This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

TOX/2023/44

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

Third Draft Statement on the Safety of Ginger Supplement Use in Pregnancy

Introduction

1. As part of the current programme of work on the maternal diet, the Committee considered the use of dietary supplements during pregnancy. A scoping paper (TOX/2020/51) was presented, reviewing the commonly used dietary supplements during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which 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 which are the responsibility of the Medicines and Healthcare Products Regulatory Agency (MHRA). Following this review, the COT agreed ginger required further investigation, noting that human, animal and *in vitro* data were available.

2. In May 2021, the Committee considered the potential effects of ginger and ginger supplements during pregnancy and lactation. Paper TOX/2021/26 (Available on the COT website) reviewed the available data on toxicity to the mother, effects on the development of the foetus or embryo, and possible interactions with drugs as well as data on potential exposure.

3. Overall, it was concluded that there were limited data. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible adverse effects and a lot of uncertainties. Ginger did not appear to be systemically toxic but did appear to have reprotoxic effects at high

supplemental doses. The Committee suggested looking at the animal data in closer detail to determine the point of departure (No Observed Adverse Effect Level - NOAEL), followed by calculating the potential exposure to supplements to determine whether there was cause for concern.

4. Paper TOX/2021/51 provided further information with respect to animal studies, contaminants and exposure to ginger supplements, primarily centred on the effect of ginger on prostaglandins, reproductive and developmental toxicity and the possible contaminants present in ginger.

5. The members noted that although the different ginger extracts were not comparable, they did appear to exhibit some biological activity in the early stages of pregnancy. It was reiterated that there was no indication of general systemic toxicity from the use of ginger.

6. A draft statement was considered in July 2022 (TOX/2022/42), drawing on the information provided in the previous discussion papers to form an overall conclusion on the safety of the use of ginger and in particular ginger supplements in the maternal diet.

7. The current statement includes additional studies identified by the COT to further inform the available database, with regard to the possible influence of ginger components on cyclooxygenase (COX) and prostaglandin activity. A summary of all the studies considered has also been tabulated in Annex B for reference.

Questions for the Committee

i. Does the additional information provided change the final conclusion of the statement?
ii. Does the information provided on red ginger need to be considered and incorporated into this statement?
iii. Does the committee have any further comments on the content and structure of this statement?

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Secretariat

November 2024

TOX/2023/44 Annex A

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

Second Draft Statement on the Safety of Ginger Supplement Use in Pregnancy

Background

1. In 2019, the Scientific Advisory Committee on Nutrition (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; this would include the effects of chemical contaminants and excess nutrients in the diet.

2. This subject was initially discussed during the COT's horizon scanning item at their January 2020 meeting with a scoping paper being presented to the COT in July 2020. This included background information on a provisional list of chemicals proposed by SACN.

3. Following a discussion at the September 2020 meeting, the COT agreed that papers on a number of compounds should be prioritised. The following paper provides the advice of the COT on whether exposure to ginger would pose a risk to maternal health.

4. As part of the current programme of work on the maternal diet, the Committee considered the use of dietary supplements during pregnancy. A scoping paper (TOX/2020/51) was presented, reviewing the commonly used dietary supplements during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which have been 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 which are the responsibility of the Medicines and Healthcare Products Regulatory Agency (MHRA).

5. Paper TOX/2020/51 provided a detailed summary of the supplements most recommended during pregnancy (ginger, chamomile, raspberry leaf, echinacea, peppermint oil and leaves, dandelion, and evening primrose oil), focusing where available, on studies relevant to pregnancy and maternal outcomes. The main areas of investigation were general toxicity to the mother, effects on the development of the foetus or embryo, and possible interactions with medicines. The COT agreed that ginger required further investigation, noting that both human and animal *in vitro* and *in vivo* data were available.

6. In May 2021, the Committee considered the potential effects of ginger and ginger supplements during pregnancy and lactation. Paper TOX/2021/26 (Available on the COT website) reviewed the available data on toxicity to the mother, effects on the development of the foetus or embryo, and possible interactions with drugs as well as data on potential exposure.

7. Overall, it was concluded that there were limited data. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible adverse effects and a lot of uncertainties. Ginger did not appear to be systemically toxic but did appear to have reprotoxic effects at high supplemental doses. The Committee suggested looking at the animal data in closer detail to determine the point of departure (No Observed Adverse Effect Level - NOAEL), followed by calculating the potential exposure to supplements to determine whether there was cause for concern.

8. Paper TOX/2021/51 provided further information with respect to animal studies, contaminants and exposure to ginger supplements, primarily centred on the effect of ginger on prostaglandins, reproductive and developmental toxicity and the possible contaminants present in ginger.

9. Members noted that although the different ginger extracts were not comparable, from animal studies they did appear to exhibit some biological activity in the early stages of pregnancy. It was reiterated that there was no indication of general systemic toxicity from the use of ginger.

10. The COT noted that intake of ginger in foodstuffs should also be considered as ginger was consumed not only as a supplement but also as part of the diet in foods such as ginger biscuits, tea and ginger beer. Therefore, aggregate exposures would need to be considered when addressing the safety of ginger supplement use during pregnancy.

Information on ginger

11. Ginger (*Zingiber officinale*) is a flowering tropical plant originating in Southeast Asia and grown in warm climates including China, India, Africa and the Caribbean. Ginger is commonly consumed in fresh root, dried root powder and capsule (encapsulated dried powder) forms, as a liquid extract, preserved in syrup or sugar and as a tea.

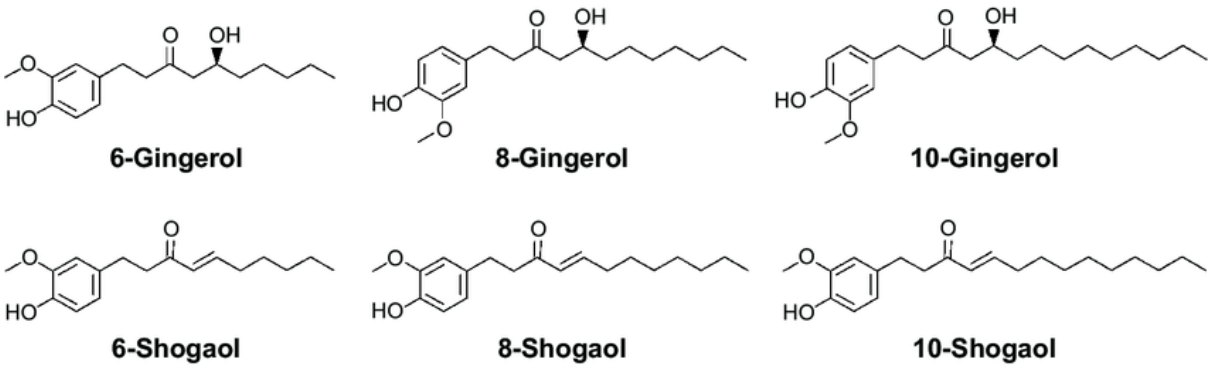
Uses

12. The rhizome (underground stem) of the ginger plant is commonly used as a spice and flavouring in many countries around the world and is increasingly growing in popularity as a natural remedy due to its purported immunomodulatory properties and also to alleviate motion sickness and post-operative nausea and vomiting. Ginger has been recommended as a nonpharmacological treatment for mild to moderate nausea and vomiting in pregnancy (NHS 2021; NICE 2021) and has also been used as a dietary supplement and a traditional remedy in many cultures. Ginger is included in the official pharmacopoeias of some western countries.

Constituents

13. Over 100 compounds have been identified in ginger extracts, most being terpenoids - mainly sesquiterpenoids (α-zingiberene, β-sesquiphellandrene, β-bisabolene, α-farnesene, ar-curcumene zingiberol) and smaller amounts of monoterpenoids (camphene, β-phellandrene, cineole, geraniol, curcumene, citral, terpineol, borneol) (EMA, 2012).

14. The ginger rhizome contains two main classes of constituents: the essential oils responsible for the aroma, and the main pungent principles, gingerols and shogaols. Organic acids are also present in smaller amounts. Depending on the area of cultivation, gingerols make up 4-7.5% of the pungent principles, the main one being 6-gingerol. Gingerols of other chain lengths are also present in smaller amounts.



Reviews by other regulatory agencies

15. Ginger is included in the official pharmacopoeias of several western countries. Ginger is classified as 'Generally Recognised as Safe' (GRAS) by the United States Food and Drug Administration (FDA) however, few specific studies have been carried out to evaluate the safety of ginger use during pregnancy and lactation. A report by the National Institute for Health and Care Excellence (NICE) cites a number of short duration trials which have been conducted in pregnant women (NICE, 2021).

