Harmful effects of substances and microorganisms in the diet during pregnancy

No. 2021/26-A5e, The Hague, June 22, 2021

Background document to:
Dietary recommendations for pregnant women
No. 2021/26, The Hague, June 22, 2021

Health Council of the Netherlands

01 introduction

This background document to the advisory report *Dietary recommendations for pregnant women* describes the harmful effects of substances (e.g. nutrients, contaminants, and aroma compounds) and microorganisms in the diet on pregnant women and their offspring. This included checks of whether there were any new scientific developments that ought to be taken into account when deriving the guidelines.

1.1 Scope

This background document addresses the following substances in the diet: acrylamide, alcohol, caffeine, furans, glycyrrhizin (liquorice), hormone-like substances – especially soy isoflavones, herbs and herbal preparations, retinol (vitamin A), and superfoods. The document also addresses probiotics and the following microorganisms: *Listeria monocytogenes*, *Toxoplasma gondii,* and other microorganisms that can cause food-borne infections.

Certain harmful substances have not been reassessed in this background document, namely the harmful substances where the intake level is known to exceed the limit value. These are specifically substances for which tolerable intake limits have been derived based on strong evidence. The 2014 advisory report *Risks of prenatal exposure to substances describes various substances* for which the evidence is strong ('demonstrated'). This applies to PCBs, dioxins, methylmercury, and lead (from lead drinking water pipes) (see Inset 1).[1] These substances are taken into account in the advisory report, based on an advisory report on lead in tap water and a separate background document on exposures from fish.[2-4]

Artificial sweeteners are also not assessed in this document. The European Food Safety Authority (EFSA) is currently re-evaluating the safety of all artificial sweeteners with E numbers that are already on the market.

Inset 1: Health Council of the Netherlands – Advisory report on the risks of prenatal exposure to substances (2014)

Prenatal exposure to PCBs is associated with impaired thyroid function at certain levels of intake. Prenatal exposure to dioxins and dioxin-like PCBs is associated with impaired immune system function. Prenatal exposure to PCBs, dioxin-like substances, lead, and methylmercury has been associated with impaired nervous system function in the unborn child. Finally, prenatal exposure to PCBs is associated with lower birth weight.[1]

1.2 Methodology

As stated in the working method document, the committee is not set up for carrying out stand-alone risk assessments.[5] The committee is therefore relying on existing risk assessments conducted by other Health Council committees and by the EFSA. Where those are not available, the committee uses risk assessments made by other organisations (Table 1).

Table 1 Organisations whose risk assessments have been used by the committee in the background document about harmful substances and microorganisms

Guiding principle
Netherlands
Health Council of the Netherlands (HCNL)
Europe
European Food Safety Authority (EFSA)
Organisations to be used when HCNL and EFSA advisory reports are outdated or unavailable
Netherlands
Netherlands Food and Consumer Product Safety Authority (NVWA)
National Institute for Public Health and the Environment (RIVM)
Europe
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES), France
Food Standards Agency, United Kingdom
Bundesinstitut für Risikobewertung (BfR), Germany
European Commission and European Parliament
United States
Food and Drug Administration (FDA)

Additionally, the committee ascertains whether there have been scientific publications on research into exposure to the specific substance in pregnant women since the risk assessment in question. Appendix A contains an overview of the searches in PubMed. The evaluation of new research is to focus in particular on whether the results provide any grounds for a new risk assessment. This may be the case if there is new research (in humans) that has not yet been taken into account in existing risk assessments and that shows an elevated risk of negative health outcomes from exposure during pregnancy.

Where possible, the committee gives a tabulated summary for each topic of the conclusions of the risk assessments and the data about intake levels.

This background document discusses the scientific basis underpinning dietary recommendations in the advisory report *Dietary recommendations for pregnant women*. At the end of each chapter, the committee draws a conclusion about whether or not the topic should be included in the advisory report *Dietary recommendations for pregnant women*.

The system used is as follows:
Are there any specific known risks in pregnancy?

- Yes → Formulate specific recommendation for pregnant women (i.e. maintain the recommendation if there already was one from the Netherlands Nutrition Centre (Appendix B), or issue a recommendation if there is not one yet. This document is looking primarily at whether we are going to make a recommendation about a particular topic in the advisory report. Exactly what that recommendation looks like is a subsequent step. Maintaining a recommendation does not automatically imply that the advice has to be identical to the existing recommendation from the Netherlands Nutrition Centre).
- No → Do not formulate a recommendation for pregnant women unless there was an existing recommendation from the Netherlands Nutrition Centre about it (Appendix B) AND questions about the matter are a hot

topic among pregnant women. The latter aspect is determined based on the committee's expert judgement.

Formulating recommendations is done in the core document – the advisory report itself – and not in this background document.

1.3 Nutrient supplements, herbs, and other plant products – legislation

There are extensive regulations for nutrient supplements at the European level. Regulating harmful substances in plant products is handled at the national level and may vary from one country to the next.

When regulating nutrient supplements that are treated as foods within the European Union, a distinction is made between nutrient supplements (supplements that contain vitamins and/or minerals) and those containing substances that are neither vitamins nor minerals. The manufacturer, importer, supplier, or distributor is responsible for the safety of supplements.[6]

European legislation specifies what compounds may be used in vitamin and mineral supplements.[7] Additionally, EFSA has defined safe upper intake levels for vitamins and minerals.[8] The European Commission has however not yet set maximum and minimum content levels for vitamins and minerals in nutrient supplements. National legislation is therefore currently in force.[9]

Actions have also been taken at the European level for ingredients in supplements that are not vitamins or minerals to protect consumers from potential health risks. For instance, a list is kept of substances that have been shown to have an undesirable effect on health or are suspected of having such an effect. Substances for which evidence of an undesirable effect is strong should not be added to supplements (or only under certain conditions). Substances for which the undesirable effect is not yet scientifically certain are described in a separate list.[10]

Herbs and other plant products can be used not only in supplements but also in other products, e.g. teas and other foods, herbal extracts, or essential oils. EFSA maintains information on herbs and other plant products that contain substances that could potentially cause health issues when incorporated into a food or supplement.[11]

The regulations in the Netherlands about harmful substances in plant products are laid down in the Commodities Act Decree on Herbal Preparations.[12] This decree under the Commodities Act lays down rules for the use of herbs in foods such as food supplements. Herbs used in the kitchen to add flavour to dishes are not covered by this decree.

The regulations have played a role in selecting the topics covered in this background document. The committee notes that there are no legal regulations in force for some of the herbal preparations that are available (pills, capsules, or other highly concentrated products made from herbs, plants, or their essential oils). These are precisely the supplements in which concentrations of harmful substances can be high. The regulations

on such supplements do not therefore provide sufficient certainty about their use by pregnant women (see also Chapter 8).

02 acrylamide

2.1 Risk assessment summary

Conclusion	Acrylamide can increase the risk of cancer in humans.
Effect size	Not known exactly.
Scientific basis	Experimental animal studies. Studies in humans are not conclusive.
New scientific knowledge about safety	New studies in pregnant women do not give reason for a new risk assessment.
Exceeding the upper level of intake	No upper level of intake has been determined.
Other information	As acrylamide cannot be eliminated from the diet entirely, efforts should be made to lower the levels in foods and to give tips for eating less of acrylamide-rich foods. Acrylamide can cross the placental barrier.[13]

2.2 Explanation

This explanation describes how acrylamide is formed, what the main sources are and what harmful effects have been mentioned in risk assessments. It then discusses new scientific findings about pregnant women and acrylamide intake levels.

2.2.1 Introduction and concepts

Acrylamide can be formed when starchy products are heated without water at above 120 degrees. It is present in the brown colouration of e.g. toast and fried potatoes. Studies using experimental animals have shown that acrylamide is harmful to animals, mainly involving peripheral neuropathy and neoplastic effects. In humans, higher intake levels of the substance may be potentially harmful.[14]

2.2.2 Sources of acrylamide

Products containing acrylamide include coffee, ‘ontbijtkoek’ (a Dutch cake product), cereals, bread (especially toasted), biscuits, crackers, and deep-fried potato products such as chips and crisps.[14,15]

2.2.3 Acrylamide during pregnancy

EFSA risk assessment

In the 2015 EFSA opinion on acrylamide[14], two prospective cohort studies were described that both found a relationship between the acrylamide intake level during pregnancy and reduced foetal growth, in terms of a lower birth weight and a high probability of having a child that is small for gestational age (with a birth weight below the 10th percentile for gestational age). One of the two studies also noted a smaller head circumference.[16,17] In one of the two studies, exposure was determined via a food frequency questionnaire among 50,561 Norwegian women; the odds ratio (OR) for having a child that was small for gestational age was 1.11 (95% CI 1.02-1.21) for women in the highest quartile of acrylamide intake (> 14.5 ng/kcal/day) compared to the lowest quartile (< 8.5 ng/kcal/day) (5,188 cases in total).[16] In the other study, acrylamide exposure was determined based on the levels of acrylamide- and glycidamide[a]-haemoglobin-adducts in the blood of 1,101 women from five different European countries who were pregnant with a single child. For every

[a] Glycidamide is a metabolite of acrylamide.

10 pmol/g increase in acrylamide-haemoglobin-adduct level, the relative risk (RR) was 1.20 (95% CI 1.08-1.33) for having a child that was small for gestational age (72 cases); for glycidamide-haemoglobin-adducts, the RR was 1.36 (95% CI 1.13-1.64).[17]

EFSA added as a caveat to these findings, that the association could also be explained by other, unknown factors and that there is no clear biological mechanism that explains it. Signs of developmental toxicity have been seen in rats and mice (including a slight reduction in body weight gain), but only at levels of exposure where maternal toxicity also occurs. Developmental effects are therefore assumed to be due to maternal toxicity. EFSA concludes that there are still too many uncertainties to make a risk assessment based on the cohort data.[14]

2.2.4 New scientific developments

Since the publication of the EFSA opinion, a French cohort study has been published into acrylamide intake levels during the last trimester of pregnancy and foetal growth (Appendix A).[18] The study covered 1,471 women with a median intake of 19.2 micrograms per day (interquartile range 11.8 to 30.3 micrograms per day). Kadawathagedara et al. found that the intake level of 10 micrograms of acrylamide per day was associated with a greater risk of the child being small for gestational age (OR=1.11; 95% CI 1.03 to 1.21) (177 cases). There was also an association with being shorter at birth (-0.05 cm; 95% CI -0.11 to 0.00) and a tendency towards a lighter birth weight (-9.8 g; 95% CI -21.3 to +1.7). The association with the head circumference was not statistically significant.

This cohort study therefore points in the same direction as the two cohort studies described by EFSA for the greater risk of a child that is small for gestational age, whereas the findings for head circumference and height at birth are contradictory. The committee has some reservations about the findings, as the chance of residual confounding cannot be excluded in cohort studies. There is also no explanation of the mechanism by which acrylamide could affect the child's development. Finally, the *critical effect* (i.e. the first adverse effect of the substance that occurs with increasing exposure) of acrylamide is the elevation of the risk of cancer.

The committee therefore concludes that the new scientific research is not sufficient reason for a new risk assessment into acrylamide intake levels during pregnancy.

2.2.5 Data about acrylamide intake levels during pregnancy

The committee has not found any data about intake levels of acrylamide by pregnant women in the Netherlands or by women of childbearing age. Data from food consumption surveys has however revealed that the median intake of acrylamide by adults in the age range 19 to 69 was 0.3 micrograms per kilogram body weight per day. The 99th exposure percentile (P99) was 1.4 micrograms per kg body weight per day. In the group that was studied, the key source was consumption of chips (32%),

followed by coffee (26%), crisps (11%), and ‘kruidkoek’ (a Dutch cake product) (7%).[15]
This consumption data may possibly be overestimated because the data about acrylamide levels in foods dates from 2005/2006 and actions have been taken in the meantime to reduce acrylamide levels in foods.[15]

2.3 Conclusion of the committee regarding recommendations for pregnant women

Acrylamide is a genotoxic carcinogen. The *critical effect* of acrylamide is the elevation of the risk of cancer. This risk is not specifically related to pregnancy or the foetus and no studies have been carried out into the association between exposure in pregnant women and the risk of cancer in the offspring.
A relationship with pregnancy outcome has also been reported for acrylamide: in the 2015 EFSA opinion statement about acrylamide, two prospective cohort studies were described that both found a relationship between the acrylamide intake level during pregnancy and reduced foetal growth, in terms of a lower birth weight and a higher probability of having a child that is small for gestational age (SGA). A further French cohort study was also published after the EFSA opinion came out. All three cohort studies of pregnant women reported a statistically significant association with an elevated risk of a baby that is small for gestational age (+11%, +11% and +20%) for intake levels that are below the average intake in the Netherlands. EFSA added as a caveat to this finding, that the relationship could also be explained by other, unknown factors and that there is no clear biological mechanism that explains it. EFSA concludes that there are still too many uncertainties to make a risk assessment based on the cohort data.[14]

Based on this state of scientific knowledge, the committee concludes that the advice for pregnant women about acrylamide can be the same as for the population as a whole: keep the exposure as low as reasonably achievable (ALARA). As there may be specific risks from acrylamide for pregnancy, this recommendation will also be included in the advisory report.

03
alcohol

3.1 Risk assessment summary

Conclusion	Alcohol consumption during pregnancy is associated with an elevated risk of unfavourable pregnancy outcomes. Those risks become greater and more severe as alcohol consumption increases. With respect to the lowest intake levels, it is not possible to set an alcohol intake level below which it can be said with certainty that alcohol consumption does not affect the foetus.
Effect size	The nature and scope of the effects depend on the exposure; the risks increase as alcohol consumption increases.
Scientific basis	Cohort studies and experimental animal studies.
New scientific knowledge about the safety of alcohol consumption up to one glass per day.	Recent research has found no relationship or an unfavourable relationship between alcohol intake of up to one glass (10 g ethanol) per day during pregnancy versus little or no alcohol and the risk of miscarriage or a child that is small for gestational age. Evidence for a relationship between alcohol consumption of up to 4 glasses per week and the risk of preterm birth is contradictory. Research into specific variants of genes coding for enzymes involved in metabolising alcohol shows that alcohol consumption of up to one glass a day during pregnancy has a small but potentially unfavourable effect on the cognitive development of the child in terms of lower IQ. Cohort studies showed no significant relationship between alcohol intake of up to one glass a day and cognition but did show a relationship between this level of alcohol intake and less favourable behavioural scores for the child.
Alcohol intake during pregnancy	In 2015, 9% of pregnant women in the Netherlands said they had consumed alcohol during their pregnancy, with those with higher education reporting it more often than those with lower education. Under-reporting cannot be ruled out here.
Other information	The Dutch dietary guidelines 2015 recommend that adults should not drink alcohol, or at any rate no more than one glass a day. That advice is not aimed at either pregnant or breastfeeding women.

3.2 Explanation

This text first discusses the Health Council's advisory report of 2005 on alcohol during pregnancy. Because the greatest uncertainty is about the effects of up to 1 glass a day[a], the committee has limited the evaluation of new scientific developments to that low intake level. The committee also describes the percentage of women who consume alcohol during pregnancy.

3.2.1 Alcohol and pregnancy: Advisory report by the Health Council of the Netherlands, 2005

The Health Council advised against drinking alcohol during pregnancy.[20] The Council concluded in this advisory report that consuming one to two standard units of alcoholic beverages a day (in the Netherlands, 1 standard unit equals 10 grams of ethanol) was likely to adversely affect the child's psychomotor development and that the risks of miscarriage, foetal death, preterm birth, and low birth weight might be increased. The evidence for these relationships became stronger at an average consumption of two to six standard units a day during pregnancy. The evidence for a relationship with alcohol intake of up to one standard unit a day during pregnancy was weaker, e.g. the risks of miscarriage, foetal death, and preterm birth were possibly increased, the spontaneous

[a] The Dutch dietary guidelines 2015 define moderate alcohol consumption as an intake level of up to 15 g alcohol per day (1.5 glasses). The earlier advisory report by the Health Council on alcohol during pregnancy made a distinction between people who drink up to 1 glass a day and those who drink 1 to 2 glasses a day. The Trimbos Institute defines light alcohol intake as 1 to 8 glasses a week and moderate as 8 to 14 glasses a week.[19]

shock movements and reactions of the foetus were possibly affected, and there was a possible negative influence on the child's psychomotor development after birth.
The council concluded that any reduction in alcohol consumption leads to a risk reduction and that it is not possible to set an alcohol intake level below which it can be said with certainty that there is no effect on the foetus and the pregnancy.

3.2.2 New scientific developments

In view of the less conclusive findings in the Health Council's advisory report of 2005 for alcohol consumption of up to one standard unit a day, the committee's evaluations of new scientific developments focus on the lowest intake levels (up to one standard unit a day). The outcome measures it uses are the risk of miscarriage and stillbirth, preterm birth, a child that is small for gestational age, and effects on psychomotor development; this is because there was the clearest evidence of these effects according to the Health Council's recommendation of 2005.
The committee has adopted the risk of a child being small for gestational age rather than the risk of low birth weight as the former is a better measure of growth retardation.
Where possible, the committee expresses alcohol intake in units of grams; however, some studies report alcohol intake in units of glasses. Enquiring about alcohol consumption in units of glasses without additional information gives a fairly inaccurate estimate of exposure. The 'standard unit' of an alcoholic beverage in the Netherlands contains 10 grams of alcohol in principle (i.e. about 12 ml), irrespective of the type of beverage; the standard unit is therefore smaller when the alcohol percentage is higher (250 ml for beer, 100 ml for wine, 35 ml for spirits). The standard units used in Britain (8 grams/unit) are smaller than the Dutch ones, whereas the American ones are larger (14 grams/unit). In addition to these differences between countries in the amount of alcohol per standard unit, more than the standard quantity is often poured into a glass in everyday practice. For example, a large glass of a craft beer often holds 2 standard Dutch glasses, and a large wine glass often holds 2.5 standard units.
Another point to pay attention to in alcohol research is the reference group used. In some studies, that group comprises pregnant women who do not drink at all and in others it comprises pregnant women who drink little to nothing. Because some people do not drink because of health problems, this can also make interpreting the findings more awkward.

Miscarriages and stillbirths

The committee found a systematic review of alcohol and foetal death in terms of miscarriages (death at up to 20 weeks) and stillbirths (death at 20 weeks or more) (Appendix A).[21] In their systematic review of alcohol consumption of up to one glass a week during pregnancy and the risk of stillbirth, Henderson et al. (2007) summarised three cohort studies and one nested case-control study but did not carry out a meta-analysis. Only one of the four studies included correction for potential confounders.

