EFSA's reference value for pregnant women is also higher. The sole study in which the total riboflavin requirement was estimated (in twelve pregnant Filipino women) supports EFSA's reference value. The committee accepts EFSA's AR and PRI for pregnant women for use in the Netherlands (Table 4.3).

Table 4.3. Reference values for riboflavin recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	1.5 mg/d	*1.3 mg/d*
Population reference intake (PRI)	1.9 mg/d[a]	*1.6 mg/d*

[a] PRI is calculated from the $AR_{scaling}$ multiplied by twice the CV:
$PRI = (AR^{non\text{-}pregnant} \times (weight^{pregnant}/weight^{non\text{-}pregnant})^{0.75}) \times 1.2$
$PRI = (1.3 \times (70.5/58.5)^{0.75}) \times 1.2$

05
Niacin (vitamin B3)

Summary and conclusion

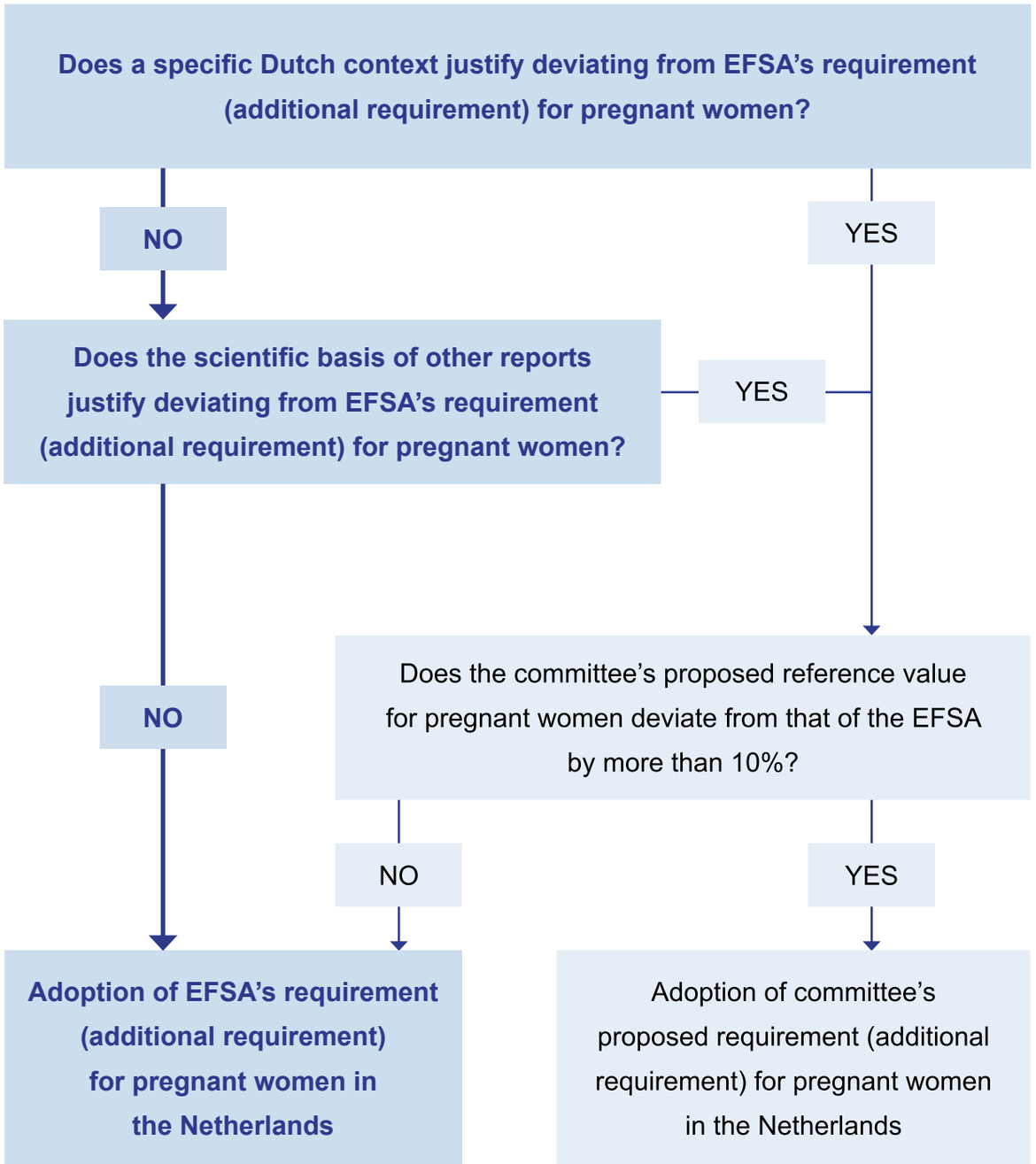
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

There appears to be a scientific consensus between the different reports concerning the use of an additive model to derive the reference values for pregnant women. The committee agrees with EFSA's choice of method for deriving the additional requirement for niacin during pregnancy. However, it also notes that the exact distribution is of the different aspects of the increased energy requirement (i.e., deposition, increased energy metabolism, etc.) during pregnancy is still unclear. The scientific basis for the method of derivation is deemed to be acceptable.

The committee accepts EFSA's PRI and AR for pregnant women for use in the Netherlands. This results in the following reference values:

- AR = 1.3 mg NE/MJ
- PRI = 1.6 mg NE/MJ (16 mg NE/d)
- Trimester
- 1st: 15 mg NE/d
- 2nd: 16 mg NE/d
- 3rd: 17 mg NE/d

Flowchart with committee's line of reasoning for niacin



5.1 Overview and comparison of values

Table 5.1. Overview of the reference values for niacin for pregnant women and the model used to derive these values, compared with the reference values for niacin for non-pregnant women

Report	Type	Value pregnant women in mg NE/ MJ (and in mg NE/d)	AR pregnant women in mg NE/ MJ (and in mg NE/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women in mg NE/ MJ (and in mg NE/d)	Value non-pregnant women in mg NE/ MJ (and in mg NE/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2014[8]	PRI	1.6 *(16)*[c] *(Trimester 1st: 15* *2nd : 16* *3rd: 17)*	1.3 (-)	10	Additive	PRI	1.6 *(14)*	1.3 (-)	10	23-70 (lowest from cereals, highest from animal products)
HCNL 2000[41] =HCNL 2014[38]	RDA	- (17)	- (12)	*(~20)*	Additive	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	1.6 *(14)*	1.3 (-)	10	23-70 (lowest from cereals, highest from animal products)
NCM 2014[42]	RI	1.65 (17)	1.3 (-)	*(~10)*	Additive	RI	1.65 (15) (Age 18-30 : 15 Age 31-60: 14)	1.3 (12)	10	"Near complete absorption of up to 3 grams of nicotinic acid. In cereals…less available"
DACH 2015[43]	RDA	1.6 (14)[d] (Trimester 2nd : 14 3rd: 16)	1.3 (-)	10	Additive	RDA	1.6 (19-24 yr: 13 25-50 yr: 12)	1.3 (-)	10	25-70 (lowest from cereals, highest from animal products)
IOM 1998[48]	RDA	- (18)	- (14)	15	Additive	RDA	- (14)	- (11)	15	30 (mature cereal grains) "Much more available" (meats) "Highly available" (beans, liver, enriched and fortified products)
WHO/FAO 2004[50]	AI	- (18)	- (-)	-	Additive	AI	- (14)	- (-)	-	-

Abbreviations: -: Not specified, N/A: not applicable, NE: niacin equivalents, niacin can be synthesized in the human body from the essential amino acid tryptophan. ~60 mg of tryptophan yields 1 mg niacin equivalent (NE)
Calculations done by the committee are depicted in brackets and in italics.

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

[b] Information on the models used for each report is specified in Table 5.2.

[c] EFSA reported the additional requirements for each trimester in Appendix K of their report. On this basis, the committee calculated the PRI for each trimester and the average PRI for pregnancy.

[d] The committee calculated the average RDA for pregnancy, assuming an RDA for the 1st trimester equal to the RDA for non-pregnant women. For this, the average was calculated from the RDA of 13 mg NE/d for 19 to 24-year-olds and the RDA of 12 mg NE/d for 25 to 50-year-olds.

Table 5.2. Overview of the model used and the basis for the requirements (additional requirements) for niacin for pregnant women

Report	Model used[a] (mg NE/d)	Absorption (%)[b]	Needed for	Basis
EFSA 2014[8]	Additive[c] **(PRI by trimester 1st: +1 2nd: +2 3rd: +3)**	"Conversion of tryptophan to niacin is more efficient in pregnant women than in other adults"	Increased energy requirement.	Assumptions: Pregnant women's niacin requirement in mg/MJ does not differ from that of non-pregnant women; increases in average energy requirements in the 1st, 2nd, and 3rd trimesters are 0.29, 1.1, and 2.1 MJ/d respectively; and the average requirement is 1.31 mg/MJ.
HCNL 2000[41] =HCNL 2014[38]	Additive (**AR +3.0** RDA +4.0)[d]	-	Increased energy requirement and niacin deposition due to growth in maternal and fetal tissue.	Assumptions: an extra 2 mg NE/d is needed for tissue growth and an extra 1 mg NE/d is needed for increased energy.
NCM 2014[42]	Additive **(RI: +2)**[e]	-	Increased energy requirement.	No further details.
DACH 2015[43]	Additive **(RDA by trimester 1st: - 2nd: +1.5 3rd: +3.5)**[f]	-	Increased energy requirement.	Assumption: increases in average energy requirements in the 2nd and 3rd trimesters are +250 kcal/d *(+1.05 MJ/d)* and +500 kcal/d *(+2.09 MJ/d)* respectively; and the average requirement is 5.5 mg/1,000 kcal *(1.31 mg/MJ)*.
IOM 1998[48]	Additive (**AR +3** RDA +4)	-	Increased energy requirement and niacin deposition due to growth in maternal and fetal tissue.	Assumption: ~20% extra is needed for tissue growth and ~10% extra is needed for the increase in energy requirement
WHO/FAO 2004[50]	Additive **(AI +4)**	-	Increased energy requirement and niacin deposition due to growth in maternal and fetal tissue.	Assumption: the estimated energy cost of pregnancy is 230 MJ; the average energy requirement is 1.34 mg NE/MJ; and IOM's estimate for tissue growth is used.[48]

Abbreviations: -: Not specified, N/A: not applicable, NE: niacin equivalents

[a] If applicable: (+ additional requirement in mg NE/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

[c] Estimates in mg NE/d are based on the reference value for niacin (mg/MJ) and the additional energy requirement (MJ/d).

[d] AR of 9 and RDA of 13 mg NE/d from HCNL 2000.[41]

[e] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for AR and RI.

[f] Using the average as calculated from DACH's RDA of 13 mg NE/d for 19 to 24 year olds and the RDA of 12 mg NE/d for 25 to 50 year olds.

5.2 Explanation of differences between reports

This evaluation focuses on differences in the method of derivation, on differences in reference values, and on the use of values per trimester in the reports.

Reference values for niacin are originally presented in mg/MJ. However, since differences in values between pregnant and non-pregnant women are not visible in mg/MJ, the values in this document are primarily presented in mg/d.

Differences in the method of derivation

All reports used an additive model for the reference value for pregnant women. EFSA and DACH used a lower additional requirement for pregnancy than the other reports, because they based their additional requirement solely on an increased energy requirement. However, in addition to this increased requirement, HCNL 2014, IOM, and WHO/FAO based their additional requirements on niacin deposition due to the growth of maternal and fetal tissues. The basis is of NCM's proposed 1-2 mg NE/d higher requirement is unclear. For this reason, no further consideration will be given to the NCM report.

EFSA cited no studies on indicators of niacin requirements during pregnancy. The additional requirement was based solely on the increase in energy requirements. Both EFSA and DACH assumed that the relationship between niacin requirement and energy requirement in pregnancy does not differ from that of other adults. Therefore, they applied the AR and PRI for non-pregnant women (expressed in mg/MJ) to pregnancy. EFSA further assumed an increase in energy requirement of 0.29, 1.1, and 2.1 MJ/d for the 1st, 2nd, and 3rd trimester respectively. These are similar to DACH's assumed increase in energy requirement of 1.05 MJ/d and 2.09 MJ/d for the 2nd and 3rd trimester respectively. EFSA's increases in energy requirements correspond to an additional requirement of 0.38, 1.43, and 2.73 mg NE/d for the 1st, 2nd, and 3rd trimester. These are similar to DACH's corresponding additional requirement of 1.38 mg NE/d and 2.74 mg NE/d for the 2nd and 3rd trimester respectively.

IOM attributed a proportion of 10% (amount in mg NE/d was not specified) to an increase in energy requirement. WHO/FAO referred to IOM (1998) for the proportion of ~2 mg NE/d attributed to increased tissue growth. HCNL 2014 also used a value of 1 mg NE/d for increased energy requirement and a value of 2 mg NE/d for increased tissue growth. This resulted in an additional requirement for pregnancy of 3 mg/d, which was used in all three reports.

Differences in the reference values

With the additive model, differences between the values given in separate reports resulted from disparities in three factors.

1. The reference value for non-pregnant women:
   EFSA and the other reports used the same value for non-pregnant women (which was higher than DACH).[4]
2. The CV used:
   EFSA and DACH used a CV of 10%, IOM of 15%, and HCNL 2014 of 20%.
3. The method used to derive the additional requirement:
   EFSA and DACH derived a lower additional requirement than HCNL 2014, IOM, and WHO/FAO, as described above.

EFSA's additional values (in mg NE/d) for pregnant women were presented in Appendix J of their report. After multiplying the additional values described above by twice the CV of 10%, these values were: 0.5, 1.7, and 3.3 for the 1st, 2nd, and 3rd trimester respectively.
The committee adds these values to the PRI for non-pregnant women to derive the following PRIs for pregnant women:

- PRI 1st trimester: 14 mg NE/d + 0.5 mg NE/d = 14.5 mg NE/d
- PRI 2nd trimester: 14 mg NE/d + 1.7 mg NE/d = 15.7 mg NE/d
- PRI 3rd trimester: 14 mg NE/d + 3.3 mg NE/d = 17.3 mg NE/d

The committee calculates an average PRI of (14.5 + 15.7 + 17.3)/3 = 15.8 mg NE/d (16 mg NE/d after rounding).

DACH's estimated PRIs for pregnant women (2nd and 3rd trimester) were estimated in Table A5 of their report. These values were obtained by multiplying by twice the CV of 10% the AR for non-pregnant women (1.31 mg/MJ) times the daily energy requirement (including the additional increment for the increased energy need): +1.05 and +2.09 MJ/d for the 2nd and 3rd trimester respectively (9.00 MJ/d and 10.05 MJ/d):

- PRI 2nd trimester: (1.31 mg/MJ x 1.2) x 9 = 14.15 mg NE/d (14 mg NE/d after rounding)
- PRI 3rd trimester: (1.31 mg/MJ x 1.2) x 10.05 = 15.80 mg NE/d (16 mg NE/d after rounding)

The committee calculates an average PRI of (13 + 14 + 16)/3 = 14.33 mg NE/d (14 mg NE/d after rounding).

HCNL 2014 estimated its PRI for pregnant women by adding the additional requirement to the AR of non-pregnant women and multiplying by twice the CV of 20%. PRI: (9 mg NE/d + 3 mg NE/d) x 1.4 = 16.8 mg NE/d (17 mg NE/d after rounding).

IOM estimated its PRI for pregnant women similarly, but with a CV of 15%. PRI: (11 mg NE/d + 3 mg NE/d) x 1.3 = 18.2 mg NE/d (18 mg NE/d after rounding).

WHO/FAO used their calculated needs above those of non-pregnant women of 1.7 mg NE/d for the 2nd and 3rd trimester, then added this amount and the amount of 2 mg NE/d required for tissue growth to the AI of non-pregnant women, resulting in an PRI of 1.7 + 2 + 14 = 17.7 mg NE/d (18 mg NE/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

EFSA and DACH differentiated their additional requirement by trimester. EFSA reported a higher energy requirement for all trimesters, whereas DACH did not report a higher energy requirement for the 1st trimester. While IOM and WHO/FAO noted that the higher requirement is especially important during the 2nd and 3rd trimester, they only but reported only one additional requirement for the entire pregnancy.

5.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no niacin deficiencies during pregnancy.[8]

Intake and associated health outcomes

EFSA reported two conflicting observational studies in relation to maternal niacin intake and infant birth weight.[8] EFSA concluded that these ambiguous data could not be used for deriving DRVs for niacin.

5.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Additive model

There appears to be a scientific consensus regarding the use of an additive model to derive the reference values for pregnant women.

Conclusion and strength of the additive model

The committee agrees with EFSA's choice of method (which is similar to DACHs) for deriving the additional requirement for niacin during pregnancy. The committee notes that the exact distribution is of the different aspects of the increased energy requirement (i.e., deposition, increased energy metabolism, etc.) during pregnancy is still unclear.

The evidence for EFSA's method of derivation for the additional niacin requirement was not supported by references. Data on niacin requirements during pregnancy are scarce and their results are ambiguous in this regard. The method of derivation was based on a plausible rationale. The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

The committee accepts EFSA's PRI and AR for pregnant women for use in the Netherlands (Table 5.3).

Table 5.3. Reference values for niacin recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	1.3 mg NE/MJ	*1.3 mg NE/MJ*
Population reference intake (PRI)	1.6 mg NE/MJ (16 mg NE/d)[a] (Trimester 1st: 15 mg NE/d 2nd: 16 mg NE/d 3rd: 17 mg NE/d)	*1.6 mg NE/MJ (14 mg NE/d)*

[a] PRI is calculated as $PRI_{non\text{-}pregnant}$ + additional requirement by trimester:
PRI 1st trimester = 14 mg NE/d + 0.5 mg NE/d
PRI 2nd trimester = 14 mg NE/d + 1.7 mg NE/d
PRI 3rd trimester = 14 mg NE/d + 3.3 mg NE/d
The average PRI for pregnancy is calculated from these PRIs by trimester.

06 Pantothenic acid (vitamin B5)

Summary and conclusion

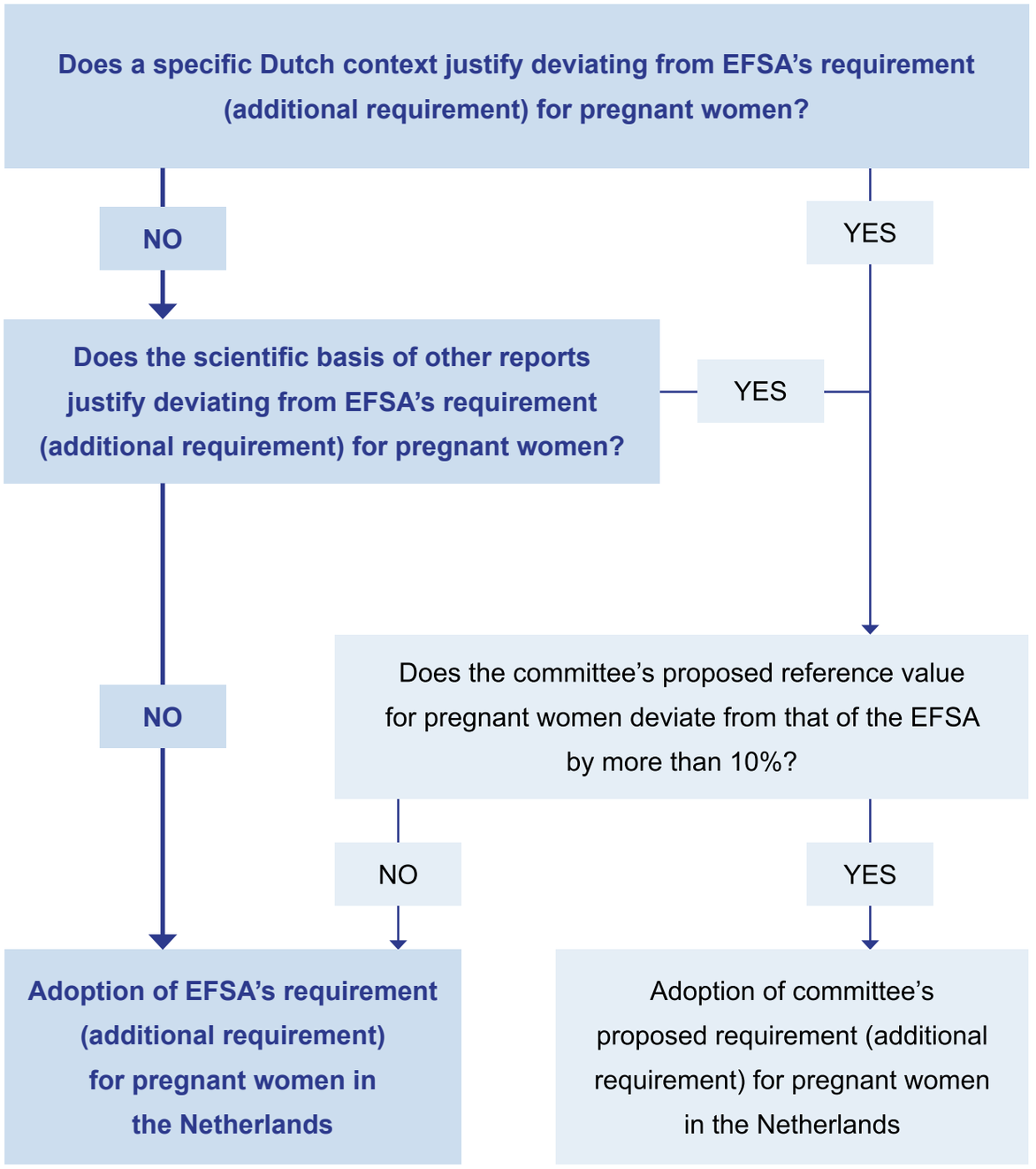
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a pantothenic acid recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The AI set for pregnant women is the same as the AI for non-pregnant women. The scientific basis for the method of derivation is weak.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 5 mg/d

Flowchart with committee's line of reasoning for pantothenic acid



6.1 Overview and comparison of values

Table 6.1. Overview of the reference values for pantothenic acid for pregnant women and the model used to derive these values, compared with the reference values for pantothenic acid for non-pregnant women

Report	Type	Value pregnant women (mg/d)	Model used	Type	Value non-pregnant women (mg/d)
EFSA 2014[9]	AI	5	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	5
HCNL 2000[41] =HCNL 2014[38]	AI	5	$AI_{pregnant} = AI_{non\text{-}pregnant}$	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	AI	5
NCM 2014[42]	-	-	No reference values derived	-	-
DACH 2015[43]	AI	6	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	6
IOM 1998[48]	AI	6	Average intake (rounding up)	AI	5
WHO/FAO 2004[50]	AI	6	Unknown.	AI	5

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.

6.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

Differences in the method of derivation

None of the reports derived an AR due to the lack of evidence regarding pantothenic acid requirements during pregnancy.

EFSA, HCNL 2014[a], and DACH[b] applied their AI for non-pregnant women to pregnant women. IOM based its AI on the rounding up of the average intake (which was 4 to 7 mg/d),[48] in the absence of information showing that usual intakes are inadequate to support a healthy pregnancy outcome. NCM did not set reference values for pantothenic acid and is therefore not discussed further. It is uncertain what the basis is of WHO/FAO's proposed AI of 6 mg/d. Therefore, no further consideration will be given to the WHO/FAO report.

Differences in the reference values

Differences in the values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   DACH used a higher value for non-pregnant women than the other reports.[4]
2. The method of derivation of the reference value:
   IOM used a different method of derivation than the other reports (as described above).

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

[a] Noting that there was no reason to assume an undesirably low pantothenic acid intake among pregnant women.
[b] Referring to IOM 1998's DRVs[48]of 5 mg/d for adults, 6 mg/d for pregnant women, and 7 mg/d for lactating women of which DACH's DRV is the average estimated to be adequate for all adults. DACH noted that IOM's very differentiated subdivision seemed not strictly necessary based on the uncertain scientific grounds.

6.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no pantothenic acid deficiencies during pregnancy.[9]

Intake and associated health outcomes

EFSA reported two prospective cohort studies on the relationship between pantothenic acid and birth outcomes.[9] EFSA concluded that data from these studies were very limited and could not be used for deriving DRVs for pantothenic acid in pregnancy.

6.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

Based on the absence of any demonstrated benefit, a pantothenic acid recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The AI set for pregnant women is the same as the AI for non-pregnant women. The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee agrees with EFSA's method of derivation of the reference value (which is the same as HCNL 2014's and DACH's), and accepts its AI for pregnant women for use in the Netherlands (Table 6.2).

Table 6.2. Reference value for pantothenic acid recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	5 mg/d	*5 mg/d*

07
Vitamin B6

Summary and conclusion

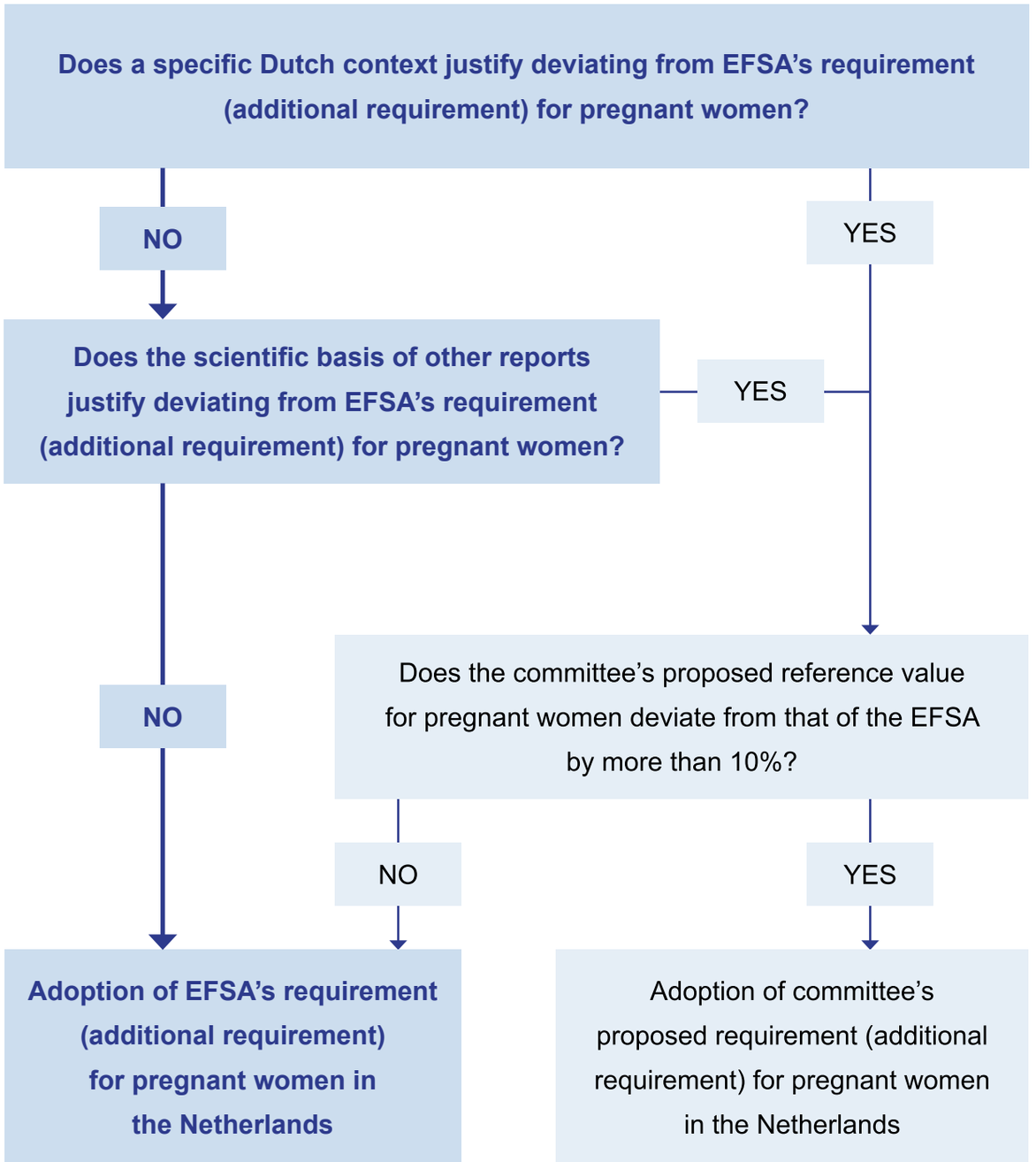
In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women.

There appears to be a scientific consensus between the different reports on the derivation of the reference values for pregnant women with an additive model. The committee agrees with EFSA's method of derivation of the additional requirement of vitamin B6 during pregnancy. The scientific basis for the method of derivation is acceptable.

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women and uses the CV of 20% (as per the reference values for non-pregnant women) to calculate the PRI, resulting in the following reference values:

- AR = 1.3 mg/d
- PRI = 1.8 mg/d

Flowchart with committee's line of reasoning for vitamin B6



7.1 Overview and comparison of values

Table 7.1. Overview of the reference values for vitamin B6 for pregnant women and the model used to derive these values, compared with the reference values for vitamin B6 for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2016[10]	PRI	1.8	1.5	10	Additive	PRI	1.6	1.3	10	75[c]
HCNL 2003[40] = HCNL 2014[38]	RDA	1.9	1.35	20	Additive	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	1.5	1.1	20	75[c]
NCM 2014[42]	RI	1.4[d]	1.2	*(~10)*	Additive	RI	1.2	1.0	10	71-79[e]
DACH 2015[43]	AI	1.9[f]	N/A	N/A	Additive	AI	1.2	N/A	N/A	0-80 (non-animal products)
IOM 1998[48]	RDA	1.9	1.6	10	Additive	RDA	1.3	1.1	10	75[c]
WHO/FAO 2004[50]	RI	1.9	1.6	10	Additive	RI	1.3	(1.1)	(10)	75[c]

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.

[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 7.2.
[c] Bioavailability from a “normal” or “mixed” diet is ~75%.
[d] As reported in Table 1.3 from NCM’s report.[42]
[e] It is unclear whether NCM used this absorption rate as they noted that the design of the study from which this range of absorption rates was derived was not optimal.
[f] From 4 months onwards in the pregnancy.

Table 7.2. Overview of the models used and the basis for the requirements (additional requirements) for vitamin B6 for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2016[10]	Additive (**AR: +0.2** PRI: +0.2)[c]	75	Vitamin B6 deposition due to maternal and fetal tissue growth.	Assumptions: the mean gestational increase in body weight is 12 kg, the vitamin B6 content is 15 nmol/g body weight (0.0037 mg/g tissue), and the bioavailability is 75%. Supportive evidence of a high transfer from mother to fetus.
HCNL 2003[40] = HCNL 2014[38]	Additive (**AR: +0.25** RDA: +0.4)[d]	-	Vitamin B6 deposition due to maternal and fetal tissue growth.	Assumptions: the vitamin B6 content of fetus and placenta is 25 mg at the end of the pregnancy (0.1 mg/d), the transfer from mother to fetus and placenta is incomplete (not quantified), and the metabolic need of the mother is increased (not quantified).
NCM 2014[42]	Additive (**AR: +0.2** RI: +0.2)[c]	-	Vitamin B6 deposition due to fetal tissue growth.	Assumption: an increased energy requirement (no further details).
DACH 2015[43]	Additive **(AI: +0.7)**	-	Vitamin B6 deposition due to tissue growth.	A biochemically detectable worsening of vitamin B6 supply mainly in the last trimester of the pregnancy (no further details).
IOM 1998[48]	Additive (**AR: +0.5** RDA: +0.6)	75	Vitamin B6 deposition due to maternal and fetal tissue growth.	Assumptions: the fetal, uterine, and placental accumulation is ~25 mg (0.1 mg/d), the weight and metabolic need of the mother are increased (not quantified), and the bioavailability is 75%.
WHO/FAO 2004[50]	Additive (**AR: +0.5** RDA: +0.6)	75	Vitamin B6 deposition due to maternal and fetal tissue growth.	IOM's estimate of the additional requirement.[48]

Abbreviations: -: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in mg/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

[c] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for AR and (P)RI.

[d] AR of 1.1 and RDA of 1.5 mg/d from HCNL 2003.[40]

7.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

WHO/FAO followed IOM (1998).

Differences in the method of derivation

All reports used an additive model for the reference values for pregnant women. The additional requirements for the PRI values varied from +0.2 to +0.7 mg/d between reports. EFSA, HCNL 2014, and IOM based their additional requirements on an increase in gestational weight and/or metabolic need, the vitamin B6 content in maternal and/or fetal tissue, and the bioavailability or the transfer from mother to fetus. The basis for NCM's proposed 0.2 mg/d higher requirement is uncertain, as is the basis for DACH's proposed 0.7 mg/d higher requirement. Therefore, the NCM and DACH reports are not discussed further.

EFSA noted that although the mechanism of vitamin B6 passage through the placenta is unclear, three studies showed evidence of a high transfer of vitamin B6 from the mother to the fetus.[57-59] EFSA used these studies as supportive evidence for the increased requirement for vitamin B6 during pregnancy. As the available data was deemed unsuitable for setting the total requirement for vitamin B6, EFSA calculated an additional requirement based on the content of vitamin B6 in the tissue acquired through gestational weight gain, taking into account the bioavailability of vitamin B6. EFSA assumed a vitamin B6 content of ~15 nmol/g body weight (equivalent to 0.0037 mg/g tissue) as analyzed in muscle biopsies in humans and labelled and non-labelled studies in other (animal) species.[60-65] They used a gestational increase in body mass of 12 kg[a] and assumed a vitamin B6 bioavailability of 75%.

Additional requirement: (vitamin B6 tissue content x gestational weight gain/bioavailability)/duration of normal pregnancy = (0.0037 mg x 12,000 g/0.75)/280 d = 0.21 mg/d (0.2 mg/d after rounding).

IOM assumed a vitamin B6 body store of 1000 µmol (or 167 mg), and a fetal, uterine, and placental accumulation of 15%, resulting in a fetal and placental accumulation of 167 mg x 0.15 = 25.05 mg (25 mg after rounding). This corresponds to an increased daily intake of 25 mg/280 days = 0.09 mg/d (0.1 mg/d after rounding). HCNL 2014[b] used IOM's calculated value. Both HCNL 2014 and IOM added an extra 0.15 mg/d for the increased maternal metabolic needs and the bioavailability percentage or incomplete transfer from mother to placenta and fetus, resulting in an additional requirement of 0.1 mg/d + 0.15 mg/d = 0.25 mg/d. IOM doubled this additional requirement to 0.5 mg/d to account for the fact that "vitamin B6 is not stored in the body to any substantial extent".

[a] Applies to women with a singleton pregnancy and a pre-pregnancy BMI in the range between 18.5 and 24.9 kg/m^2.[54]

[b] Assuming the desired increase in protein intake during pregnancy (+0.1 g/kg body weight/d) falls within the range of usual protein intake, and thus would not require additional vitamin B6.

Differences in the reference values

With the additive model, differences in the reference values between reports resulted from differences in three aspects.

1. The reference value for non-pregnant women:
   EFSA used a higher value for non-pregnant women than the other reports.[4]
2. The CV used:
   EFSA and IOM used a CV of 10%, whereas HCNL 2014 used a CV of 20%.
3. The method of derivation of the additional requirement:
   EFSA based its additional requirement mainly on the vitamin B6 content in relation to the gestational weight gain, whereas HCNL 2014 and IOM based their additional requirement mainly on fetal and placental accumulation of vitamin B6, as described above.

EFSA's PRI was based on the additional requirement added to the AR of non-pregnant women multiplying by twice the CV of 10%: (1.3 mg/d + 0.2 mg/d) x 1.2 = 1.8 mg/d.
IOM's PRI was estimated in the same way: (1.1 mg/d + 0.5 mg/d) x 1.2 = 1.92 mg/d (1.9 mg/d after rounding).
HCNL 2014's PRI was estimated in the same way, but with a CV of 20%: (1.1 mg/d + 0.25 mg/d) x 1.4 = 1.89 mg/d (1.9 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

IOM acknowledged that the surplus of their additional requirement may overestimate the additional need in early gestation, but considered it "judicious to err on the side of ensuring sufficiency throughout pregnancy".

7.3 Pregnancy-related health outcomes

EFSA described no pregnancy-related vitamin B6 deficiencies and no studies showing intake levels associated with pregnancy-related health outcomes.[10]

7.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women, which were based on the lower cut-off value for plasma PLP of ≥20 nmol/L (contrasting EFSA's cut-off value of 30 nmol/L).[4]

Additive model

There appears to be a scientific consensus on the derivation of the reference values for pregnant women with an additive model.

Conclusion and strength of the additive model

EFSA and HCNL 2014 derived a similar additional requirement. IOM initially also derived a similar additional requirement but doubled this value to ensure a sufficient intake later in pregnancy as vitamin B6 is not stored in the body to any substantial extent. However, EFSA reported no

pregnancy-related deficiencies[10], IOM indicated that there is no evidence of significant problems in vitamin B6 status despite reduced levels of biomarkers,[48] and HCNL 2014 reported no differences in the course and the result of the pregnancy in clinical supplementation studies[40]. Therefore, the committee finds it unnecessary to double the additional requirement and agrees with EFSA's method of derivation of the additional requirement of vitamin B6 during pregnancy.

The committee used the same method to calculate the additional requirement as EFSA, with an increase in body weight of 13.8 kg, which resulted in the same additional requirement as calculated by EFSA.

Data on vitamin B6 requirements during pregnancy are scarce and provide only supportive evidence.[57-59] The evidence of EFSA's method of derivation for the additional vitamin B6 requirement was based on the content of vitamin B6 in the tissue acquired through gestational weight gain during pregnancy. The committee deems the scientific basis for the method of derivation to be acceptable (based on a plausible rationale).

Reference values for pregnancy

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women and uses the CV of 20% (as per reference values for non-pregnant women) to calculate the PRI (Table 7.3).

Table 7.3. Reference values for vitamin B6 recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	1.3 mg/d	*1.1 mg/d*
Population reference intake (PRI)	1.8 mg/d[a]	*1.5 mg/d*

[a] PRI is calculated as ($AR_{non\text{-}pregnant}$ + additional requirement) multiplied by twice the CV: PRI = (1.1 mg/d + 0.2 mg/d) x 1.4.

