Toxicology Overview

In this guide

28. It was noted that some studies reported effects of ginger on the testes and, though not relevant for females, they were nevertheless regarded as indicating a potential reprotoxic effect. Studies suggest that ginger affected the viability of pregnancy at high doses; however, with no strong human data, the COT concluded that more work was required. Further, possible fetotoxicity based on evidence from animal data, genotoxicity and possible drug interactions should be further investigated.

29. Discussion paper TOX/2021/26 reviewed the available studies on cytotoxicity, mutagenicity, acute, reproductive and developmental toxicity, lactation and possible drug interactions as well as data on potential exposure in pregnancy, covering both animal and human studies. The results from these reports were variable due to the differences in the forms and extracts of ginger tested and as a result, some findings were contradictory.

30. Paper TOX/2021/51 provided further information with respect to animal studies, contaminants and exposure to ginger supplements, primarily centred on the effects of ginger on prostaglandin production, reproductive and developmental toxicity and the possible contaminants present in ginger. The Committee noted that the papers reviewed covered ginger in a range of forms including fresh, aqueous, dried and alcohol extracts.

31. The toxicological data in this report have been divided into two sections: the first includes studies in which ginger was administered in forms similarly to those in traditional culinary uses; and the second includes studies using ginger extracts and other concentrated forms.

32. Dry ginger powder was administered in some of the studies. Where the dose was ≤ 4 g/day (equivalent to approximately 2 teaspoons) they have been included in the section on traditional culinary uses, and if it was > 4 g/day they were included in the extracts section.

Toxicology of ginger root in traditional culinary uses

Reproductive and developmental toxicity

Animal studies

33. Reproductive and developmental toxicity has been investigated in studies in rats. In a study by Wilkinson (2000), three groups of pregnant Sprague-Dawley rats were administered either a control (unspecified), or 20 g/L or 50 g/L ginger tea - prepared by the infusion of grated ginger in water then filtered and administered via the drinking water - during days 6 to 15 of gestation. No further details were provided regarding specific compounds of interest. While no maternal toxicity was observed, embryonic loss in the treated groups was found to be twice that of the controls. Exposed fetuses were found to be significantly heavier than controls but showed no gross structural malformations. The authors concluded that the results of this study suggest that *in utero* exposure to ginger tea results in early embryonic loss and increased growth in surviving fetuses.

Human studies - exposures in pregnancy

34. In a double-blind randomised crossover trial, 27 pregnant women were administered capsules containing either 250 mg ginger in powdered root

form or 250 mg lactose as a placebo, four times per day, for four days followed by a wash out period of 2 days prior to a further 4 days administration of ginger or placebo alternative to the treatment during phase 1 (Fischer-Rasmussen et al., 1990). Two subjects did not carry to term: one subject from the ginger group had a spontaneous abortion, one elected. Of the remaining 25 subjects, no adverse effects were observed.

35. Of the available human studies, few explicitly addressed the safety of ginger consumption during pregnancy, most being incidental to other studies. In a double-blind study by Vutyavanich et al. (2001), 32 women were given 1 g of dried ginger in capsule form for 4 days. Of those in the ginger group, one spontaneous abortion was reported compared to 3 in the placebo group. Equally, for delivery by caesarean section, there was no difference between the groups. No congenital abnormalities were observed in any baby carried to term. The group concluded that there were no significant adverse effects of ginger on pregnancy outcome.

36. An observational study in humans examined 187 pregnant women who took ginger in their first trimester and compared them to 187 pregnant women exposed to nonteratogenic drugs that were not antiemetic drugs (Portnoi et al., 2003). Three major malformations were reported in the ginger group, ventricular septal defect (VSD), right lung abnormality, and kidney abnormality (pelviectasis) and one child was diagnosed with idiopathic central precocious puberty at age 2 years. The mother was reported to have taken 250 mg of ginger in capsules four times a day from 11 to 20 weeks of gestation in addition to dimenhydrinate and doxylamine/vitamin B6 (Diclectin) during the first trimester of pregnancy. In the comparison group, there were two major malformations, consisting of a VSD and bladder exstrophy. The authors concluded that the results suggested ginger does not increase the rate of major malformations above the baseline rate of 1%-3%. No significant difference between the two groups in terms of live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age were reported, however the comparison group had more infants weighing less than 2,500 g (12 vs 3, P0.001) and the ginger group had 8 sets of twins (i.e. approximately 4 in 100 births), compared with an expected background rate of 1 in 80 to 1 in 100 births. There were no twins reported in the control group.

37. Ensiyeh et al. (2009), investigated the effectiveness of ginger versus vitamin B6 for treatment of nausea and vomiting in pregnancy (NVP) in women before 17 weeks’ gestation. Seventy women were randomised to receive either

ginger at a dose of 1 g per day or B6 at 40 mg per day for 4 days. The ginger group reported 2 spontaneous abortions, compared to one in the B6 group. Of the babies brought to term, no congenital anomalies were observed, and all babies were discharged in good health.

38. Whilst also examining the use of ginger in the treatment of nausea and vomiting in pregnancy, Smith et al. (2004) noted 3 spontaneous abortions in the group taking 1.05 g ginger compared to 9 in the group taking 75 mg B6 daily for 3 weeks, however the overall risk of pregnancy complications did not differ by study group.

39. Chittumma (2007) compared the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in pregnancy. One hundred and twenty-six pregnant women, with a gestational age of 16 weeks received either 650 mg of ginger or 25 mg of vitamin B6 three times per day for 4 days. Ginger and vitamin B6 significantly reduced nausea and vomiting scores from 8.7 ± 2.2 to 5.4 ± 2.0 and 8.3 ± 2.5 to 5.7 ± 2.3 respectively, (p 0.05). There were some minor side effects in both groups, 25.4% and 23.8% (p = 0.795) respectively, such as sedation, heartburn, arrhythmia.

40. Heitmann et al. (2013) analysed data on ginger use during pregnancy from the Norwegian Mother and Child Cohort study. Among the 68,522 women in the study, 1,020 (1.5 %) women reported using ginger during pregnancy. The use of ginger during pregnancy was not associated with any increased risk of congenital malformations. No increased risk for stillbirth/perinatal death, preterm birth, low birth weight, or low Apgar score was detected for the women exposed to ginger during pregnancy compared to women who had not been exposed.

41. The COT considered the possible mode of action of the purported benefits of ginger on nausea. It was theorised that ginger might decrease prostaglandin levels, which were linked to nausea. The effects on prostaglandin levels are covered from paragraph 105 onwards

42. Overall, it was concluded that there were limited data on the effects of ginger in traditional culinary uses during pregnancy. The human data presented were not strongly indicative of any toxicological concern but there were many uncertainties. Ginger did not appear to be systemically toxic but reprotoxic effects have been reported in animal studies. However, there is no convincing evidence for such effects in human studies.

Lactation

43. With respect to lactation, the focus of available studies (Lamxay *et al.*, 2011; Kaygusuz *et al.*, 2021; Dilokthornsakul *et al*., 2022) was on the effect of ginger on milk production and volume rather than safety and therefore, the effect of exposure during lactation has not been fully investigated.