16. In 2008, the Danish company Ferrosan A/S withdrew their product GraviFrisk – a product containing 6 g of dried ground ginger - from market, due to concerns surrounding the lack of safety data with respect to the use of supplements containing highly concentrated ginger extracts by pregnant women (Dietz *et al*., 2016).

17. In their 2012 report on ginger root in powdered form, the European Medicines Agency (EMA) concluded “The ginger extract dosages to provoke acute toxicity are high and much higher than usually administered dosages (factor of 10-15 for an adult). There is some evidence that ginger root may cause rodent testicular weight to increase by repeated high dosages of ginger root extract (2000 mg/kg). Ginger root has mutagenic as well as antimutagenic properties in microbial test systems. Developmental toxicity studies in rats are difficult to interpret, however, it is probably not a cause for concern. In general, toxicity studies of ginger are considered inadequate at least regarding genotoxicity, carcinogenicity and, partially, reproductive and developmental toxicity.”

18. The Norwegian Food Safety Authority have issued a warning regarding the use of ginger supplements and ginger-containing shots during pregnancy. This was based on a risk assessment carried out by the Danish Technical University and the Danish Veterinary and Food Administration (DTU, 2018). The assessment, based on animal studies, including one in which rats were treated with a fresh grated ginger preparation with ginger at concentrations of 20-50 g/L in water, found that even in the 20 g/L treatment group – the equivalent of 1,784 mg/kg bw increased the incidence of abortion in rats. The Norwegian Food Safety Authority concluded that while a woman of 70 kg would consume less ginger (124 mg to 329 mg) there remains cause for concern and fetal risk cannot be excluded.

19. Recently, the Finnish Food Authority issued a recommendation against the use of products containing ginger concentrate or extract, ginger tea and food supplements containing ginger by pregnant and breastfeeding women, infants and toddlers, schoolchildren, elderly and individuals with weakened immunity (Finnish Food Authority, 2019). It was noted that the concentrates contained substances which may be harmful and safe consumption levels were unknown.

20. The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of ginger-derived ingredients for use in cosmetics and determined that they are safe in cosmetics in the present practices of use when formulated to be non-sensitising (Belsito, 2021). The report describes a short-term toxicity study where seventy participants were given an oral dose of either steamed ginger extract (200 mg in capsule form; n = 36), or a placebo (n = 34), daily. All clinical test results were normal, and all participant completed the study. No extract-related adverse effects were observed.

Health-based guidance values

21. There are currently no health-based guidance values (HBGV) with respect to ginger or its main components. Exposure to ginger was considered based on information found on supplement and tincture composition and background diet, but the variability of available supplements meant exposure also varied, which made comparison difficult.

22. The NHS and NICE support the use of ginger tea and biscuits as a non-pharmacological intervention for nausea and vomiting in pregnancy (NHS, 2021; NICE, 2021). Generally, amounts of 1 g ginger per day are probably safe (NHS, 2022). Anecdotally, 1-1.5 g per day has also been advised during pregnancy (Healthline, 2020; Mother and baby, 2022). It is advised that supplements should be used only under the advice and supervision of a medical professional.

Red ginger

23. In traditional medicine, red ginger is used for treating headaches, indigestion, nausea, vomiting, and cancer. In addition, it is widely used to treat autoimmune diseases (psoriasis), hypertension, hypercholesteremia, hyperuricemia and bacterial infections. (Zhang et al., 2022).

24. The consumption of red ginger in the diet is not common due to the difference in taste when compared with common ginger. There is limited evidence to suggest that red ginger is commonly purchased or consumed in the UK.

25. Health claims relating to red ginger reference the benefits of consuming red ginger for emesis and pain during and following pregnancy however studies in this area are primarily from hospital obstetrics settings in Asia (largely Indonesia) where red ginger is grown and readily available.

26. There is limited toxicological data available on red ginger and studies looking at the medicinal potential of red ginger do not assess or comment on effects outside of those of interest. There are some examples of comparisons of red vs common ginger on toxicological literature. In these studies, red ginger has an enhanced effect when compared to common ginger.

27. Red ginger is discussed in Annex D.

Toxicology Overview

28. It was noted that some studies reported effects on male testes and, though not relevant for females, they were nevertheless regarded as indicating a potential reprotoxic effect from ginger. Studies suggest that ginger affected the viability of pregnancy; however, with no strong conclusive human data, the COT concluded that more work was required, especially as these studies suggested a link between first trimester loss and ginger use. Further, the 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 varied due to the

differences in the forms and extracts 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 effect of ginger on prostaglandins, 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 similarly to 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 is ≤4 g/day (equivalent to approximately 2 teaspoons) it has been included in traditional culinary uses, and if it is >4 g/day the study is included in the extracts section.

Toxicology of ginger root used traditionally

Reproductive and developmental toxicity

Animal studies

33. Reproductive and developmental toxicity has been investigated in rat studies. 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 double that of the controls. Exposed foetuses were found to be significantly heavier than controls and showed no gross structural malformations. The authors conclude that the results of this study suggest that in utero exposure to ginger tea results in early embryonic loss and increased growth in surviving foetuses.

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 groups. No congenital abnormalities were observed in all babies 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. The results suggested that the ginger group did not have an increased rate of major malformations above the baseline rate of 1%–3% (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. 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, $P<0.001$) 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, investigated the effectiveness of ginger versus B6 for treatment of nausea and vomiting in pregnancy (NVP) in women before 17 weeks' gestation (2009). 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. 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 (2004).

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. p. 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. 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 prostaglandins are covered from paragraph 103 onwards.

41. Overall, it was concluded that there were limited data. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible effects and 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 this outcome in human studies.

Lactation

42. With respect to lactation, the focus of available studies (Lamxay *et al.*, 2011; Kaygusuz *et al.*, 2021; Dilokthornsakul *et al*., 2021) has been 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

43. Ginger was found to have a significant inhibitory effect on CYP3A4, CYP2C9, and P-glycoprotein activities in vitro (Kimura *et al*., 2010; Zhang and Lim, 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

44. Krüth *et al.* reported the possible over-anticoagulation resulting from a possible ginger-phenprocoumoun interaction (2003). 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.

45. Young *et al.* 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 (2006). In a five-part study, the two groups comprising of 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).

46. Platelet aggregation in the presence of collagen, ADP and epinephrine was 44.1%, 44.5% and 42.1% in normal subjects and 64.2%, 67.7% and 62.9% in hypertensive patients, respectively. Platelet aggregation induced by collagen, ADP or epinephrine was found to be higher in hypertensive patients than normal patients. Following administration of ginger alone, platelet aggregation was measured as 35.2%, 37.8%, 35.9% with collagen, ADP and epinephrine respectively. When administered ginger and nifedipine in combination, the percentage inhibition of platelet aggregation induced by collagen, ADP and epinephrine was 79.8%, 75.2%, 69.3% respectively.

47. Al Askar *et al.* (2020) investigated the effect of ginger on platelet aggregation using agonists adenosine diphosphonate, arachidonic acid, collagen, ristocetin and epinephrine. Forty healthy male and female participants were randomized (1:1) to consume ginger tea at an amount of 4 g powered ginger in 150 ml of boiling water once daily vs. 4 g twice daily for five consecutive days. Comparisons were with pre-treatment changes. Four grams of ginger powder administered daily resulted in reduced platelet aggregation in subjects using epinephrine only. No such effect was seen in the higher dose group. Essentially, ginger had no effect on platelet

aggregation in this study. Platelet aggregation inhibition was found to be higher in women using arachidonic acid.

48. 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 ~5g of fresh ginger for 7 days, ginger was found to inhibit eicosanoid biosynthesis *in vivo*.

49. Lumb found that a dose of 2g of ginger in powder form daily produced no significant differences in platelet aggregation/function than the placebo. The authors concluded that previously reported effects on thromboxane synthetase activity may be dose dependent or attributed to fresh ginger (1994).

50. 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). However, a single 10g dose of powdered ginger, administered to CAD patients resulted in a significant decrease in induced platelet aggregation.

Toxicology of ginger extracts

Cytotoxicity

51. The cytotoxicity of ginger extracts has been investigated with varied results. Plengsuriyakarn *et al*. (2012) examined 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. The median inhibitory concentration, (IC_{50}) 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.

52. Zaeoung *et al.* (2005) reported that the IC_{50} of aqueous and methanolic extracts of ginger was greater than 39.2 µg/ml against breast (MCF7) and colon (LS174T) cell lines.