Because this study from 2002 was not included in the Health Council's advice about alcohol in 2005, it is now being described here. Kesmodel et al. (2002) did not find a significant relationship between alcohol intake of 12 to 24 grams per week or 25 to 48 grams per week versus less than 12 grams per week during the first months of pregnancy (median of 103 days) and the risk of foetal death in the first or second trimester (RR=1.3; 95% CI 0.8-2.1). At intake levels of 60 grams a week and above, the risk was significantly higher (RR=2.96; 95% CI 1.37-6.41) when compared to less than 12 grams a week.[21,22]

There are three more recent cohort studies into the relationship between alcohol intake of up to one glass a week and the risk of miscarriages and stillbirths (Appendix A).[23-25] The findings have been summarised in Table 2.

In a Danish cohort, Andersen et al. (2012) found a relationship between alcohol consumption in the first trimester of pregnancy as compared to no alcohol and a higher risk of foetal death (miscarriages and stillbirths combined) that was not statistically significant at a consumption level of 0.5 to 1.5 glasses a week but was significant at 2 to 3.5 glasses a week. In subgroup analyses, significant relationships were only found for miscarriages in the first trimester and between 13 and 16 weeks, but not for later miscarriages (from 16 to 22 weeks) or stillbirths.[23]

In an American study among Afro-American women, Chiodo et al. (2012) analysed the relationship between alcohol intake during the first 20 weeks of pregnancy and the risk of miscarriage (before 20 weeks of the pregnancy has passed) as a linear dose-response relationship. The authors found a significant relationship between intake levels at 28 grams of alcohol per day and the risk of a miscarriage. The average intake level was approximately 34 grams of alcohol per day. It is unclear whether the linearity of the relationship was tested.[25]

In an American cohort study, Aliyu et al. (2008) found no evidence of a relationship between 1-2 glasses per week or 3-4 glasses per week during pregnancy versus no alcohol and the risk of stillbirth (from 20 weeks onwards), whereas an intake level of 5 glasses a week or more was associated with a higher risk of stillbirth, with the risk being greater for early stillbirths (between 22 and 28 weeks; RR=1.8; 95% CI 1.2-1.7) than late ones (from 28 to 44 weeks; RR=1.2; 95% CI 1.0-1.6).[24]

Recent cohort studies have therefore reported no relationship or an unfavourable relationship between alcohol intake of up to one glass a day and the risk of miscarriages and stillbirths. At intake levels of above 1 glass a day, the risk increases as the intake level goes up. The committee concludes that this recent study does not give grounds for a new risk assessment.

Table 2 Cohort studies into the relationship between alcohol intake of up to one glass a day and the risk of miscarriages and stillbirths.

Author and year	Alcohol intake: exposure versus control	N participants	N cases	RR estimate[a] (95% CI)
Kesmodel 2002[22]	12-24 g/week versus < 12 g/week	24,768	116[b]	1.3 (0.8-2.0) for miscarriages in the first trimester 1.2 (0.9-1.7) for miscarriages in the second trimester
Kesmodel 2002[22]	25-48 g/week versus < 12 g/week	24,768	116[b]	0.8 (0.4-1.7) for miscarriages in the first trimester 1.1 (0.7-1.9) for miscarriages in the second trimester
Aliyu 2008[24]	Drinking versus not drinking	665,979	120	1.4 (1.2-1.7) for stillbirths
Aliyu 2008[24]	1-2 glasses/week versus not drinking	665,979	62	1.1 (0.9-1.4) for stillbirths
Aliyu 2008[24]	3-4 glasses/week versus not drinking	665,979	9	1.1 (0.6-2.1) for stillbirths
Aliyu 2008[24]	≥5 glasses/week versus not drinking	665,979	15	1.7 (1.0-3.0) for stillbirths
Andersen 2012[23]	0.5 to 1.5 glasses/week versus 0 glasses a week	91,843	3,595[b]	1.08 (0.99-1.16) for miscarriages and stillbirths
Andersen 2012[23]	2-3.5 glasses/week versus 0 glasses/week	91,843	3,595[b]	1.42 (1.28-1.58) for miscarriages and stillbirths
Andersen 2012[23]	≥4 glasses/week versus 0 glasses/week	91,843	3,595[b]	2.07 (1.75-2.44) for miscarriages and stillbirths
Chiodo 2012[25]	Per 28 g/day[c]	302	23[b]	2.37 (1.25-4.48) for miscarriages

CI: confidence interval; N: number; RR: relative risk.

[a] In the articles used, this may also be an odds ratio (OR) or hazard ratio (HR).

[b] Total number of miscarriages and/or stillbirths in the entire cohort.

[c] The article expresses the risk per ounce of ethanol per day. According to the authors, a standard American glass contains roughly half an ounce of ethanol, i.e. 14 grams.

[d] Measured over the entire pregnancy; scaled from 0-100.

Preterm birth

There are two recent systematic reviews and one pooled analysis looking at the relationship between alcohol intake at a level of up to one glass a day during pregnancy and the risk of preterm birth (< 37 weeks) (Appendix A).[26-28] The findings of Mamluk et al. (2017) and Strandberg-Larsen et al. (2017) have been summarised in Table 3. The committee has disregarded Patra et al. (2011)[26] because the authors' systematic review combined findings of case-control studies with those of cohort studies. This is because the committee prefers systematic reviews of cohort studies (if available), as these are less susceptible to recall bias.[26] Mamluk et al. (2017)[27] have summarised prospective cohort studies and quasi-experimental research into the relationship between alcohol consumption of less than 32 grams per week (which corresponds to three alcoholic beverages a week in the Netherlands) versus no alcohol consumption. The authors did not find a significant relationship with preterm birth. There was considerable heterogeneity in the size of the effect in particular, which was ascribed to a Danish study in which a risk level was found that was clearly higher than in other studies. Strandberg-Larsen et al. (2017)[28] carried out a pooled analysis of the individual data from nine European cohorts. The average alcohol intake level was low: only 7% of the pregnant women drank more than two glasses of alcoholic beverages a week. Strandberg-Larsen et al. found that alcohol consumption of up to four glasses a week was associated with a significantly lower risk of preterm birth and consumption of

seven glasses a week or more with a non-significantly elevated risk. The reference group comprised women who did not drink alcohol. During the study period, the percentage of women who said that they did not drink alcohol during their pregnancy rose by 36 percentage points, from 50% before 2000 to 61% in the period 2000-2004 and 86% in the period 2005-2011. The association was the same in all periods of the study.

The committee did not find any more recent cohort studies into alcohol consumption of up to one glass a day and the risk of preterm birth (Appendix A).

Evidence for a relationship between alcohol consumption of up to four glasses per week and the risk of preterm birth is contradictory: a meta-analysis showed no significant relationship whereas a pooled analysis said that this level of consumption was associated with a lower risk. The committee concludes that these recent studies into alcohol intake at levels of up to one glass a day do not give grounds for a new risk assessment.

Table 3 Results of the meta-analysis by Mamluk et al. (2017) and the pooled analysis by Strandberg-Larsen et al. (2017) of cohort studies into the relationship between alcohol intake of up to one glass a day and the risk of preterm birth.

Type of study	N studies	N participants	N cases	Estimated RR[a] 95% CI	Heterogeneity (I^2), %
Meta-analysis [27]	8	At least 51,295	At least 2,061	1.07 (0.92-1.24) for alcohol consumption of > 0 to ≤ 32 g/week versus none	59
Pooled analysis [28]	9	193,747	8,787	0.92 (0.87-0.98) for alcohol consumption of > 0 to < 1 glass/week versus none. 0.89 (0.81-0.96) for alcohol consumption of 1 to < 2 glasses/week versus none. 0.86 (0.76-0.97) for alcohol consumption of 2 to < 3 glasses/week versus none. 0.66 (0.52-0.84) for alcohol consumption of 3 to < 4 glasses/week versus none. 0.88 (0.66-1.18) for alcohol consumption of 4 to < 5 glasses/week versus none. 0.89 (0.58-1.36) for alcohol consumption of 5 to < 6 glasses/week versus none. 0.84 (0.43-1.61) for alcohol consumption of 6 to < 7 glasses/week versus none. 1.25 (0.87-1.79) for alcohol consumption of ≥ 7 glasses/week versus none.	n/a

CI: confidence interval; N: number; n/a: not applicable, RR: relative risk.

[a] In the articles used, this may also be an odds ratio (OR) or hazard ratio (HR).

Small for gestational age

There are two recent systematic reviews and one pooled analysis into the relationship between low alcohol intake during pregnancy and the risk of a child that is small for gestational age (Appendix A).[26-28] The findings of Mamluk et al. (2017) and Strandberg-Larsen et al. (2017) have been summarised in Table 4. The committee has disregarded Patra et al. (2011)[26] because the authors' systematic review combined case-control studies with cohort studies. This is because the committee prefers systematic reviews of cohort studies (if available), as these are less susceptible to distortion of the results through recall bias.[26]

Mamluk et al. found that low alcohol intake levels of up to 32 grams a week went hand in hand with an 8% higher risk of a child that is small for gestational age as compared to no alcohol consumption. There was heterogeneity here. The results were however largely driven by an American study: 95% of the participants in the meta-analysis came from that single study.[27]

In their pooled analysis, Strandberg-Larsen et al. found that the relative risk of having a child that is small for gestational age was about 1 for consumption of up to four glasses a week and increased from four glasses a week upwards, with the risk being significantly higher from seven glasses a week. The reference group comprised women who did not drink alcohol. The publication does not however give a definition of how much alcohol a single glass contained.

During the inclusion period, the percentage of women who said that they did not drink alcohol during their pregnancy rose by 36 percentage points, from 50% before 2000 to 61% in the period 2000-2004 and 86% in the period 2005-2011. The association with the risk of having a child that is small for gestational age changed over time: before 2000, consuming either two to three or three-plus glasses of alcohol a week was associated with a higher risk, whereas there was no relationship in the later periods. The authors note that it was impossible to distinguish if the bias was attributable to a change of unmeasured confounding factors over time, or to cohort heterogeneity. There were too few cohorts with data over multiple periods for this to be done. They conclude that bias seemed to be in play in their findings, so that it was not possible to make a statement about the safety of a low level of alcohol consumption during pregnancy.[28]

The committee did not find any additional recent cohort studies into alcohol consumption of up to one glass a day and the risk of a child that is small for gestational age (Appendix A).

Evidence for a relationship between alcohol consumption of up to four glasses per week and the risk of having a child that is small for gestational age is therefore contradictory, given that a meta-analysis linked it to an elevated risk whereas a pooled analysis showed there was no significant relationship. From one glass a day upwards, the risk was significantly increased. The committee concludes that this recent study does not give grounds for a new risk assessment.

Table 4 Results of the meta-analysis by Mamluk et al. (2017) and the pooled analysis by Strandberg-Larsen et al. (2017) of cohort studies into the relationship between alcohol intake of up to one glass a day and the risk of having a child that is small for gestational age.

Type of study	N studies	N participants	N cases	Estimated RR[a] 95% CI	Heterogeneity (I^2), %
Meta-analysis [27]	7	at least 15,295	at least 825	1.08 (1.02-1.14) for alcohol consumption of > 0 to ≤ 32 g/week versus none.	59
Pooled analysis [28]	9	193,747	18,544	1.00 (0.96-1.05) for alcohol consumption of > 0 to < 1 glass/week versus none. 0.95 (0.90-1.01) for alcohol consumption of 1 to < 2 glasses/week versus none. 0.97 (0.89-1.06) for alcohol consumption of 2 to < 3 glasses/week versus none. 1.03 (0.91-1.17) for alcohol consumption of 3 to < 4 glasses/week versus none. 1.13 (0.93-1.36) for alcohol consumption of 4 to < 5 glasses/week versus none. 1.12 (0.85-1.48) for alcohol consumption of 5 to < 6 glasses/week versus none. 1.37 (0.93-2.02) for alcohol consumption of 6 to < 7 glasses/week versus none. 1.40 (1.10-1.77) for alcohol consumption of ≥ 7 glasses/week versus none.	n/a

CI: confidence interval; N: number; n/a: not applicable RR: relative risk.

[a] In the articles used, this may also be an odds ratio (OR) or hazard ratio (HR).

Cognition and behaviour

The committee found two recent meta-analyses looking at the relationship between alcohol consumption of up to one glass a day during pregnancy and the child's cognitive development and behaviour (Appendix A).[27,29] Flak et al. (2013) summarised seven studies of cognitive development and three of behaviour. Mamluk et al. (2015) described two studies into cognitive development (one of which was also summarised by Flak et al.) and two looking at behaviour.[27,29] Given that just one study overlapped in the two systematic reviews, the committee has described the results of both. The lack of overlap can be explained by the fact that Mamluk et al. adopted the inclusion criterion that the alcohol intake could be converted into grams of alcohol per week, whereas Flak et al. also included studies based on the number of glasses a week.

Flak et al. categorised alcohol intake levels into alcohol consumption of up to 41 grams a week, up to 82 grams a week, and up to 82 grams a week in which at least some individuals consumed more than 41 grams a week (Table 5). When Flak et al. summarised all the studies, irrespective of quality, there were no significant relationships between alcohol consumption of up to 41 or 82 g/week compared to no alcohol consumption for various neuropsychological outcomes (cognition, behaviour, attention span, visual and motor development, and language skills). Based on three high-quality cohort studies, in which the adjustment for confounders included socioeconomic status, Flak et al. did however find a significant relationship between alcohol consumption of up to 82 g/week (with at least some women consuming more than 41 g/week) and

unfavourable effects on child behaviour. Different questionnaires were however used in each of the three studies.[29]

Table 5 Results of the meta-analysis by Flak et al. (2013) [29] of cohort studies into the relationship between alcohol intake levels of > 0 to 82.2 grams per week versus 0 grams per week and the child's behavioural and cognitive scores.

Outcome	N studies	N participants	Cohen's d (95% CI)	Heterogeneity (I^2), %
Behaviour	3	approx. 11,900[a]	-0.15 (-0.28 to -0.03)	0
Cognition	8	approx. 10,000[b]	0.04[c] (0.00 to 0.08)	0

CI: confidence interval; N: number.

[a] Children aged between 9 months and 5 years.

[b] Children aged between 6 months and 14 years.

[c] Children aged between 9 months and 14 years.

The systematic review by Mamluk et al. summarised the relationship between alcohol consumption of up to 32 g per week and the risks of cognitive impairment, behavioural problems and delayed development.[27] The researchers concluded that most of the research results could not be summarised by meta-analysis because of divergent outcome measures or incompleteness of the published data. There were for example some cohort studies with behavioural outcome measures that did not find evidence of a relationship with internalising problems (RR 1.01; 95% CI 0.98-1.04; two cohort studies) and/or externalising problems (OR 0.97; 95% CI 0.93-1.01; three cohort studies). In contrast, another cohort study looking at behavioural problems and hyperactivity (in the same externalising domain) found a relationship between alcohol consumption of up to 32 grams per week and a higher risk. This latter study could however not be combined in the meta-analysis because of differences in the outcome measures.

The committee found a single more recent cohort study (Appendix A). Eilertsen et al. (2017) examined the relationship between alcohol consumption during pregnancy and the risk of symptoms and diagnosis of ADHD.[30] The authors made no distinctions in the amount of alcohol consumed during pregnancy, however, and this study therefore provides no information about the relationship between alcohol intake levels of up to one glass a week and the risk of symptoms or diagnosis of ADHD. Therefore, the committee has disregarded the study in its further considerations.

Mendelian randomisation study and meconium studies into alcohol and cognition

A publication about the British ALSPAC cohort examined the effect of the mother's genetic variants as an indicator of prenatal alcohol exposure on the child's school performance. This publication gives a Mendelian randomisation estimate that suggests a small but potentially unfavourable effect of small increases in prenatal alcohol exposure on school attainment at ages 14 to 16.[31] Meconium studies point in the same direction.[32-34]

Causality

One limitation of the cohort studies into alcohol intake is that alcohol consumption during breastfeeding and other lifestyle factors of the mother and child can also influence the child's cognitive development and behaviour. Because there was little or no correction for this in the studies mentioned above, it is not possible to say with certainty whether the associations with cognition and behaviour are distorted or actually causal. Research into the effects of certain genetic variants does however point in that direction. In the British ALSPAC cohort, five variants of genes coding for enzymes involved in alcohol metabolism were associated with the children of women who drank one to six glasses a week having a lower IQ at age eight. There was no relationship found for the children of mothers who did not drink alcohol during pregnancy. This finding supports the hypothesis that alcohol consumption during pregnancy is associated with the child having a lower IQ.[35]

3.2.3 Data about alcohol consumption during pregnancy

Data from a nationwide survey in the Netherlands in 2015 shows that the percentage of women who said they consumed alcohol during pregnancy has fallen from 22% in 2007 and 19% in 2010 to 9% in 2015. The percentage of women who said they drank alcohol during pregnancy increased with the level of education. In 2015, just under 8% of less highly educated women said this, as opposed to over 8% of women with average levels of education and 12% of more highly educated women. The difference between the women with medium and higher levels of education was significant. The data was collected through a questionnaire that was completed after the birth. Because the numbers of more highly educated women responding were greater, the percentages are weighted for the level of education. The authors do state that under-reporting is inevitable.[36]

3.3 Conclusion of the committee on recommendations for pregnant women

Recent studies into alcohol consumption during pregnancy have found either no relationship or an unfavourable one between alcohol intake levels of up to one glass a day during pregnancy versus little or no alcohol, for the risk of miscarriage or having a child that is small for gestational age. From one glass a day upwards, both these risks increase with increasing intake.

Evidence for a link between alcohol consumption of up to 4 glasses a week and the risk of preterm birth is contradictory.

Research into specific variants of genes coding for enzymes involved in metabolising alcohol shows that alcohol consumption of up to one glass a day during pregnancy has a small but potentially unfavourable effect on the cognitive development of the child in terms of lower IQ. Cohort studies found no significant relationship between alcohol intake of up to one glass a day and cognition but did find one between this level of alcohol intake and less favourable behavioural scores for the child.

The committee concludes that it is still not possible with the recent studies to set an alcohol intake level below which it can be said with certainty that alcohol consumption does not affect the unborn child. There is no need for a new risk assessment and the recommendation not to consume alcohol during pregnancy is retained.
This recommendation will also be included in the advisory report.