08
Folate

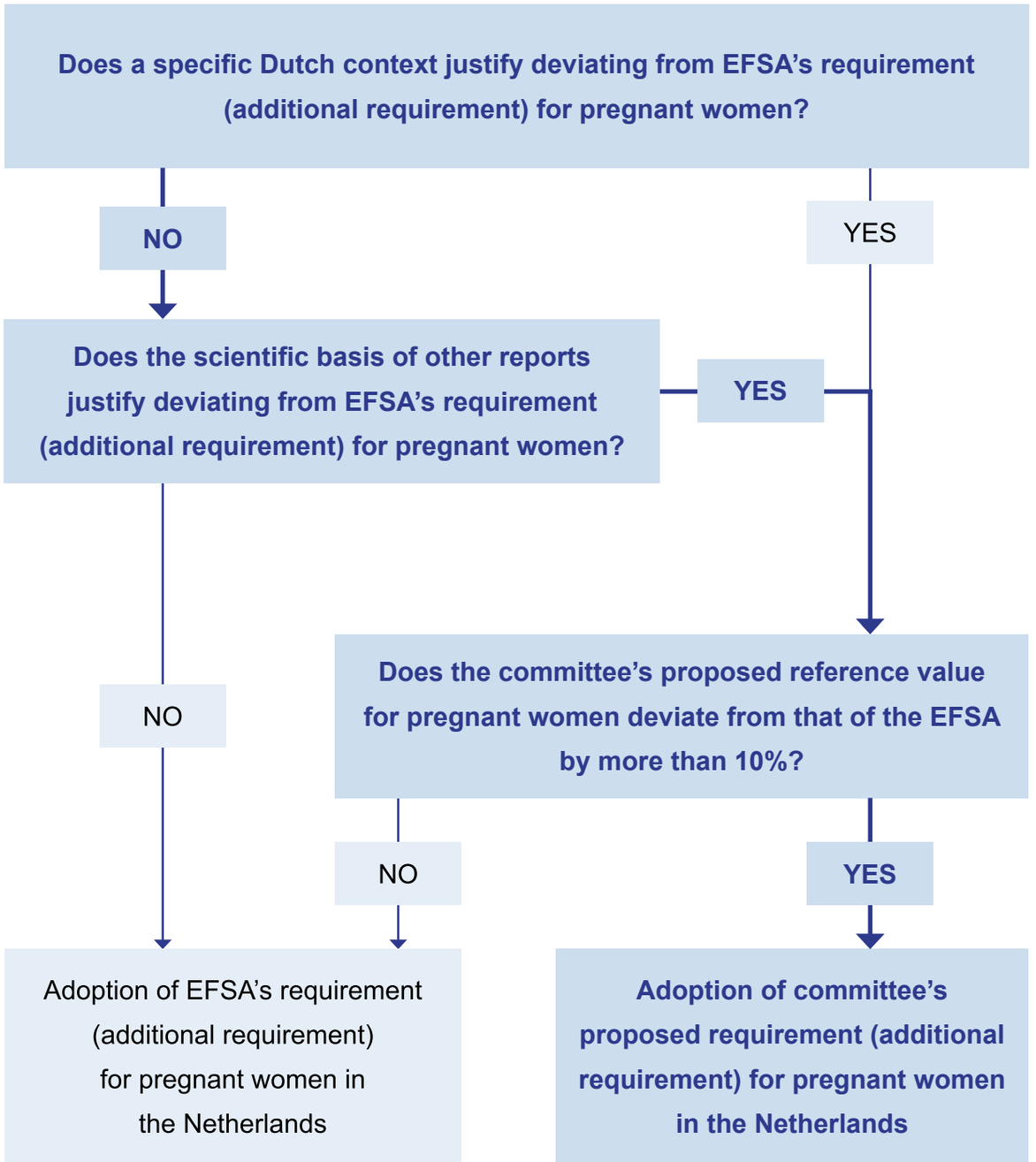
Summary and conclusion

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women. There seems to be no scientific consensus on the value of the increased requirement during pregnancy between EFSA/NCM, HCNL, and IOM, nor on the underlying basis. EFSA and NCM used a total requirement model, whereas IOM and HCNL used an additive model. The committee maintains HCNL's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 400 µg dietary folate equivalents (DFE)/d

On top of this reference value for folate throughout pregnancy, in the Netherlands, as in many countries, women are advised to take a supplement of 400 µg/d of folic acid (the synthetic variant of folate) for one month before and during the 1st trimester of pregnancy to prevent neural tube defects.

Flowchart with committee's line of reasoning for folate



8.1 Overview and comparison of values

Table 8.1. Overview of the reference values for folate for pregnant women and the model used to derive these values, compared with the reference values for folate for non-pregnant women

Report	Type	Value pregnant women (µg DFE/d)	AR pregnant women (µg DFE/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (µg DFE/d)	AR non-pregnant women (µg DFE/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2014[11]	AI	600	N/A	N/A	Total requirement	PRI	330	250	15	50 (food folate) 85 (folic acid from fortified foods or folic acid supplement ingested with food) 100 (folic acid supplement on an empty stomach)
HCNL 2003[40] = HCNL 2014[38]	AI	400	N/A	N/A	Additive	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	300	200	25	50 (food folate) 85 (folic acid from fortified foods) 100 (folic acid supplement on an empty stomach)
NCM 2014[42]	RI	500	-	-	Total requirement	RI	400	200	25	-
DACH 2015[43]	RDA	550	420	15	Additive	RDA	300	220	15	-
IOM 1998[48]	RDA	600	520	10	Additive	RDA	400	320	10	50 (food folate) 100 (folic acid supplement on an empty stomach)
WHO/FAO 2004[50]	RNI	600	520	10	Additive	RDA	400	320	10	50-75 (natural folates) ≥85 (synthetic folic acid)

Abbreviations: -: Not specified, N/A: not applicable, DFE: Dietary Folate Equivalents
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 8.2.

Table 8.2. Overview of the models used and the basis for the requirements (additional requirements) for folate for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2014[11]	Total requirement	N/A	Folate deposition due to growth in maternal and fetal tissue and prevention of deficiency symptoms.	Controlled metabolic study: intakes of 630-680 µg DFE/d resulted in mean concentrations of status markers well above cut-offs for folate adequacy.
HCNL 2003[40] = HCNL 2014[38]	Additive **(AI = RDA +100)**[c]	N/A	Folate deposition due to growth in maternal and fetal tissue and prevention of deficiency symptoms.	Due to hemodilution, the amount of folate needed to normalize folate deficiency is higher in pregnant women than in non-pregnant women; In a German observational study the provision of 360 µg DFE/d resulted in maintenance of sufficient folate status (red blood cell folate > 320 nmol/l)
NCM 2014[42]	Total requirement	-	Folate deposition due to growth in maternal and fetal tissue and prevention of deficiency symptoms.	Reference values from NNR 2004.[53] Controlled metabolic study: evidence for an RDA of 600 µg/d. Assumption: women enter pregnancy with moderate folate stores due to the recommendation of 400 µg/d for all women “capable of becoming pregnant”.
DACH 2015[43]	Additive (**AR +200** RDA +250)	-	Folate deposition due to growth in maternal and fetal tissue and prevention of deficiency symptoms.	IOM’s estimate of the additional requirement.[48]
IOM 1998[48]	Additive (**EAR +200** RDA +200)[d]	-	Folate deposition due to growth in maternal and fetal tissue and the prevention of deficiency symptoms.	Population-based studies: low dietary folate intake + 100 µg/d of supplemental folate were inadequate to maintain normal folate status. Controlled metabolic study: supportive evidence for an RDA of 600 µg/d.
WHO/FAO 2004[50]	Additive (**EAR +200** RNI +200)[d]	-	Folate deposition due to growth in maternal and fetal tissue and the prevention of deficiency symptoms.	IOM’s estimate of the additional requirement.[48]

Abbreviations: -: Not specified, N/A: not applicable, DFE: Dietary Folate Equivalents

[a] If applicable: (+ additional requirement in µg DFE/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

[c] RDA of 300 µg DFE/d from HCNL 2003.[40]

[d] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for EAR and RDA/RNI.

8.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

DACH and WHO/FAO followed IOM 1998.

Differences in the method of derivation

EFSA and NCM based their reference value for pregnant women on a total requirement, whereas HCNL 2014 and IOM used an additive model. EFSA used a 270 µg DFE/d higher AI for pregnant women than their PRI for non-pregnant women. IOM used an additional requirement of +200 µg DFE/d for their PRI value. NCM used a 100 µg DFE/d higher PRI for pregnant women than their PRI for non-pregnant women. HCNL 2014 used an additional requirement of +100 µg DFE/d for their AI value.

All reports based their folate requirement on deposition due to growth in maternal and fetal tissues and on the prevention of deficiency symptoms. Please note that the folate requirements for pregnant women are not based on the prevention of neural tube defects. Regarding the prevention of neural tube defects, there is international consensus on the importance of *periconceptional folic acid* supplementation on top of the dietary reference value of folate (see Box Folic acid supplementation and the prevention of NTDs.).

EFSA, NCM, HCNL, and IOM reported a controlled metabolic study (Caudill et al) from 1997 among 12 pregnant American women in their 2nd trimester (week 14 to 26 of the pregnancy) and 12 non-pregnant controls who were fed a controlled diet of 120 µg/d dietary folate(=120 µg DFE/d).[66] Six of the pregnant women and their non-pregnant controls received an additional 330 µg/d synthetic folic acid (total intake: 120 + 1.7*330=680 µg DFE/d), the other six received an additional 730 µg/d synthetic folic acid (total intake: 120+1.7*730=1,360 µg DFE/d). After 12 weeks of supplementation, the pregnant women in the group consuming 680 µg DFE/d had a mean serum folate concentration (27 nmol/L, SD: ±9) similar to their non-pregnant controls (26 nmol/L, SD: ±11), well above the cut-off value of ≥6.8 nmol/L for adequacy. Moreover, throughout the study period, all subjects had serum folate concentrations of >13.6 nmol/L. Mean red blood cell (RBC) folate concentrations were similar in pregnant and non-pregnant women at baseline (1,383 nmol/L, SD: ±158 and 1,114 nmol/L, SD: ±397, respectively). These values were maintained after 12 weeks with no significant difference between pregnant and non-pregnant women and were also well above the cut-off value of ≥317 nmol/L for adequacy. A subsample (n=4) was followed up in the 3rd trimester of pregnancy. They received daily supplementation of 200 µg/d folic acid in addition to an estimated mean dietary folate intake of 293 µg/d (total intake: ~630 µg DFE/d). This subsample also sustained high folate status biomarker values during this period of pregnancy.

Selected findings of study by Caudill et al.[66]

Biomarker of folate status	Cut-off value for folate deficiency used by EFSA	Value after intervention (12 weeks) with 680 µcg DFE/d	
		6 pregnant women	6 non-pregnant women
Serum folate	<7 nmol/L	27 [SE 9] nmol/L	26 [SE 11] nmol/L.
RBC folate	<317 nmol/L	1453 [SE 252] nmol/L	1000 [SE 387] nmol/L

From this study, EFSA concluded that intakes of 630-680 µg DFE/d resulted in mean concentrations of folate status biomarkers being well above cut-offs for adequacy as defined by EFSA, although it is not known whether this might also have been achieved with a lower folate intake. EFSA acknowledged that the data for folate requirements for pregnant women are weaker than the data for non-pregnant women and therefore considered it not possible to set an AR for pregnant women. Therefore, EFSA set an AI for folate for pregnant women.

NCM and IOM referred to the conclusions of the authors (Caudill et al.) that ~600 µg DFE/d was sufficient to maintain folate status in pregnant women, although a lower intake might have been sufficient. NCM maintained their reference values from 2004(~500 µg DFE/d) due to the absence of new data.[53] They reasoned that women enter pregnancy with moderate folate stores due to the recommendation of 400 µg DFE/d for all women “capable of becoming pregnant”. Taken together with the results of the abovementioned study, NCM considered 500 µg DFE/d sufficient to meet the increased requirement from fast-growing tissues.

IOM also noted that 600 µg DFE/d seemed adequate to obtain/maintain normal folate status (compared with non-pregnant women), while referring to the article described above. However, their additional requirement was based on data from population-based studies showing that low folate intake (~200 µg DFE/d) was inadequate to maintain normal folate status in a significant percentage of population groups assessed.[67-70]

One population-based study was done in 350 Scottish pregnant women beginning at 12 weeks of gestation who received a folic acid supplement of 0, 100, 350, or 450 µg/d in addition to a dietary folate intake estimated to be <100 µg/d.[67,68] A supplementation level of 100 µg/d was insufficient to prevent deficient serum concentrations (defined as <7 nmol/L, or 3 ng/mL) in 33% of the group (where 5% is normal), with a mean serum folate concentration of 4.1 ng/mL (SD: ±3.17).[67] The group receiving 350 µg/d of supplemental folate, on the other hand, maintained a mean serum folate concentration comparable with the mean in healthy non-pregnant control subjects and prevented megaloblastic anemia.[67,68]

Another population-based study in the UK among 25 pregnant women beginning at 28 weeks of gestation found that taking 150 µg/d of folate supplements in addition to the diet resulted in low serum folate concentrations (<7 nmol/L, or 3 ng/mL) in 30% of the group at delivery.[69]

A Swedish experimental study was done in 95 healthy non-anemic pregnant women who received a folic acid supplement of 50, 100, 200, or 500 µg/d from the 20th-24th week until the 36th-38th week and a control group receiving a placebo supplement.[70] In this study, 100 µg/d of folic acid plus diet was insufficient to prevent serum folate reduction (with a mean concentration in healthy non-pregnant women of 6.2 ng/ml and slight or suspected megaloblastic changes generally at <2 ng/mL) in 15% of the group, whereas a folate supplement of 500 µg/d resulted in a mean serum folate concentration of 13 nmol/L (or 6 ng/mL).

From these studies, IOM concluded that the quantity of 200 µg DFE/d[a] should be added to the AR for non-pregnant women.

HCNL 2014 (based on HCNL 2003) estimated an additional requirement of +100 µg DFE/d, resulting in an AI of 400 µg DFE/d.[40] There were two main lines of reasoning: 1) pregnant women need a higher amount of folate to normalize folate status (low serum folate levels) than non-pregnant women.[40,67,68,71,72] Based on hemodilution, serum folate levels decrease during pregnancy. Supplementation of 100 µg/d of folic acid can prevent this decrease, 2) Based on a longitudinal observational study (n=109 pregnant women), 360 µg DFE/day consumed by lacto-ovo-vegetarian (n=27) women resulted in the maintenance of a sufficient folate status (RBC folate > 320 nmol/l) throughout pregnancy. The levels of RBC folate increased until week 20 of gestation, whereas plasma folate decreased. A similar pattern was observed in women in the control group consuming a Western diet (n=39) with an intake of approximately 250 µg DFE/d. Please note that the committee in 2003 also mentioned being unaware of pregnancy complications related to folate intake, which was at that time estimated to be approximately 250 µg DFE/d.

HCNL 2003 also referred to the metabolic study on which the EFSA recommendation of 600 µg DFE/d was primarily based (Caudill et al). HCNL 2003, however, did not use this metabolic study to derive the reference value. Although metabolic studies in pregnant women are rare and of primary interest for DRVs, this metabolic study is, to the opinion of the committee, not sufficiently specific to derive the requirement for pregnant women because of insufficient dose-response information. An intake of 630–680 µg DFE/day, which is much higher than the current dietary intake of folate in the Netherlands, resulted in concentrations of biomarkers of folate status well above cut-offs for folate adequacy as established in non-pregnant adults. For that reason, EFSA acknowledged that it was not known whether this could have been achieved with a lower folate intake. Moreover, based on additional evidence as collected for the advisory report *Dietary recommendations for pregnant women*,[35,73] there are no data available that indicate a benefit of folic acid supplementation throughout pregnancy. The committee decided, also based on the

[a] Equivalent to a low dietary folate intake + 100 µg/d of supplemental folate.

described concerns of the dose-response information of the metabolic study by Caudill et al., to deviate from EFSAs DRV and to maintain the previous Dutch AI of 400 µg DFE/day.

Differences in the reference values

Differences in the reference values between reports resulted mainly from differences in the method of derivation.

1. Total requirement:
   EFSA and NCM based their reference values for pregnant women on a total requirement derived from the literature, as described above. EFSA acknowledged that the database for pregnant women was weaker than that for non-pregnant women and therefore considered it not possible to set an AR for pregnancy. As a result, EFSA set an AI for folate for pregnancy. NCM, on the other hand, set a PRI based on the same evidence as EFSA.
2. Additional requirement:
   IOM based its reference values for pregnant women on an additional requirement derived from the literature, as described above.
   IOM's PRI was based on the additional requirement added to the AR of non-pregnant women multiplying by twice the CV of 10%: (320 µg DFE/d + 200 µg DFE/d) x 1.2 = 624 µg DFE/d (600 µg DFE/d after rounding). HCNL based its reference values for pregnant women on an additional requirement of 100 µg DFE/d added to the adequate intake of 300 µg DFE/d, resulting in an adequate intake of 400 µg DFE/d.

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

8.3 Pregnancy-related health outcomes

Deficiencies

EFSA described the predominant feature of folate deficiency to be megaloblastic anemia.[11] An initial fall in serum folate concentrations (<6.8 nmol/L, or 3 ng/ml), followed by a period of progressive depletion of folate stores, triggers bone marrow to generate macrocytic cells (unusually large red blood cells) with abnormal nuclear maturation. It takes several weeks before the decrease in red blood cell folate concentration, the increase in mean cell volume, the appearance of irregularly shaped red blood cells in the circulation, and the decline in both hemoglobin concentration and red blood cell number can be detected. Megaloblastosis can affect the epithelial cells of the entire gastrointestinal tract, impair the absorption of folate, and further exacerbate the deficiency state.

Intake and associated health outcomes

Neural tube defects (NTDs) are a group of congenital malformations (anencephaly and spina bifida) which are the result of incomplete closure of the neural tube during early embryonic development (days 21-28 of embryonic life). An NTD is considered to be of multifactorial etiology with possible involvement of genetic and environmental factors. EFSA considered that although women with NTD-affected pregnancies are

rarely folate deficient, they were reported to have lower serum and RBC folate and higher plasma total homocysteine concentrations than women whose pregnancies were not affected by NTD.

Periconceptional supplementation with folic acid plays a well-established protective role against both first occurrence and recurrence of NTDs, resulting in worldwide consensus on recommendations for the prevention of the first occurrence of an NTD, such that women of child-bearing age should consume supplemental folic acid at a dose of 400 µg/day for at least one month before and during the first trimester, in addition to consuming food folate from a varied diet (see Box).[11]

The EFSA Panel acknowledges the observed impact of ingestion of 400 µg/day of supplemental folic acid for at least one month before and during the first trimester of pregnancy on reducing the risk of NTD. The Panel notes that the use of supplemental folic acid is needed in addition to dietary folate intake and considers that the available data on folic acid intake and NTD risk cannot be used for deriving the requirement for folate, as the evidence for the protective effect of dietary folate is considered weak owing to the observational design of studies and the general inherent inaccuracy of dietary assessment methods.

8.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women, which were based on lower cut-off values for serum (7 nmol/L) and erythrocyte (300 nmol/L) folate levels than EFSA's (10 nmol/L and 340 nmol/L respectively) and were associated with the prevention of clinical deficiency as opposed to the lowering of plasma homocysteine concentrations.[4]

Model used

EFSA and NCM used a total requirement model, whereas HCNL and IOM used an additive model. There seems to be no scientific consensus on the value of the increased requirement during pregnancy between EFSA/NCM and HCNL, IOM, nor on the underlying basis.

Conclusion and strength of the model

The committee does not agree with EFSA's method of derivation of the reference value (which is similar to NCM's).

The evidence of HCNL's method of derivation for the AI of folate during pregnancy was based on metabolic studies and one observational study. The committee deems the evidence of the method of derivation to be acceptable.

Reference values for pregnancy

The committee maintains HCNL's AI for pregnant women for use in the Netherlands (Table 8.3). On top of this reference value, the Netherlands has a supplementation advice of 400 µg/d of folic acid for one month before and during the 1st trimester of pregnancy, in line with the international consensus on the importance of folic acid for the prevention of neural tube defects.

Table 8.3. Reference value for folate recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	400 µg DFE/d	*AR: 200 µg DFE/d* *PRI: 300 µg DFE/d*

Box Folic acid supplementation and the prevention of NTDs.

EFSA reported the global consensus on recommendations for the prevention of NTDs, while referring to the well-established protective role of periconceptional supplementation against both first occurrence and recurrence of NTDs.[11]

The advice provided by the reports on folic acid supplementation for the prevention of the first occurrence of NTDs:

- EFSA, HCNL 2014, DACH, and WHO/FAO: 400 µg/d in addition to the PRI for one month before and during the 1st trimester of pregnancy.[11,40,43,50]
- NCM: no supplementation, but a recommended intake of 400 µg/d for all women of reproductive ages to reduce the risk in planned as well as in unplanned pregnancies.[42]
- IOM: recommendation of 400 µg/d of folate from supplements, fortified foods, or both, in addition to consuming food folate in agreement with the PRI for all women "capable of becoming pregnant".[48]

The advice provided by the reports on folic acid supplementation for the prevention of the recurrence of NTDs:

- WHO/FAO: 4,000 µg/d.[50]
- IOM: "an even larger dose of folate".[48]
- DACH: "the adequate dose is the responsibility of the attending physician".[43]
- EFSA, HCNL 2014, and NCM: no recommendation.[11,40,42]

EFSA reported two publications showing that a much higher folate status than just above the cut-offs for adequacy may be required for NTD prevention.[11] One case-control study showed a levelling off of the NTD incidence at a serum folate concentration of ≥15.9 nmol/L (cut-off for adequacy: ≥6.8 nmol/L) and a red blood cell folate concentration of 906 nmol/L (cut-off for adequacy: ≥317 nmol/L). The other study combined the data of two trials in Chinese women: one community intervention study and one randomized trial, both with 400 µg/d of folic acid. Results showed that the estimated risk of NTDs was approximately six times lower for a red blood cell folate concentration of 1,000 nmol/L than for one of 340 nmol/L.

09 Vitamin B12 (cobalamin)

Summary and conclusion

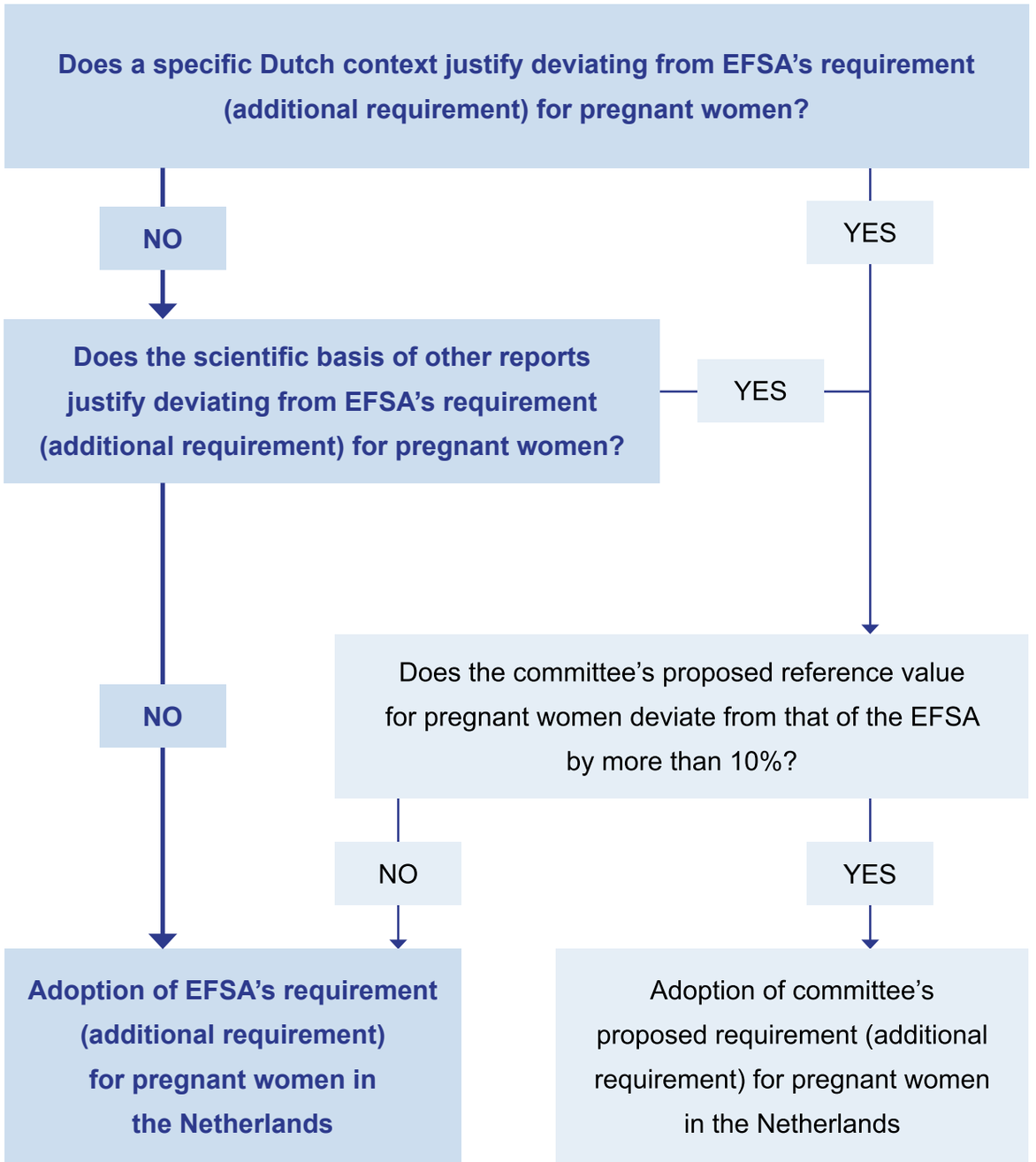
In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women.

There appears to be a scientific consensus between the different reports on the derivation of the reference values for pregnant women with an additive model. The committee agrees with the method of derivation for the additional requirement for vitamin B12 during pregnancy used by EFSA. The scientific basis for the method of derivation is acceptable.

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women, and uses the CV of 20% (as per the reference values for non-pregnant women) to calculate the PRI, resulting in the following reference values:

- AR = 2.4 µg/d
- PRI = 3.3 µg/d

Flowchart with committee's line of reasoning for vitamin B12



9.1 Overview and comparison of values

Table 9.1 Overview of the reference values for vitamin B12 for pregnant women and the model used to derive these values, compared with the reference values for vitamin B12 for non-pregnant women

Report	Type	Value pregnant women (µg/d)	AR pregnant women (µg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (µg/d)	AR non-pregnant women (µg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[12]	AI	4.5	N/A	N/A	Additive	AI	4	N/A	N/A	40[c]
HCNL 2003[40] = HCNL 2014[38]	RDA	3.2	2.3	20	Additive	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	2.8	2.0	20	50[d]
NCM 2014[42]	RI	2.0	1.4	15	$RI_{pregnant} = RI_{non\text{-}pregnant}$	RI	2.0	1.4	15	50
DACH 2015[43]	RDA	3.5	-	-	Additive	RDA	3.0	2.0	*(25)*	50
IOM 1998[48]	RDA	2.6	2.2	10	Additive	RDA	2.4	2.0	10	50[d]
WHO/FAO 2004[50]	RI	2.6	2.2	10	Additive	RI	2.4	2.0	10	50[d]

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 9.2.
[c] EFSA noted that the absorption of cobalamin is highly variable, depending on the dietary source, the amount ingested, the ability to release cobalamin from food and the proper functioning of the gastric intrinsic factor system.
[d] For healthy individuals with a normal gastric function.

Table 9.2. Overview of the models used and the basis for the requirements (additional requirements) for vitamin B12 for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2015[12]	Additive **(AI + 0.5)**	40	Vitamin B12 deposition due to growth in fetal tissue.	Assumptions: liver contains about half of the body's vitamin B12 content, accumulation of vitamin B12 in the fetus is 0.2 µg/d, and absorption is 40%.
HCNL 2003[40] = HCNL 2014[38]	Additive (**AR + 0.3** RDA + 0.4)[c]	Indications that absorption is more efficient in pregnancy[d]	Vitamin B12 deposition due to growth in fetal tissue and (active) transfer from mother to fetus.	Assumptions: liver contains about half of the body's vitamin B12 content, accumulation of vitamin B12 in the fetus is 0.1-0.2 µg/d, maternal body stores are of relative unimportance to the fetus, absorption is 50%.
NCM 2014[42]	$RI_{pregnant} = RI_{non\text{-}pregnant}$	-	-	Reference values from NNR 2004.[53] Assumption: pregnant women have adequate stores to cover extra requirements of 0.1-0.2 µg/d.
DACH 2015[43]	Additive **(RDA + 0.5)**	-	Vitamin B12 deposition due to growth in fetal tissue and the prevention of deficiency symptoms.	Precaution in case of pre-existing vitamin B12 deficiency and "maintaining a high nutrient density".

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
IOM 1998[48]	Additive (**AR + 0.2** RDA + 0.2)[e]	Indications that absorption is more efficient in pregnancy[c]	Vitamin B12 deposition due to growth in fetal tissue.	Assumptions: liver contains about half of the body's vitamin B12 content, accumulation of vitamin B12 in the fetus is 0.2 µg/d, and maternal body stores are of relative unimportance to the fetus.
WHO/FAO 2004[50]	Additive (**AR + 0.2** RI + 0.2)[e]	-	Vitamin B12 deposition due to growth in fetal tissue.	IOM's estimate of the additional requirement.[48]

Abbreviations: -: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in µg/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

[c] AR of 2.0 and RDA of 2.8 µg/d from HCNL 2003.[40]

[d] Available data were deemed insufficient to draw conclusions about the changes in bioavailability of vitamin B12 during pregnancy.

[e] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for AR and RDA.

9.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The WHO/FAO report followed the IOM (1998 report).

Differences in the method of derivation

All reports except NCM used an additive model for the reference values for pregnant women. NCM applied their PRI for non-pregnant women to pregnant women as the recommendation for adults is already "on the high side" and as pregnant women usually have adequate stores to cover extra requirements.[53]

EFSA and DACH used a higher additional requirement (+0.5 µg/d) than HCNL 2014 (+0.3 µg/d) and IOM (+0.2 µg/d). DACH did not describe the origin of their data; it is uncertain what the basis is for their proposed 0.5 mg/d higher requirement. Therefore, no further consideration will be given to the DACH report. All reports based their additional requirement on the accumulation of vitamin B12 in the fetus's liver. Differences between reports resulted mainly from differences in absorption rates used.

EFSA, HCNL 2014, and IOM referred to three studies on the liver content of infants.[74-76] The first study from 1962 in 9 pregnant Indian women with a vitamin B12 deficiency (7 of whom gave birth to apparently normal babies, 2 of whom gave birth to stillborn fetuses) compared the accumulation of vitamin B12 in the livers of the two stillborn fetuses with the livers of 17 stillborn fetuses of different ages from mothers with normal serum vitamin B12 levels.[74] The total vitamin B12 content of the livers in control fetuses increased with increasing fetal age, reaching a maximum of 20-25 µg

at birth. The second study from 1977 assessed the liver vitamin B12 content of 77 fetuses with gestational ages ranging from 22-45 weeks and body weights from 0.4-6.5 kg.[75] The third study from 1975 determined the liver vitamin B12 content in 13 immature, 27 premature, and 21 full-term fetuses.[76] The average reserve (concentration x liver weight) of hepatic vitamin B12 for the immature group was 4.1 µg, for the premature group 10.7 µg, and for the full-term group 27.3 µg. From these studies, IOM (followed by WHO/FAO, in turn followed by EFSA and HCNL 2014) estimated that the fetus accumulates an average of 0.1-0.2 µg/d of vitamin B12. All reports assumed that the maternal body stores are a negligible source of vitamin B12 for the fetus. EFSA and IOM further assumed that the liver contains half the total body vitamin B12 content.

EFSA calculated the additional requirement by considering a fetal accumulation of 0.2 µg/d and an absorption of 40%[a] (which corresponds to an adjustment factor of 2.5): 0.2 µg/d x 2.5 = 0.5 µg/d.

HCNL 2014 calculated the additional requirement in the same way, but with an absorption of 50% (which corresponds to an adjustment factor of 2) and for the range of fetal accumulation: 0.1-0.2 µg/d x 2 = 0.2-0.3 µg/d and used the 0.3 µg/d.

[a] EFSA referred to an analysis suggesting that the generally assumed fractional cobalamin absorption of 50% from a typical meal may overestimate cobalamin absorption at habitual cobalamin intake levels in Europe.[77] Therefore, EFSA considered a cobalamin absorption of 40% a more conservative estimate.

IOM argued, based on a fetal deposition of 0.1-0.2 µg/d and evidence that maternal absorption becomes more efficient during pregnancy, that the additional requirement is 0.2 µg/d.

Differences in the reference values

With the additive model, differences in the reference values between reports were due to differences in three aspects.

1. The reference value for non-pregnant women:
   EFSA used a higher value for non-pregnant women than the other reports.[4]
2. The CV used:
   EFSA did not use a CV (as their reference value was an AI).
   HCNL 2014 used a CV of 20%, and IOM used a CV of 10%.
3. The method of derivation of the additional requirement:
   EFSA derived a higher additional requirement than the other reports, as described above.

EFSA's AI was based on the additional requirement added to the AI of non-pregnant women: 4.0 µg/d + 0.5 µg/d = 4.5 µg/d.
HCNL 2014's PRI was based on the additional requirement added to the PRI of non-pregnant women multiplying by twice the CV of 20%: (2.0 µg/d + 0.3 µg/d) x 1.4 = 3.22 µg/d (3.2 µg/d after rounding).
IOM's PRI was derived in the same way but with a CV of 10%: (2.0 µg/d + 0.2 µg/d) x 1.2 = 2.64 µg/d (2.6 µg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

HCNL 2014 noted that accumulation presumably takes place mostly in the 2nd and 3rd trimester. They calculated the additional requirement within a range, of which the lower limit was the additional requirement for the entire pregnancy, and the upper limit was the additional requirement for the 2nd and 3rd trimester.

9.3 Pregnancy-related health outcomes

Deficiencies

EFSA reported the most frequent clinical expression of vitamin B12 deficiency to be megaloblastic anemia, affecting all types of blood cells and resulting in symptoms such as fatigue and shortness of breath due to impaired oxygen delivery.[12] Because of the interrelated functions of vitamin B12 and folate, anemia and its mechanisms are identical in deficiencies of both vitamins, but the onset occurs later in vitamin B12 deficiency.

EFSA also noted that the neonatal period is thought to be a period of special vulnerability to vitamin B12 insufficiency and deficiency.[12] They mentioned a summary of case studies into infants of mothers with undetected pernicious anemia or adhering to strict veganism, indicating that clinical symptoms of deficiency appear in infants at around four to seven months of age. After treatment with vitamin B12 injections (typically 1 mg intramuscular for four days), a reversal of neuromuscular manifestations was observed in most cases, whereas psychomotor and cognitive development delays were not reversed in ~40-50% of cases.

Intake and associated health outcomes

EFSA described no studies showing vitamin B12 intake levels associated with pregnancy-related health outcomes.[12]

9.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women, which were based on the prevention of deficiency (contrasting EFSA's higher reference values for which they showed no evidence of providing additional health benefits).[4]

Additive model

There appears to be a scientific consensus on the derivation of the reference values for pregnant women with an additive model. Only NCM did not use an additive model. Instead, they applied the PRI for non-pregnant women to pregnant women as well. As vitamin B12 deposition occurs in the fetus, and maternal liver stores seem to be a less important source for the fetus, the committee considers an additive model appropriate.

Conclusion and strength of the additive model

The committee agrees with the method of derivation of the additional requirement for vitamin B12 during pregnancy used by EFSA, which was based on the accumulation of vitamin B12 in the fetus's liver and a more conservative estimate of the absorption rate than HCNL 2014's and IOM's, referring to an analysis suggesting that the generally assumed absorption (50%) may overestimate vitamin B12 absorption in Europe.

The evidence of EFSA's method of derivation for the additional vitamin B12 requirement during pregnancy was based on three observational studies[74-76] from weak to acceptable quality. The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch PRI for non-pregnant women (as per EFSA adding the additional value to their AI for non-pregnant women) to calculate the PRI (Table 9.3).

Table 9.3. Reference values for vitamin B12 recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	2.4 µg/d	*2.0 µg/d*
Population reference intake (PRI)	3.3 µg/d[a]	*2.8 µg/d*

[a] PRI is calculated as ($PRI_{non\text{-}pregnant}$ + additional requirement).

10 Vitamin C (ascorbic acid)

Summary and conclusion

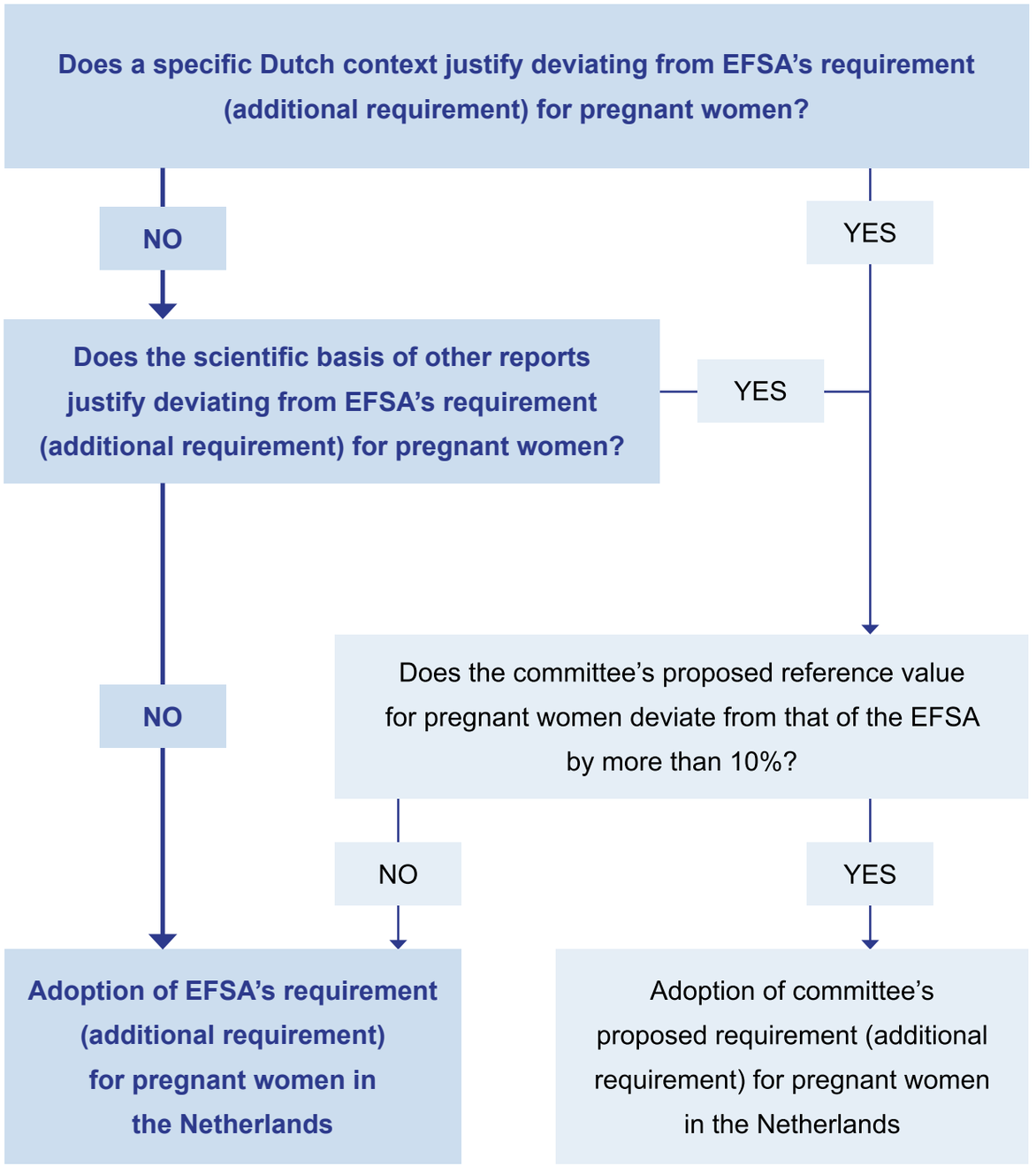
In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women.