53. Abudayyak *et al*. (2015) found the aqueous and methanolic extracts of ginger exhibited no cytotoxic activity when assessed using an MTT test (a colourimetric assay for assessing cell metabolic assay) in the rat kidney, NRK-52E cell line. The chloroform extract resulted in an IC_{50} value of 9.1 mg/mL.

54. However, it was noted that the inhibitory concentration (IC_{50}) values presented in the studies reviewed were based on a small amount of 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 would not have been assessed.

Mutagenicity

55. Nakamura and Yamamoto (1982) found that the juice of ginger rhizome possessed both mutagenic and anti-mutagenic properties, and that 6-gingerol in particular was a powerful mutagen. The group also demonstrated that 6-shogaol was much less mutagenic (strain Hs30 of Escherichia coli) than 6-gingerol (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 and exposed to benzo(a)pyrene was found to display a significant reduction in mutagenicity as indicated by a reduced number of TA98 and TA100 revertants at all ginger concentrations (Nirmala *et al*. 2007) when tested in an Ames assay.

56. In another Ames assay, an ethanolic extract of ginger (Soudamini *et al.* 1995) and an essential oil from ginger (Sivaswami *et al*. 1991) 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 between 10 and 200 µg/plate, and gingerol and shogaol were mutagenic in strains TA100 and TA1538 with metabolic activation by rat liver S9 mix, while zingerone did not display mutagenic effects (Nagabhushan *et al*. 1987).

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

58. 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 was not shown to be mutagenic *in vivo* (Nirmala, Prasanna Krishna and Polasa, 2007).

Acute toxicity

59. An acute toxicity study (Malik and Sharma, 2011) in male Wistar rats showed no signs of toxicity or mortality. The animals were administered doses of 250, 500 and 1000 mg/kg lyophilised ginger powder by gastric 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).

Short term repeat dose studies

60. 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. The results demonstrated that 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.

61. 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 and systemic toxicity (Alnaqeeb et al. 2003). Neither oral nor intraperitoneal administration resulted in mortality. Orally administered aqueous ginger extract resulted in increased levels of serum aspartate aminotransferase (AST) and decreased levels of alanine aminotransferase (ALT).

62. Jeena et al. (2011) conducted a sub chronic toxicity study of the essential oil of ginger in Wistar rats following oral administration at concentrations of 100, 250, and 500 mg/kg per day once daily for 13 consecutive 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.

63. An increase in serum sodium levels was observed in 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 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

64. Mohammed *et al* investigated the effects of herbal extracts, including ginger and 6-gingerol, on chick embryonic heart micromass and mouse D3 embryonic stem

cell systems (ESD3) (2016). The team observed that a different study had concluded that the use of 6-gingerol l remedies in the first trimester of pregnancy may affect foetal development (Park, 2012). However, 6-gingerol-treated primary embryonic chick cardiomyocytes showed no significant changes in contractile and cellular activity or changes in total protein content in comparison to the control. At concentrations of 0.75–6 μM, 6-gingerol treated primary embryonic chick cardiomyocytes exhibited no significant changes in contractile activity, 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 the cellular activity and protein content in a dose-dependent manner.

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

Animal studies

66. 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 highlighted to affect some essential embryonic developmental processes, such as the disruption of angiogenesis. Kim *et al*, demonstrated the ability of 6-gingerol to inhibit proliferation and 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 through its anti-angiogenic activity (Kim et al., 2005).

67. The teratogenicity of EV.EXT 33, a patented Zingiber officinale extract (comprising 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 & Sigwart, 2001). The extracts were administered orally by gastric intubation at concentrations

of 100, 333 and 1000 mg/kg, to three groups of pregnant rats from days 6 to 15 of gestation. Their bodyweight, food and water were monitored during the treatment period. The study 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 1000 mg/kg bw.

68. Shalaby and Hamowieh, (2010) investigated fertility, serum testosterone and acute toxicity 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 (prepared using 100 g dry ginger roots soaked in 500 ml water or 500 ml methyl alcohol 90%) 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 were recorded. The oral lethal doses (LD_{50}) 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 does up to 5 g/kg bw. Both extracts increased fertility index, sexual organ weight, and sperm motility and count after 65 consecutive days (see below).

69. To investigate the effect of ginger extracts on serum testosterone levels, male rats had their fertility reduced by inducing diabetes, a condition shown to reduce male fertility. 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 $P < 0.001$) 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 (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.

70. The study also investigated fertility based on 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 at doses of 100 and 200 mg/kg bw for 65 consecutive days and water extracts at doses of 150 and 300 mg/kg bw and compared to a diabetic control group.

71. Histopathological examination of the testes of diabetic rats showed mild to moderate degenerative changes of spermatogenic cells, diffuse oedema and incomplete arrest of spermatogenesis. The testes of rats orally administered 300 mg/kg bw of water extract of ginger root showed 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, showing fewer signs of degradation, suggesting a LOAEL 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 impotency.

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

73. Hosseini et al. (2015, abstract only) investigated the effect of ethanolic ginger extract on serum testosterone, LH and FSH as well an effect on spermatogenic cell lines in male mature offspring rats. In this study, 72 female rats, sorted 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 and saline was used as a control. Following puberty, LH, FSH, numbers of Sertoli cells, spermatogonia, spermatocytes and spermatids were counted in 8 male rat offspring from each group. Ginger was found to significantly increase testosterone levels and the number of spermatogenic cells and at doses of 100 and 200 mg/kg bw, alcoholic extract of ginger 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.”

74. Dissabandara & Chandrasekara (2007) also examined the effect of powdered ginger extract administered prenatally on the postnatal development of rats. A period of administration of the dry powdered extract orally at doses of 500 mg/kg/day 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.

75. 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 at 250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract. These were investigated in 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.

76. 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, the length of the oestrous cycle was prolonged with 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 at this dose group was also

16.6% higher than the control group. The authors considered that this may reflect a dose-dependent antifertility (anti-implantation) effect.

77. 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 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 was 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.

78. 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.

79. When evaluating the effect of the aqueous extract of Ginger rhizomes on the sexual parameters of rats. Peneme et al. (2023) initially determined the acute toxicity of the aqueous extract of ginger rhizomes in accordance with OECD guideline no. 423. Rats were given 5000 mg/kg aqueous ginger extract by gavage. No change in the general condition or behaviour of the mice compared with the control batch was observed. No animal mortality was observed after 48 hours or 14 days of observation. This experiment was followed by administering aqueous ginger extract

at doses of 300 and 600 mg/kg, 17β-oestradiol at a dose of 1 mg/kg or distilled water, orally to rats for 14 days. A non-significant increase and decrease in body weight was observed at doses of 300 and 600 mg/kg respectively. The authors state that rats treated with 17 β-oestradiol also showed a reduction in body weight, as with the ginger extract at 600 mg/kg, and they considered this to confirm an oestrogenic effect. The eosinophil indices for the 600 mg/kg group were similar to the 17β-oestradiol indicating disruption of the oestrus cycle. A significant increase in oestradiol levels was observed in the rats treated at 300 mg/kg, and a non-significant decrease at 600 mg/kg compared with the control batch. The rat batch treated with the reference molecule 17 β-oestradiol at 1 mg/kg also showed a drop in oestradiol levels.

80. The Committee considered the animal studies to be inconclusive.

81. ElMazoudy and Attia (2018) noted reductions in bodyweight and deaths in mice dosed 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 up to 500 mg/kg ginger extract.

82. However, the Committee noted that the database was limited, and the extraction and concentration of ginger varied between the studies. 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 were unable to determine a point of departure, to reach a conclusion.

Human studies - exposures in pregnancy

83. 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. One spontaneous abortion was observed in the placebo group.

84. In an observational study conducted by Laekman 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. 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 rate 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 states that there was no relationship between the events affecting the mother and child and the number of EXT.GR10 tablets taken.

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

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

In silico

86. 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 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

87. 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 an inhibitory effect on CYP enzymes CYP3A4, CYP2C9 (Kimura *et al.*, 2010), CYP2C19 (Kim *et al.*, 2012), and CYP1A2 and CYP2C8 with IC_{50} values as low 1μM, (e.g., 6-shogaol on CYP1A2; Mukkavilli *et al.*, 2014).

Animal studies

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

89. 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, two 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 per oral on the third day. Ginger significantly increased the absorption and plasma half-life and significantly decreased the elimination rate constant and clearance of metronidazole.

90. 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.

91. 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).

92. 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 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.

Human studies

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

94. Conversely, whilst investigating the effects of ginger on the pharmacokinetics or 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 had no effect on international normalized ratio (INR) or *ex vivo* platelet aggregation in response to arachidonic acid.

Anti-platelet aggregation activity

In vitro studies

95. 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.

