Risk characterisation - Raspberry leaf tea

In this guide

47. 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 the literature search identified only a limited number of animal studies and most of those on systemic toxicity were very old. Therefore, they did not meet current test guidelines, nor 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, but it was noted that there was considerable uncertainty associated with them.

48. The Committee was unable to establish a point of departure for raspberry leaf due to the absence of suitable data and significant uncertainties

associated with the few studies available. The main sources of uncertainty identified included: the lack of data available on the active components of raspberry leaf and on characterisation of the test material used; the potential for the method of sampling and preparation to affect the activity of the supplement, as well as unknown batch to batch variation; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction (described in detail in TOX/2022/50)), 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 (see TOX/2022/50, TOX/2022/50 The Potential Health Effects of Raspberry Leaf in the Maternal for details).

49. Another source of uncertainty was the absence of any specific data on the pharmacokinetics of the constituents of raspberry leaf. However, it was noted that there were indications in the literature that it was less toxic when administered orally than parenterally in mice (Burn and Withell, 1941; Beckett et al., 1954), suggesting reduced oral bioavailability of the toxic constituents. Members also noted that there was limited data on the reproductive toxicity of raspberry leaf and that only one study, conducted in ICR male mice given one dose level of different extracts or raspberry leaf over a two-week period (100 mg/kg bw/day), could be identified in which it had been evaluated it for sub-acute toxicity (Yang et al., 2019).

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

51. The Committee considered the reproductive toxicity study conducted by Hastings-Tolsma *et al*. (2022). The authors of the study reported finding a statistically significant reduction in litter size among C57BL/6N Tac mice given 1.78 or 2.66 mg/mL aqueous raspberry leaf extracts orally throughout pregnancy, compared with untreated controls. Members noted that there were a number of limitations in this study. The mouse strain chosen (C57BL/6NTac) is known not to have good mothering behaviour and is associated with high spontaneous litter mortality. Animals were examined only in the morning, and as mice typically litter overnight the precise time of birth could not be determined. No necropsies were performed on the animals, so it was not possible to assess implantation rates and whether there might have been any maternal cannibalism of offspring. Few of the differences reported were statistically or biologically significant. The few differences reported as significant (pup weight, maternal fluid consumption and

pup mortality) showed overlap of their standard error bars with those of the controls, and in the case of pup mortality, were not analysed appropriately (ANOVA was used for incidence data). It was unclear as to exactly how much raspberry leaf extract mice were exposed to, as the animals were given free access to water bottles containing the extract. The Committee concluded that, in view of these appreciable uncertainties, the results of this study in themselves do not give rise to undue health concern from consumption of raspberry leaf.

52. 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 and/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).

53. 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 12.4 g/person/day), based on data collected from online sources by the FSA's exposure team, was 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.

54. The Committee also took into account that there had been very few 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, despite the reported high prevalence of use of raspberry leaf in pregnancy. 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, which would not have been caused by raspberry leaf, 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 effects and gave birth to a normal, liveborn infant at 40 weeks.

55. Members considered that one of the other reasons that raspberry leaf appeared to be of low concern to human health was the apparent poor bioavailability of the toxic constituents (based on indirect evidence). However, concern was expressed that if raspberry leaf extracts were micronised, or otherwise formulated to increase bioavailability, they may need to be evaluated separately in terms of safety.