Effect on P450 (CYP) Enzymes and Herb-Drug Interactions

44. Ginger was found to have a significant inhibitory effect on CYP3A4, CYP2C9, and P-glycoprotein activities in vitro (Kimura *et al*., 2010; Zhang et al. 2008). It was this effect that was thought to be responsible for reported hepatic cytolysis in a 48-year-old woman being treated with crizotinib. The patient, who was being treated with 250 mg crizotinib twice a day, had been taking ginger as a tea (amounts unknown) concomitantly during treatment. A subsequent diagnostic evaluation showed an increased crizotinib concentration, 1.8-fold higher than that measured two months prior.

Anti-platelet aggregation activity

Human studies

45. Krüth *et al.* reported possible over-anticoagulation resulting from a ginger-phenprocoumon interaction (2004). A 76-year-old woman on long-term phenprocoumon therapy presented with epistaxis and an international normalized ratio (INR) of >10. Partial thromboplastin time (PTT) was also found to be prolonged (84.4 seconds; normal 35). For several weeks prior to the event, the woman had a regular ginger intake of dried ginger pieces and tea from ginger powder. Following treatment with vitamin K, the patient’s INR and PTT returned to within therapeutic range.

46. Young et al. (2006) investigated the synergistic effect of ginger and nifedipine on anti-platelet aggregation in healthy volunteers aged 25-60 years old and hypertensive individuals aged 35-60 years old. In a five-part study, the two groups comprising 10 males and 10 females, were administered 75 mg of acetylsalicylic acid (ASA), 1 g of ginger, 10 mg nifedipine, 1 g dried ginger and 10 mg nifedipine in combination and 1 g dried ginger and 75 mg ASA in combination daily for one week each following a washout period (7 days following ASA administration, 10 days thereafter).

47. Young et al. found that platelet aggregation in the presence of collagen, ADP and epinephrine was 44.1%, 44.5% and 42.1% in normal subjects, compared to 64.2%, 67.7% and 62.9% in hypertensive patients. Following administration of

ginger alone to normal subjects, the percentage inhibition of platelet aggregation induced by collagen, ADP and epinephrine was 35.2%, 37.8%, 35.9%, respectively. Following nifedipine administration to such subjects, platelet aggregation induced by collagen, ADP and epinephrine was inhibited by 20.2%, 22.6% and 23.4 %, respectively. When normal subjects were administered ginger and nifedipine in combination platelet aggregation induced by collagen, ADP and epinephrine was inhibited by 79.8%, 75.2%, 69.3%, respectively, which values were significantly different from those with either ginger or nifedipine alone, suggesting a synergistic effect of the combined treatments. This synergistic effect was also seen in hypertensive patients. The authors concluded that ginger could potentiate the anti-platelet effect of nifedipine.

48. AlAskar *et al.* (2020) investigated the effect of ginger on platelet aggregation using ADP, arachidonic acid, collagen, ristocetin and epinephrine as agonists. Forty healthy male and female participants (numbers of each not specified, presumably 20 of each) were randomized (20 per group) to consume ginger tea comprising either 4 g powered ginger in 150 ml of boiling water once daily or 4 g twice daily, for five days. Comparisons were with pre-treatment values. Administration of 4 or 8 g ginger powder daily for 5 days as a tea had no effect on platelet aggregation induced by any of the agonists, or than modest inhibition in the 4 g per day group with epinephrine as agonist (by 12%), Essentially, ginger had no effect on platelet aggregation in this study.

49. Srivastava (1989) investigated the effect of fresh ginger on blood platelet thromboxane synthesis in humans. In a study on 7 women aged between 25-65 years, where volunteers consumed ~5 g of fresh ginger for 7 days, ginger was found to inhibit thromboxane B2 biosynthesis *in vivo* by 36%.

50. Lumb (1994) found that after a single dose of 2 g of dried ginger in powder form there were no significant differences in platelet aggregation/function at 3 and 24 hours post-dose compared to those after a lactose placebo. The authors concluded that previously reported effects of ginger on thromboxane synthetase activity may have been due to the use of higher doses or fresh ginger.

51. Bordia *et al.,* (1997) found that 4 g powdered ginger administered daily over the course of 1.5 and 3 months had no effect on ADP and epinephrine-induced platelet aggregation in individuals with coronary artery disease (CAD) (who were all taking nitrates and aspirin). However, a single 10 g dose of powdered ginger, administered to CAD patients resulted in a significant decrease in induced platelet aggregation (by approx 30%)

Toxicology of ginger extracts and other concentrated forms

Cytotoxicity

52. The cytotoxicity of ginger extracts has been investigated with varied results. Plengsuriyakarn *et al*. (2012) examined the cytotoxicity of ethanolic ginger extracts in a cholangiocarcinoma (CCA) cell line 6 (CL-6) model, compared to hepatocarcinoma (HepG2) and normal human renal epithelium (HRE) models, using calcein-AM release and Hoechst 33342 assays to assess cell viability and apoptotic activity, respectively. The median inhibitory concentration, (IC50) values, for cytotoxicity of the crude ethanolic extract of ginger ranged from 11 – 245 µg/mL across the 3 cell lines and the two assays.

53. Zaeoung *et al.* (2005) reported that the IC50 of aqueous and methanolic extracts of ginger was greater than 39.2 µg/ml against breast (MCF7) and colon (LS174T) cell lines.

54. Abudayyak *et al*. (2015) found that aqueous and methanolic extracts of ginger exhibited no cytotoxic activity when assessed using an MTT test (a colourimetric assay for assessing cell metabolic activity) in the rat kidney, NRK-52E cell line. A chloroform extract resulted in an IC50 value of 9.1 mg/mL.

55. However, it was noted by the COT that the inhibitory concentration (IC50) values presented in the studies reviewed were based on limited data, from only a few different cell lines and therefore firm conclusions could not be drawn. Also, the purpose of most of these studies was an attempt to identify possible anti-cancer agents, rather than as an assessment on the safety of ginger as a supplement and therefore relevant endpoints were often not assessed.

Mutagenicity

56. Nakamura and Yamamoto (1982) found that the juice of ginger rhizome contained both mutagenic and anti-mutagenic substances, and that 6-gingerol in particular was a powerful mutagen. Ginger juice itself had anti-mutagenic activity. The group also demonstrated that 6-shogaol was much less mutagenic (strain Hs30 of *Escherichia coli*) than 6-gingerol and zingerone was much weaker still (Nakamura & Yamamoto 1983). In a *Salmonella typhimurium* reverse mutation (Ames) assay, the urine of rats fed diets containing 0.5, 1 and 5% powdered ginger for 1 month showed no mutagenicity with either strain TA98 or TA100. The

rats were then treated with a single intraperitoneal injection of benzo(a)pyrene. The urine from benzo(a)pyrene-treated animals caused an increase in the number of revertants in both strains of *Salmonella*, with and without metabolic activation. Urine from those rats that had also received ginger was found to display a significant reduction in mutagenicity, at all ginger concentrations, when tested in the Ames assay (Nirmala *et al*. 2007).