There appears to be a scientific consensus between the different reports on the derivation of the reference values for pregnant women with an additive model. The committee agrees with the additional requirement for vitamin C during pregnancy used by EFSA and with adding this additional requirement to the PRI. The scientific basis for the method of derivation is acceptable.

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch PRI for non-pregnant women, resulting in the following reference value:

- PRI = 85 mg/d

Flowchart with committee's line of reasoning for vitamin C



10.1 Overview and comparison of values

Table 10.1. Overview of the reference values for vitamin C for pregnant women and the model used to derive these values, compared with the reference values for vitamin C for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2013[13]	PRI	*(105)*[c]	-	-	Additive	PRI	95	80	10	80 (intake: 100 mg/d) 75 (intake: 1,000 mg/d)[d,e]
NCM 2014[42] = HCNL 2014[38]	RI	85	-	-	Additive	RI	75	50	25	-
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	75	50	25	-
DACH 2015[43]	RDA	105[f]	87	10	Additive	RDA	95	77	10	≥80 (intake: 15-100 mg/d) <50 (intake >1,250 mg/d)[e]
IOM 2000[44]	RDA	85	70	10	Additive	RDA	75	60	10	70-90 (intake: 30-180 mg/d) ≤50 (single dose >1,000 mg)
WHO/FAO 2004[50]	RI	55[g]	-	-	Additive	RI	45	25-30	*(25-40)*	85[e] "Almost completely" (low doses) 75 (intake: 30-180 mg/d)

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 10.2.
[c] The committee calculated the PRI based on the PRI +10 as reported in Table 6 of EFSA's report.[13]
[d] Data on vitamin C absorption have mainly been collected in men.
[e] The efficiency of absorption decreases with increasing doses and vice versa.
[f] From 4 months onwards in the pregnancy.
[g] WHO/FAO noted that this is the amount required to half saturate body tissues with vitamin C in 97.5% of the population and that larger amounts may often be required to ensure adequate absorption of non-heme iron.

Table 10.2. Overview of the models used and the basis for the requirements (additional requirements) for vitamin C for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2013[13]	Additive **(PRI + 10)**	-	The prevention of deficiency symptoms	WHO/FAO's estimate of the additional requirement.[50] Approach: adding this value to the PRI (contrasting IOM, adding it to the AR).
NCM 2014[42] = HCNL 2014[38]	Additive **(RI + 10)**	-	Vitamin C deposition due to growth in maternal and fetal tissue.	A study suggesting an estimated additional requirement of 10 mg/d for growth of the fetus and catabolized vitamin C.
DACH 2015[43]	Additive (**AR + 10** RDA + 10)[c]	-	Vitamin C deposition due to growth in maternal and fetal tissue and the prevention of deficiency symptoms.	Studies suggesting estimated total requirements of 67-100 mg/d to 200 mg/d and estimated additional requirements of 5-10 mg/d for maternal losses and 7 mg/d for infant's scurvy prevention.
IOM 2000[44]	Additive (**AR + 10** RDA + 10)[c]	-	The prevention of deficiency symptoms.	Studies suggesting estimated additional requirements of 7 mg/d for infant's scurvy prevention.
WHO/FAO 2004[50]	Additive **(RI + 10)**	-	The prevention of deficiency symptoms.	A study suggesting an estimated additional requirement of 8 mg/d for infant's scurvy prevention.

Abbreviations: -: Not specified, N/A: not applicable
[a] If applicable: (+ additional requirement in mg/d).
[b] This column presents any information on absorption during pregnancy if provided by the report.
[c] Due to the CV of 10% and rounding to 1 decimal point, the additional value is equal for AR and RDA.

10.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

All reports used an additive model for the reference values for pregnant women. Also, all reports used the same additional requirement of 10 mg/d. However, DACH and IOM added this additional requirement to their AR, whereas EFSA, NCM, and WHO/FAO added this additional requirement to their PRI.

DACH and NCM both based their additional requirement on the increased needs due to fetal growth and maternal losses. DACH also based its

additional requirement on the amount needed for scurvy prevention. IOM and WHO/FAO (followed by EFSA) based their additional requirement solely on the amount needed for scurvy prevention.

Differences in the reference values

With the additive model, differences in the reference values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   EFSA and DACH used the same values for non-pregnant women, which were higher than the values for non-pregnant women of the other reports.[4]
2. The summation of the additional requirement:
   EFSA, NCM, and WHO/FAO added the additional requirement to their PRI, whereas DACH and IOM added the additional requirement to their AR.

DACH's PRI was based on the additional requirement added to the AR of non-pregnant women multiplied by twice the CV of 10%: (77.15 mg/d + 10 mg/d) x 1.2 = 104.58 mg/d (105 mg/d after rounding).

IOM's PRI was derived in the same way: (60 mg/d + 10 mg/d) x 1.2 = 84.0 mg/d (85 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

DACH's reference value is advised from 4 months onward in the pregnancy. WHO/FAO acknowledged that the need for vitamin C particularly increases during the last trimester due to the rapidly growing fetus. To meet these additional needs, WHO/FAO's proposed additional requirement for the entire pregnancy should enable reserves to accumulate.

10.3 Pregnancy-related health outcomes

Deficiencies

Maternal vitamin C deficiency can lead to infant scurvy. EFSA noted that infant scurvy may have important effects on bone tissue, with impaired bone growth and ossification.[13]

Intake and associated health outcomes

EFSA described no studies showing intake levels associated with pregnancy-related health outcomes.[13]

10.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women[a] as the committee judged there was insufficient evidence for more health benefits using EFSA's saturated body pool of vitamin C (1.5 g) and plasma ascorbate concentrations of 50 nmol/L as

[a] Which were the reference values from the NCM report.[42]

the basis for setting the reference values, as opposed to NCM's plasma ascorbate concentrations of 32 nmol/L.[4]

Additive model

There appears to be a scientific consensus on the derivation of the reference values for pregnant women with an additive model. There also seems to be a scientific consensus on the value of the additional requirement during pregnancy.

Conclusion and strength of the additive model

The committee agrees with the additional requirement for vitamin C during pregnancy used by EFSA (which was the same for all reports). This additional requirement of 10 mg/d provides a margin above the increased needs, as reported in the literature described in Table 10.2. The committee agrees with EFSA with regard to adding this additional requirement to the PRI, as NCM and WHO/FAO did (instead of adding it to the AR as DACH and IOM did).

The evidence of EFSA's method of derivation for the additional vitamin C requirement during pregnancy was based on WHO/FAO's method of derivation. WHO/FAO's additional requirement was based on one experimental study included in a review from 1976 on scurvy prevention.[78] The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch PRI for non-pregnant women (Table 10.3).

Table 10.3. Reference value for vitamin C recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	-	*50 mg/d*
Population reference intake (PRI)	85 mg/d[a]	*75 mg/d*

[a] PRI is calculated as ($PRI_{non\text{-}pregnant}$ + additional requirement):
PRI = 75 mg/d + 10 mg/d.

11 Vitamin D (ergocalciferol and cholecalciferol)

Summary and conclusion

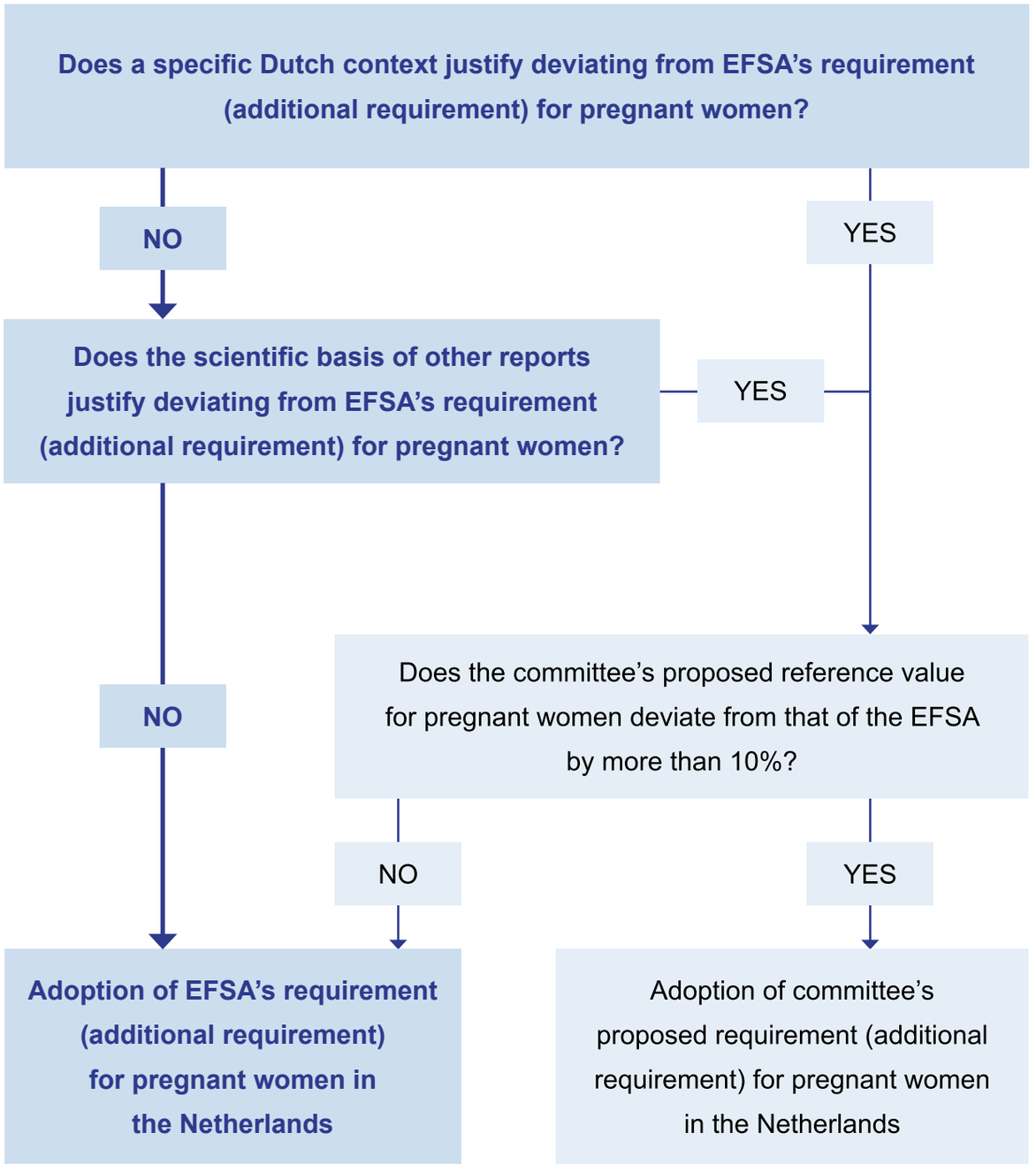
In 2018, the committee maintained HCNL 2014's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a vitamin D recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee maintains HCNL 2014's AI for pregnant women for use in the Netherlands. The scientific basis for the method of derivation is weak.

The committee maintains HCNL 2014's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 10 µg/d

Flowchart with committee's line of reasoning for vitamin D



11.1 Overview and comparison of values

Table 11.1. Overview of the reference values for vitamin D for pregnant women and the model used to derive these values, compared with the reference values for vitamin D for non-pregnant women

Report	Type	Value pregnant women (µg/d)	AR pregnant women (µg/d)	CV[a] pregnant women (%)	Model used	Type	Value non-pregnant women (µg/d)	AR non-pregnant women (µg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2016[14]	AI	15[b]	N/A	N/A	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	15[b]	N/A	N/A	~80 (55-99)
HCNL 2012[39]= HCNL 2014[38]	AI	10[b]	-	-	$AI_{pregnant}$ = $AI_{non-pregnant}$	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	10	N/A	N/A	-
NCM 2014[42]	RI	10[c,d] *(20)*[b]	7.5[d]	*(17)*	$RI_{pregnant}$ = $RI_{non-pregnant}$	RI	10[d] *(20)*[b]	7.5[d]	*(17)*	80
DACH 2015[43]	AI	20[b]	N/A	N/A	$AI_{pregnant}$ = $I_{non-pregnant}$	AI	20[b]	N/A	N/A	~80
IOM 2011[45]	RDA	15[b]	10[b]	*(25)*	$RDA_{pregnant}$ = $RDA_{non-pregnant}$	RDA	15[b]	10[b]	*(25)*	-
WHO/FAO 2004[50]	AI	5[b]	N/A	N/A	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	5[b]	N/A	N/A	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Under conditions of assumed 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.
[c] As reported in Table 1.3 from NCM's report.[42]
[d] The RI set by NCM applies to conditions of normal cutaneous vitamin D synthesis; NCM used an RI for people with little or no sun exposure of 20 µg/d.

11.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

Differences in the method of derivation

None of the reports derived an additional requirement due to the lack of evidence regarding vitamin D during pregnancy. All reports applied their reference values for non-pregnant women to pregnant women.

Differences in the reference values

Differences in the reference values between reports resulted from differences in the reference values for non-pregnant women. EFSA used the same reference value as IOM, whereas DACH used a higher reference value and HCNL 2014, NCM, and WHO/FAO used a lower reference value.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

11.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no vitamin D deficiencies during pregnancy.[14]

Intake and associated health outcomes

EFSA reported several prospective studies on the relationship between 25(OH)D (a biomarker of vitamin D intake) and health outcomes, described below.[14]

25(OH)D concentrations[a] and health outcomes

- EFSA concluded that the evidence of an association between maternal serum 25(OH)D concentration and the risk of pre-eclampsia was inconsistent. One RCT and two out of six prospective studies reported no association, whereas four out of six observational studies showed some suggestive evidence of an increased risk at 25(OH)D concentrations <50 nmol/L.
- EFSA concluded that the evidence of an association between maternal serum 25(OH)D concentration and the risk of being born small-for-gestational-age was inconsistent. Two out of four prospective studies found no association, whereas the other two studies showed some suggestive evidence for increased risk at 25(OH)D concentrations <25-37.5 nmol/L.
- EFSA concluded that one nested case-control study found no association between 25 (OH)D concentration and the risk for preterm birth in a population with a high baseline median 25(OH)D value (~90 nmol/L).
- EFSA concluded that one prospective study reported that maternal 25 (OH)D ≤43 nmol/L was associated with the child's bone outcomes at birth, which did not persist at the age of 1 year, possibly due to infant vitamin D supplementation starting at 2 weeks of age.

On the relationship between vitamin D intake and 25 (OH)D concentrations, EFSA mentioned the following: one RCT showed that women who received a 12.5 µg/d vitamin D3 supplement had a higher mean serum 25 (OH)D concentration (57 ±11 nmol/L) than women who did not receive a supplement (25 ±2 nmol/L). EFSA did not use these studies for setting the DRVs for vitamin D during pregnancy.

[a] EFSA noted that the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends a serum 25 (OH)D concentration of >50 nmol/L to indicate sufficiency.

Vitamin D intake (from supplements) and health outcomes

EFSA reported RCTs (while referring to IOM 2011 and SACN 2016) showing no association between vitamin D intake (supplementation doses: 25-100 µg/d) and incidence or risk of pre-eclampsia, preterm birth, birth length or weight, or neonatal whole-body bone mineral content. Information on vitamin D supplementation advice from the different reports is presented in the Box at the end of this section.

11.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014's reference value for non-pregnant women, which was based on the absence of signs that all Dutch adults would require vitamin D supplementation.[4] The committee considered that the scientific evidence for the cut-off value of 50 nmol/L for 25(OH)D was not strong for adults <70 years.

Model used

The committee agrees with the method of derivation used by EFSA (which is in line with all reports), i.e., adopting the reference values for non-pregnant women for use during pregnancy. The committee maintains HCNL 2014's AI for pregnant women for use in the Netherlands. Based on the absence of any demonstrated benefit, a vitamin D recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The (supplementation) studies that have been performed in pregnant women show inconclusive results; this may be attributable to design weaknesses.[14] HCNL 2014 does not refer to a study reporting a comparable vitamin D requirement of pregnant women when compared with non-pregnant women. The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee maintains HCNL 2014's AI for pregnant women for use in the Netherlands (Table 11.2).

Table 11.2. Reference value for vitamin D recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	10 µg/d[a]	*10 µg/d*[a]

[a] Under conditions of assumed 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.

12 Vitamin E (alpha-tocopherol)

Summary and conclusion

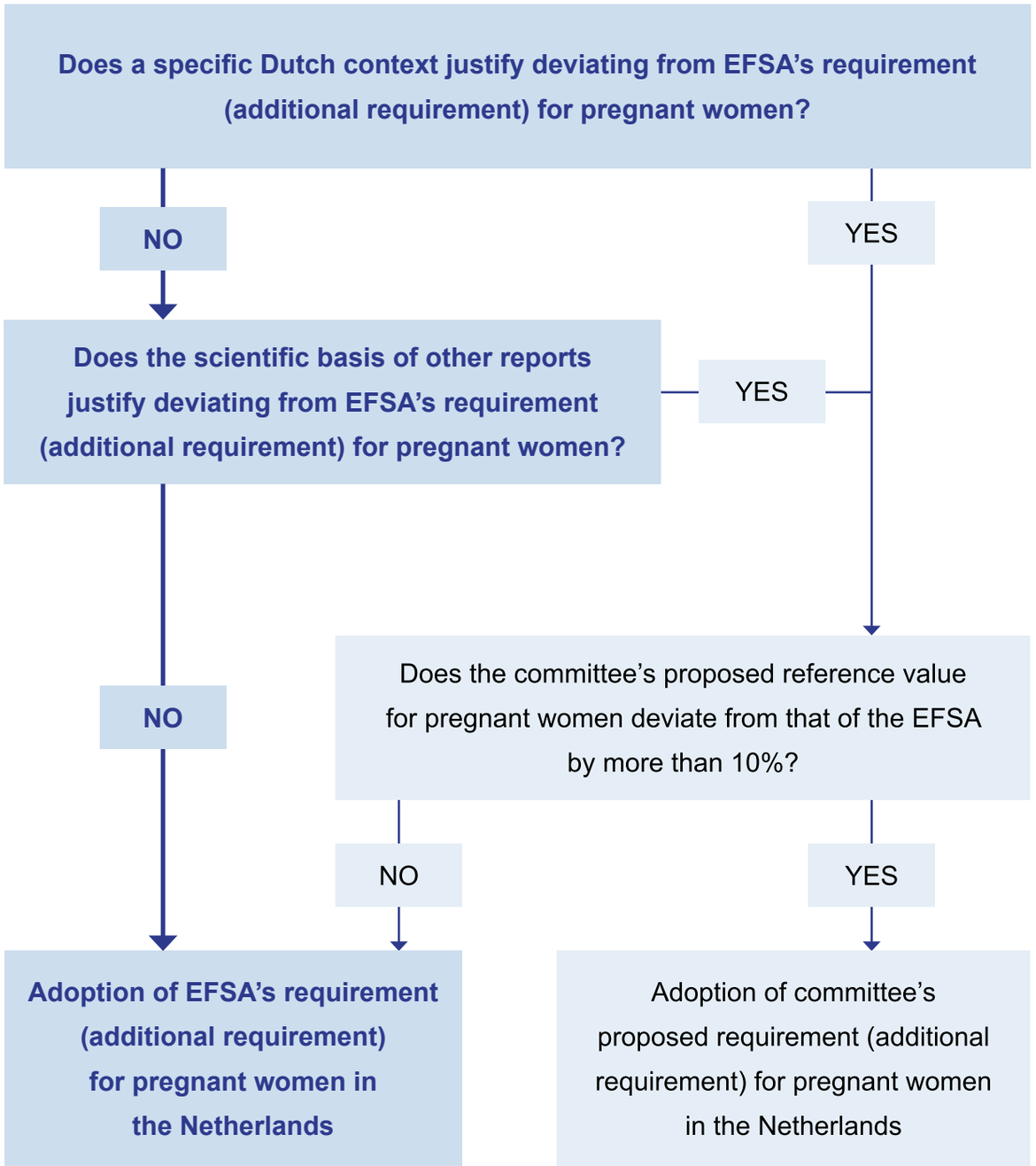
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

A vitamin E recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is strong.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 11 mg αTE/d

Flowchart with committee's line of reasoning for vitamin E



12.1 Overview and comparison of values

Table 12.1. Overview of the reference values for vitamin E for pregnant women and the model used to derive these values, compared with the reference values for vitamin E for non-pregnant women

Report	Type	Value pregnant women (mg αTE/d)	AR pregnant women (mg αTE/d)	CV[a] pregnant women (%)	Model used	Type	Value non- pregnant women (mg αTE/d)	AR non- pregnant women (mg αTE/d)	CV[a] non- pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[15]	AI	11	N/A	N/A	$AI_{pregnant}$ = $AI_{non\text{-}pregnant}$	AI	11	N/A	N/A	75
NCM 2014[42] = HCNL 2014[38]	RI	10[b]	-	-	Unknown	RI	8	5	*(30)*	-
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	11	N/A	N/A	75
DACH 2015[43]	AI	13	N/A	N/A	Unknown	AI	12	N/A	N/A	30[c]
IOM 2000[44]	RDA	15	12	10	$RDA_{pregnant}$ = $RDA_{non\text{-}pregnant}$	RDA	15	12	10	-
WHO/FAO 2004[50]	-[d]	-	-	-	Unknown	AI	7.5	N/A	N/A	-

Abbreviations: -: Not specified, N/A: not applicable, αTE: alpha-tocopherol equivalents

Calculations done by the committee are depicted in brackets and in italics.

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

[b] As reported in Table 1.3 from NCM's report.[42]

[c] Dose-dependent, with an average fat intake of 12 mg: 54%, with an intake of 24 mg: 30%, and with a pharmacological dose of 200 mg: 10%.

[d] WHO/FAO reported that "no specific recommendations concerning the vitamin E requirements in pregnancy and lactation have been made by other advisory bodies (*UK, USA*), mainly because there is no evidence of vitamin E requirements being different from those of other adults and, presumably, also because the increased energy intake during these periods would compensate for the increased needs for infant growth and milk synthesis.". The committee finds it unclear whether WHO/FAO follows the UK and USA, or whether they did not set recommendations for vitamin E during pregnancy.

12.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

EFSA and IOM applied their reference values for non-pregnant women to pregnant women due to the lack of evidence for an increased vitamin E requirement during pregnancy. It is uncertain what the basis is for NCM's and DACH's proposed +2 and +1 mg αTE/d higher requirement. It is unclear whether WHO/FAO established reference values for pregnant women (see footnote d below Table 1). Therefore, the NCM, DACH, and WHO/FAO reports are not discussed further.

EFSA noted that, despite the presence of α-TTP in the placenta and the existence of a correlation between maternal plasma and chorioamnion α-tocopherol concentrations, the α-tocopherol concentration of cord blood is much lower than that of maternal blood. In addition, maternal supplementation increases maternal but not cord plasma α-tocopherol concentrations. Both EFSA and IOM noted that the placental transfer of α-tocopherol is relatively constant throughout gestation. IOM additionally mentioned the absence of vitamin E deficiency during pregnancy and the absence of evidence that supplementation would prevent deficiency symptoms in premature offspring. EFSA additionally reported the mean α-tocopherol and α-TE intakes from the Latvian survey on pregnant adult women to be, respectively, 12.4 and 12.5 mg/d[a]. The committee notes that these intakes provide a margin above EFSA's proposed AI.

Differences in the reference values

Differences in the reference values between reports resulted from differences in the reference values for non-pregnant women. EFSA used a lower reference value than IOM.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

12.3 Pregnancy-related health outcomes

Deficiencies

EFSA noted that the origin of the discovery of vitamin E lies in the need for α-tocopherol to prevent fetal resorption in pregnant rats fed lard-containing diets.[15] The chemical name 'tocopherol' stems from its essentiality for normal reproduction in animals, even though this essentiality has never been demonstrated in humans. EFSA did, however, describe a human case report on a woman with recurrent spontaneous abortions, who

[a] From the EFSA intake assessment, as reported in appendix D and F of their report.

successfully delivered a healthy baby after administration of 300 mg/d of tocopherol nicotinate.[15]

Intake and associated health outcomes

EFSA reported four prospective cohort studies with inconsistent results regarding the association between maternal vitamin E intake from foods and supplements during pregnancy (intake not specified by EFSA) and the risk of wheeze, asthma, eczema, and/or hay fever in children at various ages over the first 10 years.[15]

12.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

A vitamin E recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by EFSA and IOM, i.e., adopting the reference values for non-pregnant women for use during pregnancy, and maintains EFSA's AI for pregnant women for use in the Netherlands.

The evidence of the method of derivation for the AI of vitamin E during pregnancy is based on studies on the presence of α-TTP in the placenta, the concentration of α-tocopherol in cord blood and maternal blood, the correlation between maternal plasma and chorioamnion α-tocopherol concentrations, the effect of supplementation and maternal and cord plasma α-tocopherol concentrations, and the placental transfer during gestation. This evidence came from several intervention and observational studies from acceptable to good quality.[15,44] The committee deems the scientific basis for the method of derivation to be strong.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 12.2).

Table 12.2. Reference value for vitamin E recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	11 mg αTE/d	*11 mg αTE/d*

13 Vitamin K1 (phylloquinone)

Summary and conclusion

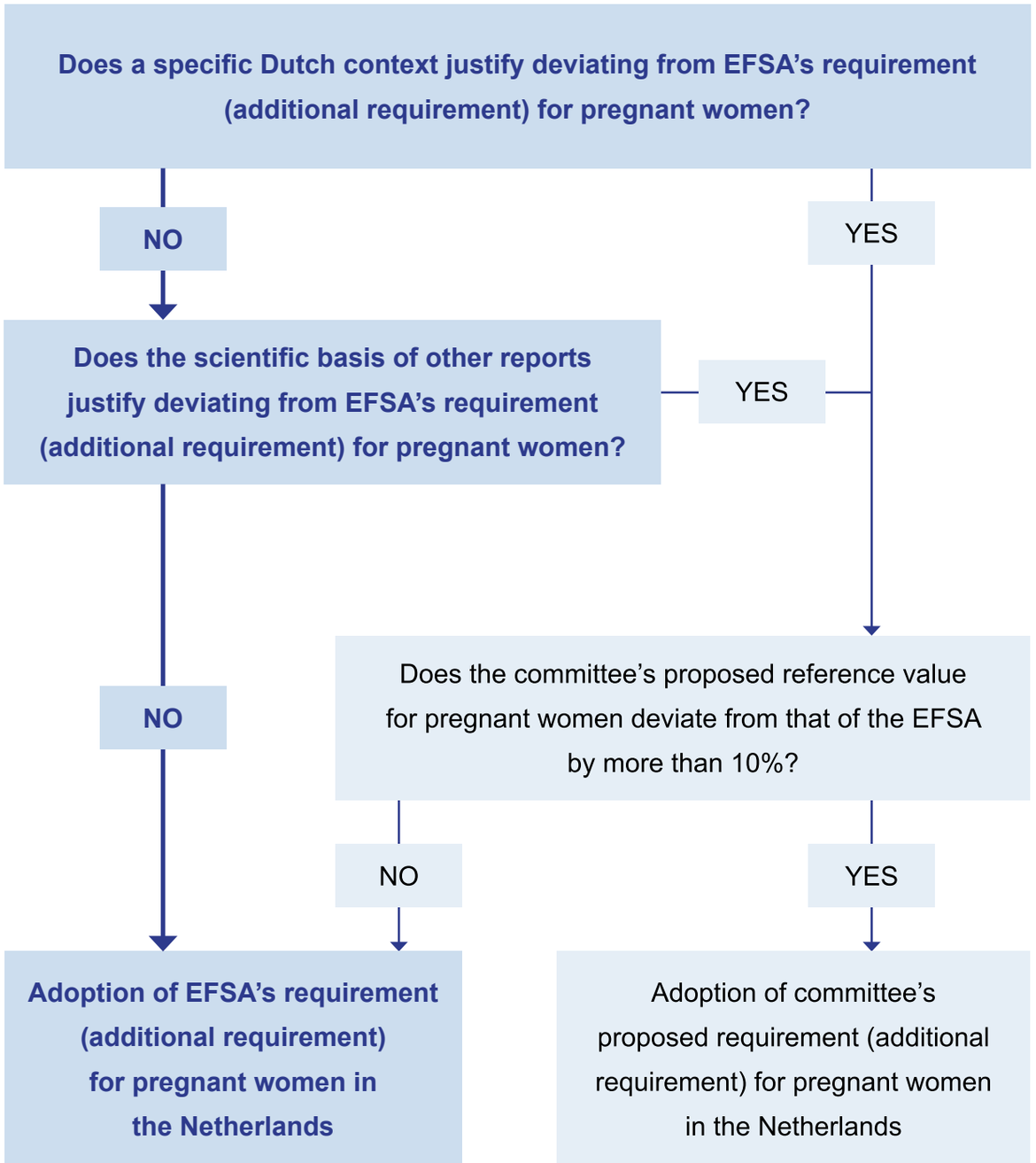
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a vitamin K1 recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by all reports (except NCM), i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is weak.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 70 µg/d

Flowchart with committee's line of reasoning for vitamin K1



13.1 Overview and comparison of values

Table 13.1. Overview of the reference values for vitamin K1 for pregnant women and the model used to derive these values, compared with the reference values for vitamin K1 for non-pregnant women[a]

Report	Type	Value pregnant women (µg/d)	Model used	Type	Value non-pregnant women (µg/d)	Absorption non-pregnant women (%)
EFSA 2017[16] = HCNL 2014[38]	AI	70	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	70	-
HCNL 2018[4]	N/A	N/A	N/A	AI	70	-
NCM 2014[42]	-	-	No reference values derived	-	-	-
DACH 2015[43]	AI	60	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	60	10-80
IOM 2001[47]	AI	90	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	90	10-80[b]
WHO/FAO 2004[50]	AI	55	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	55	10-80[b]

Abbreviations: -: Not specified, N/A: not applicable

Calculations done by the committee are depicted in brackets and in italics.

[a] Apart from MK-4 that is formed via metabolic conversion of phylloquinone during its absorption in the intestinal mucosa and in other organs, menaquinones are produced by bacteria capable of food fermentation and specific anaerobic bacteria of the colon microbiota.

[b] Boiled spinach (eaten with butter) as an example of green leafy vegetables: no greater than 10%, phylloquinone in its free form: ~80%.

13.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the EFSA report.

Differences in the method of derivation

None of the reports derived an additional requirement due to the lack of evidence regarding vitamin K1 during pregnancy. All reports applied their reference values for non-pregnant women to pregnant women. NCM did not set DRVs for vitamin K1 due to a lack of sufficient evidence.

Differences in the reference values

Differences in the reference values between reports resulted from differences in the reference value for non-pregnant women. EFSA used a lower reference value than IOM and a higher reference value than DACH and WHO/FAO.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

13.3 Pregnancy-related health outcomes

Deficiencies

EFSA reported that phylloquinone concentrations were undetectable in cord blood of infants of unsupplemented mothers unless the pregnant women received phylloquinone intravenously before delivery.[16] Liver tissue contents of phylloquinone and of menaquinones in neonates were low or undetectable, although these low vitamin K stores seemed sufficient to maintain normal hemostasis during fetal life.

Intake and associated health outcomes

EFSA described no studies showing intake levels associated with pregnancy-related health outcomes.[16]

13.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

Based on the absence of any demonstrated benefit, a vitamin K1 recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used in all reports (except NCM), i.e., adopting the reference values for non-pregnant women for use during pregnancy, and maintains EFSA's AI for pregnant women for use in the Netherlands.

The evidence of the method of derivation for the AI of vitamin K1 during pregnancy is very limited; data on vitamin K1 requirements during pregnancy is scarce. The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 13.2).

Table 13.2. Reference value for vitamin K1 recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	70 µg/d	*70 µg/d*

14 Biotin

Summary and conclusion

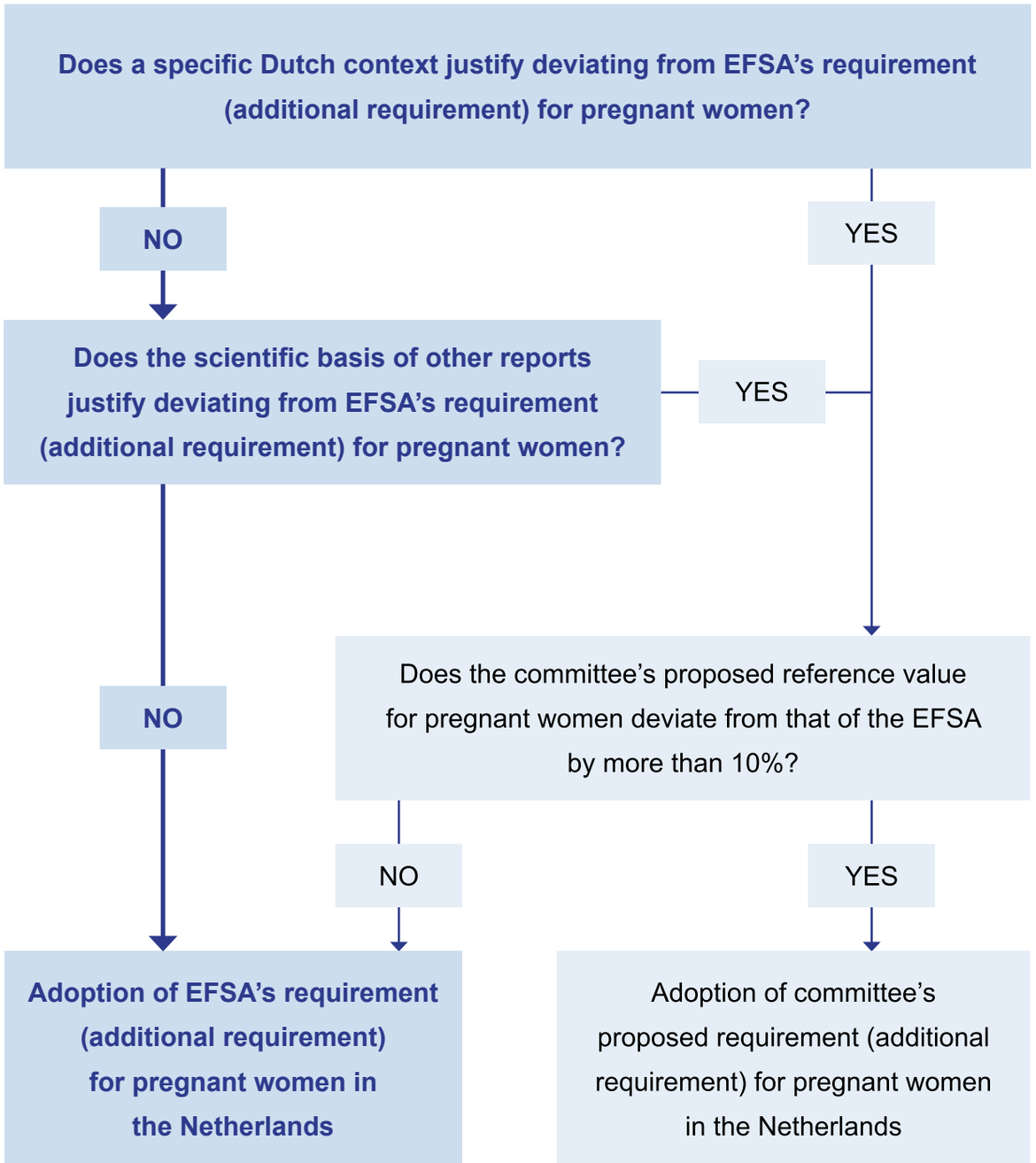
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a biotin recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used in all reports (except NCM), i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is weak.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 40 µg/d

Flowchart with committee's line of reasoning for biotin



14.1 Overview and comparison of values

Table 14.1. Overview of the reference values for biotin for pregnant women and the model used to derive these values, compared with the reference values for biotin for non-pregnant women

Report	Type	Value pregnant women (µg/d)	Model used	Type	Value non-pregnant women (µg/d)	Absorption non-pregnant women (%)
EFSA 2014[17] = HCNL 2014[38]	AI	40	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	40	"uncertain"
HCNL 2018[4]	N/A	N/A	N/A	AI	40	"uncertain"
NCM 2014[42]	-	-	No reference values derived	-	-	-
DACH 2015[43]	AI	30-60	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	30-60	"no confirmed findings"
IOM 1998[48]	AI	30	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	30	"not well characterized"
WHO/FAO 2004[50]	AI	30	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	30[a]	"limited"

Abbreviations: -: Not specified, N/A: not applicable

Calculations done by the committee are depicted in brackets and in italics.

[a] In the HCNL 2018 report, it was accidentally noted that WHO/FAO did not establish reference values for biotin for adults.[4] WHO/FAO reported reference values for biotin in Table 9.7 of their report.[50]

14.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the EFSA report.

Differences in the method of derivation

None of the reports derived an additional requirement due to the lack of evidence regarding (an additional requirement for) biotin in pregnant women. As a result, NCM did not set DRVs for biotin. The other reports applied their reference value for non-pregnant women to pregnant women.

Differences in the reference values

Differences in the values between reports resulted from differences in the reference value for non-pregnant women. EFSA used a higher reference value than IOM and WHO/FAO, and DACH set a range for its AI which included EFSA's AI.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

14.3 Pregnancy-related health outcomes

Deficiencies

EFSA reported that biotin deficiency during pregnancy had been shown to be teratogenic in several species, including mice, hamsters, chicken, and turkeys, but no data is available to indicate an increased incidence of human fetal malformations.[17]

Intake and associated health outcomes

EFSA noted that urinary excretion of 3-hydroxyisovaleric acid (a biomarker sensitive to biotin depletion) has been observed to be higher in pregnant women than in non-pregnant women, while results on urinary biotin excretion were inconsistent.[17] However, biotin intake levels were not reported, and the relevance of these findings with respect to biotin status in pregnancy was unclear. EFSA also reported one study in unsupplemented pregnant women, of which the study duration (2 weeks) was deemed insufficient to draw conclusions with respect to changes in biomarkers of biotin status.[17]

14.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

Based on the absence of any demonstrated benefit, a biotin recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used in all reports (except NCM), i.e., adopting the reference values for non-pregnant women for use during pregnancy, and maintains EFSA's AI for pregnant women for use in the Netherlands.

The evidence of the method of derivation for the AI of biotin during pregnancy is very limited; data on biotin requirements during pregnancy is scarce. The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 14.2).