04
caffeine

4.1 Risk assessment summary

Conclusion	Intake levels of more than 200 mg caffeine a day during pregnancy are associated with an elevated risk of growth restriction (foetal growth restriction and children who are small for gestational age) and miscarriage/stillbirth.
Effect size	Risk of growth retardation: OR=1.5 at 200-299 mg/day compared to less than 100 mg/day.[37] The risk of having a child that is small for gestational age is significantly greater at intake levels of between 50 and 200 mg caffeine per day compared to less than 50 mg per day (the OR ranged from 1.09 to 1.18). The risk of having a child that is small for gestational age is greatly increased at intake levels of more than 200 mg/day (the OR ranged from 1.27 to 1.62).[38]
Scientific basis	Cohort study, case-control study.
New scientific knowledge relating to unfavourable effects of caffeine during pregnancy	There are no new insights relating to growth restriction. Research into miscarriages and stillbirths does not justify a new risk assessment either.
Exceeding the upper level of intake	About 40% of pregnant women in the Netherlands had caffeine intake levels of more than 200 mg per day.[39]
Other information	None.

4.2 Explanation

Sources of caffeine, previous risk assessments, new scientific developments, and current caffeine intake levels for pregnant women are discussed below.

4.2.1 Sources of caffeine

Caffeine is found in coffee, energy drinks and shots, tea, iced tea, cola, chocolate and chocolate drinks, guarana drinks, certain types of chewing gum, sweets, food supplements (including sports supplements) and painkillers, as well as water to which caffeine has been added (often along with flavours or vitamins). Coffee and energy drinks and shots are high in caffeine; black and green tea contain around 65% less caffeine than coffee.

4.2.2 Unfavourable effects of caffeine during pregnancy

The Netherlands Nutrition Centre has based its advice on a 2008 advisory report from the UK Food Standards Agency recommending that pregnant women should limit their intake of high-caffeine products to less than 200 mg caffeine per day.[40] This is based on a British cohort study showing that high caffeine intake (more than 200 mg a day) is associated with an elevated risk of foetal growth restriction. Foetal growth restriction was defined as a birth weight below the 10th percentile, corrected for maternal height, weight, ethnicity and parity, and gender of the child.[37] According to the UK Food Standards Agency, there is some further evidence that suggests high caffeine intake levels can cause miscarriages.[40]

4.2.3 More recent guidelines about caffeine

EFSA opinion on caffeine (2015)

The European food safety authority (EFSA) came to a similar conclusion in 2015 to that of the Food Standards Authority in Britain, i.e. that normal intake levels of up to 200 milligrams of caffeine a day during pregnancy are not associated with foetal safety concerns.[41] This conclusion is based

on two large prospective cohort studies that showed a dose-dependent relationship between caffeine intake during pregnancy and the risk of foetal growth restriction and children who are small for gestational age (more than two standard deviations below average or below the 10th percentile).[37,38] The choice of these two outcome measures was driven by previous risk assessments of caffeine carried out by other organisations. This showed that associations with other pregnancy outcomes were less consistent.

The EFSA opinion lists caffeine intake as associated with a higher risk of foetal growth restriction and children that are small for gestational age in the two cohort studies, with no evidence of a threshold. The risk only became clinically relevant, however, above an intake level of 200 mg caffeine per day. The risk of miscarriage or stillbirth was also examined; the effect was deemed to be clinically relevant at above 300 mg caffeine per day. Because this is higher than the previously established figure of 200 mg caffeine a day, EFSA has not addressed that finding further in its conclusions.

In the first study (n = 2,635), the risk of foetal growth restriction was only significantly elevated at intake levels above 200 mg caffeine a day (OR=1.5 at 200-299 mg/day compared to < 100 mg per day). The period of the pregnancy during which caffeine was consumed did not have an effect.[37] In the other study (n = 59,123), the risk of having a child that is small for gestational age was significantly greater at intake levels of between 50 and 200 mg caffeine per day compared to less than 50 mg per day (the OR ranged from 1.09 to 1.18), with the risk increasing sharply at intake levels above 200 mg per day (OR ranging from 1.27 to 1.62). Caffeine consumption was measured over the first five months of the pregnancy.[38]

Furthermore, EFSA describes one RCT in which reducing caffeine intake from about 300 mg a day to about 100 mg a day in the third trimester of pregnancy did not affect foetal growth (either birth weight or risk of being small for gestational age).[42]

The EFSA panel notes here that prospective cohort studies cannot demonstrate causal relationships. However, in the context of the safety assessment, the panel has assumed that it is a causal relationship, given the consistency of the association, the dose-response relationship in both studies, and the plausibility of the explanation of how caffeine could affect foetal development.[41]

4.2.4 New scientific developments regarding the effect of caffeine on growth retardation and miscarriage

The committee searched PubMed for recent articles on the effect of caffeine on the risk of growth retardation and miscarriages (Appendix A). The committee focused on these particular outcome measures as they were central to the risk assessments by EFSA and the UK Food

Standards Agency. ‘Growth retardation’ here refers specifically to delayed fetal growth and children who are born small for gestational age. The risk of low birth weight was not considered as this outcome measure is less significant for the child’s health.

Foetal growth restriction and small for gestational age

Several meta-analyses of the effects of caffeine on growth were published in the year that the EFSA risk assessment came out (2015) and in the years that followed.[43-47]

Jahanfar et al. (2015) summarised RCTs looking at the effect of restricting caffeine intake on perinatal and pregnancy outcomes.[43] Because the authors have described the same RCT for growth retardation as EFSA used in its scientific opinion, that meta-analysis will not be considered further here.[41,42]

In two reviews of reviews, Poole et al. (2017) refer to the systematic review by Rhee et al. (2015), and Grosso et al. (2017) refer to systematic reviews by Rhee et al. (2015) and Chen et al. (2014).[44-46,48] Rhee et al. (2015) and Chen et al. (2014) summarise cohort studies and case-control studies according to the relationship between caffeine intake during pregnancy and the risk of low birth weight. Because the authors did not study the relationship with growth retardation or the child being small for gestational age, the committee has disregarded these systematic reviews.[44,48]

The systematic review by Wikoff et al. (2017) contains a summary of the relationship between intake levels of over 300 mg caffeine a day versus less than 300 mg caffeine a day and the effects on foetal growth. As this cut-off level is above the safe intake limit of 200 mg caffeine per day, this systematic review provides no new information on relationships at around that level. The committee has therefore also disregarded this systematic review.[47]

Two individual cohort studies have been published since the beginning of 2015 looking at the relationship between caffeine intake levels during pregnancy and the risk of the child being small for gestational age.[39,49] Neither cohort study reported a significant relationship (see Table 6). The small numbers of cases in both the Japanese cohort study and the Dutch one may play a role.

Table 6 Cohort studies of the relationship between caffeine intake and the risk of having a child that is small for gestational age

Cohort	n/N caffeine	n/N control	Estimated RR[a] 95% CI
Osaka Maternal and Child Health Study 2015[49]	20/215	15/214	1.52 (0.72-3.18) at a caffeine intake level of 175-257 versus < 175 mg/day
Osaka Maternal and Child Health Study 2015[49]	18/215	15/214	1.19 (0.59-2.55) at a caffeine intake level of 258-372 versus < 175 mg/day
Osaka Maternal and Child Health Study 2015[49]	14/214	15/214	1.11 (0.49-2.52) at a caffeine intake level of ≥ 373 versus < 175 mg/day
Osaka Maternal and Child Health Study 2015[49]	NR[b]	NR	1.05 (0.89-1.25) per 100 mg caffeine/day
Leidsche Rijn Wheezing Illness Study, 2017[39]	NR[c]	NR	0.92 (0.71-1.19) per 100 mg caffeine/day

CI: confidence interval; n/a: not applicable; n/N: number of cases/total number of participants; NR: not reported; RR: relative risk.

[a] In the articles used, this may also be an odds ratio (OR) or hazard ratio (HR).

[b] 7.8% of the 858 children born in total were small for gestational age.

[c] There were 29 cases of children who were small for gestational age among 847 births.

At the end of the advisory process, the committee noted a new review: James (2020).[50] The author of that review concluded that a safe threshold for caffeine intake cannot be determined. This is a narrative review, though, and so it does not provide a systematic overview of the literature. The committee has therefore only used the article to identify cohort studies that it had not previously found. There was one cohort study found by James (2020) that the committee was not yet aware of, the cohort study by Kobayashi et al. (2019).[51] The remaining articles included by James (2020) have already been described in documents used by the committee.

Kobayashi et al. (2019) report results for children who are small for gestational age based on the Japan Environment and Children's Study.[51] They found a statistically significant association with an increased risk of the child being small for gestational age at intake levels of 87 milligrams caffeine per day upwards versus intake levels of below 87 milligrams per day (RR 1.07; 95% CI 1.00-1.15). The committee does not however consider the results of the study suitable for inclusion because of reservations it has about the study's methodology. For example, the committee believes there is a potential for bias in the results from unmeasured confounding, possibly due to smoking. The authors themselves are also not very confident about their results. Moreover, the committee does not deem the study relevant for the Dutch context because the main source of caffeine investigated in the study (green tea) differs substantially from customary caffeine sources in the Netherlands and because the pregnancy characteristics of the population studied are very different from the Dutch situation.

The committee concludes that the new publications do not give grounds for a new risk assessment.

Mendelian randomisation study into foetal growth

In a prospective cohort study, Sasaki et al. (2017) studied whether foetal growth was affected by genetic variation in CYP1A2, an enzyme that breaks down caffeine. Sasaki et al. reports no association between caffeine intake level and average body length and weight at birth (neither in the full cohort, nor in the subgroups of participants by CYP1A2 genotype).[52] Because this is only a cohort study, the committee believes that more research is needed before a conclusion can be drawn.

Miscarriages

There are three systematic reviews on the relationship between caffeine intake levels and the risk of miscarriages or stillbirths.[45-47]

The umbrella reviews by Grosso et al. (2017)[46] and Poole et al. (2017)[45] both describe the systematic review by Li et al. (2015).[53]

The publication by Wikoff et al. (2017)[47] contained a summary of the relationship between intake levels of over 300 mg caffeine a day versus less than 300 mg caffeine a day on the risk of repeated miscarriages. As this cut-off figure is above the safe intake limit of 200 mg caffeine per day, this systematic review provides no new information on relationships at around that level. The committee has therefore disregarded this systematic review.

As well as the systematic review by Li et al. (2015)[53], there are two further systematic reviews by Chen et al. (2015)[54] and Lyngso et al. (2017).[55] Lyngso et al. (2017) summarise three cohort studies with several case-control studies.[55] Two of the three cohort studies are also summarised by Li et al. (2015), along with six other cohort studies.[53] Chen et al. (2015) summarise thirteen cohort studies[54], six of which overlap with Li et al. (2015).

Because the overlap between Chen et al. (2015) and Li et al. (2015) is only partial, the committee has described both systematic reviews below. The committee has also described a more recent cohort study (Table 7).

Chen et al. (2015) used studies that reported caffeine intake levels that were based on reports of either caffeine or coffee consumption, with the caffeine intake in some cases being calculated by Chen et al. (2015) based on the reported coffee consumption. Li et al. (2015) present two meta-analyses, one looking at coffee consumption and the other at caffeine intake, based on the exposures as reported in the original studies. The meta-analysis by Li et al. (2015) for caffeine therefore covers the cohort studies in which the original publications reported findings on caffeine intake; only two of the ten cohort studies in their meta-analysis of caffeine intake also appear in their meta-analysis of coffee consumption, and both studies are relatively small (Fenster 1997 and Savitz 2008). These two meta-analyses by Li et al. are consequently virtually

independent of each other. The findings for coffee consumption and caffeine intake point in the same direction, namely to associations with the risk of miscarriage and stillbirth; they therefore reinforce each other. The findings for caffeine are presented below. The findings for coffee can be found in the background document on foods and dietary patterns.[56]

Chen et al. (2015) found that caffeine intake levels were associated with an elevated risk of miscarriages and stillbirths. In the dose-response analysis, every additional 100 mg caffeine was associated with a 7% higher risk. There was considerable heterogeneity that could be partly explained by the age of the participants: the link was stronger in women aged over 30 versus women aged under 30 (RR=1.23; 95% CI 1.09-1.38 versus RR=1.05; 95% CI 1.04-1.07). The relationship was also stronger in studies in which caffeine intake was determined during pregnancy (RR=1.11 per 100 mg/day; 95% CI 1.05-1.17) than when this was done before the pregnancy (RR=1.02; 95% CI 0.97-1.07). There was, furthermore, evidence of publication bias. Even so, a subgroup analysis that was limited to large cohorts (> 2,500 participants) produced a similar relative risk per 100 mg caffeine: RR=1.06; 95% CI 1.03-1.10).[54]

Li et al. (2015) also found a relationship between caffeine intake and the risk of pregnancy loss (miscarriages and stillbirths). In this systematic review, the relationship was significant for intake levels of 301 mg caffeine per day or more versus zero or very little caffeine. There was moderate heterogeneity that was not investigated further as the analysis of the cohort studies was already a subgroup analysis.[53]

There is one more recent cohort study that found a relationship between daily caffeine intake levels of 100 mg or more early in pregnancy versus less than 100 mg a day and an increased risk of miscarriage. There was no evidence of a dose-response relationship in this study.[57]

The intake levels at which a significantly higher risk of miscarriage was found in the meta-analyses are around 300 mg caffeine a day or above. Over 200 milligrams a day has been flagged as unsafe in previous safety assessments. One exception to this is the Danish cohort study, which did find a higher risk at lower intake levels (100 to 199 mg/day and 200 to 299 mg/day versus less than 100 mg/day), although there was no evidence of a dose-response relationship.[57]

Given the evidence of heterogeneity and publication bias in one of the meta-analyses plus the fact that the meta-analyses only gave the risk as being significantly higher from 300 or 350 mg caffeine per day upwards, the committee concludes that these findings do not justify a new risk assessment.

Table 7 Results of the meta-analyses by Chen et al. (2015) and Li et al. (2015) of cohort studies and the Snart-Gravid cohort study of the relationship between caffeine intake and the risk of miscarriages and stillbirths.

Type of study	N studies	n/N caffeine	n/N control	Estimated RR[a] (95% CI)	Heterogeneity (I^2), %
Meta-analysis [54]	8	NR[b]	NR	1.02 (0.85-1.24) for caffeine intake levels of 50-149 versus < 50 mg per day	28
Meta-analysis [54]	11	NR[b]	NR	1.16 (0.94-1.41) for caffeine intake levels of 150-349 versus < 50 mg per day	50
Meta-analysis [54]	8	NR[b]	NR	1.40 (1.16-1.68) for caffeine intake levels of 350-699 versus < 50 mg per day	19
Meta-analysis [54]	4	NR[b]	NR	1.72 (1.40-2.13) for caffeine intake levels of ≥ 700 versus < 50 mg per day	0
Meta-analysis [54]	13	NR[b]	NR	1.07 (1.03-1.12) per 100 mg caffeine/day	81
Meta-analysis [53]	NR[c]	NR	NR	1.05 (0.91-1.22) for < 150 mg caffeine/day versus non-drinkers and individuals with the lowest intake levels	0
Meta-analysis [53]	NR	NR	NR	1.16 (0.95-1.42) for 150-300 mg caffeine/day versus non-drinkers and individuals with the lowest intake levels	0
Meta-analysis [53]	NR	NR	NR	1.54 (1.21-1.97) for ≥ 301 mg caffeine/day versus non-drinkers and individuals with the lowest intake levels	32
Cohort study [57]	1	93 / 10,417	392 / 66,210	1.62 (1.19-2.22) for caffeine intake levels of 100-199 versus < 100 mg/day	n/a
Cohort study [57]	1	164 / 15,375	392 / 66,210	1.48 (1.03-2.13) for caffeine intake levels of 200-299 versus < 100 mg/day	n/a
Cohort study [57]	1	83 / 8,299	392 / 66,210	1.23 (0.61-2.46) for caffeine intake levels of ≥ 300 versus < 100 mg per day	n/a

CI: confidence interval; n/a: not applicable; n/N: number of cases/total number of participants; NR: not reported; RR: relative risk.

[a] In the articles used, this may also be an odds ratio (OR) or hazard ratio (HR).

[b] 130,456 participants with 3,429 cases.

[c] 8 cohort studies used in the overall analysis.

4.2.5 About caffeine intake levels during pregnancy

In the Leidsche Rijn Dutch Wheezing Illness Study's cohort, 92% of the mothers had used tea, coffee, or both during pregnancy. The average caffeine intake level was 178 mg a day (ranging from 60 to 345 mg/day) with 58% of the caffeine coming from tea. About 60% of the women had caffeine intake levels of below 200 mg per day. Because the average birth weight, child's body length, and incidence of hypertensive disease were comparable with national data, the authors have assumed that the cohort is representative of the Dutch population at large.[39]

In contrast, coffee contributed about 70% of caffeine intake in the Generation R cohort. The average caffeine intake level was not reported in this study.[58] Data from the ABCD cohort showed that the average caffeine intake from caffeinated beverages was 174.9 mg/day. This level of intake applied in particular for women with a Dutch background and a high level of education. Women with non-Dutch origins were more likely to have lower caffeine intake levels.[59]

All three studies show that a substantial proportion of women consume more than 200 mg caffeine a day.

4.3 Conclusion of the committee on recommendations for pregnant women

EFSA has reported that intake levels of more than 200 mg caffeine a day during pregnancy are associated with an elevated risk of growth restriction (foetal growth restriction and children who are born small for gestational age) and with miscarriage/stillbirth. The committee concludes that the recent scientific findings do not give any reason to reject EFSA's risk assessment and therefore intends to retain the recommendations aimed at limiting pregnant women's caffeine intake. The recommendations are further clarified in the advisory report.

Moreover, the committee notes that the Dutch dietary guidelines 2015 advised the general population to replace unfiltered coffee with filtered coffee, as the filter ensures that no fats from the coffee beans get into the drink. These fats increase the risk of cardiovascular disease.[60]

The committee notes that the intake of these coffee fats will be limited if pregnant women drink no more than two cups of coffee per day.