57. The mutagenicity of aqueous and DMSO extracts of fresh, boiled and fried ginger paste and powder was assessed in an Ames test using *S. typhimurium* strains TA98 and TA100 with and without metabolic activation, at concentrations of 1, 2 and 3 mg/plate of ginger paste and 0.5, 1 and 1.5 mg/plate of ginger powder, respectively. None of the preparations caused any increase in the number of revertants. All of the ginger preparations reduced the mutagenicity of benzo(a)pyrene *in vitro* (Nirmala *et al*. 2007).

58. In other Ames assays, an ethanolic extract of ginger (Soudamini *et al.* 1995) demonstrated mutagenic activity in *S. typhimurium* strains TA100 and TA1535 at concentrations of 25-50 mg/plate and 5-10 mg/plate, respectively. Similarly, an ethanolic ginger extract at concentrations of between 10 and 200 µg/plate, gingerol at concentrations between 5 and 200 µg/plate, and shogaol at concentrations between 5 and 200 µg/plate, were mutagenic in strains TA100 and TA1538 with metabolic activation by rat liver S9 mix, while zingerone (5 and 200 µg/plate) did not display mutagenic effects (Nagabhushan *et al*. 1987).

59. Abudayyak *et al*. (2015) found that an aqueous ginger extract exhibited mutagenic activity when assessed using the Ames assay on *S. typhimurium* TA98 strain (in the presence of S9 mix) over a concentration range of 0.78–25 ug/mL. However, no activity was exhibited on the TA100 strain. No activity was observed with chloroform and methanolic extracts.

60. Based on the available data, ginger showed some mutagenicity in TA100, TA1535, and TA98 strains, but this is low compared with established mutagens. An aqueous extract of ginger did not show any mutagenicity *in vivo* (Nirmala et al. 2007).

Acute toxicity

61. An acute toxicity study (Malik and Sharma, 2011) in male Wistar rats showed no signs of toxicity or mortality with ginger. The animals were administered doses of 250, 500 and 1000 mg/kg lyophilised ginger powder by gavage. The authors stated that the three dose levels used in the study

corresponded to 5, 10 and 20% of the NOAEL of the powder (5000 mg/kg).

62. Preliminary to a study of the effects of an aqueous extract of ginger rhizomes on sexual parameters in rats, Peneme et al. (2023) (see below) determined the acute toxicity of the extract in accordance with The Organisation for Economic Co-operation and Development (OECD) guideline no. 423. Mice received 5000 mg/kg aqueous ginger extract by gavage. No change in the general condition or behaviour of the mice compared with the control animals was observed. No mortality was observed after 48 hours or 14 days of observation. Hence, the LD50 was above 5000 mg/kg.

Short term repeat dose studies

63. Rong et al. (2009) evaluated the safety of powdered Japanese ginger (mainly containing 6-gingerol galanolactone and 6-shogaol) by conducting a 35-day toxicity study in rats. Both male and female rats were treated with 500, 1000 and 2000 mg/kg bw/day by gavage. Oral administration of up to 2000 mg/kg to male and female rats did not result in any increase in mortality, or changes to behaviour, growth, the general condition of the animals (including: changes in skin, fur, eyes, and mucous membranes, occurrence of secretions, excretions and autonomic activity), food and water consumption. At the highest dose tested (2000 mg/kg), ginger led to slightly reduced absolute and relative weights of testes (by 14.4% and 11.5%, respectively). No effects were apparent in the females.

64. The effect of oral and intraperitoneal administration of aqueous extracts of ginger root over 28 days in female rats at two dose levels (50 mg/kg and 500 mg/kg) was examined for haematological, serum enzymes and systemic toxicity (Alnaqeeb et al. 2003). Neither oral nor intraperitoneal administration resulted in mortality. Orally administered aqueous ginger extract resulted in increased serum levels of serum aspartate aminotransferase (AST) and decreased levels of alanine aminotransferase (ALT) at 500 mg/kg. Intraperitoneal administration had no effect on either AST or ALT levels.

65. Jeena et al. (2011) conducted a sub chronic toxicity study of essential oil of ginger in Wistar rats following oral administration at doses of 100, 250, and 500 mg/kg per day once daily for 13 weeks to assess the oral safety of ginger oil. No mortality was observed. No unusual changes in behaviour or locomotor activity were observed during the period of the study, nor were any abnormal changes observed in the relative organ weights of liver, kidney, spleen, lungs, brain, and stomach with respect to body weight in ginger oil-treated animals

when compared to vehicle control animals.

66. An increase in serum sodium levels was observed in the male rats treated with 500 mg/kg per day but in the absence of changes in sodium levels in females, this change was not considered significant. A slight increase in total bilirubin level was observed in female rats treated with ginger oil along with a decrease in AST and ALT levels, however, there were no significant changes in hepatic function parameters such as alkaline phosphatase, total protein, albumin, and globulin content.

Reproductive and developmental toxicity

In vitro studies

67. Mohammed et al. (2016) investigated the effects of herbal extracts, including ginger and 6-gingerol, on primary chick embryonic cardiomyocyte micromass and mouse D3 embryonic stem cell (ESD3) systems. Primary embryonic chick cardiomyocytes treated with 6-gingerol at concentrations of 0.75–6 µM showed no significant changes in contractile or cellular activity or changes in total protein content in comparison to the control. At concentrations of 12.5–50 µM, inhibition in contractile activity was observed at 48h. All high 6-gingerol concentrations, 12.5–100 µM, tested in micromass, significantly altered both cellular activity and protein content in a dose-dependent manner.

68. The same concentrations of 6-gingerol used in the micromass system were used to treat the ESD3, which showed a significant decrease in cardiomyocyte differentiation with all tested concentrations above 0.75 µM. The cellular activity and protein content of stem cell-derived cardiomyocytes also exhibited a significant decrease with exposure to increasing 6-gingerol concentrations.

Animal studies

69. To date, the number of studies on the safety of the use of ginger supplements during pregnancy is limited. The ginger component, 6-gingerol, was shown to affect some essential embryonic developmental processes, such as the disruption of angiogenesis. Kim *et al*, demonstrated the ability of 6-gingerol (10 µM) to inhibit proliferation and capillary-like tube formation of primary cultured human endothelial cells in rat aorta by down regulation of cyclidin D and the ability to inhibit tumour growth in mice (3 mg/kg) through its anti-angiogenic

activity (Kim et al., 2005).

70. The teratogenicity of EV.EXT 33, a patented ethanol extract of dry rhizomes of *Zingiber officinale* Roscoe (comprising largely 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, and 8-shogaol, which made up 1.9 w/w of the extract) was investigated in Wistar rats (Weidner and Sigwart, 2001). The extract was administered orally by gastric intubation at concentrations of 100, 333 and 1000 mg/kg, to pregnant rats from days 6 to 15 of gestation. Their bodyweight, food and water were monitored during the treatment period. The study authors concluded that treatment with EV.EXT 33 during the period of organogenesis resulted in neither maternal nor developmental toxicity at daily doses of up to 1,000 mg/kg bw.

