This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

TOX/2024/23

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

First Draft Statement on the Potential Health Effects of Raspberry Leaf Tea in the Maternal Diet

Introduction

1. As part of the COT's current programme of work assessing risks from the maternal diet, to feed into the Scientific Advisory Committee on Nutrition's (SACN) review of nutrition and maternal health, focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery, in 2020 the COT considered a scoping paper which reviewed commonly used herbal supplements during pregnancy. These were promoted by anecdotal evidence and unofficial sources as having various purported benefits.

2. The review was confined to herbal dietary supplements which would be regulated as foods and which would not be considered to be traditional herbal medicines within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA). Among those investigated was raspberry leaf, which is most commonly taken during pregnancy to stimulate and facilitate labour and to shorten its duration.

3. The COT agreed that raspberry leaf required further consideration, noting that human, animal and *in vitro* data were available. The main areas of concern included general toxicity to the mother, effects on the development of the fetus or embryo and possible interactions with drugs. Others included potential effects on offspring and on uterine contractility. A more extensive literature search was undertaken to evaluate the safety of raspberry leaf use during pregnancy, and a scoping paper produced, which was considered by the COT at its September 2022 meeting.

4. Members considered that the risk associated with raspberry leaf consumption during pregnancy was low, but with a high level of uncertainty. This conclusion was based primarily on the results of two human studies identified in the literature search, a retrospective cohort study and a double-blind, placebo-controlled, randomised trial. Neither study reported adverse effects to mother or child associated with raspberry leaf consumption during pregnancy. However, Members did note that the dose of raspberry leaf tea tested in the trial was several times lower than an exposure estimate based on data provided by the FSA's exposure assessment team.

5. In addition, a limited number of reports of raspberry leaf exposure during pregnancy had been received by the UK Teratology Information Service (UKTIS) since its inception in 1983 to the present date, with no evidence of adverse effects at normal consumption levels.

6. COT Members considered that it was not possible to identify any point of departure for use in risk assessment for various reasons. These included the lack of data available on the active components of raspberry leaf; the potential for the sampling and the preparation method to affect the activity of the supplement; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction), which appeared to depend on a number of factors, such as the species, preparation and whether it was tested *in vitro* or *in vivo*; and uncertainty regarding the most appropriate animal model for studying raspberry leaf's effects in humans. Limited data were available on the pharmacokinetics of raspberry leaf, although there were indications in the literature that it was less toxic when administered orally rather than parenterally. Limited reproductive toxicity data were available, and only one study, in mice, appeared to have evaluated it for sub-acute toxicity. Finally, the potential for contaminants such as cadmium, and pesticide residues, was noted.

7. Members commented that one of the reasons why raspberry leaf appeared to be of low concern to human health, based on the safety data available, was low bioavailability. However, concern was expressed that if raspberry leaf extracts were

reformulated, such as by micronisation or microencapsulation, as has been done for some other supplements such as cannabidiol (CBD) and turmeric, this might increase bioavailability. The safety of any such products may need to be evaluated separately.

8. The scoping paper (TOX/2022/50) and minutes of the meeting are available online at COT Meeting: 6th September 2022 | Committee on Toxicity (food.gov.uk).

9. A draft Statement has been prepared, incorporating Members' comment, which is included at Annex A.

Questions for the Committee

The Committee are asked to consider the following questions:

a) Does the Committee have any comments on the structure or content of the draft Statement?

b) Does the Committee consider that any further information should be included in the risk characterisation and/or conclusions sections on the results of animal studies?

c) Does the Committee have any other comments?

Secretariat
June 2024

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Annex A to TOX/2024/23

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

First draft statement on the potential health effects of raspberry leaf tea in the maternal diet

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on “The influence of maternal, fetal and child nutrition on the development of chronic disease in later life” (SACN, 2011) and on “Feeding in the first year of life” (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.

2. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery. SACN agreed that, where appropriate, other expert committees would be consulted and asked to complete relevant risk assessments. A provisional list of chemicals was proposed by SACN Members. However, this was subject to change following discussion by the COT. A scoping paper was presented to the Committee to define the scope of the work from a toxicological safety perspective, and also requesting their input on the selection of candidate chemicals or chemical classes that could be added or removed.

3. As part of this work, the Committee decided it would be useful to consider the use of herbal supplements during pregnancy. A scoping paper reviewed the commonly used herbal supplements during pregnancy. These were promoted by anecdotal evidence and unofficial sources as having various purported benefits. The

review was confined to herbal dietary supplements which would be regulated under food law and which would not be considered to be traditional herbal medicines within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA). Among those investigated was raspberry leaf, which is most commonly taken during pregnancy to stimulate and facilitate labour and to shorten its duration.

4. Following this review, the COT agreed that raspberry leaf required further investigation, noting that human, animal and *in vitro* data were available. The main areas of concern included general toxicity to the mother, effects on the development of the fetus or embryo and possible interactions with drugs. Others included potential effects on offspring and on uterine contractility.

5. Based on the COT's recommendations, a more extensive literature search was undertaken to evaluate the safety of raspberry leaf use during pregnancy (for full details of the search method, see Appendix 1). This statement summarises the conclusions drawn by the Committee.

Background

Uses

6. Leaves of the red raspberry plant (**Rubus idaeus**) have been used medicinally in Europe since as early as the sixth century (Beckett *et al*., 1954). The plant is native to Europe, North America and temperate Asia. However, it is mainly grown for commercial use in central and eastern Europe, especially Bulgaria, Macedonia and Romania (European Medicines Agency (EMA), 2014).

7. Traditionally, raspberry leaf has been used for a range of applications, including relieving menstrual cramps and diarrhoea, as an astringent mouthwash and as a treatment for conjunctivitis (EMA, 2014). However, it is most commonly consumed during pregnancy to stimulate and facilitate labour and to shorten its duration, with a prevalence of use among pregnant women as high as 38%, based

on a recent survey in Australia (Farnaghi and Braniff, 2022). In a survey of herbal remedy use performed at the antenatal clinic at Norfolk and Norwich University hospital between November 2007 and February 2008, 23.7% of expectant mothers who responded to the survey reported taking raspberry leaf (Holst *et al*., 2011). Typically, it is taken as tea or tablets but occasionally as a tincture (Simpson *et al*., 2001). Other alleged benefits of raspberry leaf during pregnancy include: alleviation of morning sickness; prevention of post-partum haemorrhage, miscarriage and Braxton Hicks contractions; and stimulation of breast milk production (Patel *et al*., 2004; EMA, 2014).