05 furans

5.1 Risk assessment summary

Conclusion	Furans cause liver damage and liver cancer in experimental animals. No studies into the effects of furans during pregnancy were found.
Effect size	Cannot be determined.
Scientific basis	Experimental animal studies and in vitro studies.
New scientific knowledge about the unfavourable effects of furans during pregnancy	None.
Exceeding the upper level of intake	Yes, based on the margin of exposure approach there is reason to be concerned about exposure to furans.
Other information	Only *Health Canada* gives a recommendation about the combination of dioxin and furans: fry less (https://www.canada.ca/en/health-canada/services/healthy-living/your-health/environment/dioxins-furans.html). Given the chemical structure of furans, it is likely that they can diffuse across membranes and therefore across the placenta. (personal communication from Prof. Rietjens)

5.2 Explanation

Furans are formed when food is heated. This applies not only to furan itself but also to related components such as 2-methylfuran and 3-methylfuran. The substances are always present in heated or heat-treated food. The heating process determines how much of various furans is produced and how much is then lost by evaporation, as furans are volatile.[61]

5.2.1 Sources of furans

Children and adolescents mainly ingest furans through cereals and foods made from grains. For adults, the main source is coffee. For babies, furans mostly come from ready-to-eat foods in jars or cans.

5.2.2 Unfavourable effects of furans during pregnancy

EFSA published an opinion on furans in 2017[61], concluding that furans cause liver damage and liver cancer in animal studies. No specific additional risks for pregnant women were described in the European Food Safety Authority report.

5.2.3 New scientific developments

The committee did not find any recent new studies on the effects of furans in pregnant women (Appendix A).

5.2.4 Data about intake levels of furans during pregnancy

For furans EFSA has adopted the margin of exposure approach, which is a method for assessing possible concerns about the safety relating to genotoxicity and carcinogenicity. The margin of exposure is the ratio between the lowest dose at which a small but measurable undesirable effect is observed and the observed level of exposure through the diet in the population in question. If the estimate is based on what is known as

the BMDL10[a] for tumour incidence in experimental animal studies, a value of at least 10,000 means that there is little cause for concern.
The EFSA report gives minimum, median and maximum estimates of the average intake level and the 95th percentile intake level. The median estimate used as the average intake level of furan in adults was between 0.32 and 0.36 micrograms per kilogram body weight per day. When intake levels of methylfurans are included, the estimated intake is 3.5 times higher.
The maximum estimate for the 95th percentile intake level in adults is between 1.18 and 1.22 micrograms per kilogram body weight per day. When intake levels of methylfurans are included, the estimated maximum is almost 4.8 times higher. Although there is still some uncertainty about the carcinogenicity of furans, EFSA's opinion – based on the margin of exposure estimates (i.e. some of the margin of exposure estimates for furans were below 100) – is that current intake levels of furans give cause for health concerns.

5.3 Conclusion of the committee on recommendations for pregnant women

Furans are genotoxic carcinogens. This risk is not specifically related to pregnancy or the foetus and there are no studies of the link between exposure to furans in pregnant women and the risk of cancer in the offspring. There are also no other studies on pregnancy-related risks of furans.
Based on the available scientific evidence, the committee concludes that there is no reason at this time to formulate a recommendation for pregnant women about furans other than what would be recommended to the population as a whole.

[a] BMDL stands for the *benchmark dose lower confidence limit*. The BMDL10 means the lower limit of the confidence interval associated with a dose that causes a 10% increase in cancer incidence compared to the cancer incidence without that exposure.

06 glycyrrhizine

6.1 Risk assessment summary

Conclusion	Glycyrrhizine, a component of liquorice root extract, can increase the blood pressure.
Effect size	For the general population, the safe upper level is 100 mg glycyrrhizine per day (approximately 120 grams of liquorice sweets, depending on the type). For certain risk groups, including pregnant women, the aforementioned safe upper level might not provide sufficient protection. That is why the recommendation for pregnant women is to limit the intake of glycyrrhizine.
Scientific basis	Based on studies in humans (clinical, prospective cohort, and case-control studies), animals, and in vitro.
New scientific knowledge	There have been no new insights that give grounds for a new risk assessment since the EFSA publication in 2008.[62]
Exceeding the upper level of intake	No upper level has been determined for pregnant women. The upper level of 100 mg glycyrrhizine per day for the general population can be attained by eating approximately 120 grams of liquorice sweets (depending on the type) or three to four glasses of liquorice tea (150 ml per cup). Liquorice sweets contain about 83 mg glycyrrhizine per 100 grams and liquorice tea contains an average of 200 mg glycyrrhizine per litre. Dutch people eat an average of 2 kg liquorice a year (5.5 grams per day). Of the 413 women of childbearing age in the 2012-2016 National Food Consumption Survey, 64 ate liquorice on at least one of the two days surveyed. The daily consumption varied from 1 gram to 530 grams. The average over two days varied from 0.5 to 265 grams. The median intake was 9 grams a day.[63]
Other	The British National Health Service has stated that moderate amounts of liquorice sweets and liquorice tea are no problem during pregnancy and gives no recommendation to avoid it. Pregnant women are advised not to use herbal medicinal products based on liquorice root, though. [64]

6.2 Explanation

Sources of glycyrrhizine, the effects of glycyrrhizine, new scientific developments, and current levels of intake are described below.

6.2.1 Introduction and concepts

Glycyrrhizine is a component of liquorice root extract, which can be obtained from the roots of the plant *Glycyrrhiza glabra L.* The substance gives the liquorice taste and is the most important ingredient of liquorice sweets.

6.2.2 Sources of glycyrrhizine

Liquorice root extract can be found in various products, such as liquorice sweets (including salted ones) and liquorice water and certain herbal teas, such as liquorice tea and ‘sterrenmix’ tisane. It can also be found in liquorice-flavoured chewing gum, liquorice-flavoured cough syrup, and cough drops, as well as certain alcoholic drinks (liquorice-flavoured beer, liqueurs such as pastis and sambuca) and tobacco. Liquorice sweets contain about 83 mg glycyrrhizine per 100 g (830 mg/kg), and liquorice tea contains an average of 200 mg glycyrrhizine per litre.[65]
In products with high levels of glycyrrhizine, the labelling (in the Netherlands) must include a mandatory statement in addition to it being included in the list of ingredients. When there is more than 100 mg/kg or 10 mg/l, the label must state that it ‘*contains liquorice*‘. When the level is above 4,000 mg/kg or 50 mg/l, it must state ‘*contains liquorice – people*

with high blood pressure should avoid excessive use'. Alcoholic beverages with more than 1.2% alcohol and more than 300 mg/l glycyrrhizine must also have this statement.[66]

6.2.3 Effects of glycyrrhizine

Upper limit for regular ingestion

Glycyrrhizine increases the blood pressure because it inhibits the conversion of cortisol into cortisone in the kidneys. This effect also occurs in the placenta. This blood pressure elevation is temporary.

In 2008, EFSA adopted the upper limit for regular ingestion of 100 mg glycyrrhizine per day, which was derived in 1991 and evaluated in 2003 by the Scientific Committee on Food. That 2003 evaluation showed that more experimental data about the effects of glycyrrhizine in humans had become available since 1991. This data gave a better scientific basis for the upper level but was still insufficient (small numbers, short duration) for deriving an ADI (Acceptable Daily Intake).

The upper limit applies for the general population. It does not, however, take into account groups with higher sensitivity such as those with high blood pressure, pregnant women and children. EFSA advises that they limit their consumption of glycyrrhizine.[62]

The American National Institute of Health gives a contra-indication during pregnancy for consuming herbal preparations that contain liquorice and eating large amounts of food containing liquorice.[67]

The British National Health Service states that moderate amounts of liquorice and liquorice tea are not a problem during pregnancy; there is no recommendation to completely avoid these products. Pregnant women are advised not to use herbal medicinal products based on liquorice root, though.[64]

6.2.4 New scientific developments

Several new studies on glycyrrhizine have appeared since 2008 (Appendix A). These studies confirm that a high intake of glycyrrhizine (more than 100 mg per day) raises blood pressure but do not give information about the effects of lower dosages in pregnant women. The committee's opinion is that these new articles do not give grounds for a new risk assessment of glycyrrhizine in pregnant women.

Effects on blood pressure

There are several recent meta-analyses of RCTs on the blood pressure elevating effect of glycyrrhizine in seemingly healthy individuals. These meta-analyses confirm the blood pressure elevating effect of glycyrrhizine.[68,69] The dosage in almost all these RCTs was above (sometimes far above) 100 mg per day. No trials were done with pregnant women. It is therefore not possible to deduce from these publications how much lower dosages affect blood pressure in pregnant women.

Finnish studies on the effects of intake during pregnancy

There are several publications about Finnish studies on the relationship between the glycyrrhizine intake during pregnancy and health effects in newborn infants and children at ages eight and twelve. The authors treated a high glycyrrhizine intake level as a model for high exposure to cortisol (stress) during pregnancy.

The first publication by Strandberg et al. from 2001 was a cross-sectional study among 1,006 Finnish women looking at the relationship between the intake of glycyrrhizine and gestational age.[70] Every 500 mg extra intake of glycyrrhizine a week (i.e. an average of 70 mg per day) was associated with the pregnancy being 1.25 days shorter. When the participants were divided into three groups, a high glycyrrhizine intake level versus a low one (500 mg or more versus less than 250 mg/week) was associated with an odds ratio of 2.5 for the risk of the gestational age being less than 38 weeks. There was no relationship with other pregnancy outcomes, birth weight, type of childbirth, or the mother's blood pressure. The Scientific Committee on Food concluded in its risk assessment (2003) that this study does not give definitive evidence that there is a relationship because confounding cannot be excluded and the study did not make a comparison with pregnant women who did not eat liquorice.[71] In addition to glycyrrhizine, Dutch liquorice sweets also contain salt, which can play a role in increased blood pressure. However, the effect of the salt in 200 grams of Dutch liquorice sweets is negligible (approximately 0.4 mmHg) compared with the effect of glycyrrhizine.[72]

A case-control study among 135 Finnish women from the same experimental group (Strandberg et al., 2002) but based on other participants, was not described by the Scientific Committee in 2003 or EFSA in 2008. It showed that a glycyrrhizine intake level of ≥ 500 mg/ week compared to < 500 mg/week was not significantly associated with a risk of preterm birth that was more than twice as high (< 37 weeks; OR=2.15; 95% CI 0.93-4.95). For births before 34 weeks, the risk was higher and statistically significant: OR=3.07 (95% CI 1.17-8.05).[73]

In two follow-up publications, part of the children of the mothers from the first study by Strandberg et al. (2001) were followed up. The participants included for the 2009 publication are a different subset than the participants from the 2017 publication; the number of overlapping participants is unclear. The relationships between high versus low glycyrrhizine intake levels during pregnancy (500 mg or more versus less than 250 mg per week) and the mental and physical development of the children were investigated.

In their publication from 2009 (n = 466), the authors reported an association between a high versus low glycyrrhizine intake during pregnancy (averaging 864 mg/ week (SD 409) and 133 mg/week (SD 57) respectively) and impaired verbal and spatial abilities and narrative

memory and more attention deficit issues, rule-breaking and aggression at age eight.[74]

In their publication from 2017 (n = 378), the authors described high versus low glycyrrhizine intake levels during pregnancy (averaging 845 mg/week (SD 405) and 47 mg/week (SD 75) respectively) as being associated with lower scores in intelligence and memory tests and a higher risk of ADHD problems at age 12. There was also an association with earlier development in height, weight, and puberty in girls.[75] For these new publications too, residual confounding cannot be excluded for these relationships and no comparison was made with pregnant women who do not eat liquorice during pregnancy. In addition to these limitations, all the studies were done by a single research group and the findings have not been replicated.

Hereditary abnormality

There is a case report of a pregnant woman with a familial history of pre-eclampsia who ate too much liquorice (the exact amount was not described) and got such severe pre-eclampsia early in the pregnancy that it had to be terminated. In three subsequent pregnancies, she did not eat liquorice sweets or other liquorice products and developed milder forms of pre-eclampsia. The authors attributed the sensitivity to a hereditary abnormality in an enzyme that plays a role in cortisol metabolism (11betaHSD2).[76] This case report is therefore not representative for pregnant women in general, but might be for pregnant women with an abnormality in the 11betaHSD2 gene (polymorphism).

Herbal preparations containing glycyrrhizine

There are two case-control studies on the association between using herbal preparations with glycyrrhizine during pregnancy and pregnancy outcomes.[77,78]

In a Korean study, they compared women who used drugstore preparations with liquorice between the fourth day and the 25th week of pregnancy to women who did not use herbal preparations. The average liquorice root intake level was 250 mg per day, varying from 1 to 2,104 mg per day. The women were followed prospectively during the pregnancy. The risk of stillbirth was not significantly higher in women who used liquorice preparations than in women who did not use herbal preparations, but the risk estimate was high (OR=7.9; 95% CI 0.9-71.5).[77] The confidence interval in this study was very broad, which limits how meaningful it is. There may also possibly have been insufficient correction for potential confounding.

In an Italian case-control study, the use of herbal preparations was surveyed retrospectively.[78] Fourteen women used liquorice regularly and the risk of impending miscarriage and premature childbirth occurred more often for them than for women who did not use liquorice. The number of women who took liquorice was low, however. The reasons they gave for using liquorice were high blood pressure, digestive problems, and

strengthening the immune system. It is not possible to tell from this study whether the unfavourable pregnancy outcomes are a result of using liquorice; the women with complaints might have been more likely to use herbal preparations and the unfavourable pregnancy outcomes could be a consequence of the underlying causes of their symptoms.

6.2.5 Exceeding the upper level of intake

In the Dutch 2012-2016 National Food Consumption Survey, 64 of the 413 women of childbearing age ate liquorice on at least one of the two days surveyed (4 of those 64 ate liquorice on both days). Daily consumption varied from 1 gram to 530 grams of liquorice. The average over the two days surveyed varied from 0.5 to 265 grams and had a skewed distribution. The median was 9 grams a day, the third quartile was 14 grams a day and the 95th percentile was 30 grams a day, whereas the mean was 17 grams a day.[63]

A food consumption survey in the 1990s showed that Dutch people eat an average of 2 kg liquorice a year (5.5 grams/day).[79]

In the Dutch 2012-2016 National Food Consumption Survey, twelve women used cough drops that may possibly have contained liquorice (the amount varied from 0.5 to 12 grams of cough drops per day), but it is not possible to determine from the data whether the cough drops actually contained liquorice. No information could be reported about the consumption of liquorice tea because tea was widely consumed but it was unclear what proportion of the tea contained liquorice.[63]

The upper level of 100 mg glycyrrhizine per day for the general population can be reached by eating approximately 120 grams of liquorice sweets (depending on the type) or three to four cups of liquorice tea (150 ml per cup). Liquorice sweets contain about 83 mg glycyrrhizine per 100 grams and liquorice tea contains an average of 200 mg glycyrrhizine per litre.[65,80]

6.3 Conclusion of the committee on recommendations for pregnant women

Glycyrrhizine can increase the blood pressure; this effect is temporary. It is general risk. However, it may be of extra concern during pregnancy, because pregnancy is a period of increased sensitivity to elevated blood pressure.

In 2008, EFSA confirmed the existing upper limit of 100 mg glycyrrhizine per day for the general population. This limit value can be reached by eating approximately 120 grams of liquorice sweets (depending on the type) or three to four cups of liquorice tea (150 ml per cup). Individuals with increased sensitivity, such as pregnant women, are advised to limit their intake of glycyrrhizine.

A single cohort study and a case-control study looking at pregnant women in particular were done by the same Finnish research group; these were not included in the 2008 EFSA opinion. They reported a relationship between glycyrrhizine intake levels of 500 mg per week or more (versus less than 500 mg per week) and a higher risk of preterm birth at < 34 weeks, as well as a relationship with an increased risk of impaired mental development and earlier development in height and weight in puberty. The significance of these findings is still uncertain, partly because it is based on a single cohort study.

According to the committee, these recent scientific publications do not give grounds for a new risk assessment and its conclusion is that advice about using glycyrrhizine products such as liquorice sweets and liquorice tea during pregnancy remains important. The recommendation is clarified further in the advisory report.

07
hormone-like substances, particularly soy soflavones

7.1 Risk assessment summary

Conclusion for soy isoflavones	There is too little research to draw a conclusion about the effects of soy isoflavones during pregnancy.
Effect size	Isoflavones have a weak oestrogenic effect.
Scientific basis	Experimental animal studies and in vitro studies.
New scientific knowledge	New studies in pregnant women do not give grounds for a new risk assessment.
Exceeding the upper level of intake	No upper level of intake has been determined at the European level. Intake levels vary from high intakes in people who take supplements with phytoestrogens, vegans and people with South Asian dietary patterns (25 to 100 mg per day) to low intakes in vegetarians (2 to 12 mg per day) and people with an omnivorous dietary pattern (<1 to 2 mg per day). Intake levels of isoflavones in adults are much higher in Asia than in Europe.
Other information:	France has a defined upper level of intake of 1 mg per kg body weight per day (as aglycone isoflavones).

7.2 Explanation

This explanatory note gives a brief description of hormone-like substances in general and soy isoflavones in particular. In the Health Council of the Netherlands advisory report on prenatal exposure to substances (2014), the conclusion was that a great deal is still unknown about hormone-like substances. There may be more substances in food that could have health effects in practice that we do not know about because not enough research has been done yet.[1]

7.2.1 Introduction and concepts

A substance is hormone-like (hormone-disrupting) if it causes an undesirable health effect in the individual or the offspring by affecting the endocrine system. A large number of substances, both natural and synthetic, can have hormone-like effects. Sometimes these effects occur only long after exposure, e.g. in adulthood or in later generations.[1] Substances that have been shown to have a hormone-like effect are banned by legislation or their use is restricted.