Animal studies

96. A study by ElMazoudy and Attia (2018) linked follicular failure to haemorrhagic effects in a study investigating the effect of aqueous ginger extract on the oestrus cycle and implantation, in female mice. The authors concluded that ginger impairs the normal growth of the corpus luteum 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. The COT noted that this might be worth further investigation. However, it was also noted that other factors could be contributing to the results observed and the study results were inconclusive.

97. The effect of an aqueous ginger extract on platelet thromboxane-B_2 (TXB_2) and prostaglandin-E_2 (PGE_2) 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 TXB_2 levels when compared to saline-treated control groups but doses at 500 mg/kg significantly reduced TXB_2 levels in serum.

98. A non-significant reduction in the level of TXB_2 was observed when ginger was injected IP. However, levels were not significantly different from the TXB_2 levels in control rats that had received saline. 50 mg/kg of ginger administered orally resulted in serum PGE_2 levels being significantly reduced and 500 mg/kg was found to be more effective in reducing PGE_2 synthesis. PGE_2 levels were reported to be significantly lower than the saline control in rats given 500 mg/kg ginger extract both orally and IP.

Human studies

99. 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, and warfarin 10 mg once day per week, 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.

100. Ginger, in powder form (5 g per day), was demonstrated to significantly ($P<0.001$) decrease ADP- and epinephrine-induced platelet aggregation in healthy male subjects who were fed 100 g of butter daily for seven days (Verma *et al.*, 1993). Conversely, 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). However, a single 10g dose of powdered ginger, administered to CAD patients resulted in a significant decrease in induced platelet aggregation.

Effects on blood pressure

Animal studies

101. 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 EC_{50} 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 preparation, when tested on the resting baseline, the ginger extract was devoid of any effect up to the dose of 10 mg/mL. The extract was then tested on high-K+ (80 mM) and phenylephrine (1 μM)-induced contractions. The extract relaxed the phenylephrine-induced vascular contraction at a dose 10 times higher than that required against K+ (80 mM)-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.

102. Ca^{2+} channel-blocking (CCB) activity was confirmed when the crude extract shifted the Ca^{2+} dose–response curves to the right, the shift being similar to that obtained with verapamil. It also inhibited the phenylephrine (1 mM) control peaks 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 N_ω-nitro-L-arginine methyl ester hydrochloride (L-NAME) (0.1 mM) or atropine (1 mM) 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

103. 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).

104. Lantz *et al.* (2007) investigated the anti-inflammatory effect of ginger extracts and the principal components thereof (6-, 8- 10-gingerols and 6-, 8-, 10-shogaols) in an *in vitro* model, U937 cells, differentiated and exposed to lipopolysaccharide (LPS) from Escherichia coli (1 µg/ml). Extracts containing predominantly gingerols were found not to be cytotoxic, while shogaols were found to be 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 (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.

105. Jolad *et al.* also demonstrated the inhibitory effect of gingerols on LPS-induced PGE_2 production in HL-60 cells stimulated with 1 µg/ml of LPS (2004). None of the compounds tested were shown to be cytotoxic.

Animal studies

106. 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. One study examining the effects of ginger extracts on prostaglandin E_2 (PGE_2) production *in vitro* (Lantz *et al.* 2007) demonstrated that crude organic extracts (dichloromethane-methanol, 1:1 v/v) of ginger were capable of inhibiting PGE_2 production and that the compounds may act at several sites. The most potent effect on lipopolysaccharide (LPS) induced prostaglandin production was noted at less than 0.1 µg/ml. It was noted that the half maximal inhibitory concentration (IC_{50}) values for a range of components were given, and it was demonstrated that the components mainly acted on COX-2. The COT

concluded further studies would be needed to determine the role of decreased prostaglandin levels in the early termination of pregnancy.

107. The composition of ginger extracts also appears to vary according to whether ginger is fresh or dried. Suekawa *et al.,* (1986, abstract only) demonstrated that (6)-shogaol, a principal component mainly found in dried ginger, inhibited carrageenan-induced swelling of rat hind paw, AA-induced platelet aggregation in rabbit and prostaglandin PGI_2 release in rat aorta, suggesting a potential inhibitory action on cyclooxygenases (COX) in both platelets and aorta tissue.

Effect on animals with induced diabetes

108. Luo et al. (2022) determined the effects of ginger on gestational diabetes in rats. In this study, 40 adult female rats were divided into 4 equal groups: pregnant rats, pregnant rats with diabetes, pregnant rats consuming ginger powder (100 mg/kg, by gavage), and pregnant rats with diabetes consuming ginger powder. The results of this study showed that one of the mechanisms of physiological metabolic adaptations during pregnancy is a change in the expression of mTORc1, SREBP-1c, PPAR-α, and PPAR-g genes. Disruption of their expression can lead to metabolic disorders and hyperglycaemia and even in advanced cases cause gestational diabetes. However, the results in the groups receiving ginger showed that ginger can significantly improve the metabolic status by modulating the expression of these genes. There were no reported adverse effects resulting from the administration of ginger when compared to the control.

109. Streptozotocin induced 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 ameliorated the levels of glucose, testosterone, and MDA. At the higher dose group elevated the levels of insulin, 17β-oestradiol, and progesterone were seen.

Contaminants

110. Differences in cultivation conditions and extraction methods could lead to possible sources of contamination from toxins, microbes, pesticides, heavy metals and residual solvents. Studies investigating contamination in ginger are limited, however of the few studies available, the main sources of contamination reported are heavy metals (Wagesho & Chandravanshi, 2015; 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*).

111. Ginger can be exposed to mycotoxin contamination during harvesting, storage and handling. Whilst information on mycotoxin contamination in 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 B_1 (AFB_1), 10 µg/kg for all aflatoxins (sum of AFB_1, AFB_2, AFG_1, and AFG_2) and 15 µg/kg for OTA, for ginger and its products.

112. 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).

113. 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 herbalists (Wagesho & Chandravanshi, 2015; Goroya *et al.*, 2019). Members queried whether there were any specific data on contaminants in ginger supplements available in the UK.

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

Exposure

115. 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 ginger from all sources described previously.

116. A number of ginger supplements (Tables 1 and 2, Annex C) are purported to support digestive and joint health, alleviate nausea, upset stomach, and travel sickness. 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.

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

118. 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 (Tables 3, Annex C) such as ginger biscuits and ginger ale, to alleviate morning sickness and nausea. Some may use these in combination with juice shots or tinctures (Table 4, Annex C).

119. Table 1 shows calculated exposures from the diet, supplements and drinks (including teas and shots). Mean acute ginger exposure from the diet of 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 exposure from drinks and supplements was more than double (%) that of those estimated from 97.5th percentile acute exposure 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.

Commodity	**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 chronic exposure* (g/day)**	**Mean chronic exposure* (g/kg bw/day)**	**97.5th percentile chronic exposure* (g/day)**	**97.5th percentile chronic exposure* g/kg bw/day**
Food[a]	NA	NA	1.7	0.026	11	0.16	0.55	0.0083	3.4	0.058
Drinks (Including tea and shots) [b1,b]	0.5 - 32.5	0.0071 - 0.46	NA	NA	NA	NA	NA	NA	NA	NA
Supplements [c]	0.010 - 24	0.00014 - 0.34	NA	NA	NA	NA	NA	NA	NA	NA

[1]This 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.

120. As previously mentioned, 1 - 1.5 g per day of ginger may be advised during pregnancy (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.

121. As the 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

122. The COT considered a number of epidemiological studies investigating the use of ginger during pregnancy (TOX/2021/26). For the most part, few studies explicitly addressed the safety of ginger consumption during pregnancy. 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.

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

124. The study results in pregnant women were also varied and the overall findings 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 directly be attributed 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 abnormalitiespost-partum following exposure to ginger.

125. In their 2003 review of interventions for nausea and vomiting in early pregnancy (first trimester), Mathews concluded high-quality consistent evidence is lacking to support advice regarding the safety of ginger during pregnancy (Mathews 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. However, in vitro results could not be extrapolated to humans and safety could be dependent on ginger quality. The majority of the studies included in this review have already been included in this draft statement. Some recent studies have been conducted evaluating the effectiveness and safety of ginger in pregnancy, and these will be discussed in detail. Overall, most studies reported gastrointestinal effects such as abdominal discomfort, vomiting and diarrhoea. Other effects included dizziness, headaches and drowsiness with some more serious effects such as spontaneous abortion also being reported in 5 out of the 14 randomized clinical studies. The review by Jewell and Young focuses on the reported effects rather than statistical significance, therefore more details on the studies reporting more serious effects are given below.

Anti-platelet aggregation activity

126. 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 in both literature and by health professionals.