Health-Based Guidance Values

8. Despite its long history of use, limited research has been undertaken to investigate the safety, efficacy or mechanism of action of raspberry leaf (Bowman *et al*., 2021). Therefore, there are no health-based guidance values (HBGVs) for raspberry leaf use during pregnancy.

Constituents

9. It is unclear what the active constituents of raspberry leaf might be (EMA, 2014). However, it is known to contain a range of different components. Some of the main groups of chemicals in raspberry leaf include: hydrolysable tannins, such as gallotannins; flavonoids, such as kaempferol, quercetin and quercetin glycosides; small quantities of volatile compounds, such as octanol; terpenoids, such as terpinolene; vitamins C and E; minerals, such as calcium, magnesium and zinc; and phenolic acids, such as caffeine and chlorogenic acid (Gudej and Tomczyk, 2004; EMA, 2014).

Existing authorisations

10. In their review on the safety of raspberry leaf, the EMA's Committee on Herbal Medicinal Products (HMPC) highlighted that while clinical studies had not found a higher incidence of adverse pregnancy outcomes associated with raspberry leaf treatment, treatment durations had generally been short and only a small number of pregnant women were included in the trials (EMA, 2014). It was also highlighted that there were insufficient data on genotoxicity, carcinogenicity, reproductive and developmental toxicity.

11. Due to a lack of genotoxicity data, including the minimum required data on mutagenicity (Ames test), the HMPC could not recommend adding raspberry leaf to the Community list of herbal substances, herbal preparations and combinations thereof for traditional medicinal products (EMA, 2014). Nor did it consider the data on clinical efficacy robust enough to meet the criteria for "well-established medicinal use," in accordance with Directive 2001/83/EC.

12. Overall, the HPMC concluded that the evidence regarding the efficacy and safety of raspberry leaf during pregnancy and lactation was lacking and that raspberry leaf could not be recommended for pregnant or lactating women, or in children and adolescents under 18 years of age (EMA, 2014).

Mechanism of action

In vitro and animal studies

13. The mechanism by which raspberry leaf may exert its alleged therapeutic effects during pregnancy is poorly understood (Bowman *et al*., 2021). Hastings-Tolsma *et al*. (2022) hypothesised that raspberry leaf's role in promoting parturition may be related to: its inflammatory, vasodilatory and antioxidant effects; its ability to promote apoptosis in cervical and myometrial cells; and the effects of the isoflavone genistein. However, limited and at times contradictory evidence was given to support these claims.

14. Six studies were identified which had investigated the effects of raspberry leaf extract(s) on uterine and other types of smooth muscle *in vitro* and or in animals (Burn and Withell, 1941; Beckett *et al*., 1954; Bamford *et al*., 1970; Rojas-Vera, Patel and Dacke, 2002; Zheng *et al*., 2010; Olson and DeGolier, 2016). However, results from these studies were highly variable, with some reporting a stimulatory effect and others reporting a relaxant effect. These differences have been attributed to differences in raspberry leaf preparations, dosages, extraction methods, animal tissue, the pregnancy status of the uterus/uterine tissue, baseline muscle tone, and whether or not the raspberry leaf was tested *in vitro* or *in vivo* (Bowman *et al*., 2021).

Human studies

15. A case series by Whitehouse (1941) reported the effects of 1.30-2.59 g crude raspberry leaf extract or 20 oz. 5 % raspberry leaf tea, administered via a uterine bag, on the uterine muscle of three post-partum women. Based on the findings, it was concluded that: “the main effect [of raspberry leaf was] relaxation of the uterine muscle.”

Toxicity studies

In vitro and animal studies

Acute toxicity

16. No adverse effects were observed in mice when aqueous raspberry leaf extract containing the equivalent of 2 g extract, was orally administered to mice (Burn and Withell, 1941). However, death was observed in mice following intravenous administration of 4 g/mL aqueous raspberry leaf extract (Burn and Withell, 1941) and in chicks following intraperitoneal administration of a raspberry leaf extract containing the equivalent of 0.1 g leaf (with cyanosis and heart dilation occurring in mice given an equivalent intraperitoneal dose of the same extract) (Beckett *et al*., 1954).

Subacute toxicity

17. Only one study was identified which had assessed the sub-acute toxicity of raspberry leaf (Yang *et al*., 2019). During the study, different raspberry leaf preparations were administered to eight-week old, ICR male mice by oral gavage over two weeks at a dose of 100 mg/kg/bw/day (containing 15-55 % gallic acid-equivalent polyphenols). The preparations included an ethanolic raspberry leaf extract (RLE); an ethanolic extract subjected to high temperature and high pressure treatment (RLE-H); and a raspberry leaf powder (RLP).

18. The study assessed body weight, adiposity, relative organ weights (heart, lung, liver, spleen, kidney, testis, fat pad) and time to exhaustion in a swimming test. None of the mice given RLP, RLE or RLE-H died or exhibited visible signs of disease over the two-week study period (Yang *et al*., 2019). Final body weight, adiposity index and body mass index in the RLE and RLE-H groups were statistically significantly decreased compared to the control and RLP groups. Relative weights of testes were statistically significantly increased in all treated groups compared to the control group. Exhaustion swimming times in the RLE and RLE-H group were statistically significantly increased compared to the control and RLP groups. Adverse intestinal flatulence was observed in the RLE and RLE-H groups, which the authors suggested may have been due to the high intakes of ellagic acid in the groups receiving these extracts. In a repeated study, RLE with pectin and sodium alginate with boiling water was prepared into a gelled food for the mice. Similar effects were observed as for RLE in the initial study, except that body weight was not decreased and intestinal flatulence was not observed.