71. Shalaby and Hamowieh, (2010) investigated the acute toxicity, effects on fertility and on serum testosterone levels of ginger in rats. One hundred and twenty male Sprague Dawley rats, separated into groups of 10, were orally administered either water or methanolic extracts of dry ginger roots in graded doses ranging from 5 to 17.5 g/kg bw (gavage doses were not specified). Following dosing, the number of dead mice in each group after 48 hours of observation was recorded. The oral lethal doses (LD50) of the methanolic and water extracts were calculated to be 10.3 and 11.8 g/kg bw respectively. No signs of toxicity were observed at doses up to 5 g/kg bw. Both extracts increased the fertility index, sexual organ weight, and sperm motility and count after 65 days of dosing (see below).

72. To investigate the effects of ginger extracts on serum testosterone levels, male rats had their fertility reduced by inducing diabetes, a condition shown to reduce male fertility (Shalaby and Hamowieh, 2010). The aim was to see whether ginger, with its antioxidant and androgenic effects, would restore fertility. Rats rendered diabetic by subcutaneous injection of 120 mg/kg bw alloxan for 3 days, were administered methanolic extracts of ginger for 65 days at doses of 100 and 200 mg/kg bw/d. Testosterone levels increased to 4.08 ± 0.10 and 7.13 ± 0.14 ng/dL (both significant at *P* 0.001) in the ginger treated groups compared to the diabetic control group, which had levels of 3.30 ± 0.03 ng/dL. Serum testosterone levels also increased in rats given water extracts of ginger (150 and 300 mg/kg bw) to 4.06 ± 0.03 and 5.04 ± 0.08 ng/dL (both significant at *P* 0.001 when compared to the diabetic control group), respectively.

73. The study also investigated fertility as assessed by the fertility index (for each male this was calculated as the percentage of the number of females that become pregnant in relation to the number of mated females) and

spermatogenesis. Rats were orally administered methanolic extracts of ginger at doses of 100 and 200 mg/kg bw for 65 days and water extracts at doses of 150 and 300 mg/kg bw and compared to a diabetic control group.

74. Histopathological examination of the testes of the diabetic rats showed mild to moderate degenerative changes of spermatogenic cells, diffuse oedema and incomplete arrest of spermatogenesis compared to normal control rats. The testes of rats orally administered 300 mg/kg bw of water extract of ginger root showed less changes in the testes, with mild degeneration of spermatogenic cells and slight oedema of interstitial cells. The testes of rats receiving orally 200 mg/kg bw of methanolic extract of ginger root showed nearly normal seminiferous tubules, with fewer signs of degradation, suggesting a LOEL of 200 mg/kg bw/day for the methanolic extract. The study concluded that the results suggest the intake of ginger root extract as a drink may be useful for diabetic patients suffering from sexual dysfunction.

75. The above study has been included for completeness and as any general mechanisms may be more widely relevant: The findings are consistent with those of Hosseini et al (2015)

76. Hosseini et al. (2015, abstract only) investigated the effect of ethanolic ginger extract on serum levels of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH), as well effects on numbers of spermatogenic cells in male mature offspring rats. In this study, 72 female rats, divided into 9 groups, were orally administered an alcoholic extract of ginger at doses of 50, 100 and 200 mg/kg bw, during their neonatal and perinatal periods, with saline as a control. Following puberty, serum levels of testosterone, LH and FSH, and testicular numbers of Sertoli cells, spermatogonia, spermatocytes and spermatids were counted in 8 male offspring from each group after puberty. Treatment with ginger significantly, and dose-dependently, increased testosterone levels and the number of spermatogenic cells and at doses of 100 and 200 mg/kg bw, significantly reduced the FSH and LH levels compared to control groups. The authors concluded that “the oral consumption of ginger during pregnancy and lactation dose-dependently increase the level of testosterone and the number of spermatogenic cells.”

77. Dissabandara & Chandrasekara (2007) examined the effect of powdered ginger extract administered prenatally on the postnatal development of rats. Administration of the dry powdered extract orally at doses of 500 or 1000 mg/kg/day (control not specified) during days 5 to 15 of gestation resulted in a lower intake of food and water and lower weight gain in dams in the ginger

treated group, with some embryonic loss. Growth and physical maturation of the offspring were unaffected. It was concluded that maternal administration of ginger during mid pregnancy resulted in reduced maternal weight gain and increased embryonic loss without affecting the surviving offspring.

78. ElMazoudy and Attia (2018) investigated the effect of powdered dried ginger root on the oestrus cycle and implantation in female mice. ICR mice were orally dosed with 250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract. There were four different experiments: (i) treatment for 90 days and throughout mating and gestation; (ii) 35-days of treatment evaluating the effects on the oestrous cycle; (iii) treatment for 20 days and throughout mating to evaluate pre-implantation loss (antifertility); and (iv) treatment for 20 days and throughout gestation to evaluate post-implantation loss (abortifacient). In the 90-day study, the dams were terminated on gestation day 20. In the mothers, one mortality was recorded in the 1000 mg/kg bw/d group on gestation day 18 and two in the 2000 mg/kg bw/d group at gestational day 16. There was a significant reduction in body weight changes in these two dose groups compared to the control group; however, food consumption was comparable.

79. In the study investigating the oestrus cycle, a significant reduction in the numbers of oestrus cycles was observed at the highest dose, with the length of the oestrus cycle in this group being significantly prolonged, 10.05 ± 0.8 days compared with 4.99 ± 0.5 days recurrent and successive oestrous cycles in control mice. At the highest dose level, there was a significant decrease in the duration of diestrous-metestrus (luteal) phase and prolonged proestrus-estrus (ovulatory) phase. In the study investigating pre-implantation loss, a significant decrease in the number of corpora lutea was observed at the highest dose. Implantation failure was also increased by 36% compared to the control group and pre-implantation loss in this dose group was also 16.6% higher than in the control group. The authors considered that this may reflect a dose-dependent antifertility (anti-implantation) effect.

80. Regarding fertility and developmental outcomes, the female copulation index was significantly reduced at 2000 and 1000 mg/kg bw/d, whereas the female pregnancy index was significantly decreased only at the highest dose. The number of implantation sites and live fetuses in the 2000 mg/kg bw/d group was lower than in the other treated and control groups. An increase in fetal resorption and post implantation loss was also seen in the highest dose group. There was no evidence of fetal malformations, however growth retardation, reduced pup weight and delay in the crown-rump length were observed in this dose group as well.

Finally, changes in ovarian histopathology were observed at 2000 mg/kg bw/d, following 90 days of treatment. Ovarian follicle atresia was observed. The atretic follicles contained cell debris and there was haemorrhage in the antral cavity.

81. Additionally, degenerated primordial follicles with pyknotic nuclei forming polycystic ovaries were noted. Deteriorated follicles were observed as a detaching of layers of granulosa cells from the basal membrane by dilation of zona pellucida and with evidence of apoptosis; non-visibility of the follicular nuclei was also evident in damaged ova. The authors considered the above observations as evidence that ginger possesses anti-ovulation properties. Overall, the authors concluded that ginger impairs the normal growth of the corpus luteum because of progesterone insufficiency during early pregnancy and that the results suggested that ginger can disrupt the oestrous cycle and blastocyst implantation without teratogenesis. They considered the lowest NOAEL to be 250 mg/kg bw.