7.2.2 Sources of hormone-like substances

PCBs

In the previous Health Council of the Netherlands advisory report from 2014 on prenatal exposure to substances, PCBs were determined to have a hormone-like effect: they influence the thyroid gland at certain levels of intake.[1] Exposure to PCBs has decreased significantly in the Netherlands in recent decades, but because these substances have long half-lives – both in humans and in nature – there are still concerns about the extent of prenatal exposure (and exposure through breastfeeding). Effects can still occur at the current exposure levels. As described in the introduction, the committee has not re-evaluated the hormone-like effect of PCBs because it is already strongly substantiated. It is however worth mentioning here that EFSA published a new risk analysis in 2018 about dioxin and dioxin-like PCBs in which the tolerable weekly intake (TWI) was made seven times as strict.[81] Because the intake of these types of PCBs can only be

reduced to a limited extent through specific dietary recommendations, the ALARA principle is used (as low as reasonably achievable). However, for fish species, the committee addresses differences between species, because consumption of some species may cause a high exposure.[3] Therefore, the committee evaluated fish species based on the levels of dioxin and dioxin-like PCBs (and also based on the levels of methylmercury and PFAS), which is described in a separate background document.[4]

Isoflavones

Isoflavones are substances that can have a hormonal effect. They can be found in legumes, linseed, and some other vegetables and cereals. Soya in particular contains a lot of isoflavones.[82]

Soya contains the isoflavones daidzein, genistein and glycitein, which can have a hormonal effect. The isoflavones in soya beans are bound to a sugar molecule and so are known as glycoside isoflavones. Digestion or fermentation of soya beans and soya products makes the sugar molecule split off, resulting in an aglycone isoflavone: daidzein, genistein or glycitein. These substances are absorbed in the intestines. The amount of isoflavones normally is expressed in the aglycone form. The amounts and types of isoflavones vary between soya products. In the intestines, daidzein is broken down by bacteria into other isoflavones (equol and *O*-desmethylangolensin or *O*-DMA) that can be absorbed in the intestines. Products with high concentrations of isoflavones are miso, mature soya beans and tempeh. Soya milk and meat substitutes made of soya generally contain less isoflavones. However, the amount of isoflavones in soya products can vary greatly between brands and different batches of the same brand, making it hard to say how exactly what amount of isoflavones a product contains.[83,84]

The text below will specifically address risk assessments about intake levels of soy isoflavones during pregnancy.

7.2.3 Effects of soy isoflavones during pregnancy

The relevance of Asian research to Western countries

Asia has a long tradition of using soya products. The composition of soya products varies between Asian and Western countries because the preparation methods and ingredients are different. In Asia, soya is often used as tofu, tempeh, or other unprocessed forms, in contrast to Western countries where supplements with soya or other products with added soya proteins are common. The consumption pattern of soya products throughout the lifecycle is also different. In Asia, people are exposed to soya their entire life except in the neonatal period during which they are breastfed. In Western countries, soya exposure can be relatively high in the neonatal period compared to the rest of someone's life because a proportion of children are given formula milk containing soya.[85] Despite the differences in soya intake, the intake levels of soy isoflavones are

higher in Asian countries than in Western countries. Whereas isoflavone intake levels in Asian countries vary between 15 and 50 mg/day, the average intake is below 2 mg/day in Western countries.[83,84]

EFSA

Isoflavones are listed in an EFSA report from 2012 about substances that occur naturally in food and may possibly have an undesirable health effect. However, no conclusions can be drawn from the report because EFSA has not made any statement about potential risks and the quality of the report's substantiation.[86] EFSA also published an advisory report in 2015 about isoflavone consumption by menopausal women. It concludes that it was not possible to determine a single guideline value or upper level of intake based purely on health effects. Instead, EFSA proposes basing the guideline value on the dose of isoflavones and the intervention duration used in the intervention studies in which no effects were found on the mammary glands, uterus, and thyroid gland.[87] EFSA published a report in 2014 about the composition of baby and infant formula.[88] One of the panel's conclusion is that concentrations of isoflavones should be kept as low as possible. The statement is based on the findings of the American Academy of Pediatrics Committee on Nutrition[89] and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition.[90] The assessment by both these committees is that no conclusions can be drawn about the possible negative effects of isoflavones in formula milk. However, the ESPGHAN committee advises limiting the amount of isoflavones in formula as a precaution. One of the studies they summarise shows that isoflavones can pass the placenta.[91] This finding has recently been reproduced.[92] The conclusions drawn by the AAP and ESPGHAN were still deemed to be valid in the recent narrative review by Testa et al. (2018).[93] That same review added that a subgroup of babies with congenital hypothyroidism are extra sensitive to isoflavones. This condition cannot be recognised beforehand.[93] The committee notes that the significance of this finding for exposure during pregnancy is unclear.

Risk evaluations in France

In 2005, AFSSA (the predecessor of ANSES – *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*) in France defined a safe upper level of intake of 1 mg per kg body weight per day (as aglycone isoflavones) for the general population, based on an analysis of the safety of soy isoflavones. The reason for this is that scientific research has confirmed that soy isoflavones are safe at normal intake levels. AFSSA has noted that patients with hypothyroidism and women with oestrogen-dependent breast cancer may be at risk from high intake levels of soy isoflavones. AFSSA has also noted that studies in experimental animals show that regular high exposure during pregnancy or after birth can be associated with changes in the development and maturation of the genitalia and sometimes also in fertility.[94]

In a 2011 evaluation of this recommendation, ANSES concluded that new scientific findings in animals and humans (from Western countries) support the upper level of intake. These are specifically studies in experimental animals looking at growth, endocrine development, the onset of puberty, and thyroid function. ANSES has expressed concern in particular about infants who are fed solely with soya-based formula. The intake level for 4-month-old babies who are fed only soya milk can be as high as 4 to 9 milligrams of isoflavones per kilogram of body weight per day.[95]
In 2016, ANSES published an opinion in which they stated that the risk of negative effects from genistein in children aged under three cannot be excluded and they therefore advise limiting the intake of genistein in this age group. They base this statement on the lowest observed adverse effect level (LOAEL) of 35 mg/kg body weight per day in rats.[96]

This French recommendation has not been followed up in countries such as Germany and Great Britain or at the European level.

7.2.4 New scientific developments

The committee searched for observational studies published since 2008[a] on the association of soy isoflavone intake during pregnancy with health outcomes in the offspring (Appendix A). The committee found two cohort studies and two case-control studies.[97-100] plus a meta-analysis in women with vegetarian diets during pregnancy.[101]

The British cohort studies investigated the relationship between exposure to phytoestrogens during pregnancy and the age of menarche among 367 mother-daughter pairs. Marks et al. (2017) found no relationship for genistein, daidzein or equol. There was however a link between high *O*-DMA exposure during pregnancy and early menarche in the offspring (OR=1.89; 95% CI 1.04-3.42).[97]

An American case-control study investigated the relationship between the intake of phytoestrogens during pregnancy and the risk of hypospadias.[98] In hypospadias, the outlet of the urethra is on the underside of the penis instead of at the very tip. The study included 1,250 women with a son with hypospadias and 3,188 women who had a son without hypospadias in the same period or at the same childbirth centre. After correcting for a large number of confounders, the analyses showed that high intake levels of genistein (> 41.8 micrograms per day) were associated with a 40% lower risk of having a child with hypospadias compared to an intake level of 10.8 to 41.7 micrograms per day (OR=0.6; 95% CI 0.4-0.9). The associations between a high intake level (≥ P90) of daidzein, glycitein, and total isoflavones compared to intakes in the range of the 10th to 90th percentile were not significant. The study suggests that there is no

[a] The date is based on the fact that the most recent observational studies in the 2011 ANSES report were published in 2008.

negative relationship between high intake levels of isoflavones and the risk of hypospadias.

The committee is furthermore aware of a recent Japanese cohort study that investigated the risk of isoflavone intake during early pregnancy and the outcome of hypospadias in baby boys.[100] Using food frequency questionnaires, they estimated the daily intake of genistein as a proxy for the total intake level of isoflavones. The study population consisted of 41,578 mothers who gave birth to a son; 51 of the babies had hypospadias. When those below the 10th percentile with the lowest intake (median intake per day of 3.3 milligrams genistein; 5.1 grams tofu, 0 grams natto) were compared to the 11th to 89th intake percentiles (median intake per day of 15.3 milligrams genistein; 20.5 grams tofu; 10.3 grams natto), it showed that mothers with low intake levels of genistein had a higher risk of a son with hypospadias (corrected OR= 2.8; 95% CI 1.4-5.8). Relationships pointing in the same direction were found for the intake of natto and tofu (soya products), although they were not statistically significant. There was no difference between the group with high intake (≥ 90th percentile; median intake per day of 45.3 milligrams genistein; 40.7 grams tofu, 32 grams natto) and the middle group. This study too suggests that there is no unfavourable association.

The committee also looked more broadly at whether women with vegetarian diets during pregnancy may possibly have had a higher risk of giving birth to a boy with hypospadias. The assumption here is that women with vegetarian diets consume more soya products than women with omnivorous diets. The committee also found a systematic review with a meta-analysis of seven case-control studies and one cohort study.[101] Two studies were done among Asian populations and six studies among a European or American population. This review covered a total of 3,111 patients with hypospadias. Five of these studies found no significant relationship between a vegetarian diet during pregnancy and the risk of hypospadias in baby boys. Three studies found an increased risk of hypospadias in baby boys with mothers who had eaten a vegetarian diet during pregnancy. The combined risk estimate was not statistically significant. OR=1.39 (95% CI 0.88-2.11). There was strong evidence for heterogeneity (I^2 74%) but that heterogeneity could not be explained in subgroup analyses and sensitivity analyses.

Finally, there is a small Malaysian case-control study that investigated the relationship between genistein intake during pregnancy and the risk of pre-eclampsia.[99] In the study, 32 women with pre-eclampsia were compared against 32 healthy pregnant women who were matched in terms of the number of children and the duration of the pregnancy. In analyses that were not corrected for potential confounders, high intake levels of genistein were associated with a significantly lower risk compared to a low intake. However, after correction for a family history of pre-eclampsia, the link was no longer significant.

The committee concludes that the new studies do not give grounds for a new risk assessment.

7.2.5 Data about soy isoflavone intake levels

Little is known about the intake of soy isoflavones by pregnant women. In 2004, the National Institute for Public Health and the Environment (RIVM) summarised the intake level of soy isoflavones for adults in Western countries.[102] The groups with the highest isoflavone intake levels are adults who take supplements with phytoestrogens (phytoestrogens contain isoflavones and lignans) (about 40 to 100 milligrams per day), vegans (about 75 milligrams per day) and people who have a traditional South Asian dietary pattern (about 25 to 100 milligrams per day). Intake levels for people with omnivorous or vegetarian dietary patterns are significantly lower (approximately < 1 to 2 milligrams per day and 3 to 12 milligrams per day respectively).

7.3 Conclusion of the committee on recommendations for pregnant women

Isoflavones have a weak oestrogenic effect and can pass the placenta. EFSA recommends keeping intake levels of isoflavones as low as possible for infants as a precaution. No upper level of intake has been determined at the European level for the general population or for pregnant women specifically.

France has derived an upper level of 1 milligram per kilogram body weight per day at the national level. This was based in particular on studies in experimental animals into exposure during pregnancy and subsequent growth, endocrine development, onset of puberty, and thyroid function.
A British cohort study showed a relationship between high *O*-DMA exposure during pregnancy and early menarche in the offspring. Additionally, in American case-control research and Japanese cohort studies, no unfavourable relationship was found between exposure to isoflavones during pregnancy (at levels up to a median intake of 45 milligrams per day) and the risk of hypospadias in baby boys. Assuming that mothers with vegetarian dietary patterns consume more isoflavones than women with omnivorous diets, the committee included a meta-analysis of cohort studies and case-control research into vegetarian dietary patterns during pregnancy in the assessment. That study also found no significantly increased risk of hypospadias in the offspring.
A small Malaysian study found no relationship with the risk of pre-eclampsia after exposure to isoflavones.
Little data is available about the intake levels of soya products during pregnancy in the Netherlands. The most recent publication is from 2004. It showed that isoflavone intake levels in Dutch people with omnivorous or vegetarian dietary patterns is very low (1 to 12 milligrams per day). Intake levels in cases of vegan dietary patterns can be higher. The same publication shows that people with vegan dietary patterns may in fact consume up to about 75 milligrams of isoflavones a day.

Overall, the committee concludes that it is not necessary at the moment to formulate recommendations about soy isoflavones for pregnant women in the Netherlands. This is because the intake remains well below 1 milligram per kilogram body weight per day in an omnivorous or vegetarian dietary pattern. However, specifically for women who use a lot of soya products – such as those with a vegan dietary pattern – the intake level can exceed the upper level of intake of 1 milligram per kilogram body weight per day used by ANSES. The committee advises such women to not exceed the upper level of intake during pregnancy as a precaution. This recommendation will be clarified further in the advisory report.

08
herbs, herbal teas and herbal preparations

8.1 Risk assessment summary

Conclusion	It is not known whether using herbal preparations and herbal teas presents specific risks during pregnancy. Allylalkoxybenzenes are genotoxic carcinogens. Pyrrolizidine alkaloids are also genotoxic carcinogens that can additionally cause severe acute, short-term effects in humans. Certain herbs and plants, including some that are used in herbal teas, contain these substances. Herbal preparations (pills, capsules or other highly concentrated products) made from herbs or plants or their essential oils can contain relatively high dosages.
Effect size	Cannot be determined.
Scientific basis	Experimental animal and in vitro studies.
New scientific knowledge about the safety of herbal preparations during pregnancy	None.
Exceeding the upper level of intake	No safe upper level of intake can be determined for genotoxic carcinogens. The risk can be assessed based on the margin of exposure, the gap between the dose that causes cancer in experimental animals and the level of intake. When using large quantities of herbs with allylalkoxybenzenes and/or moderate to large quantities of teas containing these herbs and when using herbal preparations (pills, capsules or other highly concentrated products) made from these herbs or their essential oils, the margin is too low and there is cause for concern.
Other information	None.

8.2 Explanation

In the following section, the committee discusses the plant toxins in the kitchen herbs aniseed, tarragon, fennel, basil, allspice, nutmeg, cinnamon, sassafras, dong quai, mace and pepper.

The unfavourable effects of these substances, new scientific developments regarding effects during pregnancy, and current levels of intake are described below. The effects of plant toxins that can be found in ordinary tea and herbal teas are also discussed.

People use herbal preparations because they believe them to be good for their health, but not all such supplements have been investigated. Moreover, there are often concerns about the safety and origins of these types of preparations. Additionally, they can also have unintended traces of other plants that may or may not be harmful. There is no direct relationship here with risks that apply specifically during pregnancy, so the committee has only evaluated these types of preparations to a limited extent.[103]

8.2.1 Introduction and concepts

Plant toxins (phytotoxins) are found naturally in some plants, for example as flavourings. The kitchen herbs aniseed, tarragon, fennel, basil, allspice, nutmeg, cinnamon, sassafras, dong quai, mace, and pepper contain the allylalkoxybenzenes estragole, safrole, methyl eugenol, and myristicin.[104] These substances are flavourings.

All sorts of plants naturally contain pyrrolizidine alkaloids, which are substances that protect the plant against natural enemies. Herbal preparations and herbal teas made from these plants also contain these substances. Plants that contain pyrrolizidine alkaloids can inadvertently be

incorporated into our food. They can for instance end up in black and green tea if certain herbs are included along with the tea leaves during harvesting.[105]

8.2.2 Sources of allylalkoxybenzenes and pyrrolizidine alkaloids

Allylalkoxybenzenes

Allylalkoxybenzenes can be found in certain herbs. There are various allylalkoxybenzenes: estragole (which can be found inter alia in aniseed, tarragon, fennel, and basil), methyl eugenol (inter alia in allspice, basil, nutmeg and tarragon), safrole (inter alia in nutmeg, cinnamon, sassafras, and dong quai) and myristicin (inter alia in nutmeg, mace, aniseed, pepper, and sassafras).

The level of allylalkoxybenzenes can vary considerably from one herb or spice to another, due to the differences in variety, growing conditions, and processing. Herbs in powder form contain lower amounts of flavourings than the fresh or frozen forms. This means that they contain less of the allylalkoxybenzenes.

The European Union has set maximum permitted levels of estragole, methyl eugenol, and safrole for addition to some foods; these substances may no longer be added to the majority of these foods. This has been set in the European regulation on the use of flavourings in foods.[7, 10] In the EU, estragole, methyl eugenol, and safrole may not be added as flavourings in a concentrated form. The herbs they can be found in (such as cinnamon, nutmeg, and aniseed) may be added to foods. The amount is then subject to a maximum depending on the risks of the substance concerned and varies per substance from 1 mg/kg to 60 mg/kg.[106]

Pyrrolizidine alkaloids

There are more than 500 different pyrrolizidine alkaloids that can be found in over 6,000 plant species. Herbal preparations and herbal teas made from these plants also contain these substances. Plants that contain pyrrolizidine alkaloids can inadvertently be incorporated into our food as well. They can for instance end up in salads or in black and green tea if certain herbs are plucked too during harvesting. The substances can also be found in honey because bees use pollen from plants that produce pyrrolizidine alkaloids.[105]

There are no maximum levels set at the European level for pyrrolizidine alkaloids in foods. The Dutch Commodities Act does set legal reference values for pyrrolizidine alkaloids in herbal preparations and herbal teas. Appendix 1 of the Commodities Act Decree on herbal preparations states which plant species contain potentially toxic pyrrolizidine alkaloids. Examples are coltsfoot, comfrey, and chickweed. Herbal teas made from these plants basically always contain excessively high levels of pyrrolizidine alkaloids. Herbal teas from such plants that exceed the legal standard for pyrrolizidine alkaloids may not be sold.

No statutory limits for pyrrolizidine alkaloids have been set for other foods.[12,107]

8.2.3 Effects of allylalkoxybenzenes and pyrrolizidine alkaloids

Allylalkoxybenzenes

Animal studies and in vitro studies in particular show that pure estragole, methyl eugenol, and safrole are genotoxic and can therefore cause cancer. There is also evidence that these substances can cause cancer in humans.[108]

Estragole, methyl eugenol, safrole, and myristicin can have hallucinogenic effects; estragole, methyl eugenol, and safrole can cause liver damage at regular high doses.

There has been very little research in humans on the effect of eating these substances in the form of herbs. That is why it is still unclear whether, and if so to what extent, these substances are harmful to people who eat these herbs or drink herbal tea.

Pyrrolizidine alkaloids

Intake of pyrrolizidine alkaloids in high amounts can cause acute liver damage (as well as damage to the lungs). Several cases of poisoning by herbal teas and supplements have been described, as have various outbreaks caused by cereals that were contaminated with weeds containing pyrrolizidine alkaloids. There have even been fatalities. Poisonings also include cases of liver damage in the foetus or the newborn child after ingestion of herbal preparations containing pyrrolizidine alkaloids by the mother during pregnancy.[105]

8.2.4 New scientific developments

Allylalkoxybenzenes

The committee did not find any new studies on the effects of allylalkoxybenzenes in pregnant women since the EFSA publication of 2009 (Appendix A). The Netherlands Food and Consumer Product Safety Authority (NVWA) has recently published a risk assessment with advice about breastfeeding teas that contain fennel, aniseed, and/or caraway.[109,110] Breastfeeding teas are recommended by manufacturers because they are said to promote milk production and/or relieve the baby's intestinal cramps. Women are often recommended to drink one to four cups of breastfeeding tea from the end of the pregnancy and throughout the entire lactation period. The composition of such teas can vary widely, usually containing fennel and/or aniseed and sometimes also caraway. These herbs contain estragole. The NVWA bases their risk assessment on the use of four cups of breastfeeding tea with aniseed, fennel, and/or caraway at the end of the pregnancy and during the lactation period. Based on this risk assessment, a health risk from estragole cannot be completely excluded for babies but the health risks for women seem acceptable, especially if fewer than four cups of tea (of 250 ml) are consumed.