Cytotoxicity

19. An aqueous raspberry leaf extract and “five-seeds” formulation were both found to exhibit cytotoxicity towards HEK 293 and Chang liver (HeLa derivative) cells *in vitro*, at concentrations of 1-100 mg/mL (Teo *et al.*, 2021). The “five-seeds” formulation contained aqueous extracts from raspberry leaf, **Lycium barbarum,**

Cuscuta chinensis Lam, Schisandra chinensis and Plantago asiatica in a 1:1:1:1:1 ratio. The formulation exhibited higher IC_{50} values than the raspberry leaf extract alone when tested on HEK 293 cells (33 mg/mL vs. 21.2 mg/mL) and Chang liver cells (38.5 mg/mL vs. 20.1 mg/mL). The proportion of SubG1 (apoptotic) Chang liver cells was also found to be considerably lower following treatment with a 25 mg/mL formulation compared with when they were treated with an equivalent concentration of raspberry leaf extract (10.17% vs. 30.37%). Therefore, the authors concluded that the “five seeds” formulation appeared to have modulated the toxicity of the individual herbs used to make it.

Genotoxicity

20. No studies which had investigated the genotoxicity or carcinogenicity of raspberry leaf were found.

Reproductive and developmental toxicity

21. Limited numbers of studies were available which had investigated the reproductive effects of raspberry leaf during pregnancy. Of those identified, three involved pregnant mice or rats given raspberry leaf extracts orally, from the point breeding was confirmed until parturition (Johnson *et al.*, 2009; Makaji *et al.*, 2011; Hastings-Tolsma *et al.*, 2022). A range of effects was reported in these studies.

22. In the first study, pregnant nulliparous Wistar rats were administered 10 mg/kg bw/day commercially available raspberry leaf extract in gelatine capsules or an equivalent dose of the raspberry leaf components kaempferol or quercetin (Johnson *et al*., 2009). Raspberry leaf exposure during pregnancy was associated with a significant increase in the length of gestation, a significant reduction in time to vaginal opening in the F1 offspring, together with significant growth restriction of F2 offspring, compared with untreated controls. There was also a non-statistically significant reduction in pregnancy success rate. Compared with the control group, dams given quercetin had significantly increased weight gain during pregnancy.

Johnson *et al*. (2009) concluded that: “in Wistar rats, exposure to raspberry leaf extract throughout pregnancy [increased] gestation length and [resulted] in altered reproductive development and function in the offspring…which [raised] concerns about the safety of this herbal preparation for use during pregnancy.”

23. In the second study, pregnant nulliparous Wistar rats were given 10 mg/kg bw/day of another commercially available extract (containing the equivalent of 0.2-0.4% quercetin and kaempferol and 2-7% ellagic acid) or an equivalent dose of the raspberry leaf components kaempferol, ellagic acid or quercetin (Makaji *et al.*, 2011). Hepatic microsomes were prepared from offspring on postnatal days (PND) 1, 21, 65 and 120 and used to test the biotransformation rates of eight substrates. Maternal consumption of raspberry leaf tea resulted in increased biotransformation rates for three of the substrates by female offspring at PND120. Similar results were also observed for quercetin and kaempferol. These were considered to be more male profiles, since biotransformation rates were higher in control male than control female offspring. The authors concluded that maternal consumption of either raspberry leaf or some of its components lead to long term alterations in the CYP activity of female offspring. If applicable to humans, they suggested that the long term effects associated with consuming raspberry leaf or its constituents during pregnancy may be inappropriately rapid biotransformation of pharmaceuticals, leading to treatment failures; increased activation of xenobiotics, leading to increased tumour formation; and altered steroid hormone biotransformation, leading to adverse reproductive health/fertility.

24. The third study gave C57BL/6N Tac mice **ad libitum** access to water bottles throughout pregnancy, containing 1.78 or 2.66 mg/mL raspberry leaf extract (Hastings-Tolsma *et al*., 2022). Compared with untreated controls, both raspberry leaf groups exhibited significant reductions in litter size (viable and non-viable). The high-dose group also exhibited increased fluid consumption and significant reductions in pup weight gain at postnatal days four and five. According to the authors, the changes in the high-dose group were accompanied by a trend towards reduced gestation length, although this was not statistically significant. There were

no statistically significant differences in measures of neurodevelopment, assessed through pup locomotive abilities including time to righting, orienting response, cliff avoidance and swimming development. However, the authors suggested there were trends towards effects with maternal raspberry leaf consumption, which were more marked in the high dose group. The authors concluded that when ingested throughout gestation in mice, raspberry leaf may impact length of gestation, fluid intake during pregnancy, litter size and viability, as well as pup development.

25. A fourth reproductive study was also identified, involving immature Sprague-Dawley rats (Graham and Noble, 1955). The authors reported that when the rats were subcutaneously injected with 0.4 mL fresh or dried raspberry leaf extracts and 100 I.U. μg^{-1} pregnant rat serum they exhibited marked reductions in ovarian weight within three days compared with untreated controls (given pregnant rat serum only). The extracts were mixed with the serum *in vitro* and contained the equivalent of 0.8-18 mg raspberry leaf. Based on the findings, the authors concluded that raspberry leaf "possessed an appreciable amount of [*in vitro* anti-gonadotrophic] activity."

Drug-herb interactions

26. A study by Langhammer and Nielsen (2014) found that ethanolic raspberry leaf extracts prepared from commercially available capsules were capable of inhibiting recombinant human CYP enzymes *in vitro*. These included CYP1A2, CYP2D6 and CYP3A4, with IC_{50} constants ranging from 44-81 µg/mL. The authors concluded that clinically relevant systemic CYP inhibitions could be possible for raspberry leaf, and that it might cause clinically relevant inhibition of intestinal CYP3A4.

