Annex A - Risk characterisation

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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.