82. Peneme et al. (2023) investigated the effects of an aqueous extract of ginger rhizomes on sexual parameters in rats, after first determining the acute toxicity of the extract in mice (see above). The extract was administered at doses of 300 and 600 mg/kg, 17β-oestradiol at a dose of 1 mg/kg or distilled water at an equivalent volume, orally to rats by gavage daily for 14 days. A non-significant increase and decrease in body weight was observed at doses of 300 and 600 mg/kg, respectively. Similarly, there was no significant change in body weight on treatment with 17 β-oestradiol. Based on the eosinophil indices, treatment with 600 mg/kg of the extract blocked the sexual cycle at the estrus stage as did 17β-oestradiol. There was no effect at 300 mg/kg of the extract. A significant increase in oestradiol levels was observed in the rats treated at 300 mg/kg compared with the control group, but treatment with 600 mg/kg or 17β-oestradiol had no significant effect.

83. ElMazoudy and Attia (2018) noted reductions in bodyweight and deaths in mice dosed with up to 2000 mg/kg bw/day ginger extract and Alnaqeeb *et al.,* (2003), observed increases in serum aspartate aminotransferase (AST) in female rats dosed with up to 500 mg/kg ginger extract.

84. However, the Committee noted that the database was limited, and the extraction and concentration of ginger varied between the studies. The Committee considered the animal studies to be inconclusive. On the basis of the available information, more data would be needed in order to allow for a robust investigation of the effects described above. Therefore, at present, the Committee are unable to determine a point of departure.

Human studies - exposures in pregnancy

85. Willetts et al. examined the effect of ginger on pregnancy induced nausea (2003). 120 women less than 20 weeks pregnant, were given 125 mg ginger extract (EV.EXT35; equivalent to 1.5 g of dried ginger) or a placebo four times per day for 4 days. However, there is some lack of clarity in the description of this study as it is stated in the discussion "Women in the treatment arm of this trial took ginger for 8 days and those in the placebo arm took ginger for 4 days." It is not clear whether this refers to the trial described. Three spontaneous abortions were observed in the group receiving ginger, although one of these had not started taking ginger at the time of abortion. One spontaneous abortion was observed in the placebo group.

86. In a clinical feasibility study on the use of ginger during pregnancy conducted by Laekeman et al. (2021), 51 pregnant women could freely use ginger tablets with a maximum of 2 tablets of 50 mg EXT.GR10 a day in case of gastrointestinal discomfort during pregnancy. EXT.GR10 is a 10-times concentrated ethanolic extract of ginger root. No strict minimum number of tablets was set, and 44 out of 51 patients (86.3%) took the ginger tablets. The 44 patients took 544 tablets or a mean of 12.4 tablets per patient, with a minimum of 1 and a maximum of 55 tablets. The incidences of stillbirth, prematurity, hypertension, and gestational diabetes were reported. There were no serious complications at birth. Four cases of dysplasia of the hip and two minor malformations were recorded in the offspring. Outcomes were compared to the rates in a Flemish population delivering during the same period. Hypertension, low birth weight and premature delivery were 15.9%, 13.6% and 20.5 % respectively in the ginger cohort compared to the representative population where the rates were 5.4%, 5.6% and 5.8% respectively. The author concluded that there was no qualitative or quantitative relationship between complications in the mother during pregnancy or malformations or complications in the newborn at delivery and the use of EXT.GR10 but emphasised that this was a pilot study with small numbers.

Effect on P450 (CYP) Enzymes and Herb-Drug Interactions

87. CYPs are a family of enzymes responsible for the biotransformation of numerous drugs. Induction or inhibition of CYP enzymes is a major determinant of the occurrence of drug-drug interactions.

In silico

88. Qiu *et al.* (2015) estimated the molecular interactions between 12 main active components (6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, ar-curcumene, β-bisabolene, β-sesquiphelandrene, 6-gingerdione, (-)-zingiberene, and methyl-6-isogingerol) and human P450 (CYP) 1A2, 2C9, 2C19, 2D6, and 3A4 and attempted to predict the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the 12 ginger components using computational methods and literature searches. This study suggests that ginger components may have the potential to regulate the activity and expression of various human CYPs, resulting in alterations in drug clearance and response with a high risk of inhibition of CYP2C9 and CYP3A4.

In vitro studies

89. Ginger extracts and the major components thereof: 6-gingerol (6G), 8-gingerol (8G), 10-gingerol (10G) and 6-shogaol (6S) were investigated in *in vitro* models and shown to have inhibitory effects on CYP enzymes CYP3A4, CYP2C9 (Kimura *et al.*, 2010), CYP2C19 (Kim *et al.*, 2012), and CYP1A2 and CYP2C8 with IC50 values as low 1 μM, (e.g., 6-shogaol on CYP1A2; Mukkavilli *et al.*, 2014).

Animal studies

90. Several reports have been published on the pharmacological properties of ginger, with varying findings. Studies have examined the herb-drug interaction in animal models, (Okonta *et al.*, 2008; Egashira *et al*., 2012) although the results of some studies are questionable.

91. A study into the effect of ginger on the pharmacokinetics of metronidazole was reported by Okonta *et al*., using rabbits (2008). In a two-phase study, five healthy local strain rabbits (3 females, 2 males) were each given 3 mg/kg oral metronidazole. Following a 2-week washout period, the rabbits were given 1 ml/kg of ginger extract orally daily for 3 days and immediately given 3 mg/kg metronidazole on the third day. Ginger significantly increased the absorption and plasma half-life and significantly decreased the elimination rate constant and clearance of metronidazole.

92. Egashira *et al.*, reported the interaction between ginger juice and tacrolimus in rats (2012). Tacrolimus (0.6 mg/kg) was administered intraduodenally in male Sprague-Dawley rats 1 h following oral administration of 10 mL/kg 50% ginger juice or water. CYP3A enzymes metabolize tacrolimus in the intestine as well as in the liver and the author states that ginger has been reported to change the activity of CYP3A4. Pre-treatment with ginger juice was

found to significantly increase tacrolimus blood concentrations compared to those in animals pre-treated with water or orange juice.

93. The possible herb-drug interaction of ginger crude extract (GCE) on glibenclamide and insulin was investigated by Al Omari *et al.*, along with its hypoglycaemic and antihyperglycemic effects in normoglycemic- and streptozotocin-induced (STZ) diabetic rats (2012). Ginger crude extract was administered to normoglycemic male rats as a single dose (1 day) and as a daily dose for 1 week. STZ diabetic rats were treated with the same GCE concentrations (25, 50 and 100 mg/kg bw) together with glibenclamide (5 mg/kg bw) or insulin (1.2 IU/kg bw).

94. Single administration of ginger crude extract resulted in a significant decrease in blood glucose level (BGL) in normoglycemic rats after 1 and 2 hours (50 mg/kg bw). In STZ- diabetic rats ginger crude extract (25 and 50 mg/kg bw) decreased non-fasting BGL (N-FBGL) significantly at 1.5, 2.5, 3.5 and 4.5 hours. Glibenclamide (5 mg/kg bw) in combination with ginger crude extract at doses of 25 or 50 mg/kg bw resulted in a significant reduction in the N-FBGL by 26.3% and 25.1% respectively after 4.5 hours, compared to glibenclamide alone which exhibited a 7.9% reduction. The authors suggested that ginger crude extract may act by affecting the release of insulin from the ß-cells of the pancreas.

Human studies

95. Human data showed possible interactions of ginger with drugs, including antibiotics, immunosuppressants, and anticoagulant medications. Although, in some cases, multiple concomitant medications were being used by the subjects, therefore, the effects observed cannot necessarily be directly attributed to ginger supplementation (Rubin *et al*., 2019).

96. Conversely, whilst investigating the effects of ginger on the pharmacokinetics and pharmacodynamics of warfarin and the effect of ginger on clotting status, Jiang *et al.,* (2005), found that neither the pharmacokinetics nor pharmacodynamics of warfarin were affected in healthy males who were treated with a single 25 mg dose of warfarin, following 7 days of pretreatment with ginger tablets (3 tablets, 3 times per day, each capsule containing extract equivalent to 0.4 g of ginger rhizome powder). Furthermore, ginger treatment had no effect on INR or *ex vivo* platelet aggregation in response to arachidonic acid.

Anti-platelet aggregation activity

In vitro studies

97. Srivastava (1986) reported an effect of ginger extracts on *in vitro* platelet aggregation. Ginger extracts in water, n-hexane, chloroform, and ethyl acetate were shown to inhibit platelet aggregation using arachidonic acid (AA), epinephrine, adenosine diphosphate (ADP), and collagen as agonists. From the paper it was difficult to determine the concentrations of ginger equivalents used.

Animal studies

98. The effects of an aqueous ginger extract on platelet thromboxane-B2 (TXB2) and prostaglandin-E2 (PGE2) production was studied by Thomson *et al*. (2002). Adult female Sprague-Dawley rats were administered an aqueous extract of raw ginger at either 50 mg/kg or 500 mg/kg daily, by either oral gavage or intraperitoneally (IP) for a period of 4 weeks. A dose of 50 mg/kg ginger administered orally, or IP did not result in any significant reduction in serum TXB2 levels when compared to the saline-treated control group but oral doses at 500 mg/kg significantly reduced TXB2 levels in serum. There was no significant effect on serum TXB2 levels when this dose (500 mg/kg) was administered IP.

99. Administration of either 50 or 500 mg/kg of the aqueous extract orally or by IP injection resulted in a significant reduction in serum PGE2 levels (reduction with 50 mg/kg IP did not reach statistical significance), which was more marked after 500 mg/kg.

Human studies

100. Rubin *et al.* (2019) reported the possible effect of ginger supplementation on the INR in a woman taking warfarin. The 70-year-old female, who had been taking clonazepam 1 mg, metoprolol succinate 25 mg, paroxetine 10 mg, phenytoin 30 mg, rosuvastatin 20 mg, warfarin 7.5 mg daily except 10 mg on Wednesdays, for at least a month prior to presentation, presented with an INR of 8, an increase from 2.7, one month after taking a “Ginger Rescue,” a daily oral, chewable, 48 mg ginger supplement that had no other herbal or active ingredients. A week following cessation of the ginger supplement, the INR declined to 2.6. Upon resuming warfarin at 7.5 mg daily, her INR remained in the therapeutic range.

101. The effects of ginger on platelet aggregation were investigated in healthy male subjects (n=20) whose diet was supplemented with 100 g butter per day for seven days. This significantly enhanced platelet aggregation. Ten of the

subjects then received ginger, in powder form (5 g per day) and the other ten received a placebo. ADP- and epinephrine-induced platelet aggregation was significantly (P0.001) reduced in the ginger-treated group, whilst there was no significant change in the placebo control group (Verma *et al.*, 1993). In addition, no change was observed in the fibrinolytic activity or fibrinogen levels in these subjects. All patients in this study were taking nitrates and aspirin; the latter was stopped 2 weeks before the start of the study. In contrast to the effects after 3 months, a single 10 g dose of powdered ginger, administered to CAD patients (n=10), resulted in a significant decrease in ADP- and epinephrine-induced platelet aggregation 4 h after dosing, as compared to that prior to treatment. There was no change in the placebo-treated controls (n=10).

Effects on blood pressure

Animal studies

102. Ghayur and Gilani (2005) reported that a crude extract of ginger administered intravenously, induced a dose-dependent (0.3–3 mg/kg) decrease in arterial blood pressure of anesthetized Sprague-Dawley rats with an EC50 value of 0.9 ± 0.1 mg/kg (mean ± SEM). In guinea pig paired atria, the crude extract exhibited cardio-depressant activity on the rate and force of spontaneous contractions with EC50 values of 0.57 ± 0.03 and 0.88 ± 0.07 mg/ml (mean ± SEM) for force and rate of contraction, respectively. In rabbit thoracic aorta preparations, when tested on the resting baseline, the ginger extract was devoid of any effect up to a dose of 10 mg/mL. The extract was then tested on high-potassium (K+) (80 mg/mL) and phenylephrine (1 µg/mL)-induced contractions. The extract relaxed the phenylephrine-induced vascular contraction at a dose 10 times that required against K+ (80 mg/mL)-induced contraction with an EC50 of 0.92 ± 0.04 mg/ml, compared with an EC50 of 0.11 ± 0.01 mg/ml against K^+-induced contraction.

103. Ca^{2+} channel-blocking (CCB) activity was confirmed when the crude extract shifted the Ca^{2+} dose–response curves of thoracic aorta preparations to the right, the shift being similar to that obtained with verapamil. It also inhibited the phenylephrine (1 mg/mL) peak responses in normal-Ca^{2+} and Ca^{2+}-free solution, indicating that it acts at both the membrane-bound and the intracellular Ca^{2+} channels. When tested in endothelium-intact rat aorta, it again relaxed the K+-induced contraction (EC50 value of 0.091 ± 0.002 mg/ml) at a dose 14 times less than that required for relaxing the PE-induced contraction (EC50 value of 1.26 ± 0.08 mg/ml). The vasodilator effect of the crude extract was endothelium-

independent because it was not blocked by Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME) (0.1 mg/mL) or atropine (1 mg/mL) and also was reproduced in endothelium-denuded preparations at the same dose range. These data indicate that the blood pressure-lowering effect of ginger is mediated through blockade of voltage-dependent calcium channels.

Effect on Prostaglandins

In vitro

104. Ginger extracts, along with many gingerols and shogaols, have been shown to suppress prostaglandin synthesis *in vitro,* through inhibition of cyclooxygenase (Jolad et al. 2005; Pan et al. 2008; Dugasani et al. 2010).