27. Holst *et al*. (2011) administered a self-completed survey of herbal remedy use during pregnancy, which looked at parallel use of other pharmaceuticals. The survey was given to 1,037 expectant mothers who were at least 20 weeks pregnant and who presented at an antenatal clinic at Norfolk and Norwich University Hospital. Of the 578 respondents (response rate 55.7 %), 232 (40.1 %) reported using both

herbal remedies and pharmaceuticals during pregnancy. It is unclear what the other pharmaceuticals were or whether the women experienced any adverse effects. However, the authors commented that four women reported simultaneous use of iron and a tannin-containing herb (raspberry leaf, chamomile or valerian). They noted that tannin-containing supplements may interfere with iron absorption, which should be taken into account in anaemic patients. However, no studies were identified in the present review which had evaluated the effects of raspberry leaf tea on iron absorption.

Human studies

28. Several human toxicity studies were identified on the safety of raspberry leaf use during pregnancy (Parsons *et al.*, 1999; Simpson *et al.*, 2001; Nordeng *et al.*, 2011). This included several case reports of adverse effects experienced by pregnant women or their newborns after taking raspberry leaf, ranging in severity from petechiae to acute liver injury (UKTIS data; MacPherson and Kilminster, 2006; Wedig and Whitsett, 2008; EMA, 2014; Cheang *et al.*, 2016; Koenig, Callipari and Smereck, 2021). However, limited information was available in these case reports about the doses taken, and it was uncertain whether the adverse effects described were related to raspberry leaf consumption or to other factors, such as the use of other herbal products described in several of them (MacPherson and Kilminster, 2006; Wedig and Whitsett, 2008; Koenig *et al.*, 2021). In some cases, the authors attributed the adverse effects to other products consumed, such as evening primrose oil (Wedig and Whitsett, 2008) or blue cohosh (MacPherson and Kilminster, 2006).

29. Two publications noted that there had been some suggestion in the lay press that raspberry leaf might promote human miscarriage or abortion (Simpson *et al.*, 2001; Johnson *et al.*, 2009). However, the authors of both papers concluded that there was limited evidence to support this.

30. One of the main human toxicity studies which the COT considered in its evaluation was a retrospective cohort study by Parsons *et al.* (1999). The study was conducted at hospitals in Sydney, Australia. It included a convenience sample of 57 postnatal women who reported using raspberry leaf during pregnancy and a control group of 51 women randomly selected from the hospital database who stated that they had not used raspberry leaf during pregnancy. The groups were otherwise considered comparable. The women in the study who consumed raspberry leaf reported having done so either as tea (56.1%), tablets (40.4%) or a combination of tea, tablets and tinctures (3.5%), from as early as eight weeks' gestation for 1-32 weeks. Doses ranged from 1-8 cups of tea or tablets daily but only included a single dose of tincture, taken by one woman. No further information was provided about the doses taken or how they were prepared.

31. Parsons *et al.* (1999) identified no adverse effects associated with raspberry leaf consumption, based on information from the hospital obstetric database and participants' medical records. There was no significant difference in maternal blood loss, babies' Apgar scores at five minutes of age, pre-labour maternal diastolic blood pressure or transfer to a special/intensive care baby unit. Nor was there any significant difference in the length of gestation, likelihood of labour augmentation, incidence of meconium liquor, need for an epidural or length of each of the three stages of labour. Raspberry leaf users had a shorter mean duration of the first stage of labour compared with the control group, though this was not statistically significant. There was also a trend towards raspberry leaf users being less likely to require an artificial membrane rupture, caesarean section, forceps or vacuum birth. The authors concluded that: "the findings [suggested] that the raspberry leaf herb [could] be consumed by women during their pregnancy…to shorten labour with no identified side effects for…women or their babies" (Parsons *et al.*, 1999).

32. The other main human toxicity study that the COT considered was a double-blind, randomised, placebo-controlled trial carried out by Simpson *et al*. (2001). The study, which was also carried out in Sydney, Australia, aimed to evaluate the safety and efficacy of raspberry leaf tablets in shortening and easing labour when

consumed from 32 weeks' gestation. The sample consisted of 192, low-risk nulliparous women (mostly Caucasian) with a healthy pregnancy, who were randomised to receive either a placebo or raspberry leaf tablets containing 2.4 g extract daily with food in two separate, 1.2 g doses (n=96 women per group).

33. There were no adverse effects that could be directly attributed to the raspberry leaf, except possibly constipation, which was exclusively observed in four of the raspberry leaf participants (Simpson *et al.*, 2001). Similarly, there were no significant differences between the raspberry leaf and placebo groups with respect to other safety outcomes, including maternal blood loss; maternal diastolic blood pressures; newborn Apgar score at five minutes; presence of meconium-stained fluid; or newborn birth weight (Simpson *et al.*, 2001). The babies in the placebo group tended to have a higher average Apgar score at five minutes, with a narrower spread of measures, but this difference was not statistically significant. A slightly higher proportion of babies from the raspberry leaf group were admitted to the Neonatal Intensive Care Unit or Special Care Nursery within 24 hours of birth (5.2% compared to 3.7%). However, no statistical evaluation of this difference was presented. The authors noted that the frequency of admissions in the raspberry leaf group was still below the average admission rate for term babies born within the participating hospital at the time of the study.

34. There were no statistically significant differences reported with respect to any of the efficacy outcomes, such as emergency caesarean rate (Simpson *et al.*, 2001). However, based on the findings, it was concluded that a raspberry leaf dose of 2.4 g/day appeared to be safe for mother and baby.

35. The COT also considered data collected by the UK Teratology Information Service (UKTIS) to be of importance in its evaluation. Since its inception in 1983, UKTIS had received six reports of accidental or "therapeutic" raspberry leaf exposure (tea or tablets) during pregnancy. Limited information was available about the dose or timing of exposure but pregnancy outcomes for the six women were normal, except for one, who gave birth to a child with cerebral palsy following a delayed

delivery. One of the women had accidentally consumed large quantities of 400 mg raspberry leaf tablets and experienced nausea and diarrhoea but no pregnancy-related symptoms. She gave birth to a normal, liveborn infant at 40 weeks.