Table 14.2. Reference value for biotin recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	40 µg/d	*40 µg/d*

15 Choline

Summary and conclusion

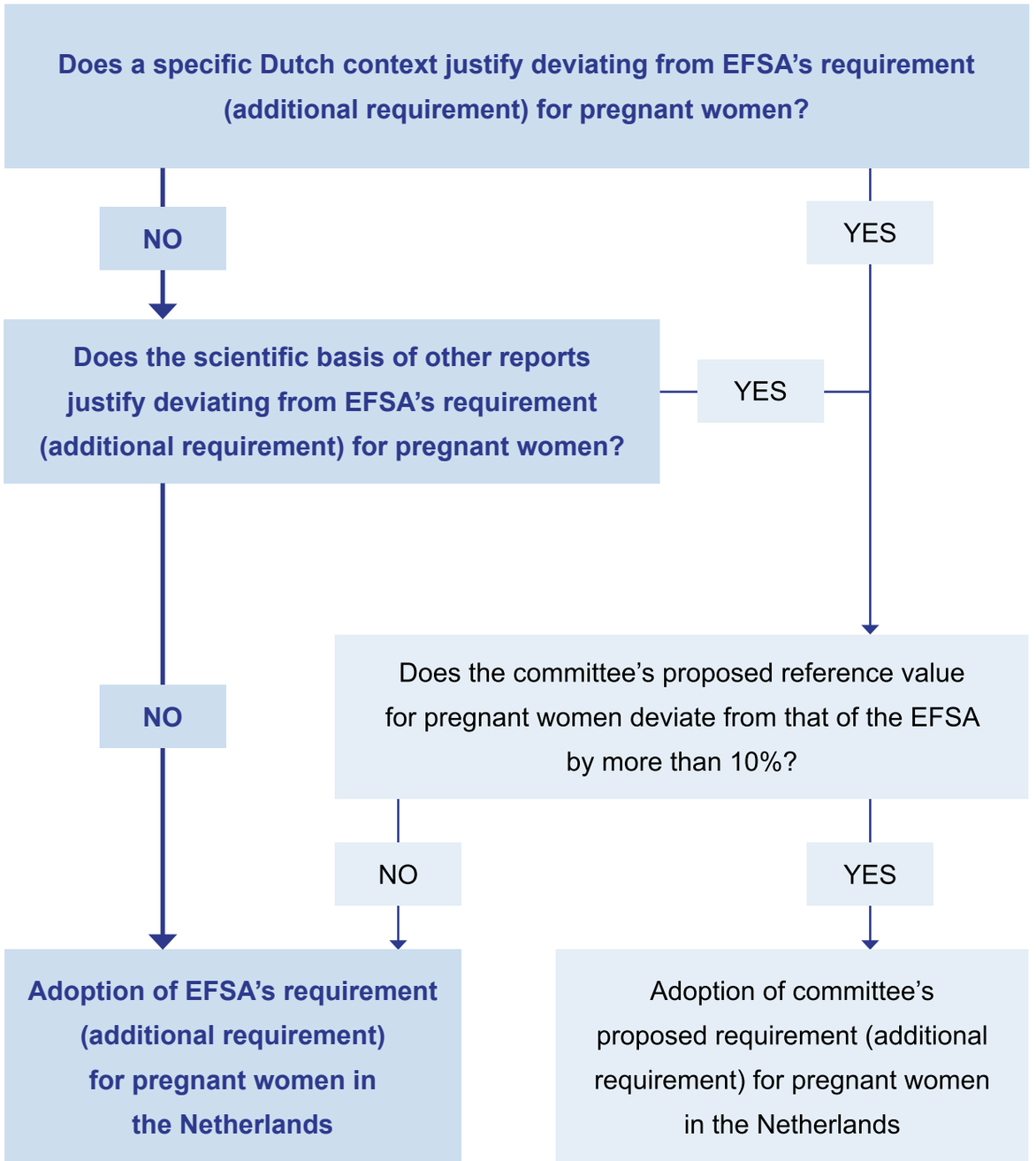
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

There seems to be no scientific consensus between the different reports on the value of the increased requirement during pregnancy, nor on the underlying basis. EFSA used isometric scaling, whereas IOM used an additive model. The committee agrees with EFSA's higher additional requirement. The scientific basis for the method of derivation is acceptable.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 480 mg/d

Flowchart with committee's line of reasoning for choline



15.1 Overview and comparison of values

Table 15.1. Overview of the reference values for choline for pregnant women and the model used to derive these values, compared with the reference values for choline for non-pregnant women

Report	Type	Value pregnant women (mg/d)	Model used[a]	Type	Value non-pregnant women (mg/d)	Absorption non-pregnant women (%)
EFSA 2016[18]	AI	480	Scaling	AI	400	-
HCNL 2014[38]	-	-	No reference values derived	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	AI	400	-
NCM 2014[42]	-	-	No reference values derived	-	-	-
DACH 2015[43]	-	-	No reference values derived	-	-	-
IOM 1998[48]	AI	450	Additive	AI	425[b]	-
WHO/FAO 2004[50]	-	-	No reference values derived	-	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] Information on the models used for each report is specified in Table 15.2.
[b] The HCNL 2018 report accidentally reported IOM's AI to be 400 mg/d, whereas their AI is 425 mg/d.

Table 15.2. Overview of the models used and the basis for the requirements (additional requirements) for choline for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Basis
EFSA 2016[18]	Scaling **(AI: +80)**	N/A	Choline deposition due to growth in maternal and fetal tissue.	Studies on choline transfer from mother to fetus and choline accretion in the fetus and placenta and supplementation studies: insufficient to establish reference values. Assumptions for scaling: reference weight of non-pregnant women is 58.5 kg and the mean gestational increase in body weight during pregnancy is 12 kg.
HCNL 2014[38]	No reference values derived	-	-	Choline was not mentioned in the report.
NCM 2014[42]	No reference values derived	-	-	Choline was not mentioned in the report.
DACH 2015[43]	No reference values derived	-	-	Choline was not mentioned in the report.
IOM 1998[48]	Additive **(AI: +25)**	N/A	Choline deposition due to growth in maternal and fetal tissue.	Assumptions: choline content of fetal and placental tissue combined is 3 mmol/kg (or 312 mg/kg), there is no extra synthesis during pregnancy nor a contribution of choline by placental or fetal synthesis, and total tissue growth is 10 kg (3 kg of fetus and 7 kg of pregnancy organs).
WHO/FAO 2004[50]	No reference values derived	-	-	Choline was not mentioned in the report.

Abbreviations: -: Not specified, N/A: not applicable
[a] If applicable: (+ additional requirement in mg/d).
[b] This column presents any information on absorption during pregnancy if provided by the report.

15.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

Differences in the method of derivation

EFSA used isometric scaling (described below) to establish the reference value for pregnant women, whereas IOM used an additive model. Based on EFSA's scaling approach, the committee calculated the additional requirement for EFSA and compared it with IOM. EFSA's additional requirement based on scaling was higher than IOM's additional requirement, which was based on the choline content of fetal and placental tissue and the increased need due to tissue growth.

HCNL 2014, NCM, DACH, and WHO/FAO did not set DRVs for choline: these reports did not mention choline in their reports, nor their lack of recommendation for this substance. Therefore, these reports are not discussed further.

In the absence of sufficient data to derive DRVs for choline for pregnant women, EFSA calculated the additional choline intake by isometric scaling from the AI of non-pregnant women (400 mg/d), using the reference body weight for non-pregnant women (58.5 kg[a]) and the mean gestational increase in body weight (70.5 kg[b]). Isometric scaling: $AI^{pregnant} = AI^{non\text{-}pregnant}$ x (70.5 kg/58.5 kg) = $AI^{non\text{-}pregnant}$ x 1.21. This corresponds to an additional requirement of +84 mg/d (+80 mg/d after rounding).

EFSA noted that this additional requirement is higher than what would have been obtained with allometric scaling[c] (+60 mg/d).

IOM estimated the fetal choline content to be ~5 mmol/kg (or 520 mg/kg) fetal weight, based on choline concentrations[d] of various adult rat tissues[79] and the assumption of a body organ weight percentage as estimated in the literature.[80] IOM further assumed that ~2 mmol choline/kg placental tissue should cover almost all pregnant women, based on an average choline content of 1.26 (SE: ±0.245) mmol/kg placental tissue in a small American sample (n=7).[81] Next, IOM added these two quantities so that the estimated average choline content of fetal and placental tissues combined is ~3 mmol/kg (or 312 mg/kg). The required dietary choline amount for the 10 kg of tissue that comprises the fetus (3 kg) and organs of pregnancy (7 kg) would then be: 10 kg x 312 mg = 3,000 mg. The additional requirement is: 3,000 mg/270 d = 11.11 mg/d (11 mg/d after rounding).

[a] The reference body weight was based on the measured body heights of 19,969 women in 13 EU Member States assuming a BMI of 22 kg/m^2.[54]

[b] Applies to women with a singleton pregnancy and a pre-pregnancy BMI in the range between 18.5 and 24.9 kg/m^2.[54]

[c] $AI^{pregnant} = AI^{non\text{-}pregnant}$ x $(weight^{pregnant}/weight^{non\text{-}pregnant})^{0.75} = AI^{non\text{-}pregnant}$ x $(70.5/58.5)^{0.75} = AI^{non\text{-}pregnant}$ x 1.15. This corresponds to an AI for pregnant women of 460 mg/d (i.e., an additional requirement of +60 mg/d).

[d] Choline concentrations in nmol/g wet weight (±SE) in liver: 141 (±5), muscle: 97 (±0.3), heart: 79 (±1), kidney: 703 (±60), plasma: 15 (±3), RBC: 34 (±0.2), brain cortex: 29 (±6), with n=3-5 rats for each tissue.[79]

Differences in the reference values

With the additive model, differences in the values between EFSA and IOM resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   EFSA used a lower value than IOM.[4]
2. The method of derivation of the additional requirement:
   EFSA derived a higher additional requirement than IOM, as described above.

EFSA's AI was estimated by isometric scaling: $AI^{pregnant} = AI^{non\text{-}pregnant}$ x (70.5 kg/58.5 kg) = $AI^{non\text{-}pregnant}$ x 1.21= 484 mg/d (480 mg/d after rounding).
IOM's AI was estimated by adding the additional requirement to the AI for non-pregnant women: 425 mg/d + 11 mg/d = 436 mg/d (450 mg/d after rounding).

EFSA reported one American randomized controlled feeding study from 2012 in 26 healthy pregnant women in their 27th gestational week (and 21 non-pregnant controls) who received either 480 or 930 mg choline/d.[82] The higher choline intake of 930 mg/d resulted in the greater maternal use of choline as a methyl donor (as evidenced by higher concentrations of dimethylglycine and sarcosine). This higher intake did not alter the urinary excretion of free choline and betaine, implying that a doubling of the choline AI did not exceed the cells' capacity to use the extra choline as a methyl donor. Choline-derived methyl groups are needed for DNA methylation, which is essential for developmental processes, including genomic imprinting and the maintenance of genome stability. Although maternal choline intake did not influence neonatal circulating concentrations of free choline or betaine, dimethylglycine was twice as high in the neonates of mothers consuming 930 mg/d as in the neonates of those consuming 480 mg/d. The authors concluded that the additional requirement of 25 mg/d as advised by IOM is insufficient to meet the choline demands of pregnant women. EFSA used this study as supportive evidence for the slightly higher AI derived with isometric scaling (which corresponded to the lower dose in this intervention study) than the AI that would have been derived with allometric scaling.
EFSA also noted that their proposed AI is higher than the mean choline intake of 356 mg/d found in 1,002 pregnant Latvian women[83] and the mean choline intake of 347 mg/d found in 600 pregnant Canadian women[84].

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

15.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no choline deficiencies during pregnancy.[18]

Intake and associated health outcomes

EFSA reported two American retrospective population-based case-control studies on the association between choline intake and neural tube defects (NTD) risk with inconsistent results.[18] One study found no association with a higher or lower risk for NTD between a choline intake below the 25th percentile (<293 mg/d) nor above the 75th percentile (>506 mg/d) compared with a choline intake between the 25th and 75th percentiles. The other study showed a significantly decreased NTD risk (OR: 0.49, 95% CI: 0.27-0.90) for the 4th quartile of periconceptional choline intake (>498 mg/d) compared with the lowest quartile (<290 mg/d). The committee notes that EFSA's proposed AI is close to the 4th quartile intakes of this study associated with a decreased risk of NTD. EFSA suggested that such associations may be influenced by the intake of other nutrients and the mothers' genotype and could not be used to derive DRVs for choline.

EFSA reported one double-blind RCT and one prospective pre-birth cohort on the relationship of choline intake and measures of cognition in the children.[18] The RCT showed no significant difference between the experimental group (supplement: 750 mg/d, diet: ~360 mg/d) and the placebo group (diet: ~360 mg/d) on any of the cognitive assessments at either age. The observational study showed no association between maternal intake from foods and supplements (1st trimester: 332 mg/d, SD: ±63, 2nd trimester: 325 mg/d, SD: ±64) and cognitive outcomes in their children at age 3. However, at age 7 the top quartile of 2nd trimester maternal intakes (median: 392 mg/d, range: 364-806 mg/d) was significantly associated (95% CI: 0.5-2.4, p trend: 0.003) with a 1.4 points higher score on a visual memory assessment than the bottom quartile (median: 260 mg/d, range: 141-288 mg/d) and with an effect estimate of 3.5 for the non-verbal intelligence assessment (95% CI: 0.1-6.9, p trend: 0.06). The associations were not significant for the 1st trimester.

The committee notes that EFSA's proposed AI provides a margin above the intake levels in the top quartile associated with higher scores on visual memory and non-verbal intelligence assessments. EFSA concluded that discrepancies in the results might suggest that, in order to investigate the effects of prenatal choline supply on visual memory of children, long-term observations are needed, that the available evidence is insufficient to demonstrate a causal relationship, and cannot be used to derive DRVs for choline.

15.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

EFSA used isometric scaling, whereas IOM used an additive model. There seems to be no scientific consensus on the value of the increased requirement during pregnancy, nor on the underlying basis.

Conclusion and strength of the model

EFSA's method of derivation of the additional requirement for choline during pregnancy (isometric scaling) differed from the method used by IOM, and resulted in a higher additional requirement.

The evidence of EFSA's method of derivation for the additional choline requirement is based on isometric scaling[a] using the mean gestational increase in body weight of 12 kg, and is supported by the findings from a small RCT on maternal choline intake and maternal and fetal biomarkers of choline metabolism.[82] EFSA's higher additional requirement is supported by this RCT in which the authors concluded that the additional requirement of 25 mg/d as advised by IOM is insufficient to meet the choline demands of pregnant women as was shown by modified maternal and fetal biomarkers. The committee agrees with EFSA's higher additional requirement and judges the scientific basis for the method of derivation as acceptable based on a plausible rationale.

The committee used the same method to calculate the additional requirement as used by EFSA, with an increase in body weight of 13.8 kg and a pre-pregnancy reference weight of 64.6 kg, which resulted in a similar (less than 1% difference) adequate intake as calculated by EFSA.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 15.3).

Table 15.3. Reference value for choline recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	480 mg/d[a]	*400 mg/d*

[a] PRI is calculated from the $AR_{scaling}$:
$AI = (AI^{non\text{-}pregnant} \times (weight^{pregnant}/weight^{non\text{-}pregnant}))$
$AI = 400 \times (70.5/58.5)$

[a] The committee deems no correction necessary for the higher reference weights of Dutch women as these weights are used solely for the isometric scaling and, thus, have a negligible effect.

16 Calcium

Summary and conclusion

In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Compared to the EFSA's report, the committee used additional data on health outcomes and derived an adequate intake (AI)*[a] for pregnant women during the second half of pregnancy. Regarding the first half of the pregnancy duration, the committee agrees with the method of derivation used in all reports (except WHO/FAO's), i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is acceptable for the first half of pregnancy and strong for the second half of pregnancy.

The committee accepts EFSA's PRIs and ARs for pregnant women during the first 20 weeks of pregnancy for use in the Netherlands, resulting in the following reference values:

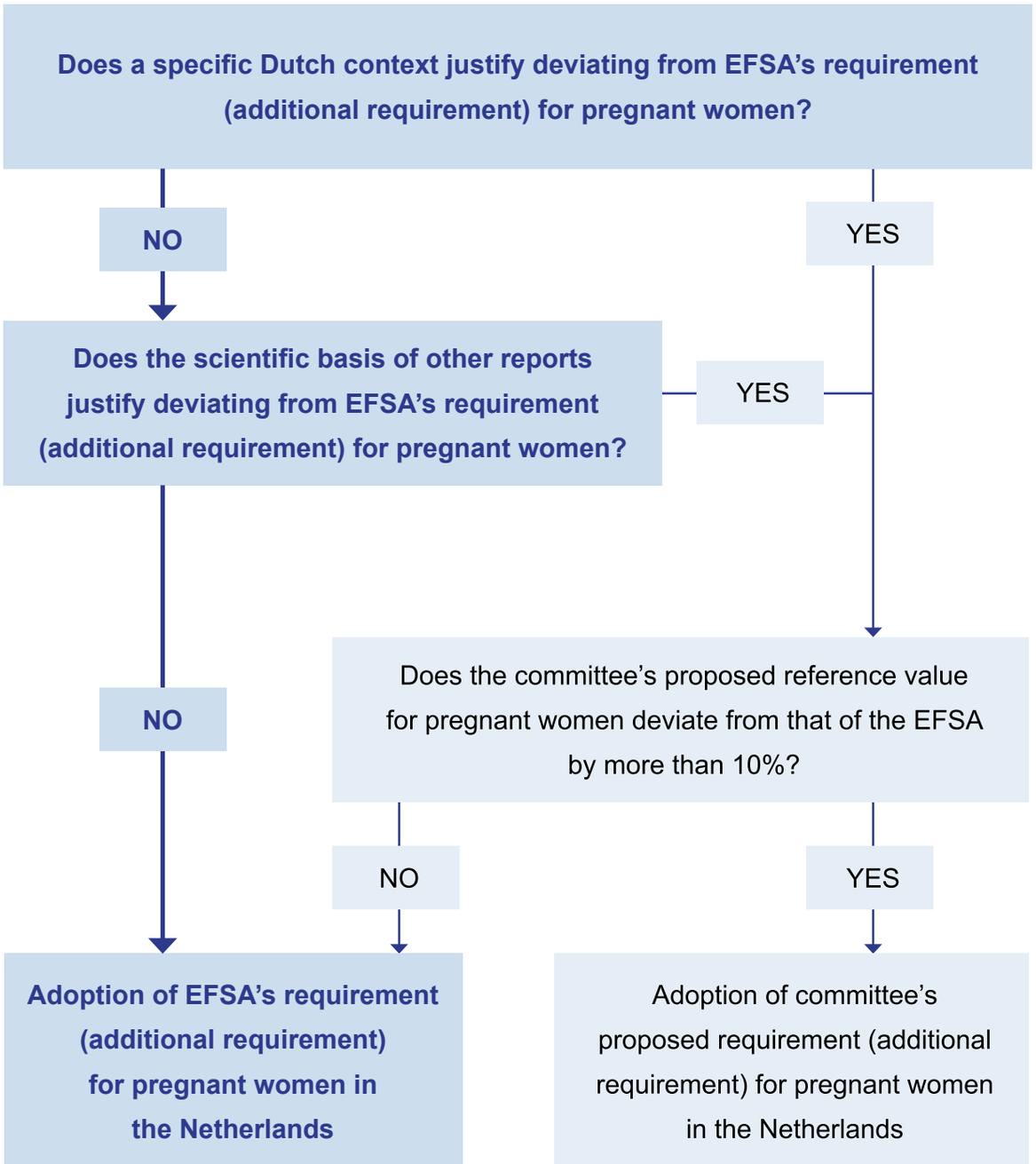
- $AR_{18\text{-}24yr}$ = 860 mg/d $AR_{\geq 25yr}$ = 750 mg/d
- $PRI_{18\text{-}24yr}$ = 1,000 mg/d $PRI_{\geq 25yr}$ = 950 mg/d.

The committee derives an AI* for pregnant women during from 20 weeks of pregnancy onwards for use in the Netherlands, resulting in the following reference value:

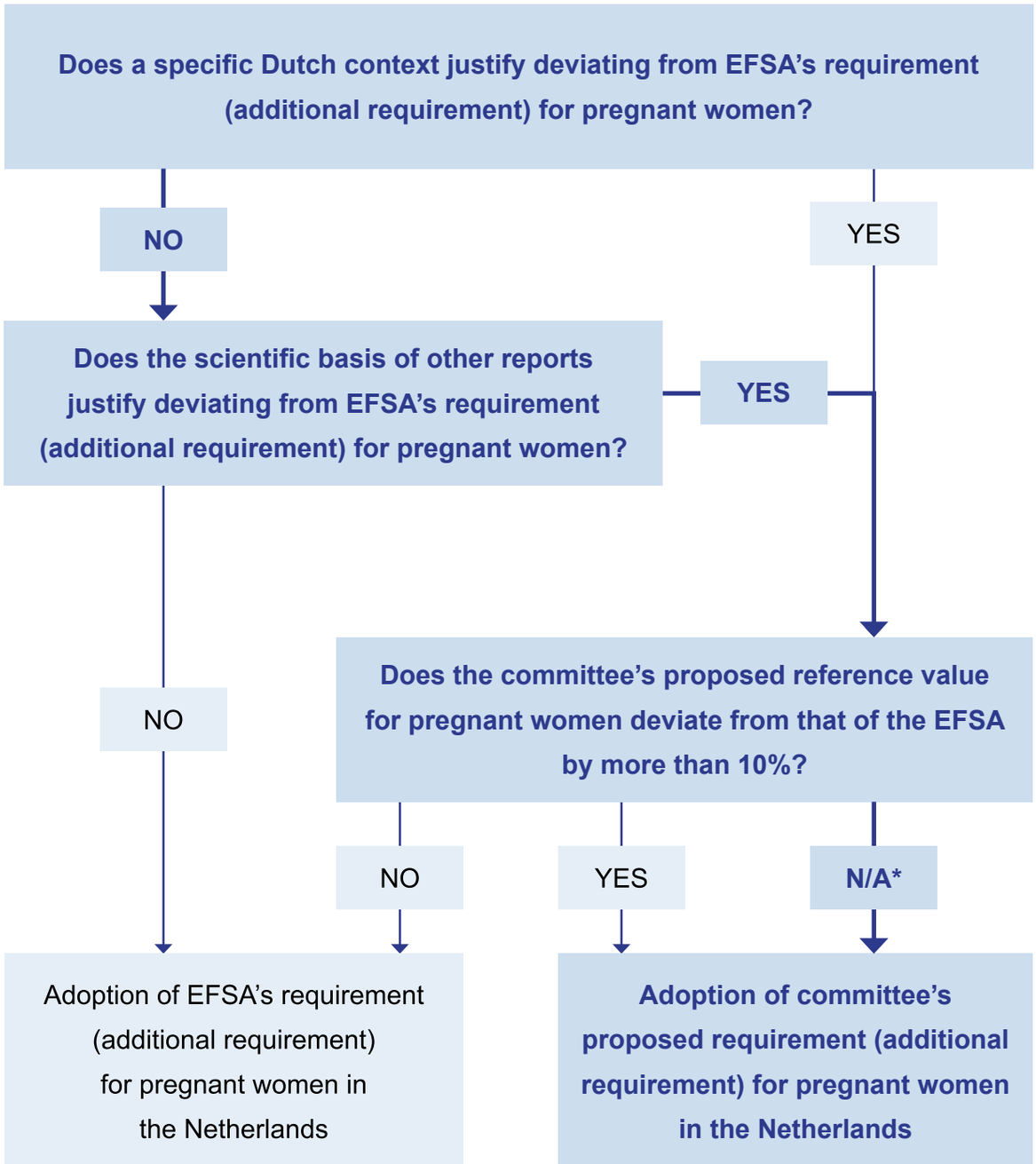
- AI* = 1,000 mg/d

[a] The committee derived an adequate intake as opposed to a PRI, because the committee concluded that an average requirement was unknown, and therefore a PRI could not be derived. The committee is aware of the fact that an adequate intake, by definition, is supposed to cover the requirement of most of the women of the population, whereas in this case, the committee concludes that all women of the population should meet the requirement of 1,000 mg/d. For this reason the adequate intake is referred to as 'adequate intake*'

Flowchart with committee's line of reasoning for calcium until 20 weeks of pregnancy



Flowchart with committee's line of reasoning for calcium from 20 weeks of pregnancy onwards



*The committee decided to change the *type* of the reference value, in combination with combining the two relevant age groups (18-24 years and ≥25 years of age).

16.1 Overview and comparison of values

Table 16.1. Overview of the reference values for calcium for pregnant women and the model used to derive these values, compared with the reference values for calcium for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[19]	PRI	18-24 yr: 1,000 ≥25 yr: 950	18-24 yr: 860 ≥25 yr: 750	10	$PRI_{pregnant}$ = $PRI_{non\text{-}pregnant}$	PRI	18-24 yr: 1,000 ≥25 yr: 950	18-24 yr: 860 ≥25 yr: 750	10	25[b]
HCNL 2000[41] = HCNL 2014[38]	AI	1,000	N/A	*N/A*	$AI_{pregnant}$ = $AI_{non\text{-}pregnant}$	N/A	N/A	N/A	N/A	N/A
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	18-24 yr: 1,000 ≥25 yr: 950	18-24 yr: 860 ≥25 yr: 750	10	25[b]
NCM 2014[42]	RI	900[c]	-	*(30)*	$RI_{pregnant}$ = $RI_{non\text{-}pregnant}$	RI	18-20 yr: 900 ≥21 yr: 800	18-20 yr: - ≥21 yr: 500	*(30)*	20-25[b]
DACH 2015[43]	RI	≥19 yr: 1,000	≥19 yr: 741	15	$RI_{pregnant}$ = $RI_{non\text{-}pregnant}$	RI	≥19 yr: 1,000	≥19 yr: 741	15	20-40[b]
IOM 2011[45]	RDA	1,000	800	*(12.5)*	$RDA_{pregnant}$ = $RDA_{non\text{-}pregnant}$	RDA	1,000	800	*(12.5)*	30[b]
WHO/FAO 2004[50]	RI	1,200	940	*(10)*	Additive	RI	1,000	840	*(10)*	35-70[b]

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] The absorption rate increases with decreasing amounts of calcium in the diet and vice versa.
[c] NCM applied the RI for non-pregnant women aged 18-20 years to pregnant women as many young women might become pregnant before termination of skeletal growth.[42]

16.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

Differences in the method of derivation

Only WHO/FAO derived reference values for pregnant women deviating from their reference values for non-pregnant women. The other reports applied their reference values for non-pregnant women to pregnant women.

EFSA acknowledged the increased need for calcium to meet the requirements of the developing fetal skeleton, which they reported to take place mainly in the second half of the pregnancy (50 mg/d at 20 weeks' gestation; 330 mg/d at 35 weeks[a]).[87] EFSA, HCNL 2000, NCM, DACH, and IOM all mentioned the increased calcium absorption during pregnancy, compensating for these increased needs.[88-96] EFSA also noted that changes are induced in calcium and bone metabolism to support the transfer of calcium from mother to child, which are generally independent of maternal calcium intake in populations where dietary intakes are close to recommendations. All reports provided evidence suggesting that these processes are physiological and provide sufficient calcium for fetal growth without relying on an increase in dietary calcium intake or compromising long-term maternal bone health, with EFSA referring to the most recent literature review (including some of the references cited by the other reports).[91] The other reports additionally referred to supplementation studies revealing no evidence of any beneficial effect[b] on mother or fetus.[97-100] Based on the above, these reports concluded that there was no evidence for an increased calcium requirement during pregnancy.

WHO/FAO used an additive model for their reference values for pregnant women. They based their additional requirement on calcium deposition due to fetal growth and on maternal urinary and skin losses. WHO/FAO assumed a fetal retention of ~240 mg/d. Combined with a maternal urinary calcium of 120 mg/d and a maternal skin loss of 60 mg/d, the absorbed calcium should be: 240 + 120 + 60 = 420 mg/d. WHO/FAO reported the optimal corresponding calcium intake to be 940 mg/d. On this basis, the committee calculated WHO/FAO's assumed absorption rate of 45% (which corresponds to an adjustment factor of 2.24). The AR is 420 x 2.24 = 940.8 mg/d (940 mg/d after rounding). Thus, WHO/FAO's additional requirement is 100 mg/d.

[a] 200-250 mg/d in the third trimester, according to IOM.[85,86]

[b] Including (but not limited to) maternal bone density and fracture risk in older age; calcium retention; fetal somatic and skeletal growth; neonatal characteristics; anthropometric measurements; bone mass in offspring at 16 years of age.

Differences in the reference values

Differences in the values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   EFSA's values for 18-24-year-olds were the same as HCNL 2014's, DACH's, and IOM's, which were higher than NCM's and lower than WHO/FAO's. EFSA's values for ≥25-year-olds were higher than NCM's and lower than the other reports.[4]
2. The method of derivation of the additional requirement:
   All reports, except WHO/FAO applied their reference values for non-pregnant women to pregnant women. WHO/FAO's PRI was calculated by multiplying the AR with twice the CV of 10%: 940 mg/d x 1.2 = 1,128 mg/d (1,200 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester. WHO/FAO acknowledged that most of the calcium is laid down in the fetus in the last trimester of pregnancy but applied the additional requirement to the entire pregnancy.

16.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no calcium deficiencies during pregnancy.[19]

Intake and associated health outcomes

EFSA reported two recent systematic reviews on the effects of calcium intake and health outcomes, targeted at different life stages, including pregnancy.[19]

One review (including 165 primary studies and 11 systematic reviews)[a] focused on vitamin D in addition to calcium and reported inconsistent results regarding bone and skeletal health, cancer, cardiovascular disease, and hypertension. EFSA listed the main limitations of this review: large variations in the methodological quality of the studies, limiting the possibilities for a meta-analysis, dose-response relationships were impossible to derive, and separating the effects of calcium and vitamin D was difficult because of their close interrelationship.

The other review was undertaken to inform the NNR 2014 on calcium requirements. The outcome measures of this review included pregnancy outcomes and growth. EFSA reported that evidence on maternal calcium intake and fetal growth, skeletal growth, BMD, and fractures was not sufficient to draw any conclusions. They listed the main limitations of this review: most were calcium supplementation studies and did not report total calcium intake, heterogeneity of study protocols was high (widely varying intake of calcium, different study duration), and dose-response studies were not reported.

[a] Including primary intervention and observational studies and excluding cross-sectional and retrospective case-control studies.

HCNL

For the advisory report *Dietary recommendations for pregnant women*,[35] HCNL presented the scientific knowledge on the effects of calcium intake from supplements during pregnancy and maternal health, pregnancy outcomes, and offspring health. The Council carried out systematic literature searches in PubMed to retrieve systematic reviews (with or without meta-analysis) of RCT's. The searches included publications until July 2019. The committee found strong evidence that calcium supplementation reduced the risk of preterm birth (<37 weeks), gestational hypertension, and the risk of pre-eclampsia from 20 weeks of pregnancy onwards. It was unlikely that calcium supplementation had an effect on the risk of a small-for-gestational-age infant. A description of methodology and conclusions is available in the background documents '*Working method for drawing up dietary recommendations for pregnant women.'*[37] *and 'Health effects of nutrient intake from supplements'.*[36]

16.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

WHO/FAO was the only organisation that derived an additional requirement. The other organisations concluded that no additional calcium was needed during pregnancy due to an increased maternal absorption. However, based on the conclusions of the parallel advisory report *Dietary recommendations for pregnant women*[35] based on calcium supplementation studies (see 16.3), the committee concluded that the average requirement for non-pregnant women of EFSA is no longer valid for pregnant women after 20 weeks of pregnancy: the distribution of the calcium requirement is unknown during this period of pregnancy. The committee therefore found it not appropriate to maintain EFSA's average requirement and PRI for this period and derived an adequate intake* for the second half of the pregnancy (≥20 weeks of pregnancy). Because the evidence based on calcium supplementation studies does not specify between age ranges, the committee derives an AI* of 1,000 mg for all pregnant women, regardless of age.

The committee deems the scientific basis for the method of derivation to be acceptable (based on a plausible rationale) for the first 20 weeks of pregnancy. The committee deems the scientific basis for the method of derivation regarding the period of 20 weeks of pregnancy onwards as strong.

Reference values for pregnancy

The committee accepts EFSA's PRI and AR for pregnant women during the first 20 weeks of pregnancy) for use in the Netherlands (Table 16.2). The committee derives an AI* for pregnant women from 20 weeks of pregnancy onwards for use in the Netherlands.

Table 16.2. Reference values for calcium recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Values for pregnant women <20 weeks of pregnancy	Values for pregnant women ≥20 weeks of pregnancy	Values for non-pregnant women
Average requirement (AR)	18-24 yr: 860 mg/d ≥25 yr: 750 mg/d	-	18-24 yr: 860 mg/d ≥25 yr: 750 mg/d
Population reference intake (PRI)	18-24 yr: 1,000 mg/d ≥25 yr: 950 mg/d	1,000 mg/d (AI)	18-24 yr: 1,000 mg/d ≥25 yr: 950 mg/d

To define the adequacy of intake of a specific nutrient on a population level, it is common practise to compare the median habitual intake of the population with the adequate intake. If the median habitual intake is higher than the adequate intake, then it is presumed that the risk of inadequacy at a population level is low. If the median habitual intake is lower than the adequate intake, a conclusion on the adequacy of intake at a population level is not possible and additional research is needed on nutrient status or health effects.

Because of the strong evidence on health effects of calcium during the second half of pregnancy, the committee concludes that this standard evaluation of nutrient intake at a population level should not be used. Instead, the committee has the opinion that the full distribution of calcium intake (including supplement intake) of pregnant women from 20 weeks of pregnancy onward should be above the AI* of 1000 mg/d.

17 Chromium (III)

Summary and conclusion

In 2018, the committee agreed with EFSA's conclusion that it is not clear whether chromium (III) is an essential trace element and with EFSA's decision not to set reference values for chromium for non-pregnant women. Due to the lack of data and the apparent absence of deficiencies in pregnancy, the committee does not establish reference values for pregnant women in the Netherlands.

17.1 Overview and comparison of values

Table 17.1. Overview of the reference values for chromium for pregnant women and the model used to derive these values, compared with the reference values for chromium for non-pregnant women

Report	Type	Value pregnant women (µg/d)	Model used	Type	Value non-pregnant women (µg/d)	Absorption non-pregnant women (%)
EFSA 2014[20] = HCNL 2014[38]	-	-	No reference values derived	-	-	-
HCNL 2018[4]	N/A	N/A	No reference values derived	-	-	-
NCM 2014[42]	-[a]	-[a]	No reference values derived	-	-	-
DACH 2015[43]	AI	30-100	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	30-100	0.5-3 (from food)
IOM 2001[47]	AI	30	Scaling	AI	25	0.4-2.5 (from food)[b]
WHO/FAO 2004[50]	-	-	No reference values derived	-	-	-

Abbreviations: -: Not specified, N/A: not applicable

Calculations done by the committee are depicted in brackets and in italics.

[a] NCM did not establish reference values for pregnant women but did refer to IOM 2001's reference values.

17.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the EFSA report.

Differences in the method of derivation

IOM used scaling (described below) to establish the reference value for pregnant women. Based on IOM's scaling approach, the committee calculated their additional requirement for IOM, which was based on the chromium deposition due to fetal growth.

DACH applied their reference value for non-pregnant women to pregnant women, without describing their argumentation for this. Therefore, no further consideration will be given to the DACH report.

EFSA, NCM, and WHO/FAO did not establish reference values for chromium. EFSA considered that there was no evidence of beneficial effects associated with chromium intake in healthy normoglycaemic subjects. NCM stated that very few relevant human studies had been conducted since their recommendations of 2004 and that data is also lacking on the requirements for chromium during pregnancy, but referred to IOM 2001's recommendations for chromium during pregnancy. WHO/FAO did not mention chromium in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

IOM stated that several reports described that chromium is depleted throughout pregnancy and with multiple pregnancies.[101-103] Additionally, they noted that tissue analyses conducted before current instruments were available indicated that chromium is higher in tissues at birth and declines rapidly with age[104], suggesting a need for deposition in the fetus from the mother. In the absence of sufficient data on which to base their reference values for chromium for pregnant women, IOM calculated the additional chromium intake themselves by extrapolating up from the AI of non-pregnant women (25 µg/d) by means of metabolic scaling[a], using the reference body weight for non-pregnant women (61 kg[b]) and the median increased body weight for pregnant women (77 kg[c]). Scaling: $AI^{pregnant} = AI^{non\text{-}pregnant} \times (77\ kg/61\ kg)^{0.75} = AI^{non\text{-}pregnant} \times 1.19$. This corresponds to an additional requirement of +4.77 µg/d (+5 µg/d after rounding).

Differences in the reference values

EFSA and NCM did not establish values for chromium during pregnancy. IOM's AI was estimated by metabolic scaling: $AI^{pregnant} = AI^{non\text{-}pregnant} \times (77\ kg/61\ kg)^{0.75} = 29.77$ µg/d (30 µg/d after rounding).

[a] Corresponding to the $^{0.75}$ in the formula.
[b] From section 2 of their report.[47]
[c] IOM referred to a study reporting a median weight gain of 16 kg among 7,002 women who had good pregnancy outcomes.[105]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

17.3 Pregnancy-related health outcomes

EFSA described no pregnancy-related chromium deficiencies and no studies showing intake levels associated with pregnancy-related health outcomes.[20]

17.4 Strength of the scientific basis and conclusions

In 2018, the committee agreed with EFSA's conclusion that it is not clear whether chromium is an essential trace element and with EFSA's decision not to set reference values for chromium for adults.[4]

Due to the lack of data, and the apparent absence of deficiencies in pregnancy, the committee does not establish reference values for pregnant women in the Netherlands.

18 Copper

Summary and conclusion

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women.

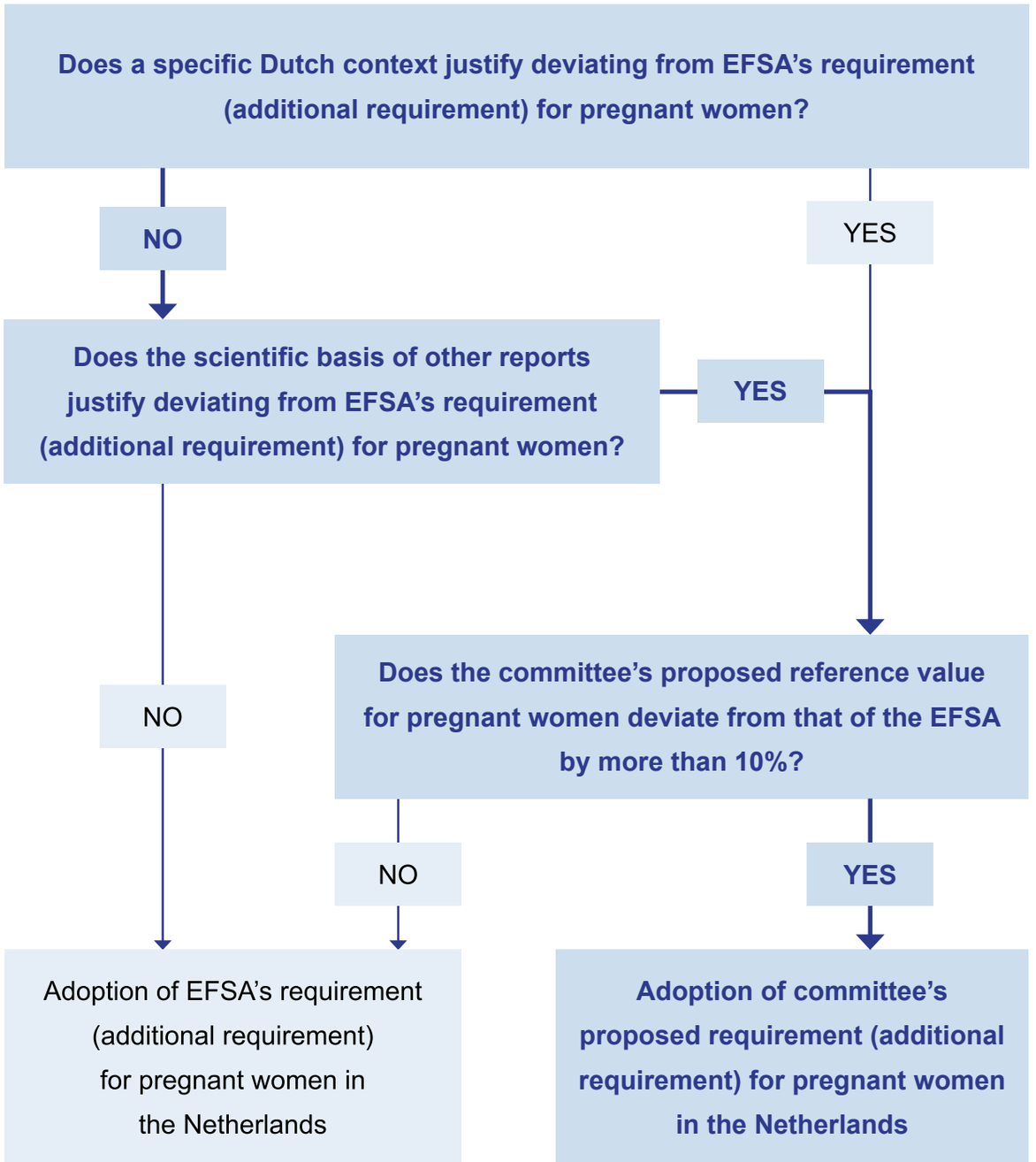
There appears to be a scientific consensus between the different reports on the derivation of the reference values for pregnant women with an additive model. The committee agrees with the method of derivation of the additional requirement for copper during pregnancy used by IOM.