105. Lantz *et al.* (2007) investigated the anti-inflammatory effect of crude organic extracts (dichloromethane-methanol, 1:1 v/v) of ginger and the principal components thereof (6-, 8- 10-gingerols and 6-, 8-, 10-shogaols) in an *in vitro* model, U937 cells (a pro-monocytic cell line), differentiated and exposed to lipopolysaccharide (LPS) from *Escherichia coli* (1 µg/ml). Extracts containing predominantly gingerols were not cytotoxic, while shogaols were cytotoxic at concentrations above 20 µg/ml. Crude extracts of ginger inhibited LPS-induced PGE2 (IC50 0.1 µg/ml) production but were much less effective at inhibiting TNF-α production (IC50 > 30 µg/ml). Extracts containing either predominantly gingerols or shogaols were highly active at inhibiting LPS-induced PGE2 production (IC50 0.1 µg/ml). Extracts containing predominantly gingerols inhibited LPS-induced COX-2 expression while shogaol containing extracts had no effect on COX-2 expression.

106. Jolad *et al.* also demonstrated the inhibitory effect of gingerols on LPS-induced PGE2 production in HL-60 cells stimulated with 1 µg/ml of LPS (2004). None of the compounds tested was shown to be cytotoxic.

107. The Committee noted the potential effect of ginger on the prostaglandin pathway, in particular cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) inhibition, and how this may affect early pregnancy. It was noted that in Lantz *et al.* (2007), the half maximal inhibitory concentration (IC50) values for a range of components in ginger were given, and it was demonstrated that these acted mainly on COX-2. The COT concluded that further studies would be needed to determine the role of decreased prostaglandin levels induced by ginger in the early termination of pregnancy.

Animal studies

108. The composition of ginger extracts appears to vary according to whether the ginger is fresh or dried. Suekawa *et al.,* (1986, only abstract in English) demonstrated that (6)-shogaol (140 and 280 mg/kg), a principal component found mainly in dried ginger, inhibited carrageenan-induced swelling of rat hind paw, arachidonic acid- and collagen-induced platelet aggregation in rabbit and ADP-induced platelet aggregation due to prostaglandin PGI2 release in rat aorta. It was further shown that at micromolar concentrations (6)-shogaol inhibited cyclooxygenase activities in rabbit platelets and microsomal fractions of rat aorta in a concentration-dependent manner and was inhibitory to 5-lipoxygenase activity in RBL-1 cells. These studies suggested a potential inhibitory action of (6)-shogaol on cyclooxygenases (COX) in both platelets and aorta tissue.

Effect on animals with induced diabetes

109. Luo et al. (2022) investigated the effects of dried, ground ginger on gestational diabetes in rats. In this study, 40 adult female rats were divided into 4 equal groups: pregnant rats, pregnant rats with streptozotocin-induced diabetes, pregnant rats consuming ginger powder (100 mg/kg, by gavage), and pregnant rats with streptozotocin-induced diabetes consuming ginger powder. The results of this study showed that one of the mechanisms of physiological metabolic adaptation during pregnancy involves reduced expression of mTORc1, SREBP-1c, PPAR-g and GLUT4 genes, with increased PPAR-α expression. Disruption of their expression can lead to metabolic disorders and hyperglycaemia and, in advanced cases, even cause gestational diabetes. Administration of ginger to diabetic animals restored expression levels of mTORc1, SREBP-1c, PPAR-g, PPAR-α, and GLUT4 in liver to those in non-diabetic animals. Ginger had no effect in non-diabetic rats. The authors concluded that these results showed that ginger can significantly improve metabolic status in gestational diabetes by modulating the expression of these genes. There were no reported adverse effects resulting from the administration of ginger when compared to the control.

110. Streptozotocin-induced diabetic rats were utilized as a diabetic model and received 200 or 400 mg/kg/day ginger extract for eight weeks. (Raoufi et al., 2023). Ginger at both levels partially ameliorated the elevated levels of glucose, testosterone, and MDA caused by diabetes. In the higher dose group, the diabetes-induced reductions in the levels of insulin, 17β-oestradiol, progesterone, and ovarian 3β-hydroxysteroid dehydrogenase transcript were also partially

offset.

Contaminants

111. Differences in cultivation conditions and extraction methods might lead to contamination of ginger from toxins, microbes, pesticides, heavy metals and residual solvents. Studies investigating contamination of ginger are limited, however of the few studies available, the main types of contamination reported are heavy metals (Wagesho & Chandravanshi, 2015; Getaneh *et al.,* 2021; Goroya *et al.,* 2019, Kilic & Soylak, 2019; Xu *et al.*, 2020) and mycotoxins (Ałtyn and Twarużek, 2020; Wen *et al., 2014;* Omotayo *et al., 2019;* Lippolis *et al., 2017*).

112. Ginger can become contaminated with mycotoxins during harvesting, storage and handling. Whilst information on mycotoxin contamination of ginger is limited, ginger has been demonstrated to be particularly exposed to aflatoxins and ochratoxin A (OTA). This is reflected in GB legislation, where maximum levels for these toxins for spices including ginger are established in Assimilated EU Law 1881/2006. Maximum levels are 5 µg/kg for aflatoxin B1 (AFB1), 10 µg/kg for all aflatoxins (sum of AFB1, AFB2, AFG1, and AFG2) and 15 µg/kg for OTA, for ginger and its products.

113. A study evaluating the heavy metal content of ginger from Turkey found that the permissible limit values in edible plants determined by FAO/WHO were exceeded for Fe, Zn, Cd, Pb and Cu (Karagözoğlu, 2023).

114. The Committee discussed the potential presence of contaminants in ginger and noted that the ginger products used in the studies reported were sourced locally in markets or from herbalists (Wagesho & Chandravanshi, 2015; Goroya *et al.*, 2019). Members queried whether there were any specific data on contaminants in ginger or ginger supplements available in the UK. However, no such information could be found.

115. The Committee noted that it was unknown how much ginger and particularly, highly concentrated juice extracts, would contribute to overall exposure to contaminants in the UK.

Exposure

116. TOX/2021/26 discussed exposure to ginger via the diet and in supplement form. TOX/2020/51 examined in more detail exposure to ginger in the form of highly concentrated juices (‘shots’). This statement reviews exposure to

ginger from all sources described previously.

117. A number of ginger supplements (Annex B, Tables 1 and 2), many of which are purported to support digestive and joint health, alleviate nausea, upset stomach, and travel sickness, are available. Currently, a number of commercially available pregnancy supplements, including ‘Seven Seas Pregnancy’ and ‘Seven Seas Pregnancy Plus Follow On’, contain ginger extracts in their formulations.

118. The availability of supplements in different forms, along with a lack of information with regards to the extraction processes involved and therefore composition of the extracts, meant that it was not possible to assess aggregate exposures. As such, ginger exposure from the diet and from supplements were considered separately.

119. In addition to supplements, pregnant women may also consume ginger as part of their general diet to various degrees. There are anecdotal reports of women consuming ginger products (Annex B, Table3), such as ginger biscuits and ginger ale, to alleviate morning sickness and nausea. Some may use these in combination with juice shots or tinctures (Annex B, Table 4).