The NVWA concludes in the risk assessment that daily use of this breastfeeding tea late in pregnancy and while breastfeeding should be discouraged as a precaution.[109] The committee has adopted that conclusion. The advice that the NVWA has given on that basis is as

follows: discourage the use of breastfeeding teas containing fennel and aniseed for women who are breastfeeding or pregnant. Based on the risk assessment presented, the committee considers it particularly important to limit levels of intake during pregnancy and in any case to not exceed four cups a day.

Pyrrolizidine alkaloids

The committee did not find any new studies on the effects of pyrrolizidine alkaloids in pregnant women since the EFSA publication on pyrrolizidine alkaloids of 2011 (Appendix A).

8.2.5 Data about the normal level of intake

Allylalkoxybenzenes

The committee is not aware of data about the intake of allylalkoxybenzenes as a group. However, there are reports by the Scientific Committee on Food from 2001 giving estimates of intake levels of the individual substances estragole, methyl eugenol, and safrole. These substances have a genotoxic effect, so no safe upper level of intake can be determined to compare these levels against.

The estimated average estragole intake for consumers was 4.3 mg per day and the 97.5% percentile for the daily intake was 8.7 mg. It was not possible to estimate the relative shares to the overall intake of the intake from foods with herbs and spices or from added flavourings.[111] The average intake of methyl eugenol was estimated at 13 mg per day (0.19 mg per kg body weight per day) and the 97.5% percentile of daily intake was 26 mg per day (0.53 mg per kg body weight per day).[112]

Intake levels of safrole can only be estimated globally and are around 0.3 mg per day with the 97.5% percentile at 0.5 mg per day.[113]

After the Scientific Committee on Food produced the above-mentioned intake estimates, EU legislation limiting the use of estragole, methyl eugenol, and safrole as additives came into force.[7] As a result, intake levels may now be lower than these estimates.

Pyrrolizidine alkaloids

In 2016, EFSA estimated pyrrolizidine alkaloid intake levels based on the concentrations in green and black tea, herbal teas and other herbal preparations, and honey. In adults, the product groups *'tea, unspecified'* and *'black tea, infusion'* were the largest sources of pyrrolizidine alkaloid intake. Estimates of the average chronic exposure to pyrrolizidine alkaloids vary from 31.1 to 41.8 ng/kg body weight per day (lower level to upper level) in adults. In the group with high exposure levels, it was 87.7 to 127.2 nanograms per kg body weight per day (lower level to upper level).[105]

For the assessment of the exposure to pyrrolizidine alkaloids, EFSA uses a margin of exposure approach, as is customary for genotoxic

carcinogens. In 2017, EFSA concluded that there is a possible concern for human health related to the exposure to pyrrolizidine alkaloids, in particular for frequent and high consumers of tea and herbal infusions.[106]
Additionally, EFSA uses a criterion based on the lowest known dose for acute, short-term toxicity, namely 2 mg per kg body weight per day.[114,115] The risks associated with acute or short-term exposure to teas, herbal teas, honey and pollen preparations is low. Herbal preparations are a different case, however, particularly those based on plants producing pyrrolizidine alkaloids. Using them can be accompanied by levels of exposure that can cause severe acute, short-term effects in humans.[115]

8.3 Conclusion of the committee on recommendations for pregnant women

Allylalkoxybenzenes and pyrrolizidine alkaloids are classed as genotoxic carcinogens. This implies that no safe level of intake can be determined for these substances. These substances can also cause liver damage at high doses. Pyrrolizidine alkaloid poisoning cases have been described in which the foetus or neonate had liver damage. There is no further research available about specific risks in pregnant women.
Allylalkoxybenzenes can be found in herbs (aniseed, tarragon, fennel, basil, allspice, nutmeg, cinnamon, sassafras, dong quai, mace, and pepper) and nutritional supplements that contain these herbs or their essential oils. Pyrrolizidine alkaloids occur in some herbal preparations[a] and herbal teas.

The committee concludes that there is no evidence that the risk to pregnant women or their foetuses is different to that for the general population. The advice for pregnant women does not therefore need to be different than for the general population. The committee concludes that the use of herbal preparations can be a cause for concern. Consuming fewer than four cups of herbal tea and using kitchen herbs as flavourings for dishes do not give cause for concern because the levels of exposure are much lower. The committee notes that pyrrolizidine alkaloids can also be present in green or black tea as a result of weeds being co-harvested. This is a form of inadvertent exposure where the amounts of pyrrolizidine alkaloids and the resulting exposure to them due to the consumption of the teas are unclear, so the committee does not make any recommendations for this. Although there is no difference between the recommendations for pregnant women and those for the general population, the advisory report does address this issue because in everyday practice there is often confusion about the use of herbs during pregnancy.

[a] The committee considers pills that are made of a herbal preparation to be ‘herbal preparations’. A herbal preparation is one that is obtained by subjecting herbal compounds to treatments such as extraction, distillation, pressing, fractionation, purification, concentration, or fermentation. Herbal compounds are entire, broken or cut plants, parts of plants, algae, fungi, and lichens in unprocessed form (generally dried but sometimes also fresh).[116]

09
retinol (vitamin A)

9.1 Risk assessment summary

Conclusion	Retinol intake levels of more than 3,000 micrograms may be associated with teratogenic effects in the first 60 days of pregnancy. This refers to intake that occurs as a one-off or several times.
Effect size	The percentage of children with a cranial neural tube defect was 0.52 in women with a daily intake of 0-1,500 mcg retinol and 1.06 in women with a daily intake of more than 3,000 mcg retinol.
Scientific basis	Based on studies in humans (clinical, prospective cohort and case-control studies) and animals.
New scientific knowledge about the teratogenicity of retinol	None compared to the EFSA report on tolerable upper levels of intake for retinol.[8]
Exceeding the upper level of intake	Using liver, liver products or high-dose nutrient supplements containing retinol may exceed the tolerable upper level of intake: 1 portion of liverwurst (22 grams per slice of bread) contains 1,156 mcg retinol and 1 portion of liverwurst spread (20 grams per slice of bread) contains 1,178 mcg retinol. In the 2012-2016 National Food Consumption Survey, 10 out of 413 women of childbearing age had a dietary intake of retinol exceeding 3,000 micrograms a day (ranging from 3,095 to 8,273 micrograms a day). When the intake from supplements was included, this applied to 13 women.[63]
Other information	Liver contains a very great deal of retinol. Legislation states that nutrient supplements specifically for pregnant women may not contain retinol. Vitamin and multivitamin supplements for other target groups may contain retinol.

9.2 Explanation

The various forms of vitamin A and their main sources are discussed below. It also describes the teratogenic effect of vitamin A, new scientific developments, and current intake patterns.

9.2.1 Introduction and concepts

Vitamin A (retinol) is obtained in two different ways: 1) from retinol and esterified retinol (retinyl esters), and 2) from the provitamin A carotenoids alpha and beta-carotene and beta-cryptoxanthin, which are converted into retinol in the body. Retinol is found in esterified forms in foods of animal origin. The commonest of these is retinyl palmitate. Both esterified retinol and the free compound can be found in food supplements and foods.

In the text, the various forms of vitamin A and its precursors are referred to as follows:

- Vitamin A = a collective term for vitamin A derived from retinol and provitamin A carotenoids.
- Retinol = vitamin A from animal-based foods, margarine, light margarine and cooking and frying products, and supplements.
- Provitamin A carotenoids = precursors of vitamin A from plant foods that are converted into vitamin A in the body.[117]

9.2.2 Sources of vitamin A

The principal sources of retinol are animal products such as milk, butter, cheese, egg yolk, liver, and certain oily fish. Furthermore, margarines

have as much retinol added to them as butter naturally contains. Liver is very rich in retinol. When a sandwich with 5 grams of margarine and 15 grams of liverwurst is consumed, 40 micrograms of retinol come from the margarine and 660 micrograms from the sausage. A similar amount of liver pâté yields 1,110 micrograms of retinol[117,118] Other animal products contain substantially less retinol.

In the Netherlands, supplements for pregnant women may only contain vitamin A in the form of provitamin A carotenoids. Vitamin and multivitamin preparations for the general population may include vitamin A in the form of retinol. No tolerable upper level has been determined for carotenoids.[8]

9.2.3 Teratogenic effects of retinol

Vitamin A in the form of retinol can cause problems in the development of the unborn child (embryogenesis). EFSA concludes that retinol intake levels of over 3,000 micrograms may be associated with teratogenic effects (both one-off and regular daily intake).[8] These teratogenic effects, also known as the retinoic acid pattern, include abnormalities of the skull, face, central nervous system, thymus, and cardiovascular system.
The critical period seems to be between the second and fifth weeks of pregnancy and it is in general considered to start from conception until the 60th day of pregnancy.
Teratogenic effects have been observed in both animals and humans.
In humans, there are case reports, case-control studies, cohort studies, and a clinical trial. The case reports of teratogenic effects are about approximately 20 women who took a retinol supplement during pregnancy. There are also five case-control studies, from which no clear conclusions can be drawn as the designs of the studies varied greatly in terms of how the congenital anomalies were classified, the number of women, the discriminating power, and in the collection of the intake data.[119-123] Additionally, there are two prospective studies from the USA and Europe.[124,125] The American cohort study followed 22,748 pregnant women, of whom 339 had babies with congenital defects; 121 of these were cranial neural tube defects. The percentage of children with cranial neural tube defects was 0.52 in women with a daily intake of 0-1,500 micrograms retinol and 1.06 in women with a daily intake of more than 3,000 micrograms retinol. When the analysis was limited to intake from nutritional supplements, the percentages were 0.46 and 2.21 respectively. Regression analysis determined a threshold of 3,000 micrograms of retinol per day. However, the number of children for mothers in the high intake group was low and only 76.5% of pregnancy outcomes were determined by doctors.[124]
In the other prospective cohort study in Europe of 423 pregnant women (311 births) who had taken more than 3,000 micrograms retinol per day in the first nine weeks of pregnancy, three children were born with serious birth defects. These cases occurred at intakes of 7,500, 9,000, and 15,000 micrograms of retinol per day. No abnormalities were reported in the children of 120 women who reported daily retinol intake levels of more

than 15,000 micrograms. The biggest limitation of this study was the discriminatory power: the sample had 80% power to show a risk that was increased by a factor of more than 2.76.[125]

Finally, there is a clinical study from Hungary in which an intake of 1,800 micrograms vitamin A (combined with folic acid) did not increase the risk of foetal abnormalities.[126]

It is not possible to derive a dose-response relationship from the available animal and human studies. However, based on the prospective cohort studies, EFSA concludes that the risk of teratogenicity is low or negligible at daily intakes of up to 3,000 micrograms of retinol over a short period. EFSA has therefore set the tolerable upper level of intake at 3,000 micrograms retinol per day. Because a single intake or several intakes above 3,000 micrograms (peak exposure) can affect embryogenesis, this tolerable upper level of intake therefore refers to short-term intakes.[8]

9.2.4 New scientific developments relating to teratogenicity

The committee found no new human studies on retinol and teratogenesis since the EFSA report on safe upper levels of intake was published in 2006 (Appendix A). There are therefore no new insights relating to the teratogenicity of retinol in humans.

9.2.5 Data about retinol intake levels

In the 2012-2016 National Food Consumption Survey, 10 out of 413 women of childbearing age had a dietary intake of retinol from foods exceeding 3,000 micrograms a day on one of the two days in which the dietary patterns were tracked (ranging from 3,102 to 7,490 micrograms a day). Based on total retinol intake from food and supplements as well, there were 13 women (ranging from 3,095 to 8,273 micrograms a day). Intake levels of more than 3,000 micrograms from supplements alone did not occur.[63]

Calculations based on the ‘Wheel of Five’ also show that consuming liver, liver products or high-dose nutrient supplements containing retinol may mean that the tolerable upper level of intake is exceeded. A daily diet according to the Wheel of Five (without liver products) contains about 700 to 800 micrograms of vitamin A, which meets the daily requirement. Roughly half (about 350 micrograms) is in the form of retinol. A 20-gram portion of liverwurst spread contains about 1,200 micrograms of retinol. Eating according to the Wheel of Five plus two 20-gram portions of liverwurst spread will yield roughly 2,700 micrograms retinol; eating three portions of liverwurst spread gives 3,300 micrograms retinol. It is therefore possible in practice to exceed 3,000 micrograms of retinol (daily).

9.3 Conclusion of the committee on recommendations for pregnant women

EFSA concludes that retinol intake levels of more than 3,000 micrograms may be associated with teratogenic effects in the first 60 days of pregnancy. These teratogenic effects include abnormalities of the skull, face, central nervous system, thymus, and cardiovascular system. This refers to intake that occurs as a one-off or several times. There are no new scientific findings about this safe upper level.

Using liver, liver products or high-dose nutrient supplements may exceed the safe upper limit. For instance, one portion of liverwurst (22 grams per slice of bread) contains 1,156 micrograms retinol and one portion of liverwurst spread (20 grams per slice of bread) contains 1,178 micrograms retinol. Two to three per cent of women of childbearing age in the Netherlands have intake levels from the diet or from supplements that exceed 3,000 micrograms a day. Legislation states that nutrient supplements specifically for pregnant women may not contain retinol.

Based on this current level of knowledge, the committee concludes that recommendations aimed at limiting retinol intake in pregnant women remain important. The recommendation is explained further in the advisory report.

10 superfoods

10.1 Risk assessment summary

Conclusion	It is not known whether superfoods in dried, concentrated forms are safe during pregnancy. Specifically regarding goji berries, there is anecdotal evidence that they can stimulate the uterus.
Effect size	Cannot be determined for superfoods in general.
Scientific basis	Because the effects of many superfoods and/or the substances they contain are not known, it is unclear whether they are safe during pregnancy in their dried, concentrated form.
New scientific knowledge relating to unfavourable effects of goji berries during pregnancy	None.
Exceeding the upper level of intake	Not applicable.
Other information	None.

10.2 Explanation

The Netherlands Nutrition Centre emphasises that people take superfoods because they believe they are healthy for them. Many superfoods fall in the category of fruit and vegetables. However, there is no scientific evidence that eating any single type of fruit provides health benefits or that any single type of vegetable provides all the nutrients found in vegetables. Some products labelled as superfoods contain not only healthy nutrients but also nutrients that are less good for your health, such as the saturated fats in chocolate. Moreover, excesses of certain superfoods may cause symptoms, such as the fact that goji berries are known to cause nausea and vomiting when consumed in large quantities. There have also been some cases of allergic reactions after eating goji berries among people who already had food allergies. Because goji berries were specifically mentioned in the old Netherlands Nutrition Centre recommendation, the committee specifically searched for new scientific understandings about the consumption of goji berries during pregnancy (Appendix A). The committee has not found any data about intake levels of goji berries by women of childbearing age.

10.2.1 Introduction and concepts

Goji berries come from a buckthorn (*Lycium babarum*) from the nightshade family.

10.2.2 Health effects of goji berries during pregnancy

The committee found a risk assessment and a review article on goji berries in relation to pregnancy.

A risk assessment by the German Bundesamt für Risikobewertung (Federal Office for Risk Assessment) states that Chinese professional literature advises pregnant women against consuming goji berries. The reason why is not stated in the risk assessment and the authors say that the original publications on this subject were not available.[127]

Ulbricht et al. (2015), working on behalf of the Natural Standard Research Collaboration, say in a systematic review of goji berries that anecdotal reports claim that goji can stimulate the uterus. There is no reference in the systematic review to the said reports.[128]

10.3 Conclusion of the committee on recommendations for pregnant women

It is not known whether superfoods in dried, concentrated forms are safe during pregnancy. Specifically regarding goji berries, there is anecdotal evidence that they can stimulate the uterus. EFSA has not carried out a risk assessment on the use of superfoods in general or on goji berries in particular, either for the general population or during pregnancy. There are therefore no recommendations at the European level in this regard either.

As there are no European recommendations and the limited scientific findings are anecdotal in nature, the committee sees no reason to draw up a specific recommendation for pregnant women on this subject.

11 probiotics

11.1 Risk assessment summary

Conclusion	RCTs have not found any unfavourable (or favourable) effects of probiotics during pregnancy.
Effect size	Not applicable.
Scientific basis	RCTs.
New scientific knowledge relating to unfavourable effects of probiotics during pregnancy	No evidence was found in RCTs that probiotics during pregnancy affect gestational duration, birth weight or the risk of preterm birth (< 34 or < 37 weeks), a child that is either small or indeed large for gestational age, gestational diabetes, premature breaking of the waters or allergic symptoms in the child.
Exceeding the upper level of intake	Not applicable.
Other information	There is wide variation in the probiotics and probiotic combinations covered by the RCTs, so it is not possible to draw conclusions about specific strains.

11.2 Explanation

Probiotics, or potentially probiotic organisms, are bacteria that are incorporated into foods and supplements with the aim of promoting health. However, there are almost no bacteria for which health effects have been conclusively determined.

The committee discusses recommendations for probiotics and EFSA's safety assessments below. Because a lot of research has been done into the effects of probiotics on health, it explores whether recent scientific developments on probiotics could be a reason for issuing a recommendation about probiotics for pregnant women. The committee has not found any data about intake levels of probiotics by women of childbearing age.

11.2.1 EFSA risk assessment

EFSA carries out safety assessments to evaluate whether certain microorganisms may be added to food. Groups of microorganisms that pass the assessment are labelled with a *qualified presumption of safety*. This label applies to any microorganism within the group. This list of authorised microorganisms is assessed every three years, during which period EFSA also carries out interim literature studies.[129]

11.2.2 New scientific developments

The committee found three recent review articles (Appendix A).[130-132] The review articles summarise RCTs of various probiotics, in particular several strains of lactobacilli and bifidobacteria. Jarde et al. (2018) found no significant effect on the risk of preterm birth (< 34 or < 37 weeks), gestational duration, or birth weight. The authors also found no evidence for children being either small or large for gestational age. Moreover, no effects were found on the risk of gestational diabetes or premature breaking of the waters. However, the number of studies on these four outcome measures was limited, making the findings less robust.[130] Zheng et al. (2018) found evidence that the use of probiotics by healthy women during pregnancy reduced insulin and HOMA-IR concentrations but had no significant effect on glucose levels.

The heterogeneity was considerable for all these findings and this was not further investigated by the authors.[131] Regarding the risk of allergy in the child, Cuello-Garcia et al. (2015) found no evidence for effects on allergic symptoms, other than a reduced risk of eczema. However, the strength of the evidence was low due to limitations in the study due to bias, inconsistencies, inaccuracy, and indirect evidence.[132]
One limitation of the systematic review articles is that there is wide variation in the probiotics and probiotic combinations covered, so it is not possible to draw conclusions about specific strains. Another point is that most RCTs have no systematic reporting of any side effects.
The committee concludes that no unfavourable effects of probiotics (or indeed favourable ones) during pregnancy have been demonstrated in RCTs.

Based on this current state of scientific knowledge, the committee concludes that there is no specific recommendation that can be formulated for pregnant women about probiotics.

11.3 Conclusion of the committee on recommendations for pregnant women

EFSA carries out safety assessments to evaluate whether certain microorganisms may be added to food. The list of authorised microorganisms is assessed every three years. Recent RCTs have not found any unfavourable or indeed favourable effects of probiotics during pregnancy. There is wide variation in the probiotics and probiotic combinations covered by the RCTs, so it is not possible to draw conclusions about specific strains.

12 listeria monocytogenes

12.1 Executive summary

Perinatal effect	Infection with ***Listeria monocytogenes*** during pregnancy can cause miscarriages, stillbirths, preterm births or severe neonatal illnesses (sepsis, meningitis).
The size of the effect	Pregnant women probably do not run a higher risk of becoming contaminated with *L. monocytogenes*, but the changes in the immune system associated with pregnancy do mean that risk of a contamination making them ill (causing a listeriosis infection) are about 20 times higher. Of the seven pregnant women who were diagnosed with listeriosis infections in the Netherlands in 2016, six had serious complications.
Scientific basis	Based on research among humans (case reports, outbreaks), in vitro research, and genetic studies of the bacteria.
Current prevalence	About seven pregnant women are diagnosed with listeriosis each year in the Netherlands.
Other	The risk of listeriosis can be reduced, in particular by giving advice about hygienic working methods and avoiding certain foods during the pregnancy.

12.2 Explanation

The effects of infection with *Listeria monocytogenes* (listeriosis) are described below, combining information from the Netherlands Nutrition Centre, the National Institute for Public Health and the Environment (RIVM) and EFSA with information from new scientific publications (Appendix A). The committee describes the key sources of *L. monocytogenes*, the effects of listeriosis, and its current prevalence.

12.2.1 Introduction

L. monocytogenes can cause listeriosis in the pregnant woman, the foetus, or the neonate.[133] Pregnant women probably do not run a higher risk of becoming contaminated with *L. monocytogenes*, but the changes in the immune system associated with pregnancy do mean that the chances of getting listeriosis after a contamination are about 20 times higher.[134-136] In theory, a single bacterium can cause an infection, although the risk of that is very small. The more bacteria there are present in a product, the greater the risk of infection. The literature shows that the risk of infection remains low as long as the number of bacteria per gram of product is below 10,000 to 1,000,000. This figure may be smaller for susceptible populations.[137] The legal maximum in Europe for ready-to-eat products intended for normal consumption (i.e. except for food for infants and food for medical use) in which *Listeria* bacteria are unable to grow is 100 colony-forming units (CFU) per gram (in five samples).[138] For ready-to-eat products in which *Listeria* bacteria can grow, the bacterium must either be absent in five samples of 25 grams or the producer must be able to demonstrate that the CFU count per gram remains below 100 until the shelf-life expiry date.[139]

12.2.2 Characteristics of Listeria monocytogenes

Listeria is a bacterium that can survive under all kinds of conditions, both with and without oxygen. The bacteria multiply readily in moist surroundings and can withstand both deep-freezing and dry conditions.

Unlike other pathogenic bacteria, *Listeria* can grow in a cold and humid climate such as a refrigerator. The bacteria can multiply at temperatures from 0 to 45°C. The temperature does affect the growth rate.
L. monocytogenes grows more slowly at 4°C than at 7°C. The bacterium can survive in products with a low moisture content but will not grow.
The bacterium can also reproduce at high salt concentrations (up to 10%) and in a pH range from 4.4 to 9.4. The bacteria can be rendered harmless by heating to at least 75°C.[133,140,141,142,138,141] Some perishable foods are pre-packed using modified atmosphere packaging (MAP); the growth of *L. monocytogenes* is reduced by an increased concentration of CO_2, but not by an increased concentration of N_2, nor by vacuum sealed packaging.[143]

Heating and storing

The hygiene code lists various general measures for controlling microbiological safety when preparing and storing food. These general precautions are important to ensure the microbiological safety of foods in a broader sense (they are not specifically aimed at *L. monocytogenes*).
With respect to *Listeria*, the committee deems heating to a core temperature of 75°C and then storing prepared products at 7°C for a maximum of two days or at 4°C for a maximum of three days to be the key measures.[144] Because the packaging is often unclear about how long pre-packed products in which *Listeria* can grow can be kept after the packaging has been opened, the committee deems the storage periods for prepared products as stated in the hygiene code as a good baseline for pregnant women to use.

12.2.3 Sources of Listeria monocytogenes

The Netherlands Nutrition Centre describes *L. monocytogenes* as occurring most frequently on foods of animal origin (e.g. fish, meat, and cheese) but plant products can also be contaminated. High-risk products are principally refrigerated products that are eaten without being reheated beforehand.
Raw or smoked fish consumed without cooking, soft cheeses (especially those made from raw milk) and cooked sliced meats are most commonly associated with *L. monocytogenes*. Other high-risk products are other processed meats, chilled pâté, hot dogs, chilled sandwiches, and chilled ready-to-eat meals such as raw vegetable salads. Leftovers are a risk too.[140]
There have also recently been scientific review articles looking at sources of *L. monocytogenes*.[134,145] The conclusions about high-risk products are largely in line with the descriptions given by the Netherlands Nutrition Centre, RIVM, and EFSA.
In a systematic review, for example, Moran et al. (2018)[145] found that women with perinatal listeriosis had eaten high-risk products more often than women who did not have perinatal listeriosis. The high-risk products in question were unpasteurised, soft, or Mexican cheese; raw, partially heated or smoked meat and pâté; melon; and ready-to-eat vegetables.

Madjunkov et al.[134] also address foods with a high risk of *L. monocytogenes*:

- Soft cheese made from unpasteurised milk.
- Hot dogs, meat products or deli meats if the meat has not been heated again to 71 degrees Celsius.
- Chilled pâté or meat spreads.
- Chilled smoked fish and shellfish (both crustaceans and molluscs) if they are not reheated to 71 degrees Celsius.
- Raw and unpasteurised milk and dairy produce.
- Raw and unwashed fruit and vegetables.
- Chilled perishable food that is not consumed within two to three days.

Dutch data from the Netherlands Controlling Authority for dairy and eggs (COKZ) shows that *L. monocytogenes* is found significantly more often in cheese (as 25 g samples) made from raw milk than in cheese made from pasteurised milk (Table 8). However, within the pasteurised cheese category, farmhouse cheeses test positive for *L. monocytogenes* significantly more often than factory cheeses. The report does not describe to what extent the bacteria levels exceeded the 100 CFU/g reference value set by the European standard, because in most cases the reference value is only exceed after *Listeria* has been able to multiply in the product. This is possible in soft cheeses (whether or not made from raw milk) because of the high moisture content of this type of product. In semi-soft or hard cheeses (e.g. types such as Gouda and Edam), *Listeria* cannot grow and will even die off.[138] Hard cheeses, whether or not they are made from raw milk, therefore pose less of a risk as far as *Listeria* is concerned.[146,147] However, there is a small risk that hard cheeses made from raw milk may contain *Listeria* (or *Toxoplasma*) that was already present in the raw milk and which, because the milk is not heated before processing, is not killed.[148] Other pathogenic bacteria such as *Salmonella* may also be present in hard cheese made from raw milk.

Table 8 Prevalence of *Listeria monocytogenes* in various cheese products (as 25 g samples) according to studies by the Netherlands Controlling Authority for dairy and eggs (COKZ) and the Dutch Food and Consumer Products Safety Authority (NVWA). Note: this table only gives a picture of the presence of *Listeria monocytogenes* in a product; it does not give information about how often the European maximum value of 100 CFU/g is exceeded.

Type of cheese	Prevalence of *Listeria monocytogenes* (%)	Standard deviation
Cheese made from raw milk	1.8	1.1-2.4
Cheese made from pasteurised milk in general	0.3	0.1-0.5
Farmhouse cheese made from pasteurised milk	2.2	0.7-4.5
Factory-made cheese made from pasteurised milk	0.1	0.04-0.3

L. monocytogenes is often found *on* products as a result of what is known as post-contamination, in other words bacteria getting onto (rather than into) the product during production or processing, for example from cutting machines or knives, or contact with surfaces previously contaminated with the bacterium.[146] The bacteria can thereby end up on products that ought

no longer normally to contain *Listeria*, e.g. products that have already been heated during the production process. Because post-contamination is an important route, *Listeria* is often found on the surfaces or cut edges of a product rather than *in* the product. There is also what is known as 'restructured meat', which looks like a continuous whole without cut surfaces but nevertheless has internal cuts from the production process in which *Listeria* can be present. Meat sometimes is injected and may be contaminated internally that way.

12.2.4 Effects of infection by Listeria monocytogenes

The incubation time for *Listeria monocytogenes* is one to 90 days. In healthy pregnant women with normal immunity, listeriosis can proceed without obvious symptoms or mild flu-like symptoms in the mother, yet the infection can at the same time lead to miscarriage, stillbirth, preterm birth, or severe neonatal illness (as sepsis or meningitis).[133,134,149] Listeriosis can occur at any point during the pregnancy but is most often diagnosed in the third trimester, from week 28 of the pregnancy onwards. The prognosis for listeriosis cases does however become more favourable the later the infection occurs in pregnancy.[133,134,150]

12.2.5 Prevalence of listeriosis and complications

Prevalence of pregnancy-related listeriosis

Listeriosis during pregnancy is a rare disease, at 1.3-2.4 cases per 100,000 pregnancies.[151] There were seven cases of listeriosis among pregnant women in the Netherlands in 2018, the same number as in 2016. These figures are more than the three cases a year in the period 2013-2015 and similar to the figures for 2012 (n=6) and 2011 (n=9).[149,152] Between 14 and 21% of all listeriosis cases are pregnancy-related. According to a study of disability-adjusted life years worldwide, 21% of all *L. monocytogenes* infections were perinatal.[153] An overview of three sets of records (Great Britain, France and the United States) gave pregnancy-related infection rates varying from 14 to 18%.[150] An article reviewing of US data states that the percentage of pregnant women who contract listeriosis in outbreaks varies greatly. It is still unclear whether this can be explained by differences between strains of *L. monocytogenes* or whether other factors are involved.[150]

Prevalence of complications

In 2016, listeriosis monitoring in the Netherlands recorded 96 patients. Those affected included seven pregnant women. One pregnant woman had a miscarriage, two babies were stillborn, and one child died after developing sepsis. One of the other three babies was premature, one developed sepsis, and the third is not known to have any symptoms.[149] For comparison with the Dutch data: a review article by Desai et al. (2017) describes data from three sets of records (Great Britain, France, and the United States) of listeriosis cases: 64% of the cases involved preterm births, 28-32% foetal death, and 3-13% neonatal death.[150] According to

one study, sepsis occurred in 31% of infected newborns and meningitis in 15%, with 9% of the infected newborns dying.[153]

European trends in listeriosis

According to an EFSA report, there is evidence at the European level that the incidence of food-borne *L. monocytogenes* infections in the general population increased from 0.30 to 0.46 cases per 100,000 from 2008 to 2015.[146] The increase occurred mainly in women between the ages of 25 and 44 (64% of cases in this group were pregnancy-related), young children aged up to 1 year (79% pregnancy-related), and in the elderly. There is no clearly substantiated explanation for the increase among pregnant women, unlike that in the elderly (explained by the increased number of older people). Other explanations suggest that the increase is linked to higher consumption of ready-to-eat products and better monitoring in some European countries. There is however only weak substantiation for that.

A model calculation in the EFSA report states that over 90% of invasive listeriosis cases are caused by consuming ready-to-eat products containing more than 2,000 CFU/g. Furthermore, according to the model, 30% of cases are due to growth after purchase, i.e. during the consumer phase.[146]

12.3 Conclusion of the committee on recommendations for pregnant women

The committee notes that the risk of pregnant women contracting listeriosis is low (the number of cases in the Netherlands annually varies from four to nine). However, when pregnant women do contract listeriosis, it is extremely likely to result in a very serious pregnancy outcome. There is no doubt about the causal relationship.

Data from 2016 shows that serious undesirable pregnancy outcomes occurred in six out of the seven infections. The committee notes that underreporting is possible, particularly with early miscarriages if the cause was not investigated further. Furthermore, this happens despite the recommendations having been in place for a long time.

The committee's conclusion is that recommendations aimed at preventing listeriosis in pregnant women remain important. The recommendation is explained further in the advisory report.

13
toxoplasma gondii

13.1 Executive summary

Perinatal effect	Infection with ***Toxoplasma gondii*** during pregnancy can lead inter alia to stillbirth or severe and irreversible harm to the baby's eyes and brain. Infected children who are born without symptoms can develop eye abnormalities later.
Effect size	Pregnant women have a greater risk of severe consequences from *T. gondii* infections than the general population.
Scientific basis	Based on research among humans (case reports, outbreaks), in vitro research and genetic studies of the parasite.
Current prevalence	Toxoplasmosis is not recorded in the Netherlands. On average, 40% of the Dutch population have been infected at some point in their lives. 18% of women of childbearing age have been infected.
Other	The risk of toxoplasmosis during pregnancy can be reduced by observing hygiene rules when processing food, wearing gloves when gardening and avoiding raw and insufficiently cooked meat, certain foods and cat faeces.

13.2 Explanation

The effects of infection with *Toxoplasma gondii* (toxoplasmosis) are described below, combining information from the Netherlands Nutrition Centre and RIVM with information from new scientific publications (Appendix A). The committee describes the sources of *T. gondii*, the effects of toxoplasmosis, and its current prevalence.

13.2.1 Introduction

T. gondii is a unicellular parasite that can cause toxoplasmosis. After a primary infection, the infection remains latent for the rest of the individual's life, providing lifelong immunity. The latent infection can however flare up again and cause symptoms, which may be severe, in people with weakened immune systems. Except for toxoplasmosis infections of the eye, a latent infection will not flare up in a healthy person or cause symptoms, according to the National Coordination Centre for Communicable Disease Control (LCI). The seroprevalence among the Dutch population increases with age. Among people aged under 20, 17.5% have had an infection at some point; that percentage rises to over 70% among people aged over 65. Women of childbearing age have therefore often not yet had an infection.[103,154,155]

If a woman comes into contact with *T. gondii* for the first time while she is pregnant and gets infected, there is a risk of congenital toxoplasmosis. There are, however, also a few case reports of congenital toxoplasmosis caused by an infection preceding the pregnancy. The most harm is done when the child is infected during the first trimester, with a high risk of severe pathology.[103,154,155] Pregnancy involves changes in the immune system, which probably leads to a higher risk of certain infections than in the general population.[136]

13.2.2 Sources of Toxoplasma gondii

T. gondii can be present in raw meat and on raw fruit and vegetables, particularly vegetables from natural soil. *T. gondii* reproduces in felines. The eggs are released in the cat's faeces and can spread that way. It takes about two to three days in the Dutch climate before those eggs can develop pathogenic properties. People run the risk of being infected

e.g. when cleaning a cat litter tray or gardening. Fruit and vegetables growing outdoors can also get contaminated by cat faeces. It is also possible for other animals to ingest these eggs and their meat can become contaminated as a result. Animals that go outside in particular run the risk of infection.[103,155,156] Fish and shellfish are also susceptible to contamination with *T. gondii*, although the risk of this is much lower than for meat and fruit or vegetables grown in natural soil.[157] Shellfish (both molluscs and crustaceans) are filter feeders that live close to shore. This biotope and the way that they feed mean that they are more susceptible to contamination with *T. gondii* than fish.[158-160]

Heating contaminated sources to a core temperature of 67 degrees Celsius or freezing raw meat for four days at a temperature of -12 degrees Celsius or three days at a temperature of -20 degrees Celsius kills the parasite.[161] Drying and salting raw meat (dry curing) is probably insufficient to render the parasite completely harmless.[162]

In a recent systematic review of case-control studies into toxoplasmosis and food consumption, the risk from raw or insufficiently cooked meat was confirmed. The review found that consuming meat that is raw or not cooked right through is in general associated with a greater risk of toxoplasmosis (five studies; OR=3.44; 95% CI 1.29-9.16). This applied in sub-group analyses specifically to consuming raw or insufficiently cooked beef (six studies; OR=2.22; 95% CI 1.57-3.12) and consuming raw or insufficiently cooked lamb (four studies; OR=3.85; 95% CI 1.85-8.00). There was too little research into the relationship with consuming raw fruit and vegetables to summarise in a meta-analysis. There was a small number of studies in which eating unwashed and/or raw vegetables and unwashed fruit (peeled or otherwise) was associated with a higher risk of toxoplasmosis.[163]

13.2.3 Effects of infection by Toxoplasma gondii

The incubation time for *T. gondii* is 10 to 23 days. Toxoplasmosis proceeds in most cases without clear symptoms; sometimes there are complaints of fatigue, restlessness, and mild fever.[154] If a woman gets toxoplasmosis during pregnancy, however, it can have severe consequences for the unborn child. A meta-analyse from 2014 looking at eight Chinese publications found that infection by *T. gondii* during the pregnancy was associated with a risk of an undesirable pregnancy outcome that was more than five times greater (RR=5.10; 95% CI 3.85-6.75). Among these undesirable pregnancy outcomes were abortion, foetal abnormalities, stillbirth, foetal growth restriction, and preterm birth, all of which occurred significantly more often.[164] The LCI guideline states the following on the matter: the risk that the mother will transmit the infection to the child increases with the duration of the pregnancy (from about 6% at 10 weeks to over 80% at 38 weeks). The symptoms of what is referred to as ‘congenital toxoplasmosis’ vary a great deal, depending on the trimester in which the mother became infected. The most harm is

done when the child is infected during the first trimester, with a high risk of severe clinical pictures such as intrauterine foetal death, brain abnormalities, eye abnormalities, and deafness. When the infection occurs in the second or third trimester of the pregnancy, the risk of harm to the child is smaller. Clinical pictures that are then observed are for example fever, rashes, and eye abnormalities (which often arise later in life).[155]