The scientific basis for the method of derivation is acceptable.

For the Netherlands, the committee accepts IOM's additional requirement for pregnant women, resulting in the following reference values:

- AR = 0.8 mg/d
- PRI = 1.0 mg/d

Flowchart with committee's line of reasoning for copper



18.1 Overview and comparison of values

Table 18.1. Overview of the reference values for copper for pregnant women and the model used to derive these values, compared with the reference values for copper for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[21]	AI	1.5	N/A	N/A	Additive	AI	1.3	N/A	N/A	~50[c]
NCM 2014[42] = HCNL 2014[38]	RI	1.0	-	-	Additive	RI	0.9	0.7	15	35-70[d]
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	PRI	0.9	0.7	15	35-70[d]
DACH 2015[43]	AI	1.0-1.5	N/A	N/A	$AI_{pregnant}$ = $AI_{non\text{-}pregnant}$	AI	1.0-1.5	N/A	N/A	35-70
IOM 2001[47]	RDA	1.0	0.8	15	Additive	RDA	0.9	0.7	15	35 (20-50)[d,e]
WHO/FAO 2004[50]	-	-	-	-	No reference values derived	-	-	-	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 18.2.
[c] From a mixed diet.
[d] The absorption rate increases with decreasing amounts of copper in the diet and vice versa.
[e] Absorption ranges from >50% at an intake of <1 mg/d to <20% at an intake >5 mg/d. ~35% of a 2 mg/d intake is absorbed. Bioavailability ranges from 75% when diet contains 400 µg/d to 12% when diet contains 7.5 mg/d.

Table 18.2. Overview of the models used and the basis for the requirements (additional requirements) for copper for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2015[21]	Additive (AI +0.2)	50	Copper deposition due to growth in maternal and fetal tissue.	Assumption: accumulation of copper in placenta and fetus is 16 mg.
NCM 2014[42] = HCNL 2014[38]	Additive (RI +0.1)	"Increased fractional absorption"	-	Reference values from NNR 2004.[53] No further details.
DACH 2015[43]	$AI_{pregnant} = AI_{non\text{-}pregnant}$	-	-	No further details.
IOM 2001[47]	Additive (EAR +0.1 RDA +0.1)[c]	65-70	Copper deposition due to growth in maternal and fetal tissue.	Assumptions: a full-term fetus contains ~13.7 mg copper, the placenta, amniotic fluid, and maternal tissue contain 4.6 mg copper.
WHO/FAO 2004[50]	No reference values derived	-	-	Copper was not mentioned in the report.

Abbreviations: -: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in mg/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

[c] Due to the CV of 15% and rounding to 1 decimal point, the additional value is equal for EAR and RDA.

18.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

EFSA, NCM, and IOM used an additive model for their reference values for pregnant women. DACH applied their reference values for non-pregnant women to pregnant women without further explanation. Therefore, no further consideration will be given to the DACH report.

WHO/FAO did not establish DRVs for copper. They did not mention copper in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

NCM and IOM used the same additional requirement of 0.1 mg/d, which was slightly lower than EFSA's additional requirement of 0.2 mg/d. It is uncertain, also from NNR 2004[53], what the basis is for NCM's additional requirement. Therefore, no further consideration will be given to the NCM report. EFSA and IOM both based their additional requirement on the accumulation of copper in the fetus and maternal pregnancy tissues. EFSA and IOM derived their additional requirement in a similar way.

Both reports estimated the copper content in the fetus and in maternal pregnancy tissues. EFSA assumed a total value of ~16 mg in placenta and fetus.[106] IOM assumed a total value of 18 mg copper in fetal and maternal tissues, of which the full-term fetus contained 13.7 mg[107] and the placenta, amniotic fluid, and maternal tissue 4.6 mg.
Both reports divided their copper content by the number of days of pregnancy (EFSA: 280 days, IOM: 270 days), and took the absorption rate during pregnancy into account (EFSA: 50%, which corresponds to an adjustment factor of 2, IOM: 65-70%, which corresponds to an adjustment factor of 1.43-1.54).
EFSA's calculated additional requirement: (16 mg/280 days) x 2 = 0.11 mg/d (which was rounded up to 0.2 mg/d in anticipation of copper requirements for lactation).
IOM's calculated additional requirement: (18 mg/270 days) x 1.43 to 1.54 = 0.096 to 0.103 mg/d (which was averaged and rounded to 0.1 mg/d).

Differences in the reference values
With the additive model, differences in the values between reports resulted from differences in three aspects.

1. The reference value for non-pregnant women:
   EFSA used a higher value for non-pregnant women than IOM.[4]
2. The method of derivation of the additional requirement:
   EFSA derived a higher additional requirement than IOM, as described above.
3. The summation of the additional requirement:
   EFSA added the additional requirement to their AI: 1.3 mg/d + 0.2 mg/d = 1.5 mg/d.

IOM's PRI was based on the additional requirement added to the AR of non-pregnant women multiplied by twice the CV of 15%: (0.7 mg/d + 0.1 mg/d) x 1.3 = 1.04 mg/d (1.0 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester
None of the reports differentiated by trimester. EFSA acknowledged that most of the fetal accumulation occurs in the last trimester of pregnancy. To allow for the additional need related to the growth of maternal tissues and fetal and placental requirements, and given the limited information on what adaptive change may occur during pregnancy, EFSA applied their additional requirement to the entire pregnancy.

18.3 Pregnancy-related health outcomes

Deficiencies
EFSA reported that Menkes disease is induced by functional copper deficiency.[21] Menkes disease is an X-linked recessive disorder due to mutations of ATP7A, one of two copper pumps involved in transferring copper across cell membranes. The copper is not taken across the gut membrane, so the deficiency is throughout the body. Babies (boys) born with Menkes disease may show the following symptoms:

- Hair changes (“kinky” hair), similar to wool changes shown in Western Australian sheep.
- Neurological deficits.
- Very lax skin (cutis laxa).
- Disrupted lamina propria of the large vessels, often resulting in early death from aortic aneurysms.

Of the many different mutations recorded in ATP7A, some do not have lethal consequences, such as those causing occipital horn syndrome. Attempts to rectify the disorder by injecting copper directly into the cerebrospinal fluid have had limited success.

Intake and associated health outcomes

EFSA described no studies showing copper intake levels associated with pregnancy-related health outcomes.[21]

18.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014’s reference values for non-pregnant women (which were the values used by NCM and IOM) because their AR appeared to have sufficient relevance for the prevention of deficiency (as opposed to EFSA’s substantially higher AI, for which the committee deemed insufficient evidence to be available for beneficial effects on the prevention of deficiency symptoms or health).[4]

Additive model

There appears to be a scientific consensus on the derivation of the reference values for pregnant women with an additive model.

Conclusion and strength of the additive model

The committee agrees with the method of derivation of the additional requirement for copper during pregnancy used by IOM. EFSA’s higher estimate is based on an anticipated increased copper requirement for lactation purposes. However, EFSA also noted that: ”The mechanisms governing the transfer of copper from blood to breast milk are not fully understood, but they do not seem to depend on the maternal intake or maternal copper reserves”. In the absence of data on copper intakes and pregnancy-related health outcomes, the committee judges IOM’s additional requirement sufficient to meet the increased needs during pregnancy.

The evidence of IOM’s method of derivation for the additional copper requirement during pregnancy was based on one study on the accumulated copper content in the fetus and pregnancy products.[107] The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

For the Netherlands, the committee accepts IOM's reference values for pregnant women (Table 18.3).

Table 18.3. Reference values for copper recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	0.8 mg/d	*0.7 mg/d*
Population reference intake (PRI)	1.0 mg/d[a]	*0.9 mg/d*

[a] PRI is calculated as ($AR_{non\text{-}pregnant}$ + additional requirement) multiplied by twice the CV: PRI = (0.7 mg/d + 0.1 mg/d) x 1.3.

19 Fluoride

Summary and conclusion

In 2018, the committee derived no reference values for fluoride for non-pregnant women. In the Netherlands, fluoride-containing dental hygiene products are used for caries prevention; contrary to EFSA, fluoride intake from foods is not considered necessary for caries prevention. There appears to be an absence of data indicating an increased fluoride requirement during pregnancy, and there appear to be no deficiencies in pregnant women. Therefore, as for other adults, the committee does not derive reference values for fluoride for pregnant women in the Netherlands as this is covered by fluoride-containing dental hygiene products.

19.1 Overview and comparison of values

Table 19.1. Overview of the reference values for fluoride for pregnant women and the model used to derive these values, compared with the reference values for fluoride for non-pregnant women

Report	Type	Value pregnant women (mg/d)	Model used	Type	Value non-pregnant women (mg/d)	Absorption non-pregnant women (%)
EFSA 2013[22] = HCNL 2014[38]	AI	2.9	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	2.9	80-90[a,b]
HCNL 2018[4]	N/A	N/A	N/A	-	-	-
NCM 2014[42]	-	-	No reference values derived	-	-	-
DACH 2015[43]	AI	3.1	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	3.1	"Almost completely"[b]
IOM 1997[49]	AI	3.0	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	3.0	≥80[a,b]
WHO/FAO 2004[50]	-	-	No reference values derived	-	-	-

Abbreviations: -: Not specified, N/A: not applicable

Calculations done by the committee are depicted in brackets and in italics.

[a] Influenced by many factors, variability in the absorption efficiency of fluoride from different foods.

[b] Absorption is lower in the presence of calcium or other cations.

19.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the EFSA report.

Differences in the method of derivation

None of the reports derived an additional requirement due to the lack of evidence regarding fluoride during pregnancy. EFSA, DACH, and IOM applied their reference values for non-pregnant women to pregnant women. NCM and WHO/FAO did not set DRVs for fluoride. NCM considered fluoride to be a non-essential trace element but referred to the IOM (1997) report, in which an AI was set for fluoride. WHO/FAO did not mention fluoride in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

EFSA's and DACH's AIs for adult women (including pregnant women) were based on the AI for children of 0.05 mg/kg body weight. For pregnant women, EFSA used the median body weight before pregnancy. This was based on measured body heights of 19,969 women (18-79 years) in 13 EU Member States, assuming a BMI of 22kg/m^2.[54] DACH did not explain their reason for applying the AI for non-pregnant women to pregnant women. Therefore, no further consideration will be given to the DACH report.

IOM referred to several studies with conflicting results on the effect of prenatal fluoride supplementation for the primary teeth.[49] IOM used the only prospective, randomized, double blind study for their conclusion that scientific evidence is insufficient to support a recommendation for prenatal fluoride supplementation.[108] In this study, 798 American children were followed until age 5. 1,400 pregnant women in their 1st trimester (from areas with fluoride-deficient drinking water) were assigned 1 mg/d of fluoride or a placebo for the last 6 months of pregnancy. In the treatment group, 92% of children remained caries-free, in the control group this was 91% (not significant).

Additionally, IOM referred to two studies[a] indicating that fluoride balances in pregnant and non-pregnant women were not markedly different.[110,111] One of these studies was performed in 10 pregnant women in the 2nd half of pregnancy and 6 non-pregnant controls.[110] They received two different low-fluoride diets (0.41 mg/d and 0.27 mg/d) for one or two 21-day periods in a metabolic unit. Both pregnant (-0.32 mg/d) and non-pregnant (-0.15 mg/d) women demonstrated small negative fluoride balances. The other study was performed in 11 pregnant women (6 in their 2nd quarter and 5 in their 4th quarter of pregnancy) and 7 non-pregnant women.[111] These women were supplemented with 1.0 mg/d (average total intake: 1.35 mg/d) over a 20-day period under confined metabolic conditions.

[a] IOM accidentally referred to a fluoride balance study performed in men.[109] The committee found the correct publication from the same author published in the same year.[110]

All groups demonstrated small positive balances; +0.16, +0.14, and +0.19 mg/d, respectively (differences between groups not significant).

From these data, IOM concluded that there is no evidence that the AI for pregnant women should be increased above the level recommended for non-pregnant women.

Differences in the reference values

Differences in the values between reports resulted from differences in the reference values for non-pregnant women. EFSA used a slightly lower reference value than IOM.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

19.3 Pregnancy-related health outcomes

Deficiencies

EFSA considered that no fluoride deficiencies have been identified in humans.[22] They further noted that 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. EFSA stated that caries is not a fluoride deficiency disease and concluded that fluoride is not an essential nutrient.

Intake and associated health outcomes

EFSA reported the same RCT as IOM mentioned in 798 children from a community with a low fluoride content in drinking water (<0.3 mg/L) reporting no positive effect of prenatal fluoride supplementation (1 mg/d) on caries incidence up to five years of age.[22] In a follow-up study, no difference was found in the fluoride content of teeth from children whose mothers had received prenatal fluoride supplements when compared with teeth from children whose mothers who had received a placebo (average fluoride concentration in surface enamel: 3,400-3,800 µg/cm^3, tooth body enamel: ~1,350 µg/cm^3, dentin: 380 µg/cm^3).[22] EFSA further acknowledged (as did IOM) that although many studies on prenatal fluoride supplementation exist, they did not use these studies to derive DRVs for fluoride for several reasons: the studies did not provide information on the total dietary fluoride intake; all studies after 1970 (as were these studies) are potentially confounded by the use of fluoride-containing dental hygiene products, and the majority of studies reviewed by EFSA (although it is uncertain whether this applies to these two studies) have not systematically assessed other factors which influence caries development (e.g., diet, environment, genetic deposition, and the aforementioned dental hygiene).

19.4 Strength of the scientific basis and conclusions

In 2018, the committee derived no reference values for fluoride for non-pregnant women.[4] In the Netherlands, fluoride-containing dental hygiene products are used for caries prevention; contrary to EFSA, fluoride intake from foods is not considered necessary for caries prevention.

There appears to be an absence of data indicating an increased fluoride requirement during pregnancy, and there appear to be no deficiencies in pregnant women. Therefore, as for the non-pregnant women, the committee does not derive reference values for fluoride for pregnant women in the Netherlands as this is covered by fluoride-containing dental hygiene products.

20 Iodine

Summary and conclusion

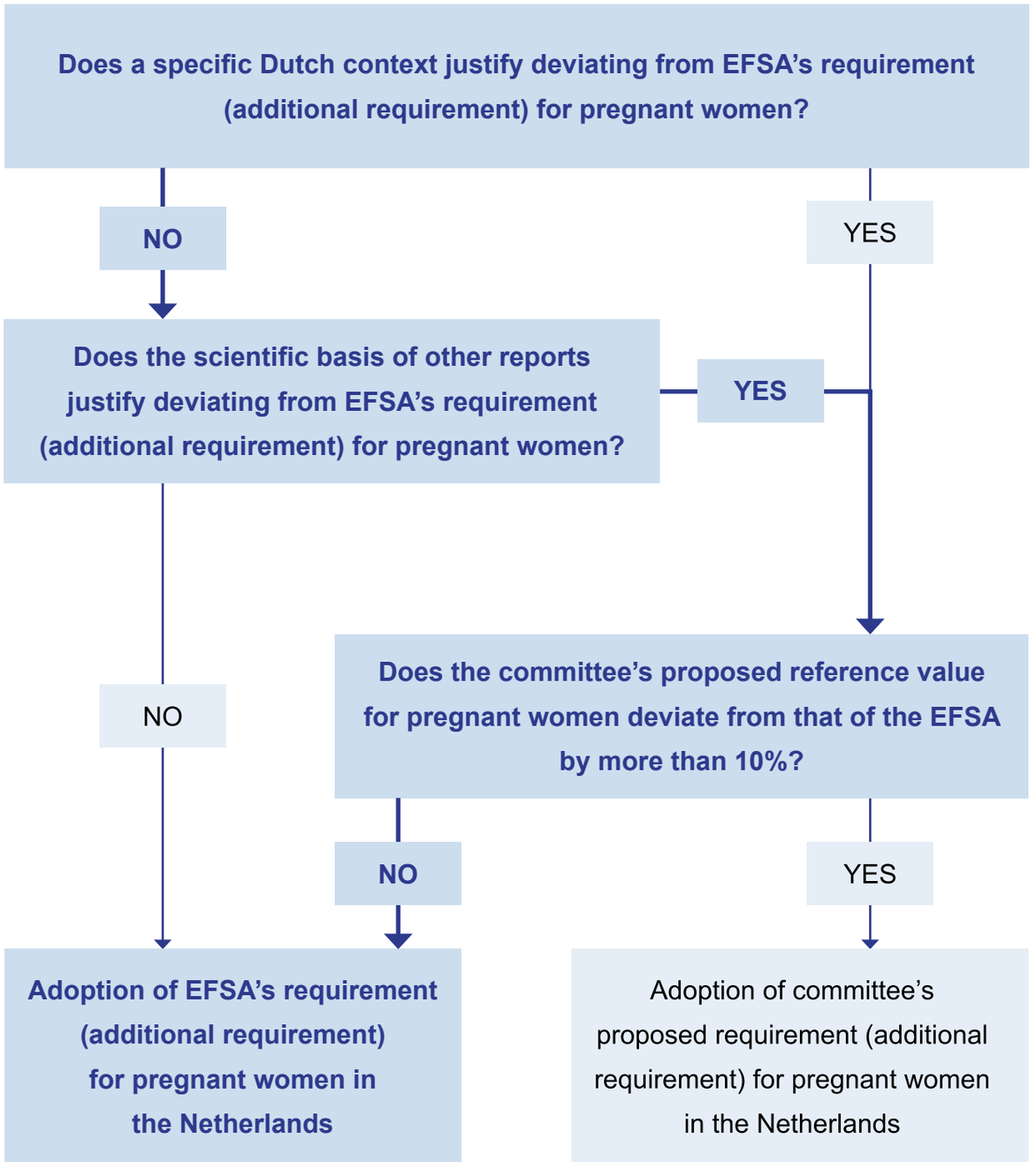
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Despite differences in the approaches used, the reference values for pregnant women from the different reports are relatively close to each other. The committee agrees with the method of derivation for the total requirement for iodine during pregnancy used by WHO/FAO and IOM, which leads to similar values as EFSA's. The scientific basis for the method of derivation is strong.

The committee prefers IOM's PRI and AR for pregnant women. However, since the difference between IOM's PRI and EFSA's AI is not more than 10%, the committee accepts EFSA's AI for use in the Netherlands, resulting in the following reference value:

- AI = 200 µg/d

Flowchart with committee's line of reasoning for Iodine



20.1 Overview and comparison of values

Table 20.1. Overview of the reference values for iodine for pregnant women and the model used to derive these values, compared with the reference values for iodine for non-pregnant women

Report	Type	Value pregnant women (µg/d)	AR pregnant women (µg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (µg/d)	AR non-pregnant women (µg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2014[23]	AI	200	N/A	N/A	Additive	AI	150	N/A	N/A	Oral inorganic iodide and T3: >90 Oral thyroxine (T4): 70-80
NCM 2014[42] = HCNL 2014[38]	RI	175[c]	-	-	Additive	RI	150	100	*(25)*	"Generally efficiently"
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	150	N/A	N/A	Oral inorganic iodide and T3: >90 Oral thyroxine (T4): 70-80
DACH 2015[43]: CH[d]	AI	200[e]	-	-	Additive	AI	150	N/A	N/A	"Almost completely"
DACH 2015[43]: DE, AU	RDA	230[e]	-	-	Additive	AI	200	N/A	N/A	"Almost completely"
IOM 2001[47]	RDA	220	160	20	Total requirement	RDA	150	95	20[f]	Dietary iodine: >90 Oral thyroxine (T4): 75
WHO/FAO 2004[50]	RI	200	-	-	Total requirement	RI	150	-	-	Iodide ion from food and water: 100[g]

Abbreviations: -: Not specified, N/A: not applicable, CH: Switzerland, DE: Germany, AU: Austria
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 20.2.
[c] As reported in Table 1.3 from NCM's report.[42]
[d] In Switzerland, iodine supply is better than in Germany and Austria as a result of a decades-long iodine salt program.
[e] In regions with a critical supply of iodine, supplementation is recommended after consultation with a doctor. In Germany, supplementation of 100 µg/d (up to 150 µg/d) is advised.
[f] The CV presented in the report was 20%, whereas the CV calculated from the AR and RDA was 29%.[g] WHO/FAO noted that absorption of iodine within thyroid hormones ingested for therapeutic purposes is not 100%, but did not state what this absorption is.

Table 20.2. Overview of the models used and the basis for the requirements (additional requirements) for iodine for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2014[23]	Additive (AI: +50)	-	Iodine deposition due to maternal and fetal tissue growth and maternal and fetal hormone production.	Assumptions: the iodine content in the placenta is 18-100 µg, in amniotic fluid 15 µg, in the fetal thyroid 100-300 µg, and in fetal blood 10 µg (cumulative total: 1 µg/d), iodine status before pregnancy is adequate, the (increased) synthesis of fetal thyroid hormones corresponds to 2-4 µg/d, of maternal thyroid hormones corresponds to 25 µg/d and the latter results in an additional requirement of 44 µg/d after applying the equation of Fisher and Oddie[112] (see "*20.2 Differences in the method of derivation*").
NCM 2014[42] = HCNL 2014[38]	Additive (RI: +25)	-	Iodine deposition due to fetal tissue growth and optimal median urinary iodine concentrations.	Reference values from NNR 2004[53]. A supplementation study: intakes of ≥150 µg/d result in optimal median urinary iodine concentrations (150-249 µg/L). A balance study: iodine retention of full-term infants is ~7 µg/kg.
DACH 2015[43]: CH	Additive (AI: +50)	-	Optimal median urinary iodine concentrations.	Assumption: increased renal blood flow and a concomitant increased urinary iodine concentration (not quantified).
DACH 2015[43]: DE, AU	Additive (AI: +30)		Optimal median urinary iodine concentrations.	Assumption: increased renal blood flow and a concomitant increased urinary iodine concentration (not quantified).
IOM 2001[47]	Total requirement	-	Iodine deposition due to fetal tissue growth and prevention of deficiency symptoms.	A balance study: EAR is 160 µg/d. Supplementation studies: an iodine intake of 150 µg/d is insufficient to prevent increased thyroid size and intakes of 200-280 µg/d prevent goiter during pregnancy.
WHO/FAO 2004[50]	Total requirement	-	Prevention of deficiency symptoms.	Recommendations from the WHO/UNICEF/ICCIDD 2001.[113] Supplementation studies: the iodine intake required to prevent deficiency symptoms is ~200 µg/d.

Abbreviations: -: Not specified, N/A: not applicable, CH: Switzerland, DE: Germany, AU: Austria

[a] If applicable: (+ additional requirement in µg/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

20.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

EFSA, NCM, and DACH used an additive model for the reference values for pregnant women. IOM additionally, and WHO/FAO solely, based their reference values on studies about the total requirement during pregnancy. IOM used a 70 µg/d higher PRI for pregnant women than for non-pregnant women. EFSA and DACH (CH) used an additional requirement of +50 µg/d for their AI values, and WHO/FAO used a 50 µg/d higher PRI for pregnant women than for non-pregnant women. DACH (DE, AU) used an additional requirement of +30 µg/d for their AI value. Finally, NCM used a substantially smaller additional requirement of +25 µg/d for their PRI value.

EFSA, NCM, and DACH used an additive model, but the underlying approach differed between these reports. It is uncertain what the basis is for DACH's proposed 30-50 µg/d higher requirement. Therefore, no further consideration will be given to the DACH report.

EFSA's estimate of the additional requirement for iodine during pregnancy originated mainly (92%) from the iodine needed for the increased thyroid hormone synthesis by pregnant women, with additional small contributions for the synthesis of fetal thyroid hormones[a] (6%) and for the iodine deposition in newly formed maternal and fetal tissue (2%). None of the other organizations use these factors as the basis for estimating the additional iodine requirement of pregnant women.

NCM adopted one of the approaches described by IOM, although IOM did not apply this estimate of the additional requirement when setting their actual reference values. NCM seemed not to consider additional maternal iodine needs during pregnancy.

Both IOM and WHO/FAO used studies estimating the total requirement in pregnant women to set their reference values. IOM used findings from a balance study in pregnant women and three European iodine supplementation studies in pregnant women to derive the RDA. WHO/FAO used findings from three publications of a large Belgian iodine supplementation study (also used by IOM) in pregnant women to derive their DRVs.

Below, a more detailed description of the differences in the method of derivation is described. These findings are summarized in Table 20.4.

[a] Note that EFSA's estimate for the deposition of iodine in the fetal thyroid gland (200 µg) is substantially larger than the estimate provided by IOM (75 µg). However, this difference has no impact, as the contribution of iodine deposition to EFSA's estimated additional requirement is negligible.

EFSA´s method of derivation

EFSA included three factors in determining the additional requirement during pregnancy.[23]

The first and most important factor was the increased synthesis of maternal thyroid hormones, corresponding to an increased iodine requirement of 25 µg/d. This was based on studies reporting a 40-60 µg/d increased need of oral thyroxine in fully T4-substituted patients with hypothyroidism during their pregnancies compared with their non-pregnant state.[114-116] EFSA assumed an absorption efficiency of oral thyroxine of ~75%, resulting in an absorption of 40-60 µg/d x 0.75 = 30-45 µg/d.

As the iodine content in T4 is 65%, the additional iodine requirement of the maternal thyroid is: 30-45 x 0.65 = 20-29 µg/d (25 µg/d after averaging).

EFSA assumed that the equation of Fisher and Oddie[a] derived in non-pregnant adults remains valid in pregnancy.[112] The increased maternal thyroid iodine requirement of 25 µg/d corresponds to an additional intake of 44 µg/d[b].

The second factor was the fetal synthesis of thyroid hormones, reported by EFSA to be ~2-4 µg/d.

The third and least important factor was the total amount of iodine deposited in maternal and fetal tissues, which EFSA reported to be: 18-100 µg in the placenta, 15 µg in the amniotic fluid, 100-300 µg in the fetal thyroid, and 10 µg in fetal blood. On this basis, the committee calculated a total iodine deposition of [(18 + 100)/2] + 15 + [(100 + 300)/2] + 10 = 284 µg. This corresponds to a daily iodine intake of 284 µg/280 days = 1.01 µg/d (1 µg/d after rounding).

Additional requirement: 44 µg/d + 2-4 µg/d + 1 µg/d = 47-49 µg/d (50 µg/d after rounding).

NCM´s method of derivation

NCM referred to the Norwegian Mother and Child Cohort Study, showing that women who used iodine-containing supplements had higher levels of urinary iodine concentration than those who did not use supplements and that inclusion of milk and seafood in the diet is important to secure optimal iodine nutrition.[117,118] Results from a subsample analysis in this study (n=119) indicated that an iodine intake of at least 150 µg/d would be required to get the median urinary iodine concentration up to the optimal range of 150-249 µg/L for pregnant women (as defined by WHO).[119] Because there was no new data supporting changes in the recommendations, NCM kept the recommendations from NNR 2004

[a] EFSA referred to two studies by Fisher and Oddie (1969) in which the authors described a positive correlation between thyroid iodine accumulation and iodine intake estimated as UI excretion (correlation coefficient r = 0.64), described by the following equation:
log (iodine accumulation in the thyroid) = 0.2456 + 0.7001 x log (UI concentration).[23]

[b] log (iodine accumulation in the thyroid) = 0.2456 + 0.7001 x log (UI concentration);
log (25 µg/d) = 0.2456 + 0.7001 x log (UI concentration);
1.3979400087 = 0.2456 + 0.7001 x log (UI concentration);
0.7001 x log (UI excretion) = 1.1523400087;
log (UI excretion) = 1.6459648745;
UI excretion = 44.25525775 µg/d (44 µg/d after rounding).

unchanged.[a] In NNR 2004, NCM referred to the same balance study as IOM (as described below) in which iodine retention of full-term babies was ~7 µg/kg.[121] NCM reported the additional requirement to be +25 µg/d. It was unclear to the committee how the additional requirement of +25 µg/d was derived from the iodine retention of ~7 µg/kg.
Therefore, no further consideration will be given to the NCM report.

IOM´s method of derivation
IOM mentioned additive models[b] but did not use these to establish their reference values. IOM based their reference values on estimates of the total requirement of pregnant women from a balance study and three supplementation studies.

The balance study from 1966 showed that 4 pregnant women[c] were at balance when consuming ~160 µg/d.[122]
The first supplementation study was performed in 35 pregnant Italian women living in an area of moderate iodine deficiency, of whom 17 received iodide salt (equivalent to a daily intake of ~120-180 µg/d) and 18 were used as a control.[123] The mean urinary iodine excretion at the 3rd trimester was significantly higher ($p<0.01$) in the treated group (100 [SD: ± 39] µg/24h) than in the control group (50 [SD: ± 37] µg/24h). At the end of pregnancy, no difference was found in thyroid size in the treated group, whereas in the control group, it increased significantly ($p<0.0001$) with a mean increase of 1.6 ±0.6 ml (or 16.2% ±6.0%). From this study, IOM concluded that an intake of ~200 µg/d prevented goiter.

The second supplementation study was performed in 54 pregnant Danish women from an area where the iodine intakes are relatively low (as shown by a median daily iodine concentration in urine of ~50 µg).[124] Of these women, 28 received iodine supplementation of 200 µg/d (in the form of drops of potassium iodine) from the 17-18th week of pregnancy until 12 months after delivery, 26 women were controls. In the treated group, urinary iodine increased from 55 to 105 µg/L (controls: from 51 to ~40 µg/L), their thyroid volume increased by 15.5% (controls: 31%), and serum thyroid stimulating hormone and serum thyroglobulin concentrations did not change (controls: +75% and +21% respectively). From this study, IOM concluded that 250-280 µg/d of iodine prevented goiter. The committee questions this conclusion based on the reported increase in thyroid function in the intervention group of 200 µg/d.
The third supplementation study was done in 180 pregnant Belgian women with low iodine intakes (as shown by a mean urinary iodine of

[a] NCM noted that Norwegian and Icelandic studies showed that pregnant women with low or no intake of dairy and/or seafood, and who do not use iodine supplements are at great risk of inadequate iodine intake.[119,120]
[b] Additive model 1: IOM's estimate of the iodine content of the newborn thyroid gland was 50-100 µg, with close to 100% being turned over daily. IOM's estimate of the daily thyroid iodine uptake was 75 µg/d.
Additive model 2: a balance study showed an average iodine retention of 6.7 µg/kg/d in 23 full-term infants with a mean age of 30 (SE: ±2) days.121 IOM assumed an average fetal weight of 3 kg. Thus, the mean retention of a fully developed fetus would be: 6.7 µg/kg/d x 3 kg = 20.1 µg/d (22 µg/d after rounding). This corresponds to an intake for pregnant women to be at balance: 95 µg/d (is $EAR_{non\text{-}pregnant}$) + 22 µg/d = 117 µg/d.
[c] Studied through 5 pregnancies from a start at 3-6 months of gestation to a finish at 1-2 months post-partum.[122]

36 µg/L)[a] and excessive thyroid stimulation[b].[125] These women were divided into three groups: group A receiving a daily placebo, group B receiving 131 µg/d of potassium iodide (KI) (corresponding to 100 µg/d of iodide), and group C receiving 131 µg/d of KI + 100 µg/d L-T4 (corresponding to 161 µg/d of iodide). Treatment was given from the day of enrolment (<16 weeks of gestation) until delivery. In group A, <10% of the women had urinary iodine values >100 µg/L at any time during gestation. In group B, this was 38-50%, and in group C 49-54%. In group A, thyroid volume increased on average by 30%, significantly higher than in group B (15%) and group C (8%). In group A, 16% of the women developed a goiter during gestation, whereas this was 10% in group B, and 3% in group C. From this study, IOM concluded that a supplement of 100 µg/d of iodine (corresponding to a total intake of ~150 µg/d) was insufficient to prevent increase thyroid size.

Based on these data, IOM set their AR at 160 µg/d.

WHO/FAO´s method of derivation

WHO/FAO based their reference values on three publications of a Belgian supplementation study where iodine intake was estimated to be 50-70 µg/d, showing that supplementation with 161 µg/d (for more details, see the last supplementation study described by IOM) prevented abnormalities such as progressive decreases in serum free-thyroid concentrations, prevented increased serum TSH and thyroglobulin, and prevented increased thyroid volume.[125-127] Based on these data, and the absence of new data contradicting the WHO/UNICEF/ ICCIDD recommendations from 2001[113], WHO/FAO set their PRI at 200 µg/d.

Differences in the reference values

Differences in the values between reports resulted mainly from differences in the method of derivation.

1. Additional requirement:
   EFSA based their reference values for pregnant women on an additional requirement derived from the literature, as described above. EFSA's AI was based on the additional requirement added to the AI of non-pregnant women: 150 µg/d + 50 µg/d = 200 µg/d.
2. Total requirement:
   IOM based their reference values on total requirements from a balance study and supplementation studies, as described above. Based on these studies, IOM derived an AR of 160 µg/d. IOM's PRI was based

[a] IOM mentioned that on a population level, iodine intake can be assessed by measuring UI concentration.[47] The following criteria based on UI concentration in school-aged children have been suggested by the WHO (2004): median UI < 20 µg/L = insufficient iodine intake and severe iodine deficiency; median UI 20-49 µg/L = insufficient intake and moderate iodine deficiency; median UI 50-99 µg/L = insufficient intake and mild iodine deficiency; median UI 100- 199 µg/L = adequate iodine intake. In addition to this classification, a UI concentration of 200–299 µg/L was considered likely adequate for pregnant/lactating women but possibly to indicate a slight risk of excess for other groups.

[b] Defined as supranormal serum thyroglobulin (>20 µg/L) associated with a low normal free T4 index (<1.23), and/ or an increased T3/T4 ratio (>25 X 10^{-3}).

on the AR multiplied by twice the CV of 20%: 160 µg/d x 1.4 = 224 µg/d (220 µg/d after rounding).
WHO/FAO based their reference values for pregnant women on a total requirement derived from a Belgian supplementation study, as described above. In the absence of new data, WHO/FAO maintained their recommendation (2001) of 200 µg/d.

Differences between the 1st, 2nd, and 3rd trimester
None of the reports differentiated by trimester.

20.3 Pregnancy-related health outcomes

Deficiencies
EFSA referred to the clinical effects of iodine deficiency as iodine deficiency disorders (IDD).[23] IDD are seen at all stages of development but are of particular concern in pregnancy and infancy because of the risk of developmental brain damage. Chronic iodine deficiency may lead to compensatory thyroid hypertrophy/hyperplasia with goiter (enlarged thyroid gland) and may subsequently cause hyperthyroidism. Goiter may cause obstruction of the trachea and the esophagus. It also increases the risk of thyroid cancer. Maternal iodine deficiency during pregnancy results in fetal iodine deficiency, accompanied by higher rates of stillbirths, abortions, and congenital abnormalities. It constitutes a threat to early brain development with consequent physical and mental retardation and lower cognitive and motor performances later in life. In areas with severe iodine deficiency, cretinism may be endemic. Cretinism is a condition of severely stunted growth and retarded physical and mental development due to untreated congenital deficiency of thyroid hormones.

The most common neurological type of cretinism is characterized by:
- Cognitive impairment.
- Congenital hearing loss resulting in inability to speak.
- Spastic diplegia.

The less common myxoedematous type is characterized by:
- Apathy.
- Hypothyroidism.
- Puffy features.
- Growth retardation.
- Delayed bone maturation.
- Retarded sexual maturation.
- Restricted growth, short stature.

Mass prevention of cretinism in areas of severe iodine deficiency has shown that improving maternal iodine status before pregnancy is most efficient.[23]

Intake and associated health outcomes

EFSA described no studies showing iodine intake levels associated with pregnancy-related health outcomes.[23]

20.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

EFSA used an additive model for pregnant women, although based on different types of data. IOM and WHO/FAO used a total requirement model. Despite differences in the approaches used, the reference values are relatively close to each other: WHO/FAO's PRI equals EFSA's AI, and IOM's PRI is <10% higher.

Conclusion and strength of the model

The committee agrees with the method of derivation of the total requirement for iodine during pregnancy used by IOM, which is even more comprehensive than WHO/FAO's method of derivation. IOM's estimate was based on balance[122] and supplementation studies[123-125] from acceptable to good quality. The committee finds it unclear for what reason EFSA did not use these balance and supplementation studies. The committee values the importance of these types of studies in deriving reference values and follows IOM in using these acceptable to good quality studies. The committee deems the scientific basis for the method of derivation to be strong.

Reference values for pregnancy

The committee prefers IOM's PRI and AR for pregnant women. However, since the difference between IOM's PRI and EFSA's does not deviate more than 10%, the committee accepts EFSA's AI for use in the Netherlands (Table 20.3).

Table 20.3. Reference values for iodine recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	200 µg/d[a]	*AI: 150 µg/d*

[a] AI is calculated as $AI_{non\text{-}pregnant}$ + additional requirement: AI = 150 µg/d + 50 µg/d.