Contaminants

36. Few studies were found which had investigated potential contaminants in raspberry leaf.

37. During a study by Veatch-Blohm *et al*. (2021), Pb, Ni and Cu were not detected in a commercial raspberry leaf supplement sold in the USA. However, Cr (0.42 µg/g) and Zn (1.90 µg/g) were both detected. The authors noted that intakes of Zn would be within the tolerable upper intake level (TUL) established by the Institute of Medicine US Panel on Micronutrients in 2001 (40 mg/day). The metal levels in this study were compliant with the limits laid down for supplements within retained EU Commission Regulation (EC) No.1881/2006, as amended.

38. Several fungal species were detected in the raspberry leaf supplement, (**Aspergillus fumigatus**, **Microsporum** sp. and **Nocardia brasiliensis**), which the authors suggested may be of concern in immunocompromised individuals (Veatch-Blohm *et al*., 2021).

39. The heavy metals Cd, Hg and Pb were detected in raspberry leaf in one study collected from farms located in eastern Poland between 2015 and 2018 at concentrations ranging from <0.005-0.613 mg/kg, while As was not detected (<0.1 mg/kg) (Kowalska, 2021). All were within WHO-recommended limits, except for Cd, which was found at levels of 0.211-0.613 mg/kg (WHO recommended limit: 0.3 mg/kg) (Kowalska, 2021). The levels of Cd, Pb and Hg were within the legal limits for supplements established by retained EU Commission Regulation (EC) No. 1881/2006, as amended.

40. Sadło *et al.* (2015) reported on the results of field studies of pesticides applied at a commercial raspberry plantation. Various pesticides were applied in accordance with current pest control programmes and according to the instructions on their labels, and residues in both the fruit and leaves were reported. Residues of boscalid, cypermethrin, pyrimethanil, pyraclostrobin and chlorpyrifos were detected in the leaves at concentrations ranging from 0.15-30.64 mg/kg on the first day of harvesting, and these residues decreased each week during the harvesting period (Sadło *et al.*, 2015). Pesticide residues in the fruit were within their respective MRLs, while residues in the leaves exceeded their respective maximum residue levels (MRLs) for herbal infusions (leaves and herbs) established by EU Regulation (EC) No. 396/2005. Dietary intakes were estimated based on an assumed daily consumption of dry leaves equivalent to a fresh weight of 7 g, and a body weight for an adult consumer of 76 kg. The highest estimated daily intake was for boscalid, which was up to 6.63% of its ADI established in the EU of 0.04 mg/kg bw, based on the analytical result for the first day of harvesting.

Exposure assessment

41. Raspberry leaf is typically consumed during pregnancy as tea (fresh or dried leaf preparations), tablets or tinctures (EMA, 2014; Bowman *et al.*, 2021). Different recommendations exist as to when women should commence raspberry leaf use during pregnancy; most online sources suggest taking it from the third trimester, typically as tea or tablets, while others suggest taking it from the second or even first trimester (Appendix 2).

42. While not specific to raspberry leaf, data from the National Diet and Nutrition Survey (NDNS) on chronic herbal and fruit tea consumption among women of childbearing age (16-49 years) may provide an indication of raspberry leaf tea intake during pregnancy and is displayed in Tables 1a and 1b (without recipes). The data suggest that women within this age group consume a mean of 4.5 mL/kg bw/day or 16 mL/kg bw/day at the 97.5th percentile, as consumed This corresponds to a mean

of 0.045 g/kg/bw/day herbal or fruit tea or 0.16 g/kg/bw/day at the 97.5th percentile on a dried basis.

43. Significantly, it is still unclear as to what the active components in raspberry leaf are (Bowman *et al.*, 2021). However, some raspberry leaf components, such as polyphenolic compounds, may vary in concentration between different raspberry leaf preparations, depending on area of cultivation, in a way which may affect their bioactivity and potentially also their toxicity (Venskutonis *et al.*, 2007). Nor does NDNS data capture consumption data for pregnant or lactating women and so while the data in Tables 1a and 1b are based on women of childbearing age, they may not necessarily be representative of the maternal diet. Therefore, consumption data for raspberry leaf tea, tablets and tinctures were also estimated during each trimester based on dose recommendations gathered from online sources by the FSA's exposure team. These are displayed in Tables 2a and 2b.

44. Assuming that one teabag represents 2 g tea, that a single cup holds 350 mL fluid and that capsules contain 100% dried raspberry leaf, online sources suggest that raspberry leaf consumption ranges from 350-1,750 mL/person/day for tea, 16-24 mL/person/day for tinctures and 900-2,400 mg/person/day for tablets during pregnancy, as consumed. In terms of dried weight, this corresponds to 2-10 g/person/day for tea, 0.014-0.021 g/person/day for tinctures and 0.9-2.4 g/person/day for tablets.

45. A retrospective cohort study suggested that at least 3.5% of women may use a combination of raspberry leaf tea, tablets and tinctures during pregnancy (Parsons *et al.,* 1999). Therefore, the FSA's Exposure Team calculated consumption values for raspberry leaf during pregnancy, assuming combined use of tea, tablets and or tinctures in order to cover different worst-case exposure scenarios. These values are displayed in Table 3 and were based on online dose recommendations during the third trimester, which is when raspberry leaf appears to be taken most commonly. It is apparent that the consumption level resulting from combined use of raspberry leaf tea, tablets and tinctures may reach up to 12.421 g/person/day.

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Table 1a. Estimated chronic consumption of herbal and fruit teas as consumed (without recipes)*[ab.]

Consumers (n)	**Mean (mL/person/day)**	**97.5th percentile (mL/person/day)**	**Mean (mL/kg bw/day)**	**97.5th percentile (mL/kg bw/day)**	**Respondents in population group (n)**
364	290	1100	4.5	16	2556

*Rounded to 2 significant figures.

[a]Based on females aged 16-49 in NDNS years 1-11.

[b]Conversion factor of 0.99 used to convert tea from dry weight to as consumed.

Table 1b. Estimated chronic consumption of herbal and fruit teas dry weight (without recipes)*[ab.]

Consumers (n)	**Mean (g/person/day)**	**97.5th percentile (g/person/day)**	**Mean (g/kg bw/day)**	**97.5th percentile (g/kg bw/day)**	**Respondents in population group (n)**
364	2.9	11	0.045	0.16	2556

*Rounded to 2 significant figures.