120. Table 1 shows estimated exposures from the diet, supplements and drinks (including teas and shots). Mean estimated acute ginger exposure from the diet in women aged 16-49 years old was 0.026 g/kg bw/day, and 97.5th percentile exposure was 0.16 g/kg bw/day. The corresponding mean and 97.5th percentile chronic exposures were 0.0083 and 0.058 g/kg bw/day, respectively. The upper value of the range of daily exposure from drinks and supplements was more than double that estimated for 97.5th percentile acute exposure from the diet, and 8-10 times that for chronic consumption from the diet.

Table 1: Estimated mean and 97.5th percentile acute and chronic ginger exposures from a variety of sources in women aged 16 – 49 years old.

Sources	**Range of daily exposures (g/day)**	**Range of daily exposures (g/kg bw/day)**	**Mean acute exposure* (g/day)**	**Mean acute exposure* (g/kg bw/day)**	**97.5th percentile acute exposure* (g/day)**	**97.5th percentile acute exposure* (g/kg bw/day)**	**Mean chro expo (g/da**

Food[a]	NA	NA	1.7	0.026	11	0.16	0.55
Drinks (Including tea and shots) [b1,b]	0.5 - 32.5	0.0071 - 0.46	NA	NA	NA	NA	NA
Supplements [c]	0.010 - 24	0.00014 - 0.34	NA	NA	NA	NA	NA

1This assumes only one serving is consumed per day.

a Data obtained from the National Diet and Nutrition surveys years 1-8 calculated from women of a childbearing age (16-49 years). (Bates *et al*., 2014; 2016; Roberts *et al*., 2018).

b Data obtained online from retailers, see Appendix 1 for further details.

c Data obtained online from retailers, see Appendix 1 for further details.

*Rounded to 2 significant figures.

121. As previously mentioned, if used during pregnancy, 1 - 1.5 g per day of ginger is advised (NHS, 2022, Healthline, 2020; Mother and Baby, 2022). Some highly concentrated ginger shots commercially available contain up to 30 g of fresh ginger per serving, over 30 times that recommended by healthcare professionals.

122. As the National Diet and Nutrition Survey (NDNS) does not provide data for pregnant women, there was uncertainty as to whether the data presented an accurate reflection of consumption during pregnancy. This uncertainty also extended to data presented for drinks and supplements, as the pattern of consumption during pregnancy to alleviate symptoms of sickness is unknown.

Toxicology conclusions

Reproductive and developmental toxicity

123. The COT considered a number of epidemiological studies investigating the use of ginger during pregnancy (TOX/2021/26). For the most part, few of these studies explicitly addressed the safety of ginger consumption. Most were focused on the use of ginger as a treatment for nausea (Fischer-Rasmussen *et al*., 1990; Smith *et al*., 2004; Ensiyeh *et al.*, 2009), age-related neurological disorders or pregnancy-induced sickness and therefore focused on efficacy (Willetts *et al.*, 2003; Stanisiere *et al.*, 2018). However, safety was considered in a few studies. The studies considered by the Committee included observational and randomised clinical studies, lasting from 4 days to 20 weeks in duration (Vutyavanich *et al.*, 2001; Portnoi *et al*., 2003). Ginger in various forms was investigated in doses ranging from 750 mg/day to the equivalent of 7 g/day.

124. The animal studies on reproductive toxicity considered in TOX/2021/26 reported a number of findings, including reduced maternal weight gain, increased fetal weight, increased serum testosterone levels in F1 generation males and an increase in embryonic loss.

125. The study results in pregnant women were also varied and overall were inconclusive. Findings reported included abdominal discomfort, vomiting and diarrhoea. There were reports of incidences of spontaneous abortion (Portnoi *et al*., 2003, Ensiyeh *et al.*, 2009), however, this effect was observed in both the treated and control groups and therefore, cannot be attributed directly to the consumption of ginger. Portnoi *et al*., reported 8 spontaneous abortions in the comparator group, compared to 3 occurring in the group taking ginger and Ensiyeh *et al.*, reported 2 spontaneous abortions in the ginger group compared to 1 in the group taking vitamin B6. This study reported no congenital abnormalities post-partum following exposure to ginger.

126. In their 2015 review of interventions for nausea and vomiting in early pregnancy (first trimester), Matthews concluded high-quality consistent evidence is lacking to support advice regarding the safety of ginger during pregnancy (Matthews et al., 2015). However, it was noted that a review by Bryer et al. (2005) concluded that maternal consumption of ginger shows no evidence of teratogenicity in infants. More recently, Stanisiere et al. (2018) conducted a review of the safety and efficacy of ginger rhizome for decreasing nausea and vomiting in women during early pregnancy, based on systematic literature searches until the end of December 2017. The group concluded that the *in vivo* results do not suggest any major concerns with respect to reproductive and developmental safety of ginger root, as no associations were found between the use of ginger and malformations in humans. *In vitro* results could not be

extrapolated to humans due to the lack of representativeness of the preparations and/or concentrations used. The authors concluded that, overall, the available evidence suggested that the use of ginger for treatment of nausea in pregnancy is safe, but that ginger quality is important from the perspective of safety. The majority of the studies included in Stanisiere et al. (2018) have already been included in this draft statement. Some recent studies have been conducted evaluating the effectiveness and safety of ginger in pregnancy and are discussed in detail. Overall, most studies reported gastrointestinal effects such as abdominal discomfort/heartburn, vomiting and diarrhoea. Other effects included dizziness, headaches and drowsiness. The review by Jewell and Young (2003) focuses on the reported effects rather than statistical significance, therefore more details on the studies reporting more serious effects were given in this statement.

Anti-platelet aggregation activity

127. Several reports have been published on the pharmacological properties of ginger, with varying results. The potential effect of ginger extract and components thereof on the reduction of platelet aggregation and their potential antithrombotic activity has been noted as a concern both in the literature and by health professionals.

128. Ginger was reported to have antiplatelet activity (Srivastava, 1986,1989; Young *et al.*, 2006), with some studies reporting effects in animals at doses of 500 mg/kg bw (Thomson *et al.*, 2002). Ginger was found to inhibit the formation of thromboxane and prostaglandin endoperoxides (PGF2α, PGE2 and PGD2) in human platelets *in vitro*, in a dose-dependent manner (Srivas, 1984).

129. With regards to the relevance of such effects in pregnancy, literature reports note that pregnancy is associated with an increased incidence of thrombotic events; mainly related to a pro-thrombotic state, physiologically useful to reduce bleeding at delivery. These changes are more pronounced in the third trimester (Patti *et al.,* 2014). It has also been hypothesised that antiplatelet agents might prevent or delay the development of pre-eclampsia (Duley *et al.*, 2019). The implications and clinical significance of the anti-platelet activity of ginger during different stages of pregnancy remain undetermined.

130. This further highlighted the need to differentiate exposure from the normal diet to that from supplements. Members noted that associations with haemorrhagic effects had been reported mainly as the result of a herb-drug interaction following supplemental exposure to ginger, (Kruth *et al.*, 2003; Rubin *et al.*, 2019; AlAskar *et al.*, 2020). though these were inconclusive.