21 Iron

Summary and conclusion

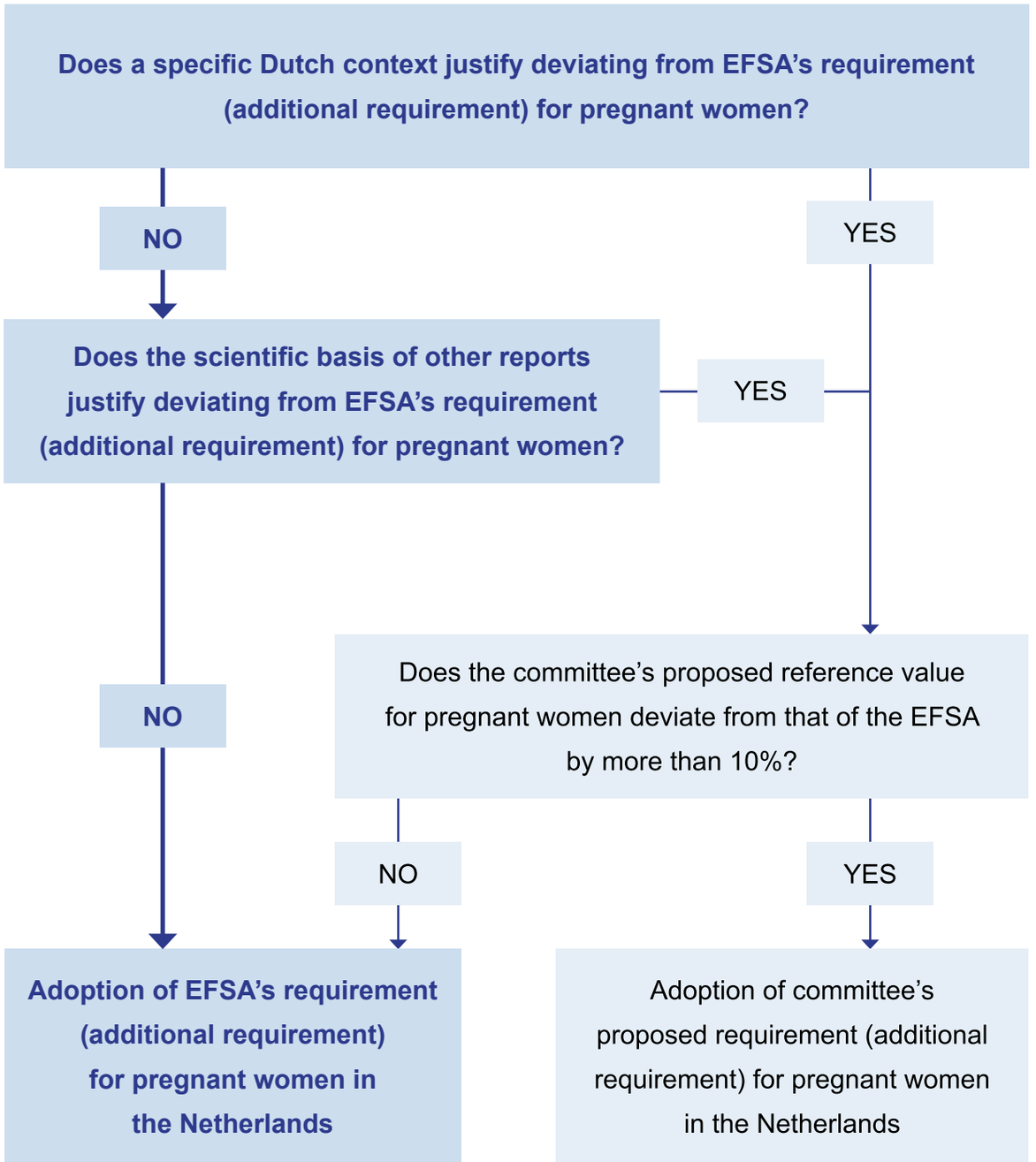
In 2018, the committee accepted EFSA's reference values for non-pregnant women.

There seems to be scientific consensus between the different reports that the need for deposition in maternal and fetal tissues increases and that iron absorption increases during pregnancy. However, there seems to be no agreement on whether the increased absorption is sufficient to meet the higher demands for iron during pregnancy. The committee agrees with applying the PRI for non-pregnant women to pregnant women used by EFSA, which was based on an increased absorption during gestation covering the higher iron demand of pregnancy. The scientific basis for the method of derivation is acceptable.

The committee accepts EFSA's PRI and AR for pregnant women for use in the Netherlands, resulting in the following reference values:

- AR = 7 mg/d
- PRI = 16 mg/d

Flowchart with committee's line of reasoning for iron



21.1 Overview and comparison of values

Table 21.1 Overview of the reference values for iron for pregnant women and the model used to derive these values, compared with the reference values for iron for non-pregnant women.[a]

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	Model used[b]	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	Absorption non-pregnant women (%)
EFSA 2015[24]	PRI	16	7	$PRI_{pregnant} = PRI_{non\text{-}pregnant}$	PRI	16	7	Haem: ~25[c]
NCM 2014[42] = HCNL 2014[38]	RI	15	*9 (or 10)*[d]	$RI_{pregnant} = RI_{non\text{-}pregnant}$	RI	15	9 (or 10)[d]	Haem: ~25[c]
HCNL 2018[4]	N/A	N/A	N/A	N/A	PRI	16	7	Haem: ~25[c]
DACH 2015[43]	AI	30	N/A	Additive	AI	15	N/A	10-15[e] (haem: >20, non-heme: >5)
IOM 2001[47]	RDA	27	22	Additive	RDA	18	8	18[c]
WHO/FAO 2004[50]	-	-	-	No reference values derived	RNI	Bioavailability[f] 15%: 19.6 12%: 24.5 10%: 29.4 5%: 58.8	-	Haem: 25[c,g]

Abbreviations: -: Not specified, N/A: not applicable

Calculations done by the committee are depicted in brackets and in italics.

[a] No CVs presented because the reference values were based on the 90th, 95th, or 97.5th percentile of losses.

[b] Information on the models used for each report is specified in Table 21.2.

[c] The absorption of non-heme iron depends on body iron stores and on meal composition.

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

[e] DACH noted that the absorption increases two- to threefold in case of iron deficiency and bioavailability may vary tenfold depending on the composition of the diet.

[f] WHO/FAO presented RNI values for four levels of bioavailability. For the comparison of reports, the HCNL 2018 report used the bioavailability of 15% because the other reports used bioavailability values of 15% or higher.[4]

[g] IOM noted that absorption of heme iron can vary from 10% during iron repletion to 40% during iron deficiency.

Table 21.2. Overview of the models used and the basis for the requirements (additional requirements) for iron for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2015[24]	$PRI_{pregnant} = PRI_{non\text{-}pregnant}$	Haem[c]: 25 Non-haem (by week) 0-23: 7.2 24-35: 36.6 36-40: 66.1	N/A	Assumptions: adaptive physiological changes take place to meet the demands of pregnancy (expansion of plasma and blood volumes and of red blood cell mass) and absorption efficiency is increased.
NCM 2014[42] = HCNL 2014[38]	$RI_{pregnant} = RI_{non\text{--}pregnant}$	"Increased during the last two thirds of the pregnancy"	N/A	Reference values from NNR 2004.[53] Assumptions: total iron requirement is 1,040 mg (of which 840 mg goes to the fetus or is lost while giving birth), increased iron demand is met by the increased absorption rate.
DACH 2015[43]	Additive (AI + 15)	-	Iron deposition due to growth in maternal and fetal tissue.	Assumptions: accumulation of iron in the fetus is 300 mg, in the placenta is 50 mg, and in the increased maternal blood volume is 450 mg.
IOM 2001[47]	Additive (AR + 14 RDA + 9)	Trimester 1st: 18 2nd: 25 3rd: 25	Iron deposition due to growth in maternal and fetal tissue.	Assumptions: basal iron losses are 250 mg, accumulation of iron in fetus and placenta is 315 mg, and in increased maternal blood volume is 500 mg.
WHO/FAO 2004[50]	No reference values derived	Trimester 1st: "marked decrease" 2nd: "increased by ~50%" 3rd: "increased by up to ~4 times the norm" (not quantified)	N/A	The iron balance during pregnancy depending not only on the properties of the diet but also and especially on the amounts of stored iron.

-: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in mg/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

[c] EFSA noted that this may be an underestimate as insufficient data are available on the efficiency of haem iron absorption throughout pregnancy.

21.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

EFSA and NCM applied their PRI for non-pregnant women to pregnant women. DACH and IOM used an additive model for the reference values for pregnant women. WHO/FAO did not set DRVs for iron because the iron balance in pregnancy depends not only on the properties of the diet but also and especially on the amounts of stored iron.

DACH used a higher additional requirement (+15 mg/d) than IOM (+9 mg/d). Both DACH and IOM based their additional requirement on the accumulation of iron in the fetus, the placenta and the increased need for the expansion of the maternal blood volume. Differences between the two reports resulted mainly from differences in the estimated amounts of iron needed to meet the requirements for the described tissues and the absorption rates used.

EFSA calculated the total quantity of iron required to support a singleton pregnancy of an average non-pregnant woman as follows: total obligatory losses[a] + iron deposited in the neonate + iron deposited in the placenta and umbilical cord + blood loss at delivery.

For the obligatory losses, EFSA used the mean basal losses in five postmenopausal women of 1.08 mg/d assuming that basal iron losses during pregnancy are the same as those of non-menstruating women.[128]
Total obligatory losses: 1.08 mg/d x 280 d = 302.4 mg (300 mg after rounding).
For the iron deposited in the neonate, EFSA used 270 mg.[129,130]
For the iron deposited in the placenta and umbilical cord, EFSA used 90 mg.[129,130]
For the iron loss through the blood loss at delivery, EFSA used the mean of values from the literature: (150 mg + 200 mg)/2 = 175 mg.[129,130]
Total quantity of iron required: 300 mg + 270 mg + 90 mg + 175 mg = 835 mg.
EFSA noted that adaptive physiological changes take place to meet the demands of the pregnancy and that iron absorption progressively increases during pregnancy.[131]
For the increased iron absorption, EFSA used an isotope study among 12 women who were fed a diet supplying 9 mg/d of non-heme iron and 4 mg/d of haem iron as given to the women for three days before the absorption study.[131] Absorption of non-heme iron was found to be 7.2%

[a] Fecal, urinary, and dermal losses.

during weeks 0-23, 36.3% during weeks 24-35, and 66.1% during weeks 36-40. EFSA assumed that the absorption of heme iron is 25% at all stages of pregnancy as there is no evidence for an increase in haem iron absorption during pregnancy[a].

Non-heme iron absorption was calculated to be:
Weeks 0-23: 9 mg/d x 0.072 = 0.65 mg/d.
Weeks 24-35: 9 mg/d x 0.363 = 3.27 mg/d.
Weeks 36-40: 9 mg/d x 0.661 = 5.95 mg/d.
Heme absorption was calculated to be: 4 mg/d x 0.25 = 1 mg/d.
The total amount of iron absorbed in each gestational period was:
Weeks 0-23 (161 days): (0.65 mg/d x 161 d) + (1 mg/d x 161 d) = 265 mg.
Weeks 24-35 (84 days): (3.27 mg/d x 84 d) + (1 mg/d x 84 d) = 358 mg.
Weeks 36-40 (35 days): (5.95 mg/d x 35 d) + (1 mg/d x 35 d) = 243 mg.
Total amount of iron absorbed: 265 mg + 358 mg + 243 mg = 866 mg.

EFSA concluded that the amount of iron absorbed during pregnancy (866 mg) covers the increased demand (835 mg).[b] Therefore, they did not derive an additional requirement for pregnancy. They also noted the importance of women entering their pregnancy with an adequate iron status.
Please note: the distribution of iron loss of non-pregnant premenopausal women is skewed due to a subgroup of women with large menstrual losses. EFSA derived a dietary iron intake level to meet the requirement of 95% of the population of non-pregnant women in their reproductive years (of which some use oral contraceptives, as is the case in the EU) instead of the 97.5% percentile of the distribution on which the PRI is usually based. EFSA considered it not possible to derive a dietary requirement for the subgroup of 5% of women with very high losses.

The committee notes that the PRI for non-pregnant women may still be influenced by the variation in iron loss due to high menstrual blood loss, although the degree is not clear. NCM, for example, used the 90% percentile of the distribution of iron loss. This uncertainty affects the PRI for pregnant women by applying the PRI of non-pregnant women to pregnant women.
NCM did not provide a calculation but arrived at the same conclusion as EFSA, acknowledging that for some women, this increased absorption may not be enough to meet the significantly increased iron demand during pregnancy. In the absence of new strong scientific evidence, NCM maintained the NNR 2004 recommendations.[53]

[a] EFSA considered that this may be an underestimate as insufficient data is available on the efficiency of heme iron absorption throughout pregnancy.

[b] EFSA also provided an alternative approach using the Dainty et al. model.[132]. Assuming serum ferritin concentrations of 30 µg/L up to week 23 associated with an iron absorption of 18% and 15 µg/L from week 24 associated with an iron absorption of 31%, the quantity of absorbed iron can be calculated.
Estimated dietary intake up to week 23: 835 mg iron required/0.18/280 d = 16.6 mg/d.
Estimated dietary intake from week 24: 835 mg iron required/0.31/280 d = 9.6 mg/d.
As ferritin concentrations fall gradually during pregnancy, EFSA used the mean value of the two estimates: (16.6 mg/d + 9.6 mg/d)/2 = 13.1 mg/d. Assuming a CV of 20%, this would correspond to a theoretical PRI of 13.1 mg/d x 1.4 = 18.3 mg/d.

DACH referred to one paper from a Nestlé nutrition workshop series from 1988 describing the iron requirement for pregnancy products: 300 mg for the fetus, 50 mg for the placenta, and 450 mg for the increased maternal blood volume.[133] The additional requirement followed based on these needs was: (300 mg + 50 mg + 450 mg)/270 days = 3.0 mg/d. It is, however, unclear how DACH arrived at the additional requirement of 15 mg/d. Therefore, no further consideration will be given to this report.

IOM used the following equation to calculate the iron requirement during pregnancy: requirement for absorbed iron = basal losses + iron deposited in the fetus and related tissues + iron utilized in the expansion of hemoglobin mass.

For the basal losses, IOM used a body weight of 64 kg for non-pregnant women and an average basal loss of 14 µg/kg[134]: 64 kg x 0.014 mg/kg = 0.896 mg/d.

For the fetal and placental iron deposition, IOM used WHO/FAO's (1988) estimated total of 315 mg[135], corresponding to different daily intakes depending on the trimester: 0.27 mg/d for the 1st trimester, 1.1 mg/d for the 2nd trimester, and 2.0 mg/d for the 3rd trimester.

For the increased hemoglobin mass, IOM also used WHO/FAO's (1988) estimate of 500 mg[135], corresponding to 0 mg/d in the 1st trimester[a] and 2.7 mg/d in both the 2nd and the 3rd trimester.[b]

IOM then used an absorption rate of 18% for the 1st trimester and 25% for the 2nd and 3rd trimester to calculate the EARs, which corresponds to adjustment factors of 5.6 and 4 respectively.

1st trimester: (0.896 mg/d + 0 mg/d + 0.27 mg/d) x 5.6 = 6.4 mg/d.

2nd trimester: (0.896 mg/d + 2.7 mg/d + 1.1 mg/d) x 4 = 18.8 mg/d.

3rd trimester: (0.896 mg/d + 2.7 mg/d + 2.0 mg/d) x 4 = 22.4 mg/d.

IOM applied the AR for the 3rd trimester to the entire pregnancy to build iron stores during the 1st trimester of pregnancy.

Differences in the reference values

EFSA's and NCM's PRIs are lower than IOM's PRI. This is because EFSA and NCM did not, and IOM did, add an additional requirement to their reference values for non-pregnant women. IOM used a 581 mg higher physiological requirement than EFSA for the increased blood mass/blood losses[c] and a 200 mg higher physiological requirement for the iron

[a] IOM noted that hemoglobin mass changes very little during the 1st trimester but expands greatly during the 2nd and 3rd trimester.

[b] IOM noted that of the 500 mg, 150-250 mg is lost at delivery, implying that of the 500 mg allowed for erythrocyte mass expansion as much as 250-350 mg remains in the body to revert to maternal stores. Nevertheless, these 250-350 mg appear to be considered as 'additional requirement' when calculating the reference values.

[c] IOM considered all iron in the increased hemoglobin mass (500 mg over pregnancy) to be additional physiological requirements, whereas EFSA only considered the iron loss through blood loss at delivery (175 mg), thus resulting in a 325 mg lower estimate. Given that IOM applied the third trimester values to calculate the reference values for the entire pregnancy, the estimate IOM used was 581 mg higher than EFSA's estimate for this factor (175 versus

deposited in the neonate plus placenta (plus umbilical cord)[a]. Please note that IOM used a 50 mg lower estimate than EFSA for the ongoing total obligatory loss for maintaining the 'pre-pregnancy maternal body' (250 versus 300 mg over pregnancy, respectively).[b]

There were also slight differences in the absorption estimates used by IOM and EFSA.

Differences between the 1st, 2nd, and 3rd trimester

EFSA and NCM both acknowledged that in the 1st trimester iron intake must cover basal losses and that iron demand (exponentially) increases during the 2nd and especially the 3rd trimester. At the same time, there is a progressive increase in the efficiency of iron absorption across the trimesters. EFSA and NCM stated that this can compensate for the higher needs, provided adequate iron stores are present at conception.

IOM, as described above, established their reference values by using the estimates for the 3rd trimester to build iron stores during the 1st trimester of pregnancy.

21.3 Pregnancy-related health outcomes

Deficiencies

EFSA reported that, in animal models, iron deficiency (with or without anemia) is associated with:

- Inefficient energy metabolism, with altered glucose and lactate utilization.
- Reduced muscle myoglobin content, reducing muscle strength and endurance.
- Reduced cytochrome c oxidase activity in muscle and the intestinal mucosa.
- Impaired collagen synthesis and osteoporosis.
- Altered vitamin A and prostaglandin metabolism.
- Reduced dopaminergic and serotonin neurotransmission in the brain and defective synapse and dendrite development.
- Altered membrane fatty acid profiles, thereby affecting neuronal function.
- Functional impairments, including delayed responses to auditory and visual stimuli and impaired memory and spatial navigation.

These manifestations provide plausible mechanistic bases for inferring that iron deficiency (with or without anemia) has similar effects in humans. The risk would be greater during periods of rapid growth (for example,

756 mg over pregnancy). IOM estimated the iron deposition in increased hemoglobin mass in trimesters 1, 2, and 3 to be 0.0, 2.7, and 2.7 mg/d, respectively. Multiplication of the average of these three values by 280 days leads to an additional requirement for increased hemoglobin mass over pregnancy of 504 mg; multiplication of the 3rd trimester value by 280 days leads to an additional physiological requirement over pregnancy of 756 mg.

[a] IOM's estimate of iron deposited in the neonate plus placenta (315 mg over pregnancy) was 45 mg higher than EFSA's estimate of iron deposited in the neonate (270 mg) plus placenta plus umbilical cord (90 mg) (in total: 360 mg over pregnancy). And again, as IOM applied the third trimester values to calculate the reference values for the whole pregnancy, therefore, the estimate IOM used was 200 mg higher than EFSA's estimate for this factor (560 versus 360 mg over pregnancy). IOM estimated the iron deposition in the neonate plus placenta in trimesters 1, 2, and 3 to be 0.27, 1.1 and 2.0 mg/d, respectively. Multiplication of the average of these three values by 280 days leads to an additional requirement for the iron deposition in the neonate plus placenta of 289 mg over pregnancy (EFSA used an estimate of 315 mg); multiplication of the 3rd trimester value by 280 days leads to an additional requirement over pregnancy of 560 mg.

[b] IOMs estimate was 0.896 mg/d; if multiplied by 280 days, this amounts to an estimated 250 mg over pregnancy.

during gestation), and the tissues involved would be those with a rapid turnover, specialized function, and high energy dependence, such as immunocytes, enterocytes, brain, and muscle. EFSA emphasized that these defects have been associated with severe iron deprivation or deficiency that are not representative of deficiencies customarily encountered in human nutrition and that there is little data to enable the construction of dose-response curves, relating these outcomes to lesser degrees of iron deficiency.[24]

Intake and associated health outcomes

EFSA described a systematic review performed for the NCM report[42] on the health effects of different intakes of iron at different life stages to estimate the requirement for adequate growth, development, and maintenance of health.[24] In this review, 55 articles were identified as relevant, and the evidence was graded. Most studies focused on vulnerable groups, e.g., women of child-bearing age. There was some evidence that prevention and treatment of iron deficiency improved certain developmental and health indicators in populations other than pregnant women. There was insufficient evidence to show negative health effects of iron intakes at levels suggested by NNR 2004[53].

EFSA also referred to a series of systematic reviews conducted by EURRECA, which included RCTs with an adequate control group. The reviews suggested a modest positive effect of iron supplementation on certain health outcomes in anemic infants and children, but there was no effect on fetal growth. A large degree of heterogeneity between study populations, iron doses, and outcomes measures prevented meta-analyses for most health outcomes[a].

EFSA also acknowledged the comprehensive literature review from SACN (2010) on the role of iron in human nutrition, concluding that although low hemoglobin concentrations have been associated with impaired physical work capacity, reproductive efficiency, and cognitive and psychomotor development, many of the studies had poorly reported outcomes and inadequate characterization of iron deficiency. Intervention studies of iron supplementation during pregnancy did not show beneficial or adverse effects on pregnancy outcomes.[24]

EFSA concluded that the following uncertainties made it difficult to determine dose-response relationships or confidently predict the risks associated with pregnancy: inaccurate estimates of iron intake and quantities of heme and non-heme iron in the diet; a poor correlation between iron intake and status; difficulties in measuring adaptive and functional responses to variations in iron intake (bioavailability); lack of sensitive and specific markers to assess the iron status and confounding by other dietary and lifestyle factors and by responses to infection and inflammation; inadequate characterization of iron deficiency anemia,

[a] Health outcomes included tiredness, physical performance, immune function, impaired thermoregulation, restless leg syndrome, and cognitive function.

and the relative role of iron deficiency and other causes of anemia in studies investigating the health consequences of iron deficiency.

21.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference values for non-pregnant women.[4]

Model used

IOM used an additive model, whereas EFSA and NCM motivated why they consider their reference values for non-pregnant women to also apply to pregnant women. WHO/FAO did not establish reference values for pregnant women. The committee agrees with the motivation by EFSA and considers that the reference values by IOM appear to be based on several estimates which are unnecessarily high.

Conclusion and strength of the model

The committee agrees with applying the PRI for non-pregnant women to pregnant women used by EFSA, which was based on an increased absorption during gestation covering the higher iron demand of pregnancy. HCNL 2014 followed NCM, which also applied their PRI for non-pregnant women to pregnant women.

The evidence of EFSA's method of applying the reference values for non-pregnant women to pregnant women was based on three studies[128-130] on iron content in maternal and fetal tissue (i.e., iron requirements during pregnancy) and one study[131] on the increased absorption during pregnancy, all of acceptable quality. The committee deems the scientific basis for the method of derivation to be acceptable (based on a plausible rationale).

Reference values for pregnancy

The committee accepts EFSA's PRI and AR for pregnant women for use in the Netherlands (Table 21.3).

Table 21.3. Reference values for iron recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	7 mg/d	*7 mg/d*
Population reference intake (PRI)	16 mg/d	*16 mg/d*

22 Magnesium

Summary and conclusion

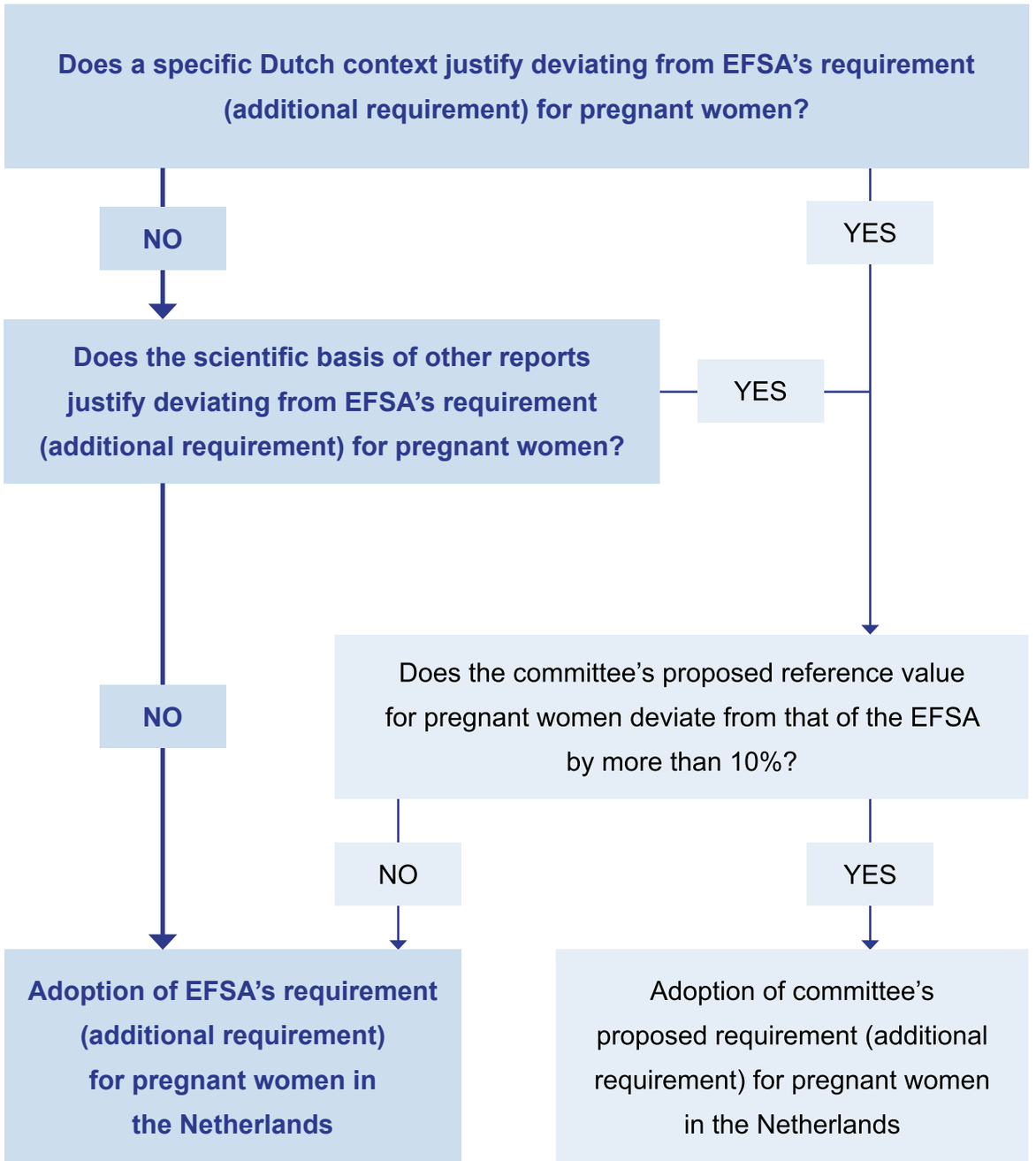
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a magnesium recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is weak.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 300 mg/d

Flowchart with committee's line of reasoning for magnesium



22.1 Overview and comparison of values

Table 22.1. Overview of the reference values for magnesium for pregnant women and the model used to derive these values, compared with the reference values for magnesium for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[25]	AI	300	N/A	N/A	$AI_{pregnant}$ = $AI_{non\text{-}pregnant}$	AI	300	N/A	N/A	Generally: 40-50 (range: 10-70)[b,c]
NCM 2014[42] = HCNL 2014[38]	RI	280	-	-	$RI_{pregnant}$ = $RI_{non\text{-}pregnant}$	RI	280	-	-	20-60[b,d]
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	300	N/A	N/A	Generally: 40-50 (range: 10-70)[b,c]
DACH 2015[43]	AI	310	N/A	N/A	$AI_{pregnant}$ = $AI_{(young)\ women}$	AI	19-24 yr: 310 ≥ 25 yr: 300	N/A	N/A	20-30[b,c]
IOM 1997[49]	RDA	19-30 yr: 350 ≥31 yr: 360	290 300	10	Additive	RDA	19-30 yr: 310 ≥ 31 yr: 320	255 265	10	15-60 [b,c,e,f]
WHO/FAO 2004[50]	RI	*220*	-	-	$RI_{pregnant}$ = $RI_{non\text{-}pregnant}$	RI	220	-	-	Studies showing: 25-75 [b,c,g,h] Net: 52 (±8)[h]

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] The absorption rate increases with decreasing amounts of magnesium in the diet and vice versa.
[c] Magnesium absorption can be inhibited and enhanced by certain nutritional factors.
[d] NCM noted that it is uncertain to what degree the composition of the diet influences absorption.
[e] In balance studies, under controlled dietary conditions in healthy older men who ingested an average of 380 mg (15.8 mmol)/day.
[f] In a study with various foodstuffs when subjects were on a constant diet.
[g] Absorption was 25% when magnesium intake was high compared with 75% when intake was low.
[h] During a 14-day balance study in 26 adolescent females consuming 176 mg magnesium daily.

22.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

Only IOM derived reference values for pregnant women deviating from their reference values for non-pregnant women, as described below. The other reports applied their reference value(s) for non-pregnant women to pregnant women.

EFSA referred to the WHO (2011) report promoting magnesium sulfate as an efficient treatment of (pre-)eclampsia.[136] However, EFSA noted that the usefulness of magnesium supplementation during pregnancy is controversial because of the lack of good-quality data. EFSA referred to a systematic review of 10 (quasi-)randomized controlled trials in 9,090 women and their infants not showing an influence of magnesium supplementation during pregnancy on infant or maternal outcomes when studied as primary outcomes.[137]

EFSA also referred to a seven-day metabolic balance study periodically throughout the pregnancy conducted in 10 pregnant white women consuming (un)supplemented self-selected diets.[90] This study reported that a mean daily magnesium intake of 269 (±55) mg led to a negative balance of -40 (±50) mg. The authors stated that the high within and between-subject variability in magnesium intake might have obscured physiological adaptations occurring in pregnancy.

EFSA reported fetal accumulation of magnesium to be 0.6-0.8 g in mature fetuses weighing 3-4 kg.[25] Placental magnesium content is supposedly low, around 36 mg.[25] Total accretion is: 600 to 800 mg + 36 mg = 636 – 836 mg. This corresponds to a magnesium transfer of 636 mg/280 days to 836 mg/280 days = 2.27-2.99 mg/d (2-3 mg/d after rounding)[a], which EFSA considered to be small.

EFSA concluded that studies with infant and maternal clinical outcomes during pregnancy, as described above, cannot be used to assess magnesium requirements but that the available evidence indicates that there is only a small additional requirement during pregnancy which may be met by adaptive metabolic changes (as stated in one study). Therefore, they applied their AI for non-pregnant women to pregnant women.

DACH reported that a fetus stores 5-7.5 mg/d during the last trimester of pregnancy, without referring to a particular study. DACH concluded that the resulting small increased need for pregnant women is covered by the recommendations for (young) women and a standard mixed diet. Because

[a] EFSA also referred to a study reporting an accretion varying from 1.8 mg/d at week 24-25 to 7.5 mg/d at week 36-37, and 5 mg/d at week 39-40. [138] The average accretion from week 24-40 thus being 4.7 mg/d.

the basis for the proposed higher requirement is uncertain, no further consideration will be given to the DACH report.

WHO/FAO assumed a fetal accumulation of 8 mg and a fetal "adnexa" accumulation of 5 mg, for a total magnesium accumulation of 13 mg during pregnancy, without referring to a particular study. WHO/FAO further assumed an absorption rate of 50%, which corresponds to an adjustment factor of 2. The 13 mg x 2 = 26 mg of magnesium thus required over a pregnancy of 40 weeks corresponds to an additional requirement of 0.09 mg/d. Like EFSA, WHO/FAO concluded that this could probably be accommodated by adaptation. Because it is uncertain what the basis is of their recommendations, no further consideration will be given to the WHO/FAO report.

NCM referred to a systematic review reporting that magnesium research has been hampered by the lack of good biomarkers of magnesium status in the body.[139] NCM stated that useful data that could contribute to the development of evidence-based dietary recommendations is limited, especially for specific vulnerable groups such as pregnant women. In the NNR 2004[53], the PRI for non-pregnant women was applied to pregnant women. This was based on one balance study reporting that an intake of 3.4 mg/kg body weight resulted in balance in almost all adult individuals, which was considered to also cover the needs during pregnancy.[42] NCM noted that no substantial new data have emerged since then indicating that these values should change.

IOM acknowledged the inconsistent findings from magnesium supplementation studies on pregnancy outcomes and the absence of data indicating that magnesium is conserved during pregnancy or that intestinal absorption is increased. IOM's additional requirement is solely based on the gain in weight associated with pregnancy. For this, IOM assumed:

- An appropriate lean body mass (LBM) of 6-9 kg, with a midpoint of 7.5 kg.[140]
- A magnesium content of 470 mg/kg LBM.[107]
- A bioavailability of 40%[141] (corresponding to an adjustment factor of 2.5).

IOM's calculation of the additional requirement: (7.5 kg/270 days) x 470 mg/kg x 2.5 = +32.64 mg/d (+35 mg/d after rounding).

Differences in the reference values

Differences in the values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   EFSA's value was higher than NCM's and lower than IOM's.[4]
2. The method of derivation of the additional requirement:

EFSA and NCM applied their reference value for non-pregnant women to pregnant women. IOM's PRI was calculated by adding the additional requirement to the AR for non-pregnant women and multiplying this by twice the CV of 10%.
19-30 yrs: (255 mg/d + 35 mg/d) x 1.2 = 348 mg/d (350 mg/d after rounding).
≥31 yrs: (265 mg/d + 35 mg/d) x 1.2 = 360 mg/d.

Differences between the 1st, 2nd, and 3rd trimester
None of the reports differentiated by trimester.

22.3 Pregnancy-related health outcomes

EFSA described no pregnancy-related magnesium deficiencies and no studies showing intake levels associated with pregnancy-related health outcomes.[25]

22.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used
Based on the absence of any demonstrated benefit, a magnesium recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. Only IOM derived an additional requirement based on the gain in weight associated with pregnancy. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. In the absence of data, the committee judges it unwarranted to calculate a higher recommendation by means of scaling, as was done by IOM.

The evidence of the method of derivation for the reference values of magnesium during pregnancy is limited; data on magnesium requirements during pregnancy is scarce. The additional requirement during pregnancy supported by two studies[142,143] seems to be small and is likely met by adaptive (metabolic) changes (as concluded by the authors of one study[90] The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy
The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 22.2).

Table 22.2. Reference value for magnesium recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	300 mg/d	*300 mg/d*

23 Manganese

Summary and conclusion

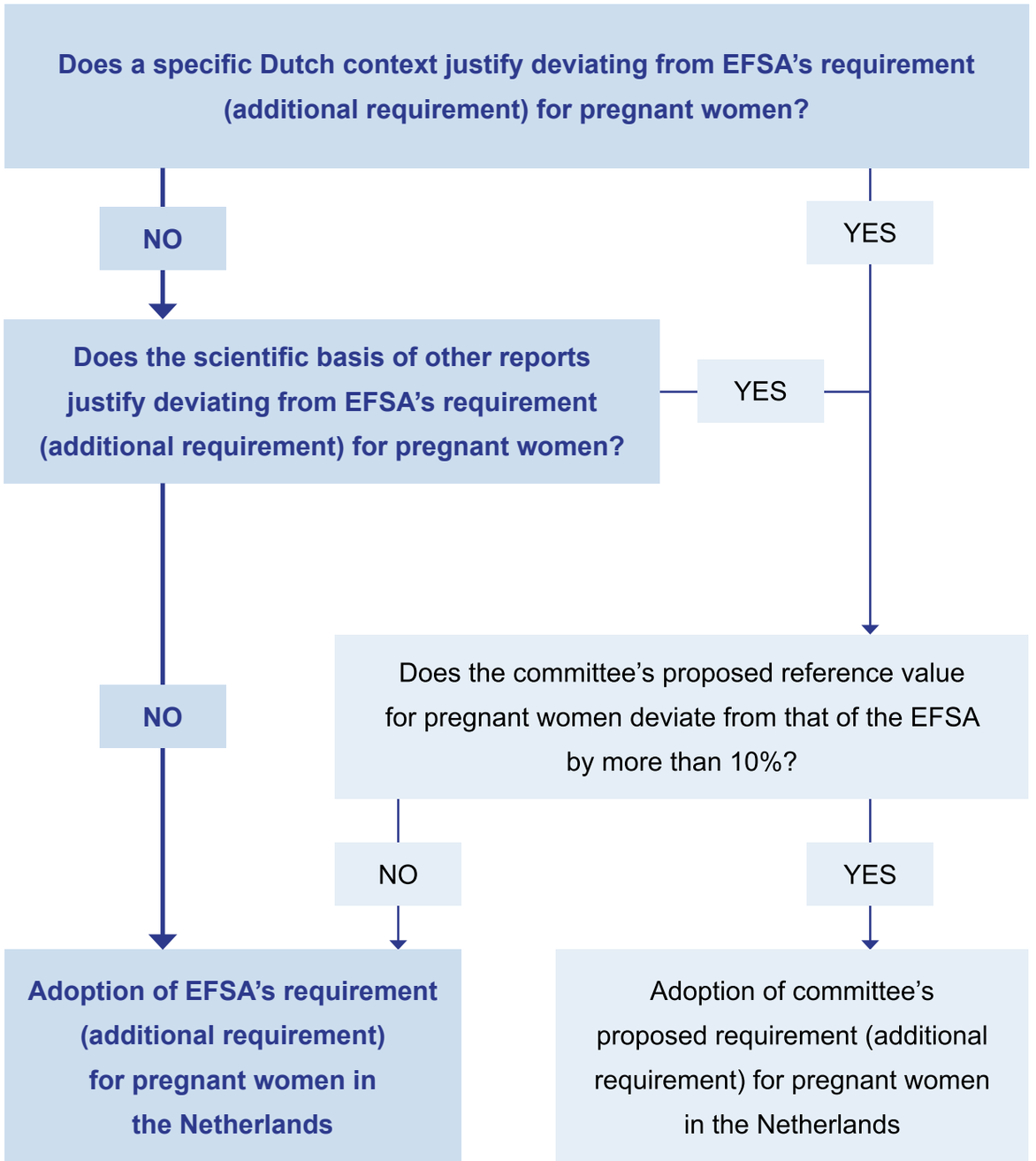
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a manganese recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is weak.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 3.0 mg/d

Flowchart with committee's line of reasoning for manganese



23.1 Overview and comparison of values

Table 23.1. Overview of the reference values for manganese for pregnant women and the model used to derive these values, compared with the reference values for manganese for non-pregnant women

Report	Type	Value pregnant women (mg/d)	Model used	Type	Value non-pregnant women (mg/d)	Absorption non-pregnant women (%)
EFSA 2013[26] = HCNL 2014[38]	AI	3.0	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	3.0	<10[a,b]
HCNL 2018[4]	N/A	N/A	N/A	AI	3.0	<10[a,b]
NCM 2014[42]	-	-	No reference values derived	-	-	-
DACH 2015[43]	AI	2.0-5.0[c]	$AI_{pregnant} = AI_{(young)\ adult}$	AI	2.0-5.0	-
IOM 2001[47]	AI	2.0	Scaling	AI	1.8	3.55 (SD: ±2.11)[d] Young adult: 5.0 (SD: ±3.1)[e]
WHO/FAO 2004[50]	-	-	No reference values derived	-	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] The absorption rate increases with decreasing amounts of magnesium in the diet and vice versa.
[b] Women absorb more manganese than men.
[c] DACH did not specify whether pregnant women are included in their recommendation for adults. The committee assumes that they are.
[d] Based on whole body retention curves at ~10-20 days after dosing with the isotope ^{54}Mn from a test meal containing 1 mg manganese.
[e] 10 Days after a test meal containing 0.3-0.4 mg of manganese.

23.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

Differences in the method of derivation

Only IOM derived reference values for pregnant women deviating from their reference values for non-pregnant women. EFSA and presumably DACH applied their reference values for non-pregnant women to pregnant women. DACH did not specify whether pregnant women were included in their recommendation for adults. Therefore, no further consideration will be given to the DACH report. NCM and WHO/FAO did not set DRVs for manganese. NCM considered data too limited to determine requirements and noted that manganese deficiency has not been observed in pregnant women. WHO/FAO did not mention manganese in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

EFSA noted that there is no data on observed manganese intakes in pregnant women and that the gain in body weight during pregnancy does not need to be accounted for given the homeostatic control of manganese.[26] Therefore, EFSA applied their AI for non-pregnant women to pregnant women.