[a]Based on females aged 16-49 in NDNS years 1-11.

[b]Conversion factor of 0.01 used to convert tea as consumed to dry weight.

Table 2a. Raspberry leaf-containing teas, tinctures and tablets summary table of suggested serving sizes on an as-consumed basis (data pooled from online sources in Appendix 2).

Stage of pregnancy	**Suggested serving size per day (as consumed) Tea (mL) *[a]**	**Suggested serving size per day (as consumed) Tincture (mL)**	**Suggested serving size per day (as consumed) Capsules/tablets (mg)**
1st trimester	350	N/a	N/a
2nd trimester	700	N/a	N/a

3rd trimester	350 – 1,750	16 – 24	900 – 2,400

*Calculated on the assumption that 1 teabag contains approximately 2 g of tea.
[a]Calculated on the assumption that a large mug holds approximately 350 mL of tea.
N/a = no sources recommending consumption.

Table 2b. Raspberry leaf-containing teas, tinctures and tablets summary table based on dry weight of raspberry leaf consumed (data pooled from online sources in Appendix 2).

Stage of pregnancy	**Suggested serving size per day (as consumed) Tea (g)***	**Suggested serving size per day (as consumed) Tincture (g)[a]**	**Suggested serving size per day (as consumed) Capsules /tablets (g)[b]**
1st trimester	2	N/a	N/a
2nd trimester	4	N/a	N/a
3rd trimester	2-10	0.014-0.021	0.9 – 2.4

*Calculated on the assumption that 1 teabag contains approximately 2 g of tea.
[a]Calculated on the assumption that the tincture was made 1:1 weight to volume ratio. Assumption that fresh leaf is 77.75 % moisture content of nettle leaves.
[b]Assumption that capsules contain 100% dried raspberry leaf tea.

Table 3. Combined consumption scenarios of raspberry leaf tea (dry weight) in the third trimester.

Estimated consumption of dry raspberry leaf (g per day) Tea	**Estimated consumption of dry raspberry leaf (g per day) Tincture**	**Estimated consumption of dry raspberry leaf (g per day) Capsule**	**Estimated consumption of dry raspberry leaf (g per day) Total consumed per day**
2-10	0.014-0.021	0.9-2.4	2.914 – 12.421
2-10	0.014-0.021	N/a	2.014 – 10.021
2-10	N/a	0.9-2.4	2.9 – 12.4
N/a	0.014-0.021	0.9-2.4	0.914 – 2.421

Risk characterisation

46. The COT considered the breadth of evidence available on the safety of raspberry leaf during pregnancy, dating back to the 1940s. It was noted that many of the animal studies identified in the literature search were older. Therefore, they did not meet the requirements for reporting of botanicals or current animal welfare regulations and ethical standards. The Committee highlighted that it did not endorse these studies but considered that they were performed in accordance with the guidelines available at the time when they were published. Therefore, information from these studies was considered in the COT's assessment.

47. The Committee was unable to establish a point of departure for raspberry leaf due to significant uncertainties. The main sources of uncertainty identified included: the lack of data available on the active components of raspberry leaf; the potential for the preparation method to affect the activity of the supplement and the sampling effect; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction), which appeared to depend on numerous factors, such as the species, preparation and whether extracts were tested *in vitro* or *in vivo*; and the lack of clarity in the literature as to the most appropriate choice of animal model for studying raspberry leaf's effects in humans.

48. Another source of uncertainty included the limited data available on the pharmacokinetics of raspberry leaf. However, it was noted that there were indications in the literature that it was less toxic when administered orally, rather than parenterally, based on studies in mice and chicks given the equivalent of 0.1 g leaf or 2 g extract (Burn and Withell, 1941; Beckett et al., 1954). Members also identified that there was limited data on the reproductive toxicity of raspberry leaf and that only one study, conducted in ICR male mice given different extracts over a two-week period (100 mg/kg bw/day), appeared to have evaluated it for sub-acute toxicity (Yang et al., 2019).

49. Limited data were available on levels of contaminants, such as heavy metals, and pesticide residues.

50. The Committee considered the reproductive toxicity study conducted by Hastings *et al*. (2022). The authors of the study reported finding a statistically significant reduction in litter size among C57BL/6N Tac mice given aqueous raspberry leaf extracts orally throughout pregnancy containing 1.78 or 2.66 mg/mL raspberry leaf extract, compared with untreated controls. Members considered that the results of the study were of low concern, as the mouse strain used was not a standard choice of animal model and the standard error bars for the treatment and control groups overlapped, casting doubt on the statistical significance of the findings. It was also unclear as to how much raspberry leaf extract the mice were exposed to, as the mice were given free access to water bottles containing the extract.

51. Although there was a high degree of uncertainty, Members considered that the available human data indicated that the risk associated with raspberry leaf consumption during pregnancy is low. This was based on the results of the two Australian human safety studies identified in the literature search. These included a retrospective cohort study by Parsons *et al.* (1999), involving a control group of 51 women and a group of 57 women who reported taking raspberry leaf for 1-32 weeks during pregnancy, including 1-8 cups/tablets, or a single tincture. The other was a double-blind, placebo-controlled, randomised trial by Simpson *et al*. (2001), involving 192 nulliparous women with a healthy pregnancy, who were randomised to receive either a placebo or raspberry leaf tablets containing 2.4 g extract daily with food from 32 weeks' gestation (as two separate 1.2 g doses).

52. Neither study reported adverse effects to mother or child associated with raspberry leaf consumption during pregnancy compared with controls. However, Members noted that the estimated consumption of raspberry leaf from tea (up to 10 g/person/day) or combined sources (up to 12.421 g/person/day), based on data collected from online sources by the FSA's exposure team, were up to four or more times higher than the raspberry leaf dose tested by Simpson *et al*. (2001). Simpson

et al. (2001) stated that they selected a conservative dose level since this was the first study of its kind.