A clinical picture of severe infection or sepsis can also be prominent, according to RIVM, with a risk of perinatal death.[154] A recent systematic review confirms this view. According to that publication, more children are born with clinical symptoms if the infection occurs in the first half of the pregnancy than in the second half (after week 24) (93% versus 16%; OR=68; 95% CI 26-181).[165]

13.2.4 Prevalence of toxoplasmosis

Occurrences of toxoplasmosis are not recorded in the Netherlands. It has been calculated, though, that antibodies to *T. gondii* are present in the child's blood in two out of every 1,000 live births in the Netherlands. This is based on studies of antibodies to *T. gondii* in the child's blood. It is unclear whether these neonates were also actually made ill as a result of the infection. Because the incidence was determined among live births, the committee assumes that it is an underestimate of the actual number, given that *T. gondii* infections can also result in miscarriages. The incidence in the Netherlands was however ten times higher than was found in Denmark and twenty times higher in Ireland, where the incidence was determined using the same method. Kortbeek et al. (2009) do not give a clear explanation for the difference in prevalence.[152,166]

On average in 2006/2007, 26% of the Dutch population had antibodies to *T. gondii* in their blood. That means that they have been in contact with the parasite at least once during their lives. Most people were unaware of it. This percentage increases with age. Among women of childbearing age, this percentage was 18% in 2006/2007, which suggests that the majority (82%) of pregnant women are susceptible to infection by *T. gondii*.[167]

13.3 Conclusion of the committee on recommendations for pregnant women

It is estimated that the incidence of congenital toxoplasmosis in the Netherlands is two, per 1,000 live births. A large proportion of women of childbearing age have not previously been infected with *T. gondii* during their lives and are therefore susceptible to infection during pregnancy. When a *Toxoplasma* infection occurs during pregnancy, the risk of a severe or very severe effect on the pregnancy outcome is greatly increased (estimated to be five times higher): stillbirth, perinatal mortality, preterm birth, small for gestational age, or abnormalities of the eyes or brain in the offspring. There is no doubt about the causal relationship. The outcomes are potentially most severe if the *Toxoplasma* infection occurs during the first trimester of the pregnancy, although the risk of the

infection reaching the foetus is lower during the first trimester than later on in the pregnancy. As the pregnancy advances, the risk of the infection reaching the foetus increases, although the consequences for the foetus are then often less severe and may be limited to skin rashes (as well as eye problems that arise later in life).

The committee concludes that recommendations aimed at preventing toxoplasmosis in pregnant women remain important. The recommendation is explained further in the advisory report.

14 other microorganisms and viruses that can cause food-borne infections

As well as *Listeria monocytogenes* and *Toxoplasma gondii*, other microorganisms such as *Salmonella* can also cause food-borne infections. Because pregnancy is associated with changes in the immune system, pregnant women may possibly run a greater risk of a more serious progression of food-borne infections or may have more symptoms.
The committee sees no reason to assess the recommendations about working hygienically because they are no different to the advice given to other groups. More attention should be paid to these hygiene precautions during pregnancy, though, because certain infections (listeriosis and toxoplasmosis) are associated with specific and severe pregnancy risks. Following hygiene precautions properly will of course also limit the risk of other food-borne infections. The substantive content of these hygiene measures is described in the advisory report.

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appendices

A search terms used in PubMed

Acrylamide

PubMed search: (acrylamide) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]). Date: 22-8-2018

Alcohol and miscarriage and stillbirth

Systematic reviews

PubMed search: ((((((((((((miscarriage[MeSH Terms]) OR miscarriage[Title/Abstract]) AND Humans[Mesh])) OR stillbirth[Title/Abstract]) OR stillbirth[MeSH Terms]) OR fetal death[Title/Abstract]) OR fetal death[MeSH Terms]) AND Humans[Mesh])) AND (((alcohol[Title/Abstract]) OR (“Ethanol”[Mesh] AND Humans[Mesh])) AND Humans[Mesh])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab])) AND Humans[Mesh])) AND (review[pt] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR meta-analysis[tiab]). Search for publications from 2004 onwards; date: 23-8-2018

Recent individual studies

PubMed search ((((((((((((((miscarriage[MeSH Terms]) OR miscarriage[Title/Abstract]) AND Humans[Mesh])) OR stillbirth[Title/Abstract]) OR stillbirth[MeSH Terms]) OR fetal death[Title/Abstract]) OR fetal death[MeSH Terms]) AND Humans[Mesh])) AND (((alcohol[Title/Abstract]) OR (“Ethanol”[Mesh] AND Humans[Mesh])) AND Humans[Mesh])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab])) AND Humans[Mesh])) AND cohort). Search for publication from 2006 onwards; date: 28-8-2018

Alcohol and preterm birth, small for gestational age and cognition and behaviour

Systematic reviews

The systematic reviews on this topic were found in the extensive search on health effects of foods, nutrients and dietary patterns in pregnancy (publications from 2008 onwards). These search terms are described in the background document on foods and dietary patterns.[56]

Recent individual studies

PubMed search ((((“Infant, Small for Gestational Age”[Mesh]) OR “Premature Birth”[Mesh] OR SGA[tiab] OR “Premature Birth”[tiab])) AND

((ethanol[MeSH Terms]) OR alcohol[Title/Abstract])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]). Search for publications from 11-7-2016 onwards; date: 23-08-2018

(((((alcohol[Title/Abstract] OR "Ethanol"[Mesh])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab])) AND (behavior[Mesh] OR behavior[tiab] OR behaviour[tiab] OR "Psychomotor Performance"[Mesh] OR "Psychomotor Disorders"[Mesh] OR Psychomotor[tiab] OR "Psychomotor Performance"[Mesh] OR "Psychomotor Disorders"[Mesh] OR Psychomotor[tiab] OR "Cognition"[Mesh] OR "cognitive function"[Title/Abstract] OR cognition[Title/Abstract])) AND cohort) Limit: humans. Search for publications from 11-7-2016 onwards; date: 29-08-2018.

Caffeine

Part of the systematic reviews on this topic were found in the extensive search on health effects of foods, nutrients and dietary patterns in pregnancy (publications from 2008 onwards). These search terms are described in the background document on foods and dietary patterns.[56]

((((((caffeine[Title/Abstract]) OR caffeine[MeSH Terms])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab])) AND Humans[Mesh])) AND (((((fetal growth[Title/Abstract]) OR small for gestational age[Title/Abstract]) OR SGA[Title/Abstract]) OR miscarriage[Title/Abstract]) AND Humans[Mesh]). Date: 18-7-2018

Furans

(("Furans"[Mesh]) OR furans[Title/Abstract])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]). Date: 4-10-2018.

Glycyrrhizine

(((glycyrrh*[Title/Abstract]) OR glycyrrhiza[MeSH Terms])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title/Abstract]) OR prenatal*[Title/Abstract]) OR perinatal*[Title/Abstract]) OR gestational*[Title/Abstract]) OR pregnant[Title/Abstract]). Date: 9-5-2018

Soy-isoflavones

PubMed search ((((((Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or

gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]))))) AND ((((((((((genestein[Title/Abstract]) OR daidzein[Title/Abstract]) OR glycitin[Title/Abstract]) OR equol[Title/Abstract]) OR isoflavone[Title/Abstract]) OR isoflavonoid[Title/Abstract]) OR “Isoflavones”[Mesh]) OR phytoestrogen[Title/Abstract])) OR “Phytoestrogens”[Mesh])))) AND (((case-control[Title/Abstract]) OR case control[Title/Abstract]) OR cohort[Title/Abstract]). Date: 29-8-2018

Allylalkoxybenzenes

((estragole OR methyleugenol OR safrole OR myristicin)) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]). Date: 4-7-2018.

Pyrrolizidine alkaloids

(((Pyrrolizidine Alkaloids[Title/Abstract]) OR “Pyrrolizidine Alkaloids”[Mesh])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]). Date: 2-10-2018.

Retinol (vitamin A)

((((vitamin A[Title/Abstract]) OR vitamin A[MeSH Terms]))) AND ((teratogen*[Title/Abstract]) OR teratogenesis[MeSH Terms]). Date: 9-5-2018

Goji berries

((((lycium barbarium[Title/Abstract]) OR goji berry[Title/Abstract]) OR goji berries[Title/Abstract])) AND ((Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab])). Date: 4-7-2018

Probiotics

(((“Probiotics”[Mesh]) OR probiotics[Title/Abstract])) AND (Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]). Date: 4-10-2018

Listeria monocytogenes

(((listeria monocytogenes[Title/Abstract]) OR listeria monocytogenes[MeSH Terms])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title/Abstract]) OR prenatal*[Title/Abstract]) OR perinatal*[Title/

Abstract]) OR gestational*[Title/Abstract]) OR pregnant[Title/Abstract])
Filters: Review; Systematic Reviews; Meta-Analysis. Date: 9-5-2018

Toxoplasma gondii

((((toxoplasma gondii[MeSH Terms]) OR toxoplasmosis[Title/Abstract]) OR toxoplasma gondii[Title/Abstract])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title/Abstract]) OR prenatal*[Title/Abstract]) OR perinatal*[Title/Abstract]) OR gestational*[Title/Abstract]) OR pregnant[Title/Abstract])
Filters: Systematic Reviews; Meta-Analysis; Review. Date: 9-5-2018

B recommendations from the Netherlands Nutrition Centre in 2018

Acrylamide

The Netherlands Nutrition Centre recommends restricting acrylamide intake levels through a varied diet and by not frying potato and grain products until they are too browned. It has not drawn up specific recommendations for pregnant women.

Alcohol

The Netherlands Nutrition Centre recommends not consuming alcohol during pregnancy because of the risks for the child that are associated with drinking alcohol. Alcohol can be harmful at all times during pregnancy. The risks of the negative effects increase as more alcohol is consumed. Alcohol during the pregnancy increases the risk of a miscarriage, preterm birth or a child with a low birth weight. Alcohol can also affect the child's later development.

Women who drink heavily during pregnancy run an increased risk of having a child with Foetal Alcohol Syndrome (FAS) with permanent effects on the body, behaviour and cognition. This syndrome is typified by growth retardation of the child, specific abnormalities of the face, abnormalities of the central nervous system and heart and deformities of the limbs. The risk increases from 6 glasses a day upwards.

The Netherlands Nutrition Centre states that it is unknown whether the risks also apply to women who drink a little during pregnancy. With the child's best interests in mind, pregnant women are advised not to consume alcohol.

Caffeine

The Netherlands Nutrition Centre advises pregnant women not to consume high-caffeine products or to limit their consumption to a maximum of one item per day. High caffeine intake levels (over 200 mg per day) during pregnancy are associated with an increased risk of foetal growth retardation. The precautionary advice is to consume no more than a single caffeinated product a day. Coffee and energy drinks are high-caffeine products: one cup of coffee (125 ml) contains for example approximately 85 milligrams of caffeine. This recommendation takes account of an average consumption of other sources of caffeine such as tea, cola and chocolate. Tea (125 ml) contains approximately 30 milligrams of caffeine. Three cups of black or green tea are therefore consistent with healthy eating habits for pregnant women. It is recommended that no more than three to four cups of tea a day should be consumed, though.

Furans

The Netherlands Nutrition Centre has not made any specific recommendations about intake levels of furans, either in general or during pregnancy.

Glycyrrhizine

Liquorice products contain glycyrrhizine, a substance that can elevate the blood pressure. As a precautionary measure, the Netherlands Nutrition Centre recommends eating a maximum of 2 to 3 liquorice sweets a day during pregnancy and drinking no more than 1 to 2 glasses of liquorice tea a day.

Hormone-like substances, particularly soy isoflavones

The Netherlands Nutrition Centre recommends a varied diet. When a harmful substance is present in a specific food, this reduces the risk of a high intake of that harmful substance during pregnancy.

Herbal preparations

Herbs and other botanicals may contain plant toxins that can be harmful, depending on the quantities consumed. Such substances are often highly concentrated in herbal preparations. People take herbal preparations because they believe them to be good for their health, but by no means all such preparations have been studied. Moreover, there are often concerns about the safety and origins of these types of preparations.

The Netherlands Nutrition Centre therefore recommends that pregnant women should not take herbal preparations (pills) and essential oils from herbs. There is also a recommendation that they should not consume too much of the kitchen herbs aniseed, tarragon, fennel, basil, allspice, nutmeg, cinnamon, sassafras, dong quai, mace and pepper. That same advice applies for the general population.

The Netherlands Nutrition Centre also recommends that people should in general not drink more than three cups of tea per day and should alternate teas and herbal tisanes with other beverages such as water.

Retinol (vitamin A)

Too much vitamin A increases the risk of birth defects. Pregnant women should therefore not consume more than 3,000 micrograms of vitamin A per day. Pregnant women are therefore advised not to take supplements containing vitamin A and to avoid liver and liver products. Liver contains very high levels of vitamin A, with 100 grams of beef liver for instance containing more than 27,000 micrograms of vitamin A and a slice of bread with liverwurst or liver pâté containing 1,000 to 1,200 micrograms of vitamin A. A single sandwich with liverwurst or liver pâté is therefore not likely to contain over 3,000 micrograms of vitamin A. If a pregnant woman wants to eat liverwurst or liver pâté, it is recommended that this should be limited to a maximum of one sandwich a day.

The Netherlands Nutrition Centre has based these recommendations inter alia on the 2008 advisory report of the Health Council of the Netherlands entitled *Towards an adequate intake of vitamin A*.

Superfoods

As a precautionary measure, the Netherlands Nutrition Centre recommends that pregnant women should not consume goji berries and not consume superfoods in dried, concentrated forms.

Probiotics

The Netherlands Nutrition Centre has not issued a specific recommendation about consuming probiotics during pregnancy.

Listeria monocytogenes

Listeria monocytogenes is a bacterium that can cause miscarriages or premature births in pregnant women. The risk of infection is very small but the consequences can be severe. *Listeria* can be present in chilled products that are consumed without being heated, such as delicatessen meat products or soft blue cheeses and white mould cheeses. Some of the recommendations do not specifically target *Listeria monocytogenes* but are aimed at pathogenic microorganisms in general.

Women can greatly reduce the risk of infection by taking the following measures:

- Store chilled items such as delicatessen meat products, pâté and ready meals in a refrigerator that is properly adjusted to 4°C.
- Discard perishable food after the expiry date and eat it within three days of opening. Chilled raw vegetable salads and pre-cut lettuce can be kept for one day after opening.
- Heat dishes right through. *Listeria* does not survive temperatures of above 70°C. Boiling, frying and roasting therefore kill the bacteria.

It is better for high-risk groups, including pregnant women, to avoid the following high-risk products:

- Soft and hard cheeses made from raw milk. The vast majority of cheese made in the Netherlands is pasteurised (from heat-treated milk) and does not therefore constitute a large risk. If a cheese has been made from raw milk, this will be stated on the label using the phrases ‘au lait cru’ or ‘gemaakt van rauwe melk’. In particular, cheese made from raw milk that has undergone ripening, such as blue cheeses or white mould cheeses, is risky. Examples include ‘Camembert au lait cru’, ‘Reblochon’ cheese and ‘Brie de Coulommiers’. Curd cheese, cottage cheese and cheese spreads use heat-treated milk and therefore do not pose a great risk.

- Ready-to-eat smoked fish, such as smoked salmon or eel from the chilled section. Because pre-packaged smoked fish may be stored for a long time, any *Listeria* bacteria can multiply to harmful levels.
- Raw animal products such as raw meat, raw egg, raw milk, raw shellfish and raw fish, such as in sushi and herring.

The products listed above can however be eaten if you heat them thoroughly.

Toxoplasma gondii

Toxoplasma gondii is a parasite that can kill the unborn child in the first months after a pregnant woman becomes infected. In the later stages of pregnancy, the disease can cause severe and permanent damage to the baby's eyes and brain. Infected children who are born without symptoms can also develop eye abnormalities later.

To prevent infections, the following advice applies for the population at large:

- Heat meat right through. So do not taste raw mince either.
- Wash cooking utensils and your hands throughout with soap and hot water after contact with raw meat.
- Wash raw vegetables and fruit thoroughly under running water. Vegetables taken from natural soil need particular attention.
- Wash your hands regularly, especially after contact with raw meat, after cleaning the cat litter, after gardening and (for children) after playing in the sandpit.
- If you have a cat, its litter tray should be cleaned daily. Do not dispose of cat litter in the organic waste container, but treat it as normal household waste.
- Children's sandpits should be covered with a lid or net so that cats cannot get in.

Freezing meat at -12°C for at least 2 days kills the *Toxoplasma gondii* parasite. Meat and meat products that have been properly frozen are safe to eat.

There are additional points that pregnant women should pay specific attention to.

- Do not eat raw meat or raw meat products such as filet américain. Do not eat raw processed meat products such as delicatessen sausages, salami and delicatessen roast beef.
- Do not eat soft raw milk cheeses, also because of the risk of *Listeria*. The ingredients label on raw milk cheeses states 'rauwe melk' or 'au lait cru'.
- Make sure the cat litter box is changed daily during pregnancy and preferably either do not do this yourself or wear gloves.
- Wear gloves when gardening.

Other microorganisms

There are no specific recommendations for pregnant women.

The recommendations for the general population for preventing food-borne infections are the following:

- Hygienic working practices let the mother-to-be minimise the risk of harm to her own health and that of the unborn child from food-borne infections. Tips for hygienic working practices have been collated in a card entitled “5x safe for pregnant women” with tips for buying, washing, separating, heating and cooling foods.
- In addition, there are specific recommendations for the products that are most frequently contaminated: Animal products, such as meat, eggs, dairy products, fish and seafood are the main causes of food-borne infections in the Netherlands. Raw animal products in particular pose a risk and are not recommended during pregnancy.
- Additionally, there have been incidents in recent years where raw fruit and vegetables have also led to relatively large outbreaks. Washing fruit and vegetables thoroughly can reduce the risk. Because vegetable sprouts are particularly susceptible to contamination, it is recommended that they should be heated before consumption.

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.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity.
The reports are available to the public.

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