127. 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 platelet thromboxane and prostaglandin endoperoxcides ($PGF_{2\alpha}$, PGE_2 and PGD_2) in human platelets, in a dose-dependent manner (Srivas, 1984).

128. 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 exposure during different stages of pregnancy remain undetermined.

129. This further highlighted the need to differentiate exposure from the normal diet to that from supplements. Members noted that associations with haemorrhagic effects were reported following supplemental exposure to ginger, (Kruth *et al.*, 2003; Rubin *et al.*, 2019; Al Askar *et al.*, 2020) though these were inconclusive.

Conclusions of the Committee

130. Ginger is commonly used as a spice and flavouring in many countries worldwide and is increasingly growing in popularity as a natural remedy, due to its purported immune system-boosting properties, for easing motion sickness and post-operative nausea and vomiting, and pregnancy related nausea.

131. Several ginger supplements are commercially available, ranging from dried root in capsule form to tincture form, all with varying amounts of ginger. In addition to this, concentrated ginger shots (liquid form), containing large amounts of pressed ginger, are increasingly becoming popular. The variability in the composition of these supplements adds uncertainty to the amount of ginger actually being consumed.

132. Study authors noted that some of the toxicity observed varied according to the nature of extraction solvent; organic solvent extracts exhibited more toxicity than aqueous extracts, which presumably indicates extraction of differentially toxic compounds. Hence, studies of individual extracts might not give the whole picture.

133. Overall, the Committee concluded that based on the available information it was not possible to determine a point of departure to use in the risk assessment of ginger when used as a supplement.

134. Members noted that although the different ginger extracts were not comparable, there did appear to be some biological activity in the early stages of pregnancy. It was stressed that in general there was no indication of systemic toxicity from the use of ginger in the diet as food.

135. The lack of safety and toxicological information available on ginger use in pregnancy make it difficult to fully characterise the risks in this respect.
The committee noted that while there was some equivocal evidence for the possible effect of ginger on reproduction, it was not possible to characterise this based on the data available.

136. Also, consumption data was based on women of childbearing age and therefore may not be representative of the maternal diet, leading to an under/overestimation of the actual exposure.

137. There is no clear indication that ginger is detrimental to pregnant women, although a signal for some adverse effects cannot be ruled out. Generally, normal

levels of consumption of ginger within a diet is not considered a health concern. The Committee noted that from the evidence presented, the potential for contamination of ginger with heavy metals and/or mycotoxins cannot be excluded.

COT Secretariat

December 2023

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TOX/2024/44 Annex B

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

Annex B: Summary of Studies

Traditional/culinary uses of ginger

Human Studies

Author/Date	Study type	Study size/No. of Patients at End	Exposure (ginger dose/day)	Study period	Length of Treatment (days)	Main outcome measures	Main results
Chittumma *et al.*, 2007	Randomized double-blind controlled trial.	126/123	Ginger powder capsules (325 mg ×2, 3x/d, = 1950 mg/day)	4 days	4	Change in nausea and vomiting scores (3 symptoms on Rhodes index); occurrence of side-effects.	Results showed that ginger is significantly more effective in relieving NVP than vitamin B6 ($p < 0.05$).
Ensiyeh *et al.,* 2005	Double-blind randomised	70/69	Ginger powder	3 months	4	Severity of nausea	two spontaneous

	controlled trial.		capsules (500 mg 2×/d =1000 mg/day).			(VAS 0–10); number of vomiting episodes; general response to treatment (5-item Likert scale); occurrence of side-effects or adverse pregnancy outcome.	abortions in ginger group, 1 in B6 group; no congenital anomalies observed in babies brough to term.
Fischer-Rassmussen *et al*., 1991	Double-blind randomised crossover trial.	30/27	Ginger powder capsules (250 mg 4 times per day = 1000 mg/day).	11 days	4	Preference of treatment period; relief scores (4-point scoring system); outcome of pregnancy.	One spontaneous abortion, One elected. No adverse effects were observed in remaining 25 subjects.
Portnoi, 2003	Not specified.	187 pregnant women.	Various, not specified.	up to 12 months post birth.	Minimum of 3 days.	Safety and effectiveness of ginger for nausea and vomiting of	Three major malformations were reported in the ginger group, ventricular

						pregnancy (NVP).	septal defect (VSD), right lung abnormality, and kidney abnormality (pelviectasis). One incidence of idiopathic central precocious puberty at age 2 years. No significant difference between the two groups in terms of live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age.

Smith, 2004	Randomized, controlled equivalence trial.	291 women, less than 16 weeks pregnant.	1.05 g ginger.	3 weeks.	3 weeks.	Ginger verses B6 for the treatment of nausea or vomiting in pregnancy.	Three spontaneous abortions in ginger group, 9 abortions in B6 group.
Vutyavanich, 2001	Double blind.	32	Ginger powder capsules (250 mg 4x/day =1000 mg/day).	5 months.	4	Severity of nausea (VAS 0–10); number of vomiting episodes; general response to treatment after 1 week (5-item Likert scale); occurrence of side-effects and adverse pregnancy outcomes.	Ginger was significantly more effective than the placebo in relieving the severity of nausea in pregnancy (p = 0.014).

Human studies – Platelet Aggregation

Author/date	Study design	Population/study size	Study Duration	Exposure	Outcome	Results	Comment
Bordia *et al.,* 1997	Placebo controlled trial.	Patients with confirmed myocardial infarction N = 60.	3 months. Outcomes measured at: baseline, 1.5 months and 3 months.	Dose: 4g per day Unstandardised capsules.	Platelet aggregation — Agonist(s): ADP and Epi;	Ginger had no significant effect on both measures of aggregation.	Ginger had no significant effect on blood lipids or blood sugar.
Bordia *et al.,* 1997	NA	NA	NA	NA	Fibrinogen;	NA	No mention of randomisation .
Bordia *et al.,* 1997	NA	NA	NA	NA	Fibrinolytic activity.		P value not reported.
Lumb. 1994	Randomised, double-blinded placebo-controlled crossover trial.	Healthy male volunteers N=8.	Total study period: 2 x 1 day, at least 14 days washout period. Outcomes measured immediately before, 3 hrs, and 24 hrs post consumption of ginger.	Dose: 2g (4 x 500 mg) dried ginger per day Unstandardized capsules.	Platelet aggregation; - Agonist(s): AA, ADP, collagen, ristocetin, ADP; Bleeding time; Platelet count; Thromboelastography.	No significant changes in any outcome at any time point.	NA
Srivastava 1989	Open-label single-arm trial.	Healthy female volunteers, N = 7.	Total study period: 7 days. Outcomes measured at	Dose: 5g raw ginger per day.	Platelet thromboxan	Ginger consumption resulted in a	NA

			baseline and 7 days post-consumption.		e B2 production.	37% inhibition of thromboxane B2 production ($p<0.01$).	
Young *et al.,* 2006	Not specified.	20	72 days.	1 g ginger (+ 10 mg nifedipine).	Synergistic effect of ginger and nifedipine on anti-platelet aggregation in normal human volunteers and hypertensive patients.	Ginger and nifedipine had synergistic effect on anti-platelet aggregation; Ginger increased anti-platelet aggregation effect of nifedipine in all patients.	NA

In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome

In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome
Wilkinson 2000	Sprague-Dawley rats, F	43	Oral, drinking water on days 6-15.	20 g/L or 50 g/L ginger tea.	20 days.	Reproductive and developmental toxicity.	Embryonic loss in the treated groups 2x that of the controls. Exposed foetuses found to be significantly

							heavier than control. No gross structural malformations observed.

Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Srivastava 1989	Open-label single-arm trial	Healthy female volunteers, N = 7	Total study period: 7 days. Outcomes measured at baseline and 7 days post-consumption.	Dose: 5g raw ginger per day.	Platelet thromboxane B2 production.	Ginger consumption resulted in a 37% inhibition of thromboxane B2 production ($p<0.01$).

Herb-drug interactions

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome

Extracts and concentrates of ginger

Human Studies

Author/Date	Study type	Study size/No. of Patients at End	Exposure (ginger dose/day)	Study period	Length of Treatment (days)	Main outcome measures	Main results
Laekman et al., 2021	Observational study, clinical trial.	51/44.	maximum of 2 tablets of 50 mg EXT.GR10 a day [limited data on actual amount administered].	During pregnancy.		Patient satisfaction pregnancy complications (including hypertension and diabetes) and birth complications (including stillbirth, premature delivery, low birth weight).	Increased incidence of premature birth, low birth weight and hypertension in treatment group when compared with general population.
Willetts *et al.,* 2003	Double-blind randomised placebo-controlled trial.	120/99.	Ginger extract capsules (125 mg 4x/d =1000 mg/day).	8 months.	4	Used RINVR to measure frequency, duration, distress. caused by nausea, vomiting and retching; long term follow-up for birth outcome.	Three spontaneous abortions observed in ginger group.