IOM stated that there is limited data on which to base an AR specific to pregnancy. They referred to one study on manganese concentrations in 40 fetuses of 22-43 weeks' gestation ranging from 0.35-9.27 µg/g dry weight[144], but they did not use this study to derive their AR. IOM also noted that in animals, manganese deficiency in utero produces ataxia and impaired otolith development, but that these defects have not been reported in humans.

IOM calculated the additional manganese intake by extrapolating up from the AI of non-pregnant women (1.8 mg/d) by means of metabolic scaling, using the reference body weight for non-pregnant women (61 kg[a]) and the median increased body weight for pregnant women (77 kg[b]). Scaling: $AI^{pregnant} = AI^{non\text{-}pregnant} \times (77\ kg/61\ kg)^{0.75} = AI^{non\text{-}pregnant} \times 1.19$. This corresponds to an additional requirement of +0.34 mg/d, which was rounded to +0.2 mg/d after rounding.

Differences in the reference values

Differences in the values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   EFSA's value was higher than IOM's.[4]
2. The method of derivation of the reference values for pregnant women:
   NCM did not establish values. EFSA applied their value for non-pregnant women to pregnant women. IOM's AI was estimated by metabolic scaling: $AI^{pregnant} = AI^{non\text{-}pregnant} \times (77\ kg/61\ kg)^{0.75} = 2.14$ mg/d (2.0 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

23.3 Pregnancy-related health outcomes

Deficiencies

EFSA described manganese deficiency symptoms in animals: impaired growth, skeletal abnormalities, reproductive deficits, ataxia of the newborn, and defects in lipid and carbohydrate metabolism. In contrast, evidence of manganese deficiency in humans is "poor". EFSA referred to SCF (1993, 2000), WHO (1996), and IOM (2001) stating that a specific deficiency syndrome has not been described in humans.[26]

[a] From section 2 of their report.[47]

[b] IOM referred to a study reporting a median weight gain of 16 kg among 7,002 women who had good pregnancy outcomes.[105]

Intake and associated health outcomes

EFSA described no studies showing manganese intake levels associated with pregnancy-related health outcomes.[26]

23.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

Based on the absence of any demonstrated benefit, a manganese recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. Only IOM derived an additional requirement based on metabolic scaling. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. In the absence of data, the committee judges it unwarranted to calculate a higher recommendation by means of scaling, as was done by IOM.

Conclusion and strength of the model

The evidence of the method of derivation for the reference values of manganese during pregnancy is limited. According to EFSA, the gain in body weight during pregnancy does not need to be accounted for given the homeostatic control of manganese.[26] Data on manganese requirements during pregnancy is scarce. The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 23.2).

Table 23.2. Reference value for manganese recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	3.0 mg/d	*3.0 mg/d*

24 Molybdenum

Summary and conclusion

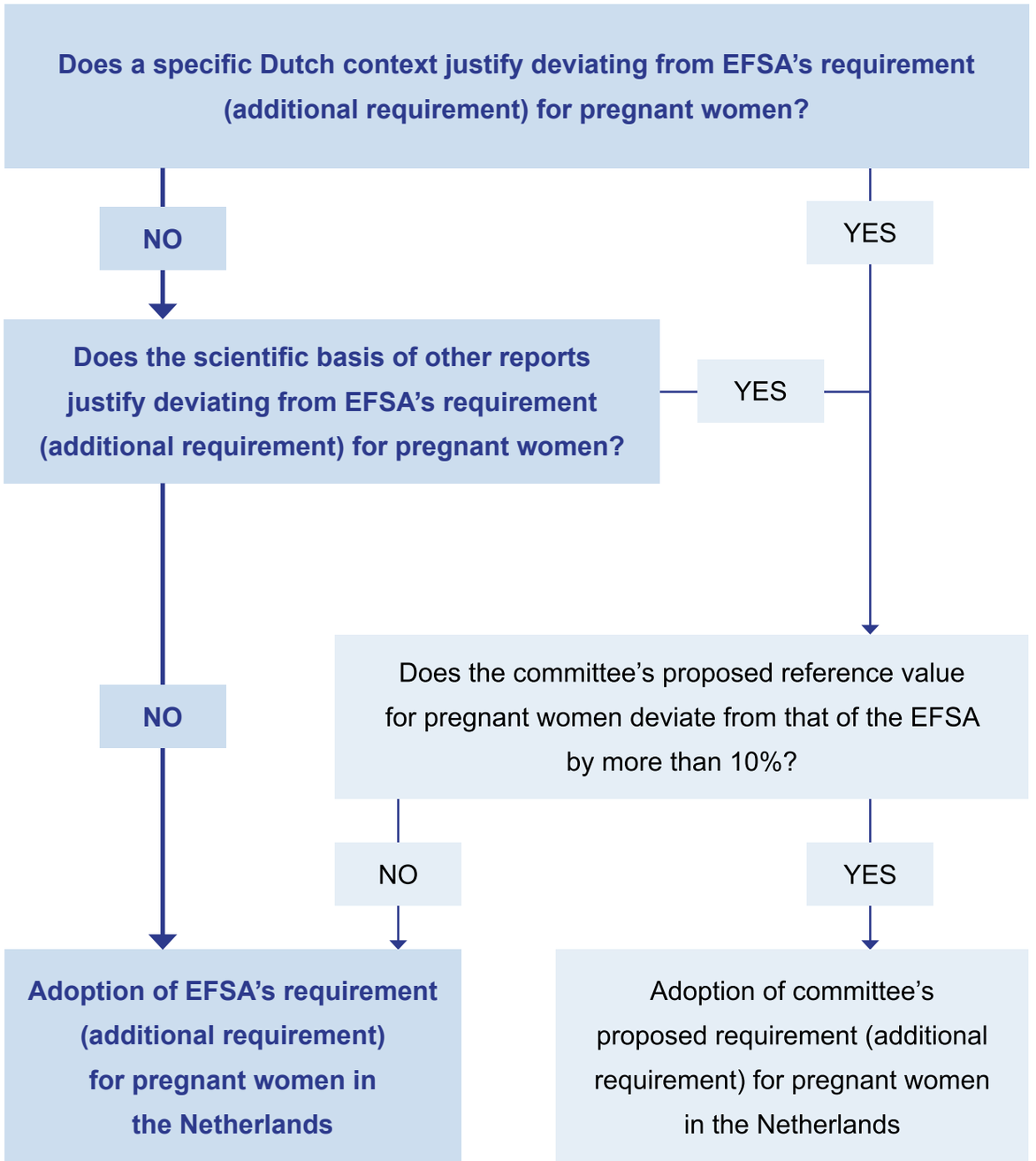
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a molybdenum recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is weak.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 65 µg/d

Flowchart with committee's line of reasoning for molybdenum



24.1 Overview and comparison of values

Table 24.1. Overview of the reference values for molybdenum for pregnant women and the model used to derive these values, compared with the reference values for molybdenum for non-pregnant women

Report	Type	Value pregnant women (µg/d)	AR pregnant women (µg/d)	CV[a] pregnant women (%)	Model used	Type	Value non-pregnant women (µg/d)	AR non-pregnant women (µg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2013[27] = HCNL 2014[38]	AI	65	N/A	N/A	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	65	N/A	N/A	100[b]
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	65	N/A	N/A	100[b]
NCM 2014[42]	-	-	-	-	No reference values derived	-	-	-	-	-
DACH 2015[43]	AI	50-100	N/A	N/A	$AI_{pregnant}$ = $AI_{non-pregnant}$	AI	50-100	N/A	N/A	~80
IOM 2001[47]	RDA	50	40	15	Scaling	RDA	45	34	15	88-93[c]
WHO/FAO 2004[50]	-	-	-	-	No reference values derived	-	-	-	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Dissolved in water and at doses up to ~1 mg. Molybdenum absorption in the presence of solid foods is lower.
[c] From widely different oral test doses of molybdenum (22-1,490 µg/d).

24.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the EFSA report.

Differences in the method of derivation

Only IOM derived reference values for pregnant women deviating from their reference values for non-pregnant women. EFSA and DACH applied their reference values for non-pregnant women to pregnant women. EFSA noted the scarcity of data on molybdenum intakes in pregnant women, which was the reason for applying their AI for non-pregnant women to pregnant women. DACH did not explain their reason for this.

Therefore, no further consideration will be given to the DACH report. NCM and WHO/FAO did not set DRVs for molybdenum. NCM referred to their NNR 2004[53] report in which they did not include recommendations for molybdenum. NCM referred to an analysis performed as preparatory work for the establishment of EFSA's DRVs[145] and concluded that the evidence regarding molybdenum in relation to setting DRVs was still limited and was considered insufficient to establish requirements. WHO/FAO did not mention molybdenum in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

IOM stated that no direct data was available for determining the additional daily requirement for molybdenum during pregnancy. Therefore, they calculated the additional molybdenum intake by extrapolating up from the AR of non-pregnant women (34 µg/d) by means of metabolic scaling, using the reference body weight for non-pregnant women (61 kg[a]) and the median increased body weight for pregnant women (77 kg[b]).
Scaling: $AR^{pregnant} = AR^{non\text{-}pregnant} \times (77\ kg/61\ kg)^{0.75} = AR^{non\text{-}pregnant} \times 1.19$.
This corresponds to an additional requirement of +6.46 µg/d (+6 µg/d after rounding).

[a] From section 2 of their report.[47]
[b] IOM referred to a study reporting a median weight gain of 16 kg among 7,002 women who had good pregnancy outcomes.[105]

Differences in the reference values
Differences in the values between reports resulted from differences in two aspects.
1. The reference value for non-pregnant women:
EFSA's value was higher than IOM's.[4]
2. The method of derivation of the reference values for pregnant women:

NCM did not establish values. EFSA applied their value for non-pregnant women to pregnant women. IOM's AR was estimated by metabolic scaling: $AR^{pregnant} = AR^{non\text{-}pregnant} \times (77\ kg/61\ kg)^{0.75}$ = 40.49 µg/d (40 µg/d after rounding). IOM's PRI was based on this AR multiplying by twice the CV of 15%: 40.49 µg/d x 1.3 = 52.64 µg/d (50 µg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester
None of the reports differentiated by trimester.

24.3 Pregnancy-related health outcomes

Deficiencies
EFSA reported that clinical signs of molybdenum deficiency have not been observed in otherwise healthy humans.[27] However, they did report that molybdenum cofactor deficiency results in a deficiency of all molybdoenzymes in humans. Molybdenum cofactor deficiency is a rare autosomal recessive syndrome with a defective hepatic synthesis of

molybdenum cofactor. This deficiency 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.
- Usually, death at an early age.

One affected child has been successfully treated using the “first detectable intermediate substance in the biosynthesis pathway of molybdenum cofactor”.

Intake and associated health outcomes

EFSA described no studies showing molybdenum intake levels associated with pregnancy-related health outcomes.[27]

24.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA’s reference value for non-pregnant women.[4]

Model used

Based on the absence of any demonstrated benefit, a molybdenum recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. Only IOM derived an additional requirement based on metabolic scaling. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. In the absence of data, and in the absence of clinical signs of molybdenum deficiency, the committee judges it unwarranted to calculate a higher recommendation by means of scaling, as was done by IOM.

The evidence of the method of derivation for the reference value of molybdenum during pregnancy is limited. Data on molybdenum requirements during pregnancy is scarce. The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee accepts EFSA’s AI for pregnant women for use in the Netherlands (Table 24.2).

Table 24.2. Reference value for molybdenum recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	65 µg/d	*65 µg/d*

25 Phosphorus

Summary and conclusion

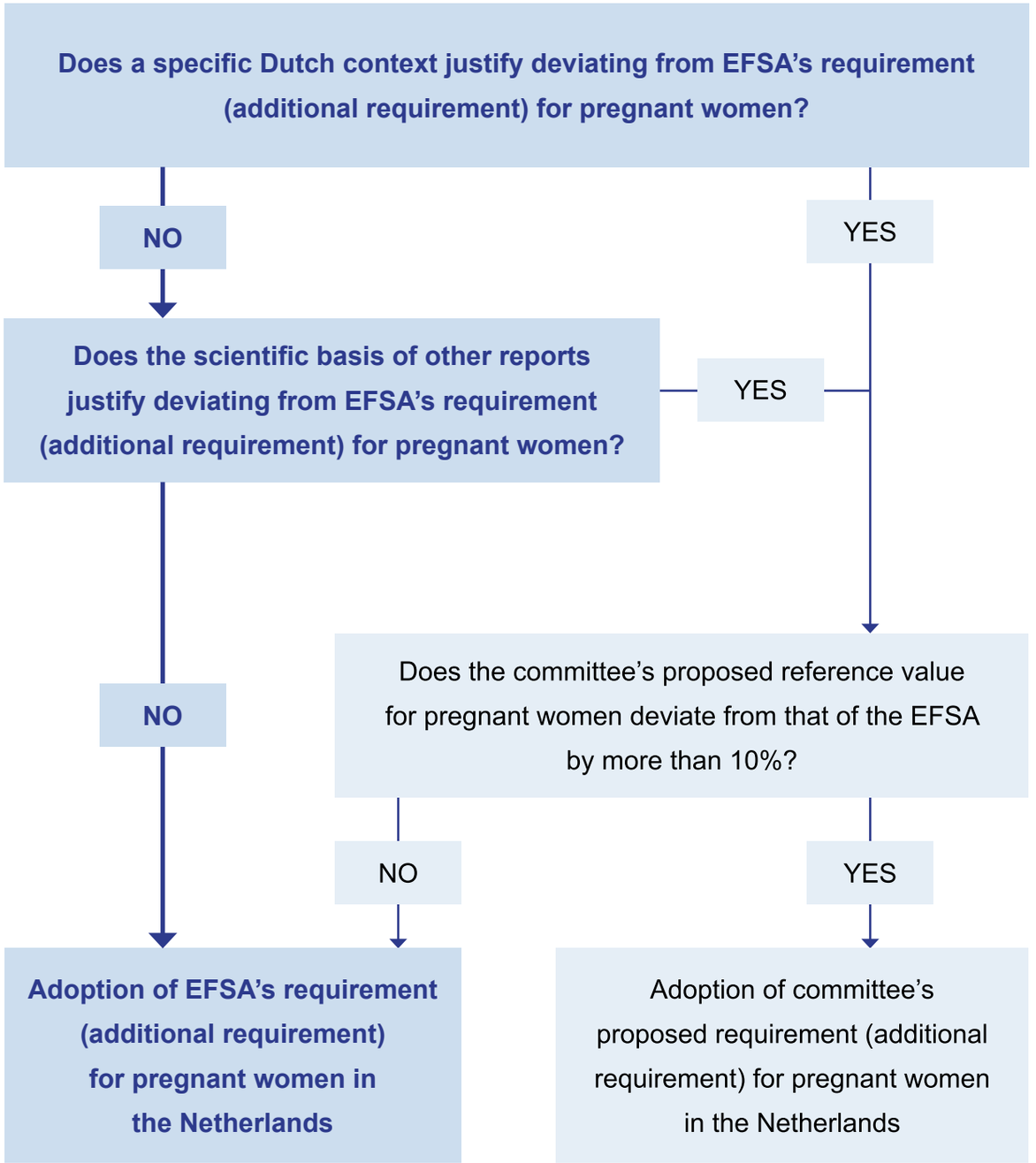
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

The available literature is limited and does not point towards an increased requirement during pregnancy. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference values for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is acceptable.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 550 mg/d

Flowchart with committee's line of reasoning for phosphorus



25.1 Overview and comparison of values

Table 25.1. Overview of the reference values for phosphorus for pregnant women and the model used to derive these values, compared with the reference values for phosphorus for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2015[28]	AI	550	N/A	N/A	$AI_{pregnant}$ = $AI_{non\text{-}pregnant}$	AI	550	N/A	N/A	55-80[b,c,d]
NCM 2014[42] = HCNL 2014[38]	RI	700[e]	-	-	Unknown	RI	600	450	*(17)*	55-70[f]
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	550	N/A	N/A	55-80[b,c,d]
DACH 2015[43]	RI	800	-	-	Additive	RI	700	580	10	55-70[g]
IOM 1997[49]	RDA	700	580	10	$RDA_{pregnant}$ = $RDA_{non\text{-}pregnant}$	RDA	700	580	10	Typically: 60-65 (range: 55-70)[d,f,g]
WHO/FAO 2004[50]	-	-	-	-	No reference values derived	-	-	-	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] EFSA noted that the intestinal phosphorus absorption tends to decrease with aging.
[c] EFSA reported the ability to absorb and use phosphorus to be affected by the total amount of phosphorus in the diet, type of phosphorus (organic versus inorganic), the food origin (animal versus plant-derived), and the ratio of phosphorus to other dietary components.
[d] EFSA and IOM noted that an important factor preventing phosphorus absorption is co-ingested calcium.
[e] As reported in Table 1.3 from NCM's report.[42]
[f] NCM and IOM reported there to be no evidence for a dose-response relationship.
[g] From a mixed diet.

25.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

EFSA and IOM applied their reference values for non-pregnant women to pregnant women. NCM and DACH derived reference values for pregnant women deviating from their reference values for non-pregnant women. NCM did not explain how they derived their additional requirement. Therefore, no further consideration will be given to the NCM report.

WHO/FAO did not mention phosphorus in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

EFSA noted that the role of dietary phosphorus during pregnancy has not been established. EFSA described a seven-day metabolic balance study (periodically throughout the pregnancy, with a maximum of six 7-day periods) conducted in 10 pregnant white women consuming supplemented or unsupplemented self-selected diets.[90] At an estimated phosphorus intake of 1,340 (±280) mg/d[a], zero phosphorus balance was observed. EFSA did not use this balance study for setting DRVs because very large intra and inter-subject variations were observed from one 7-day experimental period to another.

EFSA also referred to one review concluding that pregnancy is associated with physiological adaptive changes in mineral metabolism independent of maternal mineral supply within the range of normal dietary intakes.[146] These processes provide the minerals necessary for fetal growth without requiring an increase in maternal dietary intake or compromising maternal bone health in the long term. EFSA acknowledged the existence of these physiological adaptive processes, possibly resulting in additional dietary phosphorus during pregnancy not being required, provided intake is close to the AI for non-pregnant women. Therefore, EFSA applied their AI for non-pregnant women to pregnant women.

IOM also referred to a balance study, albeit a different one than EFSA, and used this study to derive their DRVs. This balance study was performed in 15 pregnant women (and 9 female controls of similar age) 24 times at various stages of pregnancy, and 5 were studied again following delivery at intervals varying from one week to three months post-partum.[88] The study demonstrated positive phosphorus balance, which increased with the length of pregnancy. Net absorption in the participants averaged 70%, which IOM compared with the 60-65% typically found in non-pregnant adults.

[a] Average calcium intake was 1,370 (±290) mg/d.

IOM reported the phosphorus content of a term infant at birth to be 17.1 g.[49] For this, a fetal phosphorus requirement of ~62 mg/d is needed.[147] IOM estimated the amount of phosphorus absorbed during pregnancy with an increased absorption rate of 70%, assuming the same EAR of non-pregnant women to be 412 mg/d. The amount of phosphorus absorbed with an absorption rate of 60% (non-pregnant) is 353 mg/d. Thus, the increase in the amount of phosphorus absorbed during pregnancy is 412 mg/d – 353 mg/d = 59 mg/d. IOM concluded that this amount approximately equals the estimated fetal phosphorus requirement of 62 mg/d and, therefore, applied their EAR of non-pregnant women to pregnant women.

DACH noted that an additional intake of 60 mg/d of phosphorus is required and that an additional intake of 100 mg/d takes the intestinal absorption into account. The committee calculated the assumed absorption as follows: 100 mg/d/60 mg/d = 1.67, or 60%. They did not explain how their additional requirement was derived. Therefore, no further consideration will be given to the DACH report.

Differences in the reference values

Differences in the values between reports resulted from differences in the reference value for non-pregnant women: EFSA's value was lower than IOM's.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

25.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no phosphorus deficiencies during pregnancy.[28]

Intake and associated health outcomes

EFSA reported three publications on the association between maternal phosphorus intake and bone mass in children.[28]

Two of these publications were based on the same Australian prospective cohort study. One publication studied the children at age 8 (n=173) and the other at age 16 (n=216[a]). At age 8 years, the bone mineral density (BMD[b]) of the femoral neck and lumbar spine were positively associated with the phosphorus density of the maternal diet, whereas total body BMD was not. At age 16 years, none of the BMD measures were associated with the phosphorus density of the maternal diet.[c] EFSA did not use these publications to derive DRVs as the participating children were originally selected based on having a higher risk of sudden infant death syndrome, as adjustments for multiple comparison were not performed, and as the self-reported maternal intake of protein, calcium, magnesium, and

[a] The populations are not identical as not all children underwent a scan at ages 8 and 16 years.
[b] Measured by dual-energy X-ray absorptiometry (DXA).
[c] Regression models were adjusted for children's current calcium intake.

phosphorus was very high (much higher than in Australian pregnant women in general, and higher than Australian reference values).

The other publication was performed in 4,451 UK mother-child pairs and evaluated the relationship between maternal diet during pregnancy (through FFQ) and bone mineral mass at 9 years of age. The mean maternal phosphorus intake was not associated with measures of bone density in children, but multivariate analyses were not adjusted for children's intakes of calcium or other micro or macronutrients.

25.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

EFSA noted that the role of dietary phosphorus during pregnancy has not been established. The available literature is limited and does not point towards an increased requirement during pregnancy. The committee agrees with the method of derivation used by EFSA and IOM, i.e., adopting the reference values for non-pregnant women for use during pregnancy, and accepts EFSA's values.

Conclusion and strength of the model

The evidence of the method of derivation for the reference values of phosphorus during pregnancy is limited and does not point towards an increased requirement during pregnancy. Data on phosphorus requirements during pregnancy are scarce. EFSA used one review[146] from acceptable quality, concluding that maternal physiological adaptive processes provide the phosphorus necessary for fetal growth, obviating the need for additional dietary phosphorus during pregnancy. The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 25.2).

Table 25.2. Reference value for phosphorus recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	550 mg/d	550 mg/d

26 Potassium

Summary and conclusion

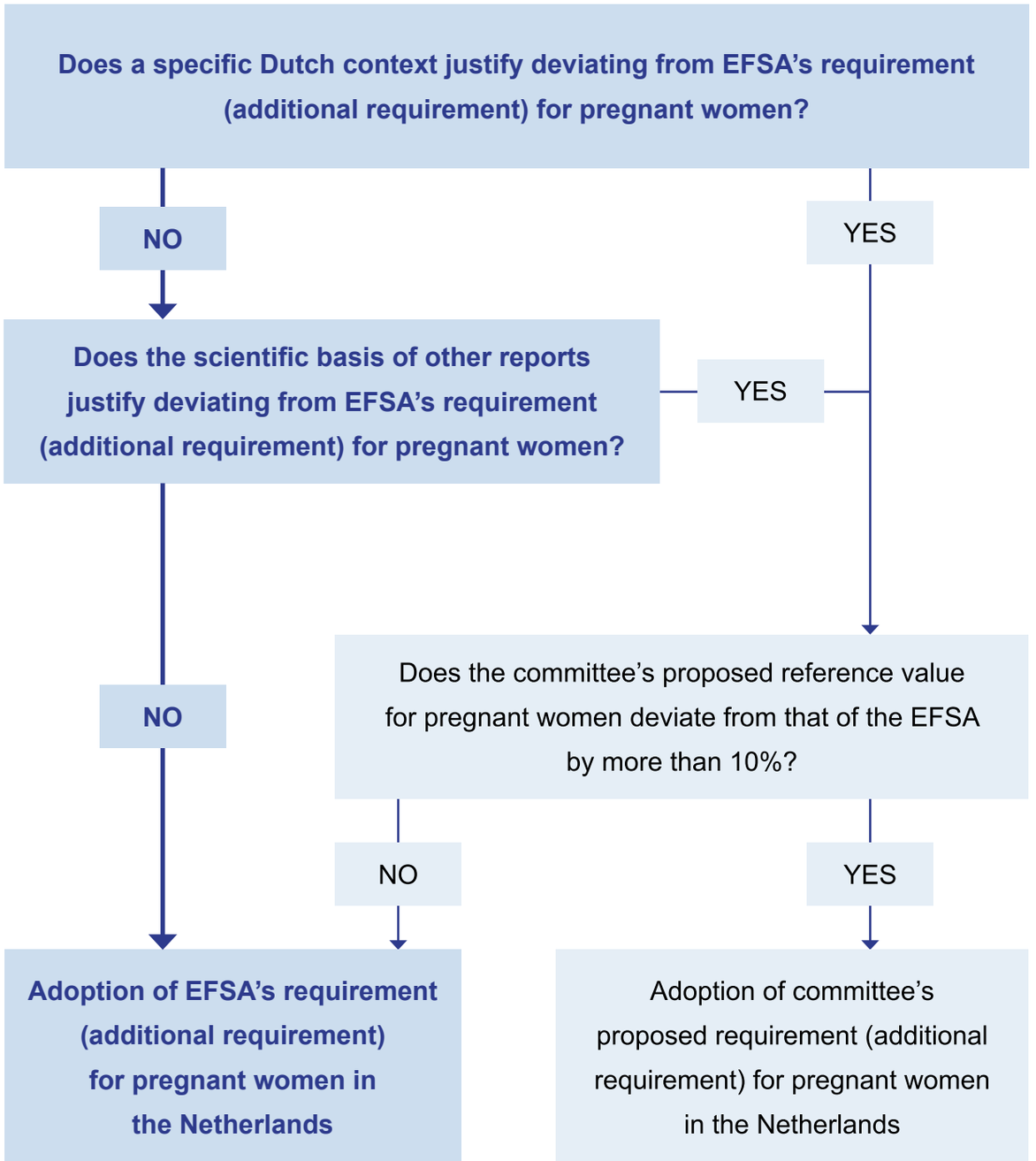
In 2018, the committee accepted EFSA's reference value for non-pregnant women.

Based on the absence of any demonstrated benefit, a potassium recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference value for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is acceptable.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value:

- AI = 3.5 g/d

Flowchart with committee's line of reasoning for potassium



26.1 Overview and comparison of values

Table 26.1. Overview of the reference values for potassium for pregnant women and the model used to derive these values, compared with the reference values for potassium for non-pregnant women

Report	Type	Value pregnant women (g/d)	Model used	Type	Value non-pregnant women (g/d)	Absorption non-pregnant women (%)
EFSA 2016[29]	AI	3.5	$AI_{pregnant} = AI_{non\text{-}pregnant}$	AI	3.5	~90
NCM 2014[42] = HCNL 2014[38]	RI	3.1	$RI_{pregnant} = RI_{non\text{-}pregnant}$	RI	3.1	~90
HCNL 2018[4]	N/A	N/A	N/A	AI	3.5	~90
DACH 2015[43]	AI	2.0	$AI_{pregnant} = AI_{(young)\ adult}$	AI	2.0	>90
IOM 2005[46]	AI	4.7	$AI_{pregnant} = AI_{(young)\ adult}$	AI	4.7	~85[a]
WHO/FAO 2004[50]	-	-	No reference values derived	-	-	-

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] In healthy persons.

26.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.
The HCNL 2014 report followed the NCM report.

Differences in the method of derivation
None of the reports derived reference values for pregnant women deviating from their reference values for non-pregnant women. EFSA, NCM, DACH, and IOM applied their reference values for non-pregnant women to pregnant women. NCM and DACH did not motivate their approach. Therefore, the NCM and DACH reports are not discussed further. WHO/FAO did not mention potassium in their report, nor their lack of recommendation for this substance. Therefore, no further consideration will be given to the WHO/FAO report.

EFSA noted that potassium excretion is kept constant through adaptive mechanisms of renal tubular potassium reabsorption, which adjust to the increased filtered potassium load and the increased retention of sodium mediated by aldosterone.[29] Therefore, healthy pregnant women do not typically develop hypokalemia, despite plasma potassium concentrations decreasing during pregnancy and filtered potassium load in the kidney

and mineralocorticoid activity increasing. EFSA referred to several (types of) studies measuring potassium accretion in pregnant women, in mature fetuses, in full-term neonates, and in placental tissues[a]. EFSA noted that there is a lack of data on potassium requirements in pregnancy, but stated that the requirement for the daily accretion of potassium in fetal and maternal tissues can be met by the adaptive changes maintaining potassium homeostasis during pregnancy.

IOM noted that there is little information on the size of body potassium stores during pregnancy and that hormonal changes may affect potassium balance and deposition. IOM referred to four studies estimating cumulative gains in the storage ranging from 100-320 mmol (3.9-12.5 g), of which 200 mmol (~7.8 g) was destined for the "products of conception".[46] Additionally, plasma and serum concentrations of potassium decrease ~0.2-0.3 mmol/L, which may not indicate hypokalemia until values decrease by 0.5 mmol, or to below 3 mmol/L. The reason for this decrease is obscure but could relate to the mild physiologic alkalemia of gestation.[46]

IOM concluded that potassium accretion during pregnancy is very small and that there is an absence of data suggesting that the potassium requirement is different during pregnancy. Therefore, they applied their AI for non-pregnant to pregnant women.

Differences in the reference values

Differences in the values between reports resulted from differences in the reference value for non-pregnant women: EFSA's value was lower than IOM's.[4]

Differences between the 1st, 2nd, and 3rd trimester

None of the reports differentiated by trimester.

26.3 Pregnancy-related health outcomes

EFSA described no pregnancy-related potassium deficiencies and no studies showing intake levels associated with pregnancy-related health outcomes.[29]

26.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

Model used

Based on the absence of any demonstrated benefit, a potassium recommendation higher than that for non-pregnant women seems unwarranted in pregnant women. The committee agrees with the method

[a] Potassium accretion in pregnant women varied from 234 mmol (~9 g) to 307 mmol (12 g). EFSA estimated daily accretion to be in the order of 3 mmol (120 mg) potassium. Potassium accretion in mature fetuses and full-term neonates was between ~100 mmol (4 g) and 150 mmol (6 g). EFSA reported daily accretion to range from 0.5 mmol/d at week 24-25 to 1.5 mmol/d at weeks 36-37 in one study and from 0.1 mmol/d at weeks 12-16 to 1.4 mmol/d at weeks 36-40 in another. EFSA estimated a net transfer of potassium to placental tissues of 22 mmol (858 mg) over the course of pregnancy.

of derivation used by both EFSA and IOM, i.e., adopting the reference value for non-pregnant women for use during pregnancy.

Conclusion and strength of the model

The evidence of the method of derivation for the reference values of potassium during pregnancy is limited. According to EFSA, the requirement for the daily accretion of potassium in fetal and maternal tissues can be met by the adaptive changes maintaining potassium homeostasis during pregnancy, which is supported by several (types of) studies.[29] Data on the potassium requirement during pregnancy is otherwise scarce. The committee deems the scientific basis for the method of derivation to be acceptable (based on a plausible rationale).

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 26.2).

Table 26.2. Reference value for potassium recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	3.5 g/d	*3.5 g/d*

27 Selenium

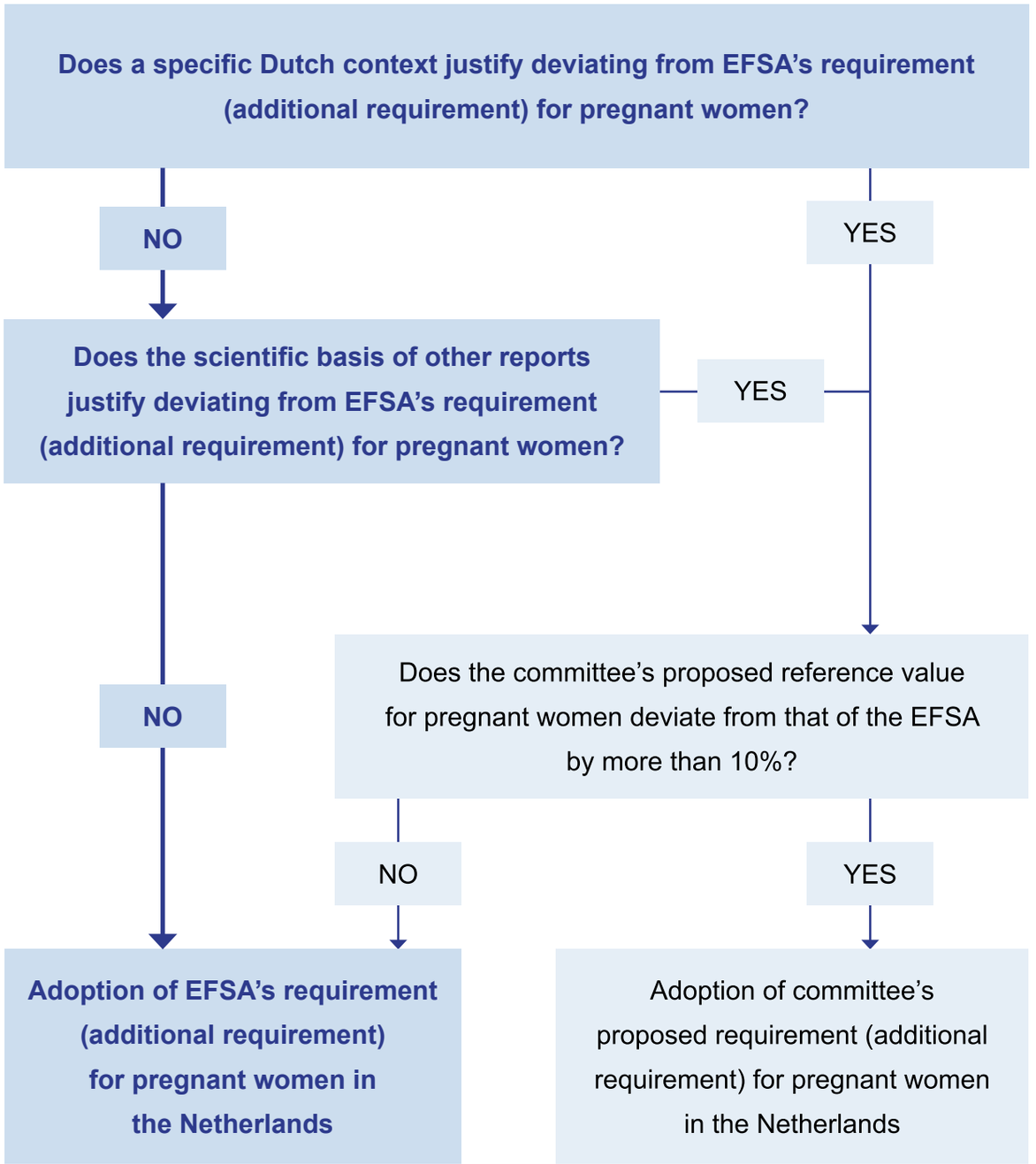
Summary and conclusion

In 2018, the committee accepted EFSA's reference value for non-pregnant women.

There seems to be no scientific consensus between the different reports on whether the reference values for pregnant women should be increased compared with non-pregnant women. The committee agrees with the method of derivation used by EFSA, i.e., adopting the reference value for non-pregnant women for use during pregnancy. The scientific basis for the method of derivation is acceptable.

The committee accepts EFSA's AI for pregnant women for use in the Netherlands, resulting in the following reference value: AI = 70 µg/d.

Flowchart with committee's line of reasoning for selenium



27.1 Overview and comparison of values

Table 27.1. Overview of the reference values for selenium for pregnant women and the model used to derive these values, compared with the reference values for selenium for non-pregnant women

Report	Type	Value pregnant women (µg/d)	AR pregnant women (µg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (µg/d)	AR non-pregnant women (µg/d)	CV[a] non-pregnant women (%)	Absorption non-pregnant women (%)
EFSA 2014[30]	AI	70	N/A	N/A	$AI_{pregnant} = AI_{non-pregnant}$	AI	70	N/A	N/A	70[c,d]
NCM 2014[42] = HCNL 2014[38]	RI	60	-	-	Unknown	RI	50	30	*(33)*	"Effectively"[e]
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	AI	70	N/A	N/A	70[c,d]
DACH 2015[43]	AI	60	N/A	N/A	$AI_{pregnant} = AI_{non-pregnant}$	AI	60	N/A	N/A	70 (50-100)[f]
IOM 2000[44]	RDA	60	49	10	Additive	RDA	55	45	10	(>50->90)[g]
WHO/FAO 2004[50]	RI	*(28)*[h] Trimester 2nd: 28 3rd: 30	-	12.5	Additive	RI	26	20	12.5	"Generally very efficiently"[i]

Abbreviations: -: Not specified, N/A: not applicable
Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR).
[b] Information on the models used for each report is specified in Table 27.2.
[c] From usual diets.
[d] Absorption of selenomethionine (and presumably as selenocysteine) is >90%. Selenium in inorganic compounds (such as selenate or selenite) is also well absorbed, selenite better than selenate. Absorption efficiency is not affected by selenium status nor plays a role in the homeostatic regulation of selenium.
[e] True for water-soluble selenium compounds and dietary selenium. Selenates and organic selenium are somewhat better absorbed than selenites.
[f] Following EFSA's absorption of 70% for dietary selenium and noting that absorption varies from ~100% for selenoamino-acids to 50% for inorganic selenium compounds.
[g] Absorption of selenomethionine (major dietary form) is >90%. Absorption of selenate (inorganic form) is almost complete. Absorption of selenite (inorganic form) is >50%. Both inorganic forms are not major dietary constituents but are commonly used to fortify foods and in supplements.
[h] The committee calculated the average RI for pregnancy, assuming an RI for the 1st trimester equal to the RI for non-pregnant women.
[i] Absorption of selenite is >80%. Absorption of selenomethionine or selenite is >90%. The rate-limiting step determining the overall bioavailability of dietary selenium is not likely to be its absorption but rather its conversion within tissues to its metabolically active forms.

Table 27.2. Overview of the models used and the basis for the requirements (additional requirements) for selenium for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Basis
EFSA 2014[30]	$AI_{pregnant} = AI_{non\text{-}pregnant}$	N/A	N/A	Assumption: adaptive changes in the selenium metabolism cover the additional needs.
NCM 2014[42] = HCNL 2014[38]	Unknown	-	Selenium deposition due to tissue growth.	EFSA's[1] and IOM's[6] estimates of the reference value, and the assumption that the recommendation should now (contrasting to NNR 2004) be based on the optimization of the plasma selenoprotein P (SePP) concentration.
DACH 2015[43]	$AI_{pregnant} = AI_{non\text{-}pregnant}$	N/A	N/A	Assumption: the additional selenium requirement is only small (2 µg/d).
IOM 2000[44]	Additive (EAR: +4 RDA: +5)	"Highly bioavailable: no adjustment is made for absorption"	Selenium deposition due to growth in fetal tissue.	Assumptions: estimated selenium content is 250 µg/kg body weight, average fetal weight is 4 kg, and the average duration of pregnancy is 270 days.
WHO/FAO 2004[50]	Additive (RI by trimester 1st: - 2nd: +2 3rd: +4)	80	Selenium deposition due to growth in fetal tissue.	Assumptions: products of conception amount to 4.6-6 kg lean tissue with a protein content of 18.5-20%, which would account for 1.0-4.5 µg/d (depending on the amount of selenium in the diet).

Abbreviations: -: Not specified, N/A: not applicable

[a] If applicable: (+ additional requirement in mg/d).

[b] This column presents any information on absorption during pregnancy if provided by the report.

27.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in reference values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

EFSA and DACH applied their reference values for non-pregnant women to pregnant women. EFSA's reasoning was that adaptive changes of the body cover the additional needs during pregnancy, and DACH's reasoning was that the additional selenium requirement is only small (2 µg/d[a], as averaged from three studies[148-150]).

IOM and WHO/FAO used an additive model to derive their additional requirement for selenium during pregnancy. Both reports based their additional requirement on the selenium deposition in the fetus.

Regarding the requirements for non-pregnant women, EFSA, DACH, and NCM based their reference value on the selenium intake level required for plasma selenoprotein P (SEPP1) to reach a plateau value, whereas IOM and WHO/FAO based their reference value on glutathione peroxidase (GPx). EFSA considered that SEPP1 is the most informative biomarker of selenium function based on its role in selenium transport and metabolism and its response to different forms of ingested selenium. EFSA notes 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 that are lower than those required for the levelling off of SEPP1. As a result of the chosen biomarker of selenium, the requirements for non-pregnant women of ION and WHO/FAO are much lower than those of EFSA, DACH, and NCM (Table 27.1).

NCM referred to the EFSA and IOM recommendations (without a literature reference) for pregnant women of 55 µg/d and 60 µg/d, and for lactating women of 70 µg/d. The NNR 2004 recommendation was 55 µg/d for both pregnant and lactating women.[53] NCM noted that "it now appears more reasonable to base the recommendation on the optimization of the plasma SePP concentration, although the usefulness of this measure has been discussed for selenium-replete populations". Based on these considerations, NCM increased their recommendation for pregnant women to 60 µg/d. It is unclear exactly how NCM derived this reference value. Therefore, no further consideration will be given to the NCM report.

EFSA noted that the available data provided some evidence that adaptive changes occur during pregnancy, as indicated by a trend of lower urinary excretion of selenium in pregnant than in non-pregnant women and a more pronounced conservation in late than in early pregnancy. This was

[a] A New Zealand study from 1982 in 16 fetuses (gestational ages: 27-42 weeks), 4 infants (4-54 months), and 41 adults (15-74 years) reported mean selenium liver concentrations of 1.26 µg/g dry weight (SD: ±0.38), 0.58 µg/g dry weight (SD: ±0.22), and 0.72 µg/g dry weight (SD: ±0.18) respectively. A German study from 1988 in 18 adult male accident victims reported a mean selenium liver concentration of 0.29 µg/g wet weight (SD: ±0.08). A Polish study from 2001 in 46 male and female accident and suicide victims reported a mean selenium liver concentration of 0.22 µg/g wet weight (SD: ±0.03).

based on one balance study from 1983 among 10 pregnant (6 in early and 4 in late pregnancy) and 6 non-pregnant American women.[151] The women were fed a defined diet providing ~150 µg/d of selenium for 20 days, and selenium balance was measured during the last 12 days. Urinary excretion was assessed by 40 µg of a stable isotope of selenium (^{76}Se) from intrinsically labeled egg. The urinary excretion was 111 µg/d (SEM: ±2) in the non-pregnant group, compared with 100 µg/d (SEM: ±6) in the early-stage pregnant group and 96 µg/d (SEM: ±2) in the late-stage pregnant group. The respective mean apparent selenium retentions were: 11 µg/d (SEM: ±2), 21 µg/d (SEM: ±4), and 34 µg/d (SEM: ±2). Net selenium retention of early-stage pregnant and late-stage pregnant groups were 10 and 23 µg/d, respectively. Based on the assumption that ~5 kg of lean tissue is deposited during pregnancy, that lean tissue contains 0.2-0.3 mg/kg of selenium, and that the pregnancy duration is 280 days, the average selenium retention was estimated to be: (0.2-0.3 mg/kg x 5 kg)/280 d = 3.57-5.36 µg/d (3.5-5 µg/d after rounding).[151] EFSA noted, however, that the inter-individual variability was high and that the results were not statistically significant. EFSA also noted that habitual selenium intake was not assessed, making the interpretation of this data difficult regarding the actual additional requirement during pregnancy.

EFSA also referred to a double-blind placebo-controlled pilot trial from 2014 in 230 pregnant UK women, randomized to selenium (60 µg/d, as selenium-enriched yeast) or a placebo, from 12-14 weeks of gestation until delivery, measuring among other things whole-blood selenium and SEPP concentration at 35 weeks.[152] However, EFSA did not use this study to draw conclusions regarding selenium requirements during pregnancy for two reasons. First, background dietary selenium intake was not assessed. Second, in the absence of information on baseline plasma SePP concentrations, it was unknown whether higher plasma SePP concentrations in the supplemented group than in the control group indicated that selenium supplementation allowed the maintenance, or rather improvement, of the selenium status of the subjects.

IOM stated that few studies provide information about the selenium requirements of pregnant women. They noted that the pregnancy requirement should, however, allow accumulation of enough selenium by the fetus to saturate its selenoproteins. IOM referred to one USA study from 1970 reporting an estimated selenium content of 250 µg/kg body weight.[44] IOM assumed a fetal weight of 4 kg, resulting in an estimated fetal selenium content of 250 µg x 4 kg = 1,000 µg. IOM further assumed a pregnancy duration of 270 days, resulting in an additional requirement of 1,000 µg/270 d = 3.7 µg/d (4.0 µg/d after rounding).

WHO/FAO stated that data from balance experiments were not sufficiently consistent for defining the increase in selenium needed to support fetal growth and development during pregnancy. WHO estimated the likely quantity of selenium incorporated into the fetal tissues. For this, WHO

assumed that the total products of conception amount to 4.6-6 kg lean tissue, with a protein content of ~18.5-20%.[153,154] Growth of these tissues could account for 1.0 µg/d of selenium in regions with a low selenium intake[155,156] (e.g., New Zealand) to 4.5 µg/d in regions with a high selenium intake[157,158] (e.g., the United States). Further, WHO/FAO assumed an absorption of 80% and a CV of 12.5%. On this basis, WHO/FAO estimated that an additional requirement of +2 mg/d would be appropriate for the 2nd trimester and +4 mg/d for the 3rd trimester. The committee finds it unclear exactly how WHO/FAO derived these values for the 2nd and 3rd trimester. Therefore, no further consideration will be given to the WHO/FAO report.

Differences in the reference values

Differences in the values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women:
   EFSA's value was higher than DACH's, which was higher than IOM's.[4]
2. The method of derivation of the reference values for pregnant women:
   EFSA and DACH applied their value for non-pregnant women to pregnant women. IOM used an additive model to derive their values for pregnant women. IOM's PRI was based on the additional requirement added to the AR of non-pregnant women multiplied by twice the CV of 10%: (45 µg/d + 4 µg/d) x 1.2 = 58.8 µg/d (60 µg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester

WHO/FAO differentiated their PRI by trimester, yet it is unclear on what basis and how the different additional requirements were calculated.

27.3 Pregnancy-related health outcomes

Deficiencies

EFSA described no selenium deficiencies during pregnancy.[30]

Intake and associated health outcomes

EFSA reported some observational studies and a small number of RCTs using selenium supplementation reporting the relationship between selenium intake and biomarkers of status and health outcomes related to fertility[a], reproduction[b], immune function[c], thyroid hormone production, and cognition.[30] These studies reported "limited and inconclusive" results. EFSA concluded that these data could not be used to derive DRVs.

27.4 Strength of the scientific basis and conclusions

In 2018, the committee accepted EFSA's reference value for non-pregnant women.[4]

[a] E.g., sperm counts, motility, morphology.
[b] E.g., pre-eclampsia, pre-term birth, miscarriage.
[c] E.g., incidence and severity of infectious episodes.

Model used

EFSA and DACH applied their reference values for non-pregnant women to pregnant women, whereas IOM used an additive model. There seems to be no scientific consensus on whether the reference values for pregnant women should be increased compared with non-pregnant women.

The committee considered the following aspects of the method of derivation used in the reports. First, regarding the requirements for non-pregnant women, the committee already agreed with using the SEPP1 biomarker, resulting in higher reference values as compared with IOM and WHO/FAO. Second, the committee feels that there is insufficient evidence that a higher reference value is needed for pregnant women compared with non-pregnant women: Based on a balance study EFSA concluded that adaptive changes would compensate for the increased need.

Conclusion and strength of the model

The evidence of the method of derivation for the reference values of selenium during pregnancy is limited. According to EFSA, the pregnancy requirement should, however, allow accumulation of enough selenium by the fetus to saturate its selenoproteins. The evidence of IOM's method of derivation for the additional selenium requirement during pregnancy was based on one observational study of acceptable quality.[44] The committee deems the scientific basis for the method of derivation to be weak.

Reference values for pregnancy

The committee accepts EFSA's AI for pregnant women for use in the Netherlands (Table 27.3).

Table 27.3. Reference value for selenium recommended for pregnant women in the Netherlands and reference value for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Adequate intake (AI)	70 µg/d	*70 µg/d*

28 Zinc

Summary and conclusion

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women.

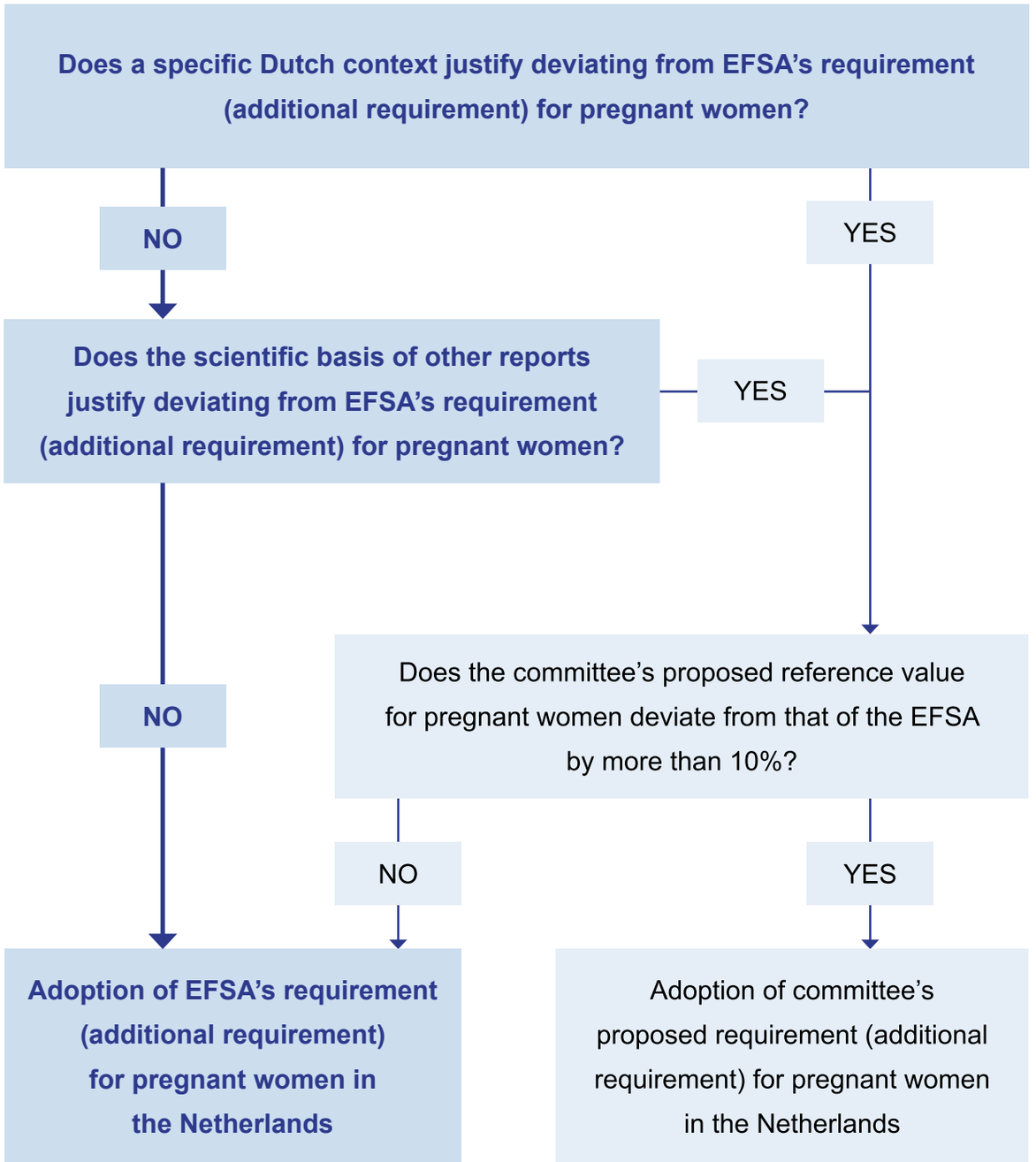
There appears to be a scientific consensus between the different reports on the derivation of the reference values for pregnant women with an additive model. The committee agrees with the method of derivation of the additional requirement for zinc during pregnancy used by EFSA.

The scientific basis for the method of derivation is acceptable.

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women, resulting in the following reference values:

- AR = 7.0 mg/d
- PRI = 9.1 mg/d

Flowchart with committee's line of reasoning for zinc



28.1 Overview and comparison of values

Table 28.1. Overview of the reference values for zinc for pregnant women and the model used to derive these values, compared with the reference values for zinc for non-pregnant women

Report	Type	Value pregnant women (mg/d)	AR pregnant women (mg/d)	CV[a] pregnant women (%)	Model used[b]	Type	Value non-pregnant women (mg/d)	AR non-pregnant women (mg/d)	CV[a] non-pregnant women (%)	Physiological requirement (mg/d)	Absorption non-pregnant women (%)
EFSA 2014[31]	PRI	+1.6	+1.3	10	Additive	PRI	Phytate intake 300 mg/d: 7.5 600 mg/d: 9.3 900 mg/d: 11.0 1,200 mg/d: 12.7	 6.2 7.6 8.9 10.2	[c]	2.9	≥60[d,e]
NCM 2014[42] = HCNL 2014[38]	RI	9.0	-	-	Additive	RI	7.0	5.7	15	2.0	- [e]
HCNL 2018[4]	N/A	N/A	N/A	N/A	N/A	RI	7.0	5.7	15	2.0	- [e]
DACH 2015[43]	RDA	10.0[f]	-	-	Additive	RDA	7.0	5.5	15	1.6	~30[g]
IOM 2001[47]	RDA	11	9.5	10	Additive	RDA	8.0	6.8	10	3.3	27[e,h]
WHO/FAO 2004[50]	RI	*(9.0)* Bioavailability high[i] 1st trimester: 3.4 2nd trimester: 4.2 3rd trimester: 6.0 Bioavailability moderate[j] 1st trimester: 5.5 2nd trimester: 7.0 3rd trimester: 10.0 Bioavailability low[k] 1st trimester: 11.0 2nd trimester: 14.0 3rd trimester: 20.0	*(6.0)* Bioavailability high[i] 1st trimester: 2.3 2nd trimester: 2.8 3rd trimester: 4.0 Bioavailability moderate[j] 1st trimester: 3.7 2nd trimester: 4.7 3rd trimester: 6.7 Bioavailability low[k] 1st trimester: 7.3 2nd trimester: 9.3 *3rd trimester: 13.3*	25	Additive	RI	*(5.9)* Bioavailability High[i]: 3.0 Moderate[j]: 4.9 Low[k]: 9.8	*(3.9)* 2.0 3.2 6.5	25	1.0	<15 to 60-70[e,l]

Abbreviations: -: Not specified, N/A: not applicable, PR: physiological requirement. Calculations done by the committee are depicted in brackets and in italics.
[a] If the coefficient of variation was not specified in the report, it was calculated as (100% x [(PRI/RI/RDA – AR)/2]/AR). [b] Information on the models used for each report is specified in Table 28.2. [c] EFSA's estimated PRI was directly based on the 97.5th percentile of reference body weights (thus, not estimated as AR + 2xCV). [d] With diets low in phytate and low in zinc (e.g., <4 mg/d). [e] Dose-dependent: absorption decreases with increasing dietary zinc, and vice versa. [f] From 4 months onwards in the pregnancy. [g] From a mixed diet. [h] As reported by IOM referring to eight studies in which dietary zinc averaged 10 mg/d. [i] 50%. [j] 30%. [k] 15%. [l] The latter percentages represent zinc administered in aqueous solutions to fasting subjects. Absorption from solid diets is less efficient. At molar ratios >6-10 zinc absorption starts to decline, at ratios >15 absorption is typically <15%.

Table 28.2. Overview of the models used and the basis for the requirement (additional requirement) for zinc for pregnant women

Report	Model used[a]	Absorption (%)[b]	Needed for	Based on
EFSA 2014[31]	Additive (**AR + 1.3** (**PRI + 1.6**)	"Some evidence of up-regulation."	Zinc deposition due to growth in maternal and fetal tissue.	Assumptions: the additional physiological requirement is 0.4 mg/d and absorption is the same as in non-pregnant adults (0.30).
NCM 2014[42] = HCNL 2014[38]	Additive **(RI + 2.0)**	"Some studies show increased absorption, whereas other studies do not."	Zinc deposition due to growth in maternal and fetal tissue.	Assumptions: the total need for the fetus, placenta, and other tissues is ~100 mg, the increase in the physiological requirement is 0.7 mg/d (with adjustment for absorption).
DACH 2015[43]	Additive **(RDA + 3)**	"An increased zinc absorption can be discussed."	-	Assumption: the average requirement of absorbed zinc is 0.8 mg/d for the 2nd half of pregnancy.
IOM 2001[47]	Additive (**AR + 2.7** RDA + 3.0)	"Increases in absorption have been reported to be non-significant."	Zinc deposition due to growth in maternal and fetal tissue.	Assumptions: zinc accumulation in maternal and embryonic/fetal tissues is 0.08, 0.24, 0.53, and 0.73 mg/d for the 1st to 4th quarters of pregnancy, with an absorption of 27%; this results in an additional requirement of 0.3, 0.9, 2.0, and 2.7 mg/d of which the 4th quarter is used for the AR; there is no compensatory change in intestinal excretion of endogenous zinc.
WHO/FAO 2004[50]	Additive *(AR + 2.1* ***RI + 3.1****)*	-	Zinc deposition due to growth in maternal and fetal tissue.	Assumptions: the total amount of zinc retained during pregnancy is 1.5 mmol (~100 mg) and the physiological requirement in the 3rd trimester is twice as high as in non-pregnant women.

Abbreviations: -: Not specified, N/A: not applicable, RE: Retinol Equivalent ; RAE: Retinol Activity Equivalent
The difference is described in the HCNL 2018 report.[4] Note that the unit of expression does not influence the outcome of EFSA's factorial method; therefore, for these DRVs, the RE and RAE are interchangeable.
[a] If applicable: (+ additional requirement in µg RE or RAE/d).
[b] This column presents any information on absorption during pregnancy if provided by the report.

28.2 Explanation of differences between reports

This evaluation focuses on the differences in the method of derivation, the differences in recommended values, and the use of values per trimester in the reports.

The HCNL 2014 report followed the NCM report.

Differences in the method of derivation

All reports used an additive model for the reference values for pregnant women. For the derivation of the additional requirements, the reports took two aspects into consideration: absorption and deposition.

1. Absorption

EFSA referred to three studies on zinc absorption during pregnancy.[159-161] The first study (also referred to by NCM and IOM) from 1997 in 13 US women measured fractional absorption of zinc (FAZ) at five time points[a]: at preconception, at 8-10, 24-26, and 34-36 weeks of gestation, and at 7-9 weeks postpartum.[159] From preconception to 34-36 weeks of gestation, FAZ increased 1.3-fold (not significant). NCM and IOM noted that non-significance may reflect the inadequate power of the study design. The second study from 2007 in 13 UK pregnant women of whom 6 received an iron supplement[b] and 7 a placebo, measured FAZ at three time points[c]: at 16, 24, and 34 weeks of gestation.[160] From 16 to 34 weeks of gestation, FAZ increased ~1.4-fold ($p<0.001$) independent of iron supplementation. The third study from 2012 was a review of published human studies on zinc homeostasis during pregnancy and lactation carried out in different populations worldwide, including the first study described above.[161] From this review, EFSA mentioned besides the 1.3-fold FAZ increase from the first study a 1.5- fold FAZ increase from 10-12 to 34-36 weeks of gestation in 10 Brazilian women[d].

NCM additionally referred to a 21-day confined metabolic study[e] from 1982 in 8 pregnant women from the USA in their 3rd trimester and 10 non-pregnant controls.[162] The pregnant women had a 1.8-fold higher absorption than the non-pregnant controls (not significant).

DACH stated that an increased absorption is “discussed”, but failed to include a literature reference.

EFSA, NCM, and IOM concluded that data was insufficient to base their additional requirements on and assumed that the absorption of non-pregnant adults could be applied to pregnant women.

WHO/FAO used the same levels of bioavailability in pregnancy as for non-pregnant adults: a high bioavailability of 50%, a moderate bioavailability of 30%, and a low bioavailability of 15%.

2. Deposition

All reports referred to the same study from 1987.[163] This study calculated a total zinc requirement for pregnancy of ~100 mg[f], of which ~60% is accumulated in “the conceptus” and ~40% in maternal tissue. Rates of

[a] With respective mean zinc intakes of 10.0 (SD: ±0.4), 10.0 (SD: ±0.7), 11.3 (SD: ±0.6), 12.3 (SD: ±0.9), and 11.2 (SD: ±0.7) mg/d.

[b] The aim of the study was to determine the effect of consuming an iron supplement on zinc status and absorption, as iron supplements are commonly advocated as a prophylactic treatment for iron deficiency during pregnancy but can interfere with the absorption of zinc.

[c] With a mean dietary zinc intake at baseline of 6.8 (SD: ±2.0) and 4.8 (SD: ±2.8) mg/d for the supplemented and placebo group, respectively. On test days, subjects received breakfast, a snack, and one of two lunch options with a total zinc content of 4.4 mg or 3.9 mg.

[d] Ingesting ~9mg/d.

[e] With a mean baseline zinc intake of 17 (SD: ±7) mg/d for the pregnant women and 12 (SD: ±9) mg/d for the controls. Subjects were fed semi-purified liquid diets providing 20 mg/d of zinc.

[f] This was calculated from a total zinc content in pregnancy products of 1,540 µmol (880 µmol in the fetus, 100 µmol in the placenta, 8 µmol in the amniotic fluid, 370 µmol in the uterus, 80 µmol in mammary tissue, and 100 µmol in blood).

zinc accumulation were calculated to be 0.08, 0.24, 0.53, and 0.73 mg/d for the four quarters of pregnancy.

EFSA calculated the average additional physiological requirement: (0.08 mg/d + 0.24 mg/d + 0.53 mg/d + 0.73 mg/d)/4 = 0.395 mg/d (0.4 mg/d after rounding). EFSA applied an absorption of 30%[a] (corresponding to an adjustment factor of 3.33), resulting in an additional requirement of 0.4 mg/d x 3.33 = 1.3 mg/d.

IOM used the additional physiological requirement of the 4th quarter of pregnancy. IOM applied an absorption of 27% (corresponding to an adjustment factor of 3.7), resulting in an additional requirement of 0.73 mg/d x 3.7 = 2.7 mg/d.

NCM stated that "The RIs are based on an increase in the physiological requirement by 0.7 mg/d, with adjustment for absorption. With adjustment for absorption, the additional dietary intake is set to 2 mg/d". The committee finds it unclear what absorption rate NCM used and how exactly they calculated their additional requirement. Therefore, no further consideration will be given to the NCM report.

DACH stated that the average increased intake of absorbed zinc is assumed to be 0.8 mg/d for the 2nd half of pregnancy but failed to include a literature reference. They further noted that even if adaptation mechanisms (i.e., increased absorption) are discussed, an additional intake of 3 mg/d is recommended from 4 months onward in the pregnancy. The committee finds it unclear what the basis is of the assumed increase of absorbed zinc of 0.8 mg/d. Therefore, no further consideration will be given to the DACH report.

WHO/FAO noted that during the third trimester, the physiological requirement of zinc is approximately twice as high as that in women who are not pregnant. The committee finds it unclear how WHO/FAO derived the additional requirements for each trimester. Therefore, no further consideration will be given to the WHO/FAO report.

Differences in the recommended values

With the additive model, differences in the reference values between reports resulted from differences in two aspects.

1. The reference value for non-pregnant women: EFSA used a higher average[b] value for non-pregnant women than IOM.[4]
2. The method of derivation of the additional requirement: EFSA used a lower additional requirement than IOM, as explained above.

[a] Corresponding to the "moderate bioavailability" as defined by WHO/FAO.

[b] Averaged for phytate intake levels.

EFSA's PRI was based on the additional requirement added to the AR of non-pregnant women, multiplied by twice the CV of 10%: (8.2 mg/d + 1.3 mg/d) x 1.2 = 11.4 mg/d.
IOM's PRI was derived in the same way: (6.8 mg/d + 2.7 mg/d) x 1.2 = 11.4 mg/d (11 mg/d after rounding).

Differences between the 1st, 2nd, and 3rd trimester
WHO/FAO presents their PRI values by trimester (in addition to three bioavailability levels).
EFSA noted that the combined estimate of the additional requirement of 0.4 mg/d calculated for the entire pregnancy probably overestimates the requirement in the 1st half of pregnancy and underestimates the requirement in the 2nd half of pregnancy.
IOM presented additional requirements per quarter of the pregnancy but applied the additional requirement for the 4th quarter of pregnancy to the entire pregnancy. IOM noted that the zinc requirement during the 1st quarter of the pregnancy is only minimally higher than the preconception requirement.

28.3 Pregnancy-related health outcomes

EFSA described no pregnancy-related zinc deficiencies and no studies showing intake levels associated with pregnancy-related health outcomes.[31]

28.4 Strength of the scientific basis and conclusions

In 2018, the committee maintained HCNL 2014's reference values for non-pregnant women, based on three arguments (for a detailed description, see background document[4]). First, the committee considered that EFSA may have over-emphasized the role of phytate intake in zinc absorption because the inhibitory effect of phytate on mineral bioavailability depends on many factors. Second, the committee noted that the concept of a percentile of *reference* body weights was unclear and not further explained by EFSA; body weights in the adult populations differ much more than indicated by this 97.5th percentile. Third, the committee considered that the average of EFSA's values was high relative to the other reports, including the NCM values used in the Netherlands at that time, which was undesirable because of the narrow margin between the PRI and the upper level (25 mg/d).

Additive model
There appears to be a scientific consensus on the derivation of the reference values for pregnant women with an additive model.

Conclusion and strength of the additive model
The committee agrees with the method of derivation of the additional requirement for zinc during pregnancy used by EFSA (which is similar to IOM's). Both reports referred to the same study reporting the zinc accumulation in maternal and fetal tissues during the four quarters

of pregnancy. Also, both reports assumed that zinc absorption during pregnancy is not increased, as data was insufficient to base their additional requirements on. IOM's higher additional requirement resulted from applying the zinc accumulation during the 4th quarter to the entire pregnancy, whereas EFSA averaged the zinc accumulation of the four quarters of pregnancy. As the margins between the PRI and the upper level are quite narrow, and studies report increased (albeit non-significantly) absorption during pregnancy, the committee prefers EFSA's approach resulting in a lower additional requirement.

The evidence of EFSA's method of derivation for the additional zinc requirement during pregnancy was based on one review of acceptable quality on zinc accumulation in maternal and fetal tissues.[163] The committee deems the scientific basis for the method of derivation to be acceptable.

Reference values for pregnancy

For the Netherlands, the committee adds EFSA's additional requirement to the Dutch reference values for non-pregnant women, and uses the CV of 15% (as per reference values for non-pregnant women) to calculate the PRI (Table 28.3).

Table 28.3. Reference values for zinc recommended for pregnant women in the Netherlands and reference values for non-pregnant women

DRV, type	Value for pregnant women	Value for non-pregnant women
Average requirement (AR)	7.0 mg/d	*5.7 mg/d*
Population reference intake (PRI)	9.1 mg/d[a]	*7.0 mg/d*

[a] PRI is calculated as ($AR_{non\text{-}pregnant}$ + additional requirement) multiplied by twice the CV: PRI = (5.7 mg/d + 1.3 mg/d) x 1.3.

summary

In total, reference values for 27 vitamins and minerals were evaluated. For most vitamins and minerals (21), the evaluations in this report resulted in the recommendation to adopt EFSA's method of derivation regarding the requirements for pregnancy (Table 29.1).

For four nutrients (folate, copper, calcium, and iodine), the committee preferred a different method of derivation than EFSA's, resulting in a different reference value or a different *type* of reference value. Because for iodine, the difference between EFSA's value and the proposed value was less than 10%, the committee still accepted EFSA's reference value. Regarding calcium, the average requirement and population reference intake was changed into an adequate intake regarding the second half of the pregnancy (≥20 weeks of pregnancy). For the first half of the pregnancy, EFSAs dietary reference values were adopted.

Regarding trivalent chromium, the committee adopts EFSA's conclusion to set no reference value. For fluoride, the committee does not accept EFSA's reference value. This is 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 value in the Netherlands.

For 17 vitamins and minerals (thiamin, riboflavin, niacin, pantothenic acid, vitamin B6, vitamin E, vitamin K1, biotin, choline, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium), the committee's reference values (adequate intake or population reference intake) are similar (have similar values) to those of EFSA. For calcium, the values are similar for the first half of the pregnancy, but not for the second half of the pregnancy. For seven nutrients (vitamin A, folate, vitamin B12, vitamin C, vitamin D, copper, and zinc), the committee's reference values are different than those of EFSA. For six out of these seven nutrients, the difference was due to differences already present in the reference values of non-pregnant women.

Table 29.1. Summary table

Nutrient	Reference value for non-pregnant women					Method of derivation for pregnant women					Reference value for pregnant women	
	Type	Value	Strength of the scientific basis	Origin (report)	If origin is not EFSA, reason:	Model	Addition value	Strength of the scientific basis	Origin (report)	If origin is not EFSA, reason:	Type	Value
Vitamin A	PRI	680 µg RAE/d	Relatively strong	New (HCNL 2018)	Dutch reference weights were used.	Additive	AR +50	Acceptable	EFSA (2015)[5]	-	PRI	750 µg RAE/d
Thiamin	PRI	0.1 mg/MJ (0.9 mg/d)	Relatively strong	EFSA (2016)	-	Additive	PRI per trimester 1e: +0.0 2e: +0.1 3e: +0.2	Acceptable	EFSA (2016)[6]	-	PRI	0.1 mg/MJ (1.0 mg/d) Trimester 1e: 0.9 mg/d 2e: 1.0 mg/d 3e: 1.1 mg/d
Riboflavin	PRI	1.6 mg/d	Relatively strong	EFSA (2017)	-	Additive	AR +0.2	Acceptable	EFSA (2017)[7]	-	PRI	1.9 mg/d
Niacin	PRI	1.6 mg/MJ (14 mg/d)	Relatively strong	EFSA (2014)	-	Additive	PRI per trimester 1e: +1 2e: +2 3e: +3	Acceptable	EFSA (2014)[8]	-	PRI	1.6 mg NE/MJ (16 mg NE/d) Trimester 1st: 15 mg NE/d 2nd: 16 mg NE/d 3rd: 17 mg NE/d
Pantothenic acid	AI	5 mg/d	Weak	EFSA (2014)	-	$AI_{non\text{-}pregnant} = AI_{pregnant}$	-	Weak	EFSA (2014)[9]	-	AI	5 mg/d
Vitamin B6	PRI	1.5 mg/d	Relatively strong	HCNL (2003)	Lower cut-off value for plasma PLP	Additive	AR +0.2	Acceptable	EFSA (2016)[10]	-	PRI	1.8 mg/d
Folate	PRI	300 µg/d	Relatively strong	HCNL (2003)	Lower cut-off values serum and erythrocyte folate levels and association with the prevention of clinical deficiency as opposed to lowering of plasma homo-cysteine concentrations.	Additive	-	Acceptable	HCNL (2003)[40]	The metabolic study as used by the EFSA may overestimate the requirement due to insufficient dose-response information.	AI	400 µg DFE/d

Nutrient	Reference value for non-pregnant women					Method of derivation for pregnant women					Reference value for pregnant women	
	Type	Value	Strength of the scientific basis	Origin (report)	If origin is not EFSA, reason:	Model	Addition value	Strength of the scientific basis	Origin (report)	If origin is not EFSA, reason:	Type	Value
Vitamin B12	PRI	2.8 µg/d	Relatively strong	HCNL (2003)	Prevention of deficiency as opposed to EFSA's higher reference values for which they showed no evidence of providing additional health benefits.	Additive	PRI +0.5	Acceptable	EFSA (2015)[12]	-	PRI	3.3 µg/d
Vitamin C	PRI	75 mg/d	Relatively strong	NCM (2014)	Insufficient evidence for more health benefits.	Additive	PRI +10	Acceptable	EFSA (2013)[13]	-	PRI	85 mg/d
Vitamin D	AI	10 µg/d	Relatively strong	HCNL (2012)	Scientific evidence for EFSA's cut-off value for 25(OH)D not strong for adults <70 years.	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Weak	EFSA (2016)[14]	-	AI	10 µg/d
Vitamin E	AI	11 mg/d	Weak	EFSA (2015)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Strong	EFSA (2015)[15]	-	AI	11 mg/d
Vitamin K1	AI	70 µg/d	Relatively strong	EFSA (2017)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Weak	EFSA (2017)[16]	-	AI	70 µg/d
Biotin	AI	40 µg/d	Weak	EFSA (2014)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Weak	EFSA (2014)[17]	-	AI	40 µg/d
Choline	AI	400 mg/d	Weak	EFSA (2016)	-	Scaling	AI +80	Acceptable	EFSA (2016)[18]	-	AI	480 mg/d
Calcium	PRI, <20wk of pregnancy	18-24 jr: 1,000 mg/d 25-50 jr: 950 mg/d	Relatively strong	EFSA (2015)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Acceptable	EFSA (2015)[19]	-	PRI	18-24 yr: 1,000 mg/d 25-50 yr: 950 mg/d
Calcium	PRI ≥20 wk of pregnancy	18-24 jr: 1,000 mg/d 25-50 jr: 950 mg/d	Relatively strong	EFSA (2015)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Acceptable	HCNL (2021)[2]	-	AI	1,000 mg/d
Chromium	No reference value											
Copper	PRI	0.9 mg/d	Relatively strong	NCM (2014)	Prevention of deficiency and insufficient evidence for more health benefits.	Additive	AR +0.1	Acceptable	IOM (2001)[47]	EFSA's estimate is based on an anticipated increased copper requirement for lactation purposes, which did not convince the committee.	PRI	1.0 mg/d

Nutrient	Reference value for non-pregnant women					Method of derivation for pregnant women					Reference value for pregnant women	
	Type	Value	Strength of the scientific basis	Origin (report)	If origin is not EFSA, reason:	Model	Addition value	Strength of the scientific basis	Origin (report)	If origin is not EFSA, reason:	Type	Value
Fluoride	No reference value											
Iodine	AI	150 µg/d	Relatively strong	EFSA (2014)	-	Total requirement	-	Strong	IOM (2001)[47] <10% EFSA (2014)[23]	Committee values the importance of balance and supple-mentation studies in deriving reference values (but difference with EFSA <10%).	AI	200 µg/d
Iron	PRI	16 mg/d	Relatively strong	EFSA (2015)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Acceptable	EFSA (2015)[24]	-	PRI	16 mg/d
Magnesium	AI	300 mg/d	Relatively strong	EFSA (2015)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Weak	EFSA (2015)[25]	-	AI	300 mg/d
Manganese	AI	3.0 mg/d	Weak	EFSA (2013)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Weak	EFSA (2013)[26]	-	AI	3.0 mg/d
Molybdenum	AI	65 µg/d	Weak	EFSA (2013)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Weak	EFSA (2013)[27]	-	AI	65 µg/d
Phosphorus	AI	550 mg/d	Weak	EFSA (2015)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Acceptable	EFSA (2015)[28]	-	AI	550 mg/d
Potassium	AI	3.5 g/d	Relatively strong	EFSA (2016)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$	-	Acceptable	EFSA (2016)[29]	-	AI	3.5 g/d
Selenium	AI	70 µg/d	Weak	EFSA (2014)	-	$AI_{non\text{-}pregnant}$ = $AI_{pregnant}$		Acceptable	EFSA (2014)[30]		AI	70 µg/d
Zinc	PRI	7 mg/d	Relatively strong	NCM (2014)	EFSA may overemphasize the role of phytate intake in zinc absorption, 'a percentile of *reference* body weights' was unclear and not further explained, and EFSA's value was higher than other reports.	Additive	AR +1.3 PRI + 1.6	Acceptable	EFSA (2014)[31]	-	PRI	9.1 mg/d

Abbreviations: - : not applicable

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annexes

A 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 adequate for virtually all apparently healthy people in a population. The AI is established when the AR (and thus the PRI/RDA) cannot be determined.
AR	Average Requirement	The AR is the level of (nutrient) intake adequate for half of the apparently healthy people in a population, given a normal distribution of requirement.
BMR	Basal Metabolic Rate	BMR is the energy expenditure in a 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 + [2 x CV/100]) times the average requirement.
DACH	Deutschland (Germany), Austria, and Confoederatio Helvetica (Switzerland)	DACH (or D-A-CH) are the German-speaking countries that establish dietary reference values together.
DFE	Dietary folate equivalent	Because the absorption efficiency of synthetic and natural folates varies, dietary folate equivalents (DFE) have been defined by IOM (1998) to take this into account for the derivation and application of Dietary Reference Values (DRVs) for folate: 1 µg DFE = 1 µg food folate = 0.6 µg folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a folic acid supplement taken on an empty stomach. For combined intakes of food folate and folic acid, DFEs can be computed as follows: µg DFE = µg food folate + (µg folic acid x 1.7).
DRV	Dietary Reference Value	A DRV is a quantitative reference value (such as AR, PRI, AI) 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 communicating 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.
HCNL	Health Council of the Netherlands	HCNL is an independent Dutch scientific advisory body tasked with 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 delivering 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 that establishes the DRVs for the USA and Canada. IOM is the former name of the Health and Medical Division program of the National Academy of Medicine (NAM). The NAM is the American nonprofit, non-governmental organization that 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).
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).
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.
P50, P97.5	50th and 97.5th percentiles of a distribution	A percentile (or a centile) is a measure used in statistics that indicates the value below which a given percentage of observations in a group of observations falls. 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 their 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 adequate for virtually all apparently healthy people in a population, on the condition that this value is established based on the average requirement (AR).
RE/RAE	Retinol Equivalent / Retinol Activity Equivalent	The biological value of substances with vitamin A activity is expressed as 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 = 1 µg of retinol = 6 µg of β-carotene = 12 µg of other provitamin A carotenoids. IOM, NCM and DACH use RAE, with 1 µg RAE = 1 µg of retinol = 12 µg of β-carotene = 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.
SEPP1	Selenoprotein P	SEPP1 is considered the most informative biomarker of selenium function based on 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 concentrations level 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 the selenium requirement is met.
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.
WHO/FAO	World Health Organization/Food and Agriculture Organization	WHO and FAO are specialized agencies of the United Nations. WHO is specialized in international public health; FAO in food and agriculture.

B 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 Values	Estimated Average Requirement (EAR)	Recommended Daily Allowance (RDA)	Adequate Intake (AI)
World Health Organization (WHO)/Food and Agricultural Organization (FAO)	-	Estimated Average Requirement (EAR)	Recommended Nutrient Intake (RNI)	Recommended Nutrient Intake (RNI)

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
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