53. The Committee also took into account the limited number of reports of adverse effects in pregnant women taking raspberry leaf or their children received by the UKTIS since its inception in 1983 to the present date. Six reports were received altogether of women who had taken raspberry leaf during pregnancy following accidental or “therapeutic” consumption. Except for one woman, who gave birth to a child with cerebral palsy following a delayed delivery, all had normal pregnancy outcomes. Limited information was available in each case about the dose, timing or duration of raspberry leaf exposure but included in one case, a woman who had taken large quantities of 400 mg raspberry leaf tablets. She experienced nausea and diarrhoea but no pregnancy-related symptoms and gave birth to a normal, liveborn infant at 40 weeks.

54. Members considered that one of the other reasons that raspberry leaf appeared to be of low concern to human health was due to its low bioavailability. However, concern was expressed that if raspberry leaf extracts were micronised, this might increase their bioavailability, meaning that they may need to be evaluated separately in terms of safety.

Conclusions

55. Overall, the COT concluded that the risk associated with raspberry leaf use during pregnancy was low but with high uncertainty. This was based on the results of the two Australian human safety studies, including a retrospective cohort study and a double-blind, placebo-controlled, randomised trial. Neither reported adverse effects in mother or child following raspberry leaf consumption during pregnancy at doses of 1-8 cups of tea/tablets per day or a single dose of tincture, or 2.4 g extract daily, respectively. However, Members noted that the estimated combined consumption of raspberry leaf from tea (up to 10 g/person/day) or from tea, tinctures and capsules combined (up to 12.421 g/person/day), based on data collected from online sources

by the FSA's exposure assessment team, was up to four or more times higher than the raspberry leaf dose tested in the randomised controlled trial.

56. The COT's conclusion was also based on the limited number of reports of adverse effects in pregnant women taking raspberry leaf or their children received by the UKTIS since its inception in 1983 to the present date. Members considered that the low bioavailability of raspberry leaf was probably also why it appeared to be of low concern to human health. However, it was recognised that micronised raspberry leaf products might exhibit increased bioavailability and may require a separate safety evaluation.

57. Members identified various uncertainties in the risk assessment of raspberry leaf. These underpinned the high level of uncertainty in their conclusion on its safety for use during pregnancy and prevented the Committee from establishing a point of departure for raspberry leaf. The main sources of uncertainty identified included: the lack of data available on the active components of raspberry leaf; the potential for the preparation method to affect the activity of the supplement and the sampling effect; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction), which appeared to depend on numerous factors, such as the species, preparation and whether extracts were tested *in vitro* or *in vivo*; and the lack of clarity in the literature as to the most appropriate choice of animal model for studying raspberry leaf's effects in humans. Other sources of uncertainty included the limited data available on the pharmacokinetics and toxicity (including reproductive toxicity) of raspberry leaf, and on levels of contaminants and residues.

Abbreviations

ADI	Acceptable daily intake
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMMC	3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4- methylcoumarin
API	Adiposity percentage
AST	Aspartate transaminase
BFC	7-benzyloxy-4-(trifluoromethyl)-coumarin
BMI	Body mass index
BQ	7-benzyloxyquinoline
bw	Body weight
CEC	3-cyano-7- ethoxycoumarin
CI	Confidence interval
CYP	Cytochrome P450
DES	Diethylbestrol
DMSO	Dimethylsulfoxide
EC_{50}	Half-maximal effective concentration
EFC	7-ethoxy-4-trifloromethyl-coumarin
EMA	European Medicines Agency
ERES	Ethoxyresorufin
FSA	Food Standards Agency
GDM	Gestational diabetes mellitus
HBGV	Health-based guidance value
HPLC	High-performance liquid chromatography
IC_{50}	Half-maximal inhibitory concentration

LCMS/MS	Liquid chromatography mass spectrometry/mass spectrometry
LOQ	Limit of quantification
MFC	7-methoxy-4-(trifuoromethyl)-coumarin
MHRA	Medicines and Healthcare products Regulatory Agency
MRES	Methoxyresorufin
MRL	Maximum residue limit
NDNS	National Diet and Nutrition Survey
NOAEL	No-observed-adverse-effect level
NP	Non-pregnant
RLE	Raspberry leaf extract
RLE-H	High-temperature, high-pressure raspberry leaf extract
RLP	Raspberry leaf powder
SACN	Scientific Advisory Committee on Nutrition
TG2	Transglutaminase 2
TDI	Tolerable daily intake
TUL	Tolerable upper intake level
UKTIS	UK Teratology Information Service
WHO	World Health Organization

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Appendix 1

Search Methodology

1. The following electronic databases were searched for relevant articles published from inception to Apr 2022: LitFetch (which includes material from PubMed, Scopus, Ebsco (Food Science Source) and Springer); ScienceDirect and Cochrane Library. Google and Google Scholar were also searched. The searches were conducted on various dates between 1st Apr 2022 and 22nd Apr 2022.

2. The search terms used included 'raspberry leaf' OR '**Rubus idaeus'** AND: ('safety' OR 'tox*' OR 'pregnan*' OR 'maternal' OR 'exposure' OR 'consumption' OR 'indications' OR 'uses' OR 'childbirth' OR 'transgenerational' OR 'transgenic' OR 'convulsion' OR 'uterine contract*' OR 'development' OR 'interactions' OR 'gestation' OR 'caesarean' or 'contaminant' OR 'heavy metal' OR 'mycotoxin' OR 'pesticide' OR 'residue').

3. The references from extracted papers were searched for citations not captured in the literature search. Only articles published in English were included, due to the linguistic abilities of the reviewer.

4. The UKTIS was also asked for information on any enquiries relating to maternal raspberry leaf use and any reports of adverse effects in pregnant women or their newborn infants received since its inception in 1983 to Apr 2022. This included information relating to the type, dosage, duration and timing of raspberry leaf taken and any pregnancy outcomes captured through follow-up.

Appendix 2

Online Dose Recommendations for Raspberry Leaf During Pregnancy

Source	Tea/Extract	Tablets	Tincture	Preparation
(Jester, no date)	Up to four cups daily.	N/a	N/a	N/a
(Edwards *et al.*, 2015)	4-8 g as an infusion daily.	N/a	4-8 mL (1:1 in 25 % alcohol) three times daily.	N/a
(Mumsnet, no date)	1-3 cups daily as tea after 36-37 weeks of gestation.	N/a	N/a	N/a
(Gerard, 1597, cited in McFarlin *et al.*, 1999)	N/a	N/a	N/a	Tea: 2 g steeped in 240 mL boiling water.
(Kothari, no date)	One cup daily at 32 weeks, increasing to 2-3 cups per day by 37 weeks.	N/a	N/a	N/a
(Birth Eat Love, 2019)	One cup daily, increasing to up to three cups per day in the third trimester, or at approx. 35 weeks.	N/a	N/a	N/a
(Grow a Good Life, 2015)	N/a	N/a	N/a	Tea: 1 tsp per 8-ounce cup of boiling water.
(Bonet, 2021)	1-3 cups daily.	N/a	N/a	N/a
(Cambridge Naturals, no date)	N/a	N/a	N/a	Tea: ‘1-2 teaspoons of dried leaf per cup of hot water’ OR ‘4 tablespoons dried herb in a quart of hot water’ OR ‘4 [tbsp] of the dried leaf in

				a quart of cold water.’
(Parsons, 1999, cited in Palmer, 2018)	Teabag cups: one cup daily during the first trimester; two cups daily during the second trimester; up to 4-5 cups during the last trimester. Loose leaf tea: 2-3 cups per day, especially after 28 weeks of pregnancy.	Two 300/400 mg tablets with each meal (three times daily) from 32 weeks.	Dose dependent on tincture strength.	Loose leaf tea: add 1 tsp of herb to a cup of boiling water, stir, sit for 10 minutes, strain and sip.
(Pregnancy, Birth and Baby, 2021)	1-2 cups daily	N/a	N/a	N/a
(Netmums, no date)	One cup of tea daily at 32 weeks, increasing every few days by one cup until taking 3-4 cups daily.	One tablet daily at 32 weeks, increasing every few days by one tablet until taking 3-4 tablets daily.	N/a	N/a
(Amuse Projects, no date)	One cup of tea per day from 27 weeks of gestation, increasing to 2-4 cups per day by week 35.	N/a	N/a	N/a
(Expectancy, 2022)	One cup daily at approx. 32 weeks, increasing gradually every few days to 3-4 cups.	One tablet (typically available as 300-400 mg doses) daily at approx. 32 weeks, increasing gradually every few	N/a	N/a

		days to 3-4 tablets.		
(Bellybelly, 2011)	At least 2-3 cups (max 4-5) daily during the third trimester but one cup per day during the first trimester is 'fine.'	Two 300-400 mg tablets with each meal three times a day from 32 weeks.	N/a	Tea: add 1 tsp of raspberry leaf to a cup of boiling water.
(Vyne Health, no date)	One cup daily or if not experiencing any uterine sensations, increase to two cups per day (provided at due date or the 37th week).	N/a	N/a	Tea: steep 1-2 tsp raspberry leaf in a cup of boiling water.
(Ellis, no date)	One cup daily, gradually increasing to 4-5 cups a day.	Two tablets, three times daily from 32 weeks.	N/a	N/a
(The best raspberry leaf teas for pregnancy 2022, no date)	One cup daily. May increase gradually at 34 weeks to 2-3 cups.	N/a	N/a	N/a
(Mommypotamus, 2019)	One cup daily at 32 weeks, gradually increasing to three cups as the due date approaches.	N/a	N/a	N/a
(Hearth and Home Midwifery, 2022)	1-2 cups daily throughout the third trimester.	N/a	N/a	Tea: steep two handfuls of the dried herb in '1 qt cold water.'
(Vegan Momma, no date)	One cup daily during the first trimester, two cups daily in the second trimester and three cups daily during the third trimester.	N/a	N/a	Tea: add 2 tsp of dried tea into a strainer and pour one cup of boiling

				water over the top.
(Darby, no date)	1-3 cups daily starting in the second trimester.	N/a	N/a	N/a
(Marie Fortier, no date)	Three cups daily during the last 3-4 weeks of pregnancy.	N/a	N/a	N/a
(Jester, no date)	1-2 cups daily in the last 6-8 weeks of pregnancy. 'Drink plenty during labor…drink postpartum to cleanse the uterus and encourage healthy breastmilk production.'	N/a	N/a	N/a
(Cleveland Clinic, 2018)	1-2 cups daily from 32 weeks of gestation.	N/a	N/a	N/a
(Teatoxlife, no date)	1-2 cups daily, gradually increasing to three cups per day.	N/a	N/a	N/a
(Healthline, 2018)	1-3 cups daily.	N/a	N/a	N/a
(Medical News Today, 2021)	1-3 cups daily.	N/a	N/a	Tea: add 1 tsp crushed or dried raspberry leaves to a cup and pour over boiling water.
(Greatist, 2022)	'1-3 cups a day is safe…if…concerned about preterm labor…drink in the third trimester.'	N/a	N/a	N/a
(Raspberry Leaf - Drugs in Pregnancy and Lactation: Tenth Edition, no date)	'Typical doses…are 1.5–2.4 g/day.'	N/a	N/a	N/a
(The Gentle Nursery, 2021)	One cup daily from as early as 14	N/a	N/a	Tea: add 1 tbsp of loose

	weeks of gestation. Increase to two cups daily during the third trimester until due date.			red raspberry leaf tea to every cup of boiling water.
(Cancer Care of Western New York, no date)	2-3 cups daily.	N/a	N/a	Tea: add one cup of boiling water to 1-2 tsp dried leaf.
(Teacurry Herbals, no date)	One cup daily from 32 weeks of gestation, gradually increasing to 2-3 cups daily until delivery.	N/a	N/a	N/a
(Mills and Bone, 2004)	12-24 g/day of dried leaf or by infusion. 12-24 mL/day of a 1:1 liquid extract. 4.5-1.4 mL/day of a 1:2 liquid extract or equivalent in tablet or capsule form.	N/a	N/a	N/a

For reference details, see main reference list.