Human studies – Platelet Aggregation

Author/date	Study design	Population/study size	Study Duration	Exposure	Outcome	Results	Comment
Bordia *et al.,* 1997	NA	20	1 day. Outcomes measured at: baseline, 4 hours post-consumption.	10 g single dose. Unstandardised capsules.	Platelet aggregation. - Agonist(s): ADP and Epi.	Reduction of both measures of platelet aggregation when compared to placebo ($p < 0.05$).	NA
Jiang *et al.,* 2004	Randomized, open label, three-way crossover trial.	Healthy male volunteers Age: 20–36 N =12.	Total study period: 3x13 days, 14 days washout period between each study period.	Dose: 3.6g (3x 0.4g, 3x per day) ginger extract Unstandardized capsules Consumed with 25 mg dose of rac-warfarin, consumed once per study period.	Platelet aggregation, Agonist: AA; INR; Plasma warfarin enantiomer protein binding & warfarin enantiomer concentrations Urinary S-	No significant changes in any outcome.	P value not reported.

					7-hydroxywarfarin.		
Rubin *et al.*, 2019	Case report.	Female, 70 yrs.	NA	48 mg daily Chewable ginger supplement for approx. 1 month.	INR - 8.0 approx. 1 month after taking ginger supplement.	INR reduced to 2.6 following cessation of ginger supplementation and pause in warfarin administration.	Patient also taking clonazepam 1 mg, metoprolol succinate 25 mg, paroxetine 10 mg, phenytoin 30 mg, rosuvastatin 20 mg, warfarin 7.5 mg, and warfarin 10 mg 10 mg.
Verma *et al.,* 1993	Randomised placebo controlled trial.	Healthy male volunteers; N = 20.	Total study period: 14 days, high calorie diet for first 7 days, high-calorie diet and ginger/placebo consumed for next 7	Dose: 5g (4 x 625 mg, twice per day); dry ginger powder - Unstandardized capsules Consumed with 100g (2x50g) butter, 2 cups of	Platelet aggregation. Agonist(s): ADP and Epi	Ginger significantly reduced platelet aggregation using both agonists when compared to placebo	Platelet aggregation reduced close to baseline but did not decrease further.

			days. Outcomes measured at baseline, 7, and 14 days.	milk, 8 slices of bread.		group ($p<0.001$).	

In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Abudayyak *et al.,* 2015	Ames: Salmonella typhimurium TA98 and TA100 strains; Cytotoxicity assay: Rat kidney NRK-52E cell line.	Cytotoxicity assay: (0.75, 1.50, 3.00, 6.00, 12.00, 25.00, 50.00, and 75.00 mg/ml, genotoxicity: 0.78, 1.56, 3.13, 6.25, 12.50, and 25.00 mg/ml.	Aq, chloroform and MeOH ginger extracts.	Cytotoxicity and genotoxicity.	Chloroform extractcytotoxic: IC_{50} = 9.08 mg/ml; aqueous extract mutagenic at all concentrations against T98 strain, in presence of S9 mix.
Mohammed *et al.,* 2016	chick embryonic heart micromass; mouse D3 embryonic stem	0.75–100 uM Micromass assay: 6 days, ESD3: 12 days.	6-gingerol.	Embryotoxicity.	no significant changes in contractile and cellular activity or changes in total protein content in 6-gingerol-treated primary

	cell systems (ESD3).				embryonic chick cardiomyocytes.
NA	NA	NA	NA	NA	inhibition in contractile activity at 12.5–50 μM.
NA	NA	NA	NA	NA	Change in both cellular activity and protein content in a dose-dependent manner at high concs (12.5–100 μM).
NA	NA	NA	NA	NA	Significant decrease in cardiomyocyte differentiation for all tested concentrations except 0.75 μM in ESD3.
NA	NA	NA	NA	NA	Significant decrease in cellular activity and protein content of stem cell-derived cardiomyocytes with increased 6-gingerol concentration exposure.
Nakamura & Yamamoto (1982)	Escherichia coli Hs30.	Not specified.	Juice of ginger rhizome, 6-gingerol.	Mutagenicity.	ginger juice supressed spontaneous mutation; 6-gingerol mutagenic in isolation.

Nakamura & Yamamoto 1983	Escherichia coli Hs30.	Not specified.	6-shogaol, 6-gingerol.	Mutagenicity.	[6]-Shogaol was 104 times less mutagenic, at a concentration of 700uM, than [6]-gingerol.
Nirmala *et al.,* 2007	Wistar rats, male.	Salmonella typhimurium strains TA 98 and TA 100.	Ginger paste and powder, unboiled, boiled, unfried, fried. Ames test: Ginger paste: 1, 2 and 3 mg; powder: 0.5, 1 and 1.5 g.	Anti-mutagenicity.	Anti-mutagenic potential unaltered by treatment of ginger.
Plengsuriyakarn *et al.,* 2012	Cholangiocarcinoma (CCA) cell line 6 (CL-6), hepatocarcinoma (HepG2) and normal human renal epithelium (HRE).	1.95, 3.90, 7.81, 15.62, 31.25, 62.5, 125, and 250 µg/ml.	Crude ethanolic ginger extract.	Cytotoxicity.	IC_{50} and cytotoxicity 10.95 and 53.15, µg/ml.
Sivaswami *et al.,* 1991 (Abstract)	Salmonella typhimurium strains TA 98, TA 100 and TA 1535.	Unknown.	Essential oil from ginger.	Mutagenicity.	Non mutagenic.

Soudamini *et al.,* 1995	Salmonella typhimurium strains TA 100, 98 and TA 1535.	25 and 50 mg/plate.	ethanolic mixture of powdered ginger.	Mutagenicity.	mutagenicity in both TA 1535 and TA 100 at both concentrations.
Zaeoung *et al.,* 2005	breast (MCF7) and colon (LS174T) cell lines.	Not specified.	aqueous extract and volatile oils.	Cytotoxicity.	IC_{50} > 39.2 µg/ml.

In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome
Alnaqeeb *et al.,* 2003 (abstract)	Rats, female.	Unknown.	Oral and intraperitoneal. 50 mg/kg and 500 mg/kg.	Aqueous ginger extract.	28 days.	NA	Increased levels of serum aspartate aminotransferase (AST) and decreased levels of alanine aminotransferase (ALT) in orally dosed rats.
Dissabandara & Chandrasekara, 2007	Sprague-Dawley rats.	15 in 3 groups, otherwise not specified.	Oral: 500 mg/kg/day and 1000 mg/kg/day during days 5	Powdered ginger extract.	Animals treated with ginger for 10 days.	Effect of powdered ginger extract administered prenatally on	Lower intake of food and water and lower weight gain in ginger treated group.

			to 15 of gestation.			postnatal developmen.	
ElMazoudy and Attia, 2018 (abstract only)	ICR mice.	Unknown.	250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract.	Powdered dried ginger root.	35-day treatment study; 20 day study (antifertility and abortifacient loss).	Effect on oestrus cycle and implantation in female mice.	Female copulation index was significantly reduced at 2000 and 1000 mg/kg bw/d groups; female pregnancy index significantly decreased at the highest dose. No. of implantation sites and live fetuses in the 2000 mg/kg bw/d group lower than the other treated and control groups.
Hosseini *et al.,* 2015 (abstract only)	Rats, female and male offspring.	72 (groups of 9).	Oral: 50, 100 and 200 mg/kg bw. during neonatal and perinatal periods.	Alcoholic ginger extract.	Unknown.	Serum testosterone, LH and FSH. Effect on spermatogenic cell lines in male mature offspring rats	Significant increase in testosterone levels and number of spermatogenic cells. Significant reduction in FSH and LH at doses of 100 and 200 mg/kg bw compared to control.
Jeena *et al.*, 2011	Wistar rat.	30.	Oral: 100, 250, and 500 mg/kg per	Ginger essential oil.	13 weeks.	Oral Toxicity.	No mortaility or abnormal changes observed in relative

			day once daily.				organ weights w.r.t. body weight. Increase in serum Na levels in male rats treated with 500 mg/kg/d. slight increase in total bilirubin in female rats, along with a decrease in AST and ALT levels. No significant changes in hepatic function parameters (alkaline phosphatase, total protein, albumin and globulin content).
Malik and Sharma, 2011	Wistar rat, male.	Not specified.	gastric gavage: 250, 500 and 1000 mg/kg, (corresponding to 5, 10 and 20% of the NOAEL of the lyophilised ginger powder (5000 mg/kg).	Lyophilsed ginger juice powder.	Experiment 2: 8 weeks. Exp 1&2 not specified.	Acute Toxicity.	no signs of toxicity or mortality.

Peneme et al., 2023	Swiss mice.	6	5000 mg/kg aqueous ginger extract.	Ginger powder extracted into water.	OECD guideline no. 423.	Acute toxicity.	no signs of toxicity or mortality.
NA	NA	20	17 β-oestradiol, (1 mg/kg) or ginger extract (300 or 600 mg/kg) per day.	Ginger powder extracted into water.	2 weeks.	Effect on oestrus cycle and plasma oestradiol levels.	Changes in body weight and eosinophil indices for 600 mg/kg bw indicated disruption of oestrus cycle.
Plengsuriyakarn *et al.,* 2012	OV and nitrosamine (OV/ DMN)-induced CCA hamsters.	90	1000, 3000, and 5000 mg/kg bw/d.	NA	30 days.	Acute Toxicity.	NA
Rong *et al.*, 2009	Sprague–Dawley rats, male and Female.	40	Gavage: 500, 1000 and 2000 mg/kg bw/day.	Powdered Japanese ginger.	37	35 day repeat dose.	No increase in mortality. Slightly reduced absolute and relative weights of testes (by 14.4% and 11.5%, respectively) at highest dose.

Shalaby and Hamowieh, 2010	Sprague Dawley rats.	120	Oral, 5 to 17.5 g/kg bw.	water or methanolic ginger extract.	65 days.	Fertility, serum testosterone and acute toxicity.	oral Lethal Doses (LD50) of the methanolic and water extracts - 10.25 and 11.75 g/kg bw respectively. No symptoms of toxicity observed at doses up to 5 g/kg bw. Both extracts increased fertility index, sexual organ weight, and sperm motility and count after 65 consecutive days.
NA	NA		NA	NA	NA	NA	Methanolic extract: Testosterone levels increased to 4.08 ± 0.10 and 7.13 ± 0.14 ng/dL (both significant at $P < 0.001$); Water extract (150 and 300 mg/kg bw): Serum testosterone levels increased 4.06 ± 0.03 and 5.04 ± 0.08 ng/dL (both significant at $P < 0.001$).

NA	NA	NA	100 and 200 mg/kg bw for 65 consecutive days and water extracts at doses of 150 and 300 mg/kg bw.	NA	NA	Fertility Index.	Mild to moderate degenerative changes of spermatogenic cells, diffuse oedema and incomplete arrest of spermatogenesis. Mild degeneration of spermatogenic cells and slight oedema of interstitial cells in testes of rats orally administered 300 mg/kg bw water extract. LOAEL of 200 mg/kg bw/day for the methanolic extract suggested.
Weidner & Sigwart, 2001	Wistar rats, pregnant female.	176 (88 Females).	Gastric intubation: 100, 333 and 1000 mg/kg from days 6-15.	EV.EXT 33, a patented Zingiber officinale extract (comprising 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, and 8-shogaol (1.9	21 days.	Teratogenicity.	No maternal or developmental toxicity observed.

				w/w of the extract).			

Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Dugasani *et al.*, 2010	Mouse leukaemic monocyte (RAW 264.7) macrophages and human polymorphonuclear neutrophils (PMN).	1, 3 and 6 uM.	[6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol	compare the antioxidant and antiinflammatory activities of gingerols and their natural analogues to determine their structure–activity relationship and molecular mechanisms.	Dose dependant inhibition of activated PGE2 release. Inhibition reached 58, 66, 73 and 87%, respectively, at 6uM.
Jolad *et al.*, 2004	HL-60 cells.	Not specified.	ginger constituents: gingerols, shogaols, 3-dihydroshogaols, gingerdiols.	Effects of ginger components on LPS-induced PGE2 production.	No cytotoxicity demonstrated.

Jolad *et al.*, 2005	HL-60 cells.	Not specified.	Ginger constituents containing gingerols, shogaols, 3-dihydroshogaols, gingerdiols.	Effects of ginger components on LPS-induced PGE2 production.	Inhibition of LPS-stimulated PGE2 production (IC_{50} = 0.05 0.08 ug/ml) with Gingerol fractions.
Kim *et al.*, 2012	Human liver microsomes.	0.05–5 ug/ml.	Aqueous ethanolic ginger extract (30% EtOH).	Inhibitory effect on CYP450-mediated drug metabolism.	Concentration-dependent inhibitory effects on CYP2C19; IC_{50} value of 3.8 g/ml.
Kimura *et al.*, 2010;	Human CYP3A4 and CYP2C9 microsomes.	Not specified.	NA	Inhibitory effect on CYP3A4 and CYP2C9 activity.	significant inhibition of CYP3A4 IC_{50} 5.1u g/ml or CYP2C9 IC_{50} (10ug/ml) activity.
Lantz *et al.*, 2007	U937 cells.	0.1 ug/ml for 6 hrs.	Ginger extract and mixtures of 6-, 8- 10-gingerols and 6-, 8-, 10-shogaols.	Effect on inflammatory mediator production.	No effect on COX-2 expression.
Mukkavilli *et al.*, 2014	Human liver microsomes.	Ginger extract: 500 mg/ml (containing 15 mg/ ml 6G, 3.4 mg/ml 8G, 3.9 mg/ml 10G, 3.0 mg/ml 6S); All individual	Ginger extract: (containing 6-Gingerol, 8-Gingerol, 10-Gingerol, 6-Shogaol). All individual components of gingerols were	effect of ginger extract and major constituents on CYP P450 enzyme activity.	Inhibition of CYP1A2 (IC_{50} - 221.5 mg/ml) by ginger extract. No effect on CYP2A6; maximum inhibition on CYP2B6: IC_{50} - 22 mg/ml; IC_{50} - 122.5 mg/mL against CYP2C8 in the presence of amodiaquine; IC_{50} - 93.5

		components of gingerols assessed at 100 mM (equivalent to 29 mg/ml 6G, 32 mg/ml 8G, 35 mg/ml 10G and 28 mg/ml of 6S).	assessed at 100 mM equivalent to 29 mg/mL 6G, 32 mg/mL 8G, 35 mg/mL 10G and 28 mg/mL of 6S.		mg/mL against CYP2C9, in the presence of diclofenac; Inhibition of CYP3A in the presence of testosterone: no effect in the presence of midazolam.

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Srivas, 1984	Human platelets and rat aorta.	NA	15-20 ul (concentrations not given).	Ginger extracts in water, n-hexane, chloroform, and ethyl acetate.	Effect of ginger extracts on *in vitro* platelet aggregation.	Inhibition of arachidonic acid (AA), epinephrine, adenosine diphosphate (ADP), and collagen-induced platelet aggregation.
Srivastava, 1986	Platelet rich plasma (no further information given).	NA	10-20 ul (concentrations not given).	NA	Effect of ginger and components on platelet aggregation and	Reduced thromboxane formation from exogenous AA; Inhibition of AA, epinephrine, ADP and collagen-induced platelet aggregation.

					eicosanoid biosynthesis.	
Suekawa *et al.*, 1986 (abstract only)	Rat hind paw and aorta, rabbits.	Unknown.	Unknown.	6-shogaol.	Effect of 6-shogaol on arachidonic acid cascade.	Inhibition of carrageenin-induced swelling of hind paw in rats and arachidonic acid (AA)-induced platelet aggregation in rabbits. Inhibition of prostaglandin 12 (PGI2) release in rat aorta. Possibly caused by COX inhibition.
Thomson *et al.,* 2002	Sprague-Dawley rats, Adult, F; *ex vivo.*	36	50 mg/kg or 500 mg/kg daily by gavage or intraperitoneally (IP) for 4 weeks.	Aqueous ginger extract, equivalent of 500 mg/ml.	*ex vivo* effect of aqueous extract of ginger on the synthesis of thromboxane-B2, prostaglandin-E2, and cholesterol, triglyceride levels in the serum of normal rats.	Serum PGE2 reduced and both dose levels; high dose significantly reduced serum TXB2 both orally and IP; A non-significant reduction in the level of TXB2 observed when ginger was injected IP but not significantly different from saline group.
NA	NA	NA	NA	NA	NA	significant reduction in levels of cholesterol in rats given high dose; No significant change in triglyceride levels with either dose either orally or IP.

Herb-drug interactions

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome
Al-Omari *et al.*, 2012	Albino rat, M.	30: 5 groups of 6; 72: 12 groups of 6.	25, 50 and 100 mg/kg bw by gavage; single dose (50 mg/kg bw) and up to one week.	Ginger crude extract.	Multiple dose: 2 weeks; single dose: 1 week.	Effect on glibenclamide and insulin; hypoglycaemic and antihyperglycemic effects in normoglycemic- and streptozotocin-induced (STZ) diabetic rats.	Significant decrease in blood glucose level (BGL) in normoglycemic rats after 1 & 2 hrs (50 mg/kg). Significant decrease in non-fasting BGL (N-FBGL) in STZ-diabetic rats.
Egashira *et al.*, 2012	Sprague-Dawley rat, M (7 weeks old).	Not specified.	10 mL/kg orally.	50% ginger juice.	1-3 days.	interaction between ginger juice and tacrolimus.	Significant increase in tacrolimus blood concentrations in rats treated with ginger juice, compared to those

							treated with water or orange juice.
Okonta *et al.*, 2008	Rabbits (3F, 2M).	5	1 ml/kg, orally.	Ginger extract.	3 days.	Effect of ginger on the pharmacokinetics of metronidazole.	Significant increase in absorption and plasma half-life; significant decrease in the elimination rate constant and clearance of metronidazole.

TOX/2024/44 Annex C

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

Annex C: Assessment of Exposure

1. The relative proportions of the active components of ginger – gingerols, shogaols and curcumin occur in varying proportions, depending on the variety of rhizome and the area of cultivation.

2. Many ginger supplements (Tables 1 and 2) are recommended to support digestive and joint health, alleviate nausea, upset stomach, and travel sickness. Currently, two commercially available pregnancy supplements – 'Seven Seas Pregnancy' and 'Seven Seas Pregnancy Plus Follow On' – contain 10 mg ginger extract.

Table 1. Sample of ginger supplements in capsule and tablet form commercially available.

Commercial Product Name	**Form**	**Composition**	**Daily dose recommended by vendor or website**
Seven Seas Pregnancy	Tablet	Ginger extract 10 mg.	1 tablet a day.
Seven Seas Pregnancy Plus Follow-On	Tablet, capsule	Ginger extract 10 mg.	One tablet and one capsule/ day.
Supplemented	Tablet	Ginger Extract 3,000 mg (20:1).	1-2 tablets daily.
Good n Natural	Capsule	Powdered root 550 mg.	2 capsules daily.
Woods Supplements	Tablet	Ginger extract 500 mg.	1 tablet daily.
Solgar	Capsules	Ginger (Zingiber officinale) Root Powder	1-2 capsules daily.

		150 mg, Standardised Ginger (Zingiber officinale) Root Powdered Extract (5% ginger gingerols) 300 mg.	
Solgar	Capsules	Ginger (Zingiber officinale) Root Powder 500 mg. Ginger (Zingiber officinale) Root Powdered Extract (4:1) 5 mg.	1-3 capsules daily.
Swanson	Capsules	Ginger Root 540 mg.	2 capsules daily.
Bio Health	Capsules	Ginger Root 500 mg.	NA
Biovea	Capsules	Ginger (root) (std. to 5% gingerols, 12.5 mg) 250 mg.	1-3 daily.
Jarrow Formulas	Capsules	Ginger root (concentrate) (Zingiber officinale) 500 mg.	1 daily.
Nature's Best	Capsule	Ginger Root 14,400 mg (provided by 120 mg of a 120:1 extract) providing 24 mg gingerols.	1 daily.
NeuLife	Tablets	Ginger Extract 12000 mg.	1-2 tablets daily.
Lifeplan	Capsule	Ginger 12:1 Extract.	1-2 tablets daily.
ALPHA01	Capsules	Ginger root powder 1100 mg.	2 capsules daily.

	Tablet	Ginger Extract 12,000 mg (20:1) standardised to 600mg 12,000 mg.	1-2 tablets daily.
Now Foods Capsules Superfood World	Capsules	Ginger Extract (Zingiber officinale) (Root) (Standardized to min. 5% Gingerols) 250 mg: Ginger Powder (Zingiber officinale) (Root) 225 mg.	1-3 capsules daily.
Viridian Ginger	Capsules	One vegetarian capsule provides: Certified organic Ginger root 400 mg.	1-3 capsules daily.

Table 2: Sample of ginger supplements in liquid and powder forms commercially available.

Commercial Product Name	**Form**	**Composition**	**Daily dose recommended by vendor or website**
Indigo Herbs	Tincture	Zingiber officinale, Alcohol, Water. Extraction Ratio: 1:3, Alcohol Volume: 25%.	1-2 ml, 2-3 times daily 20 drops from the glass dropper equals ~ 1ml.
Nature's Answer	Tincture	Ginger (Zingiber officinale) root extract: 145 mg.	1 ml (28 drops) three times per day.
Herb Pharm	Tincture	Ginger rhizome (Zingiber officinale) extract 598 mg (Extraction rate 140 mg herb per 0.7 ml).	"1 full squeeze of the dropper bulb to 2 oz. of water or juice, 2 - 5 times per day.

Indigo Herbs	Powder	100% Pure Zingiber officinale Powder.	1/3 teaspoon powder in water 3 times a day. (1 tsp = 3g)
Organic Herbal Remedies	Tincture	herb to pure grain alcohol of 1:3. 1ml is the equivalent of 333mg of dried ginger root. W.	0.2ml to 0.4ml three times a day in a little water. Children 6-12 years old 0.1ml to 0.2ml three times a day.
Biovea	Tincture	Fresh Organic Ginger (root) (667 mg per 1 ml serving).	30 drops (~ 1 ml), 1-3 times daily or as needed.
Epigenar	Tincture	Purified water, organic alcohol, organic ginger (Zingiber officinale) (amounts not specified).	15 drops, 3 times daily Max 60 drops per day unless otherwise advised. Children aged 4-15 years, 3 times daily, one drop per number of years of age.

Consideration of ginger from other sources

3. 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 using ginger products such as ginger biscuits and ginger ale, to alleviate morning sickness and nausea. Some may use these in combination with juice shots or tinctures.

Table 3: Sample of ginger-containing foods commercially available.

Commercial product name	Form	Composition
Border Biscuits Dark Chocolate & Ginger	Ground ginger	Ground ginger 1.5 %.
Sainsbury's Stem Ginger Cookies, Taste the Difference	Stem ginger	Candied Stem Ginger (17%) (Australian Stem Ginger, Sugar); ginger powder.
Sainsbury's Dark Chocolate & Ginger Cookies, Taste the Difference	Stem ginger	Candied Stem Ginger (13%) (Australian Stem Ginger, Sugar); ginger powder.
Nairn's Wheat Free, Ginger Biscuits	Stem ginger	Stem Ginger (6.4%) (Stem Ginger, Sugar); Ground Ginger.
Sainsbury's Ginger Nut Biscuits, SO Organic	Powdered ginger	Ginger Powder (0.6%).
Nooro Lemon + Ginger CBD Bar	NA	Ginger (0.5%).
Rhythm 108 Lemon, Ginger & Chia Biscuit Share Bag	Dried ginger powder	Organic gluten free oat flour (33%), organic coconut oil (24%), organic coconut flower sugar, organic almonds, organic chia seeds (5%), organic lemon zest (1.3%), organic lemon oil, organic ginger powder (0.4%).

Table 4: Ginger containing teas, juices and drinks commercially available.

Commercial Product Name	Form	Composition
Gimber	liquid concentrate	38% organic and high-quality ginger, organic lemons, herbs and spices.
Moju	liquid	Apple, Ginger Root (25%), Lemon, Antioxidant: Ascorbic Acid.
James White Drinks Organic Ginger Zinger Shot 70ml	liquid	Organic Apple Juice (73%), Organic Ginger Juice (27%), Water, Antioxidant: Ascorbic Acid.
James White Drinks Organic Xtra Ginger Zinger Shot 70ml	liquid	Organic Apple Juice (59.5%), Organic Ginger Juice (40%), Organic Chilli Flavouring (0.5%), Antioxidant: Ascorbic Acid.
Twinings Lemon & Ginger Tea	Tea	Ginger Root* (37%), Natural Lemon Flavouring with Other Natural Flavourings (25%), Lemongrass*, Blackberry leaves*, Lemon Peel, Sweet Fennel*, Natural Ginger Flavouring with Other Natural Flavourings (3.5%).
Pukka Organic Ginger, Galangal & Golden Turmeric Tea	Tea	Ginger Root (52%).
Belvoir Ginger Cordial		Pressed Ginger Juice 2%, Ginger Extracts.
Old Jamaica Ginger Beer	Drink	Ginger root extract.
Fever Tree Ginger Beer Light	Drink	Ginger Root, Natural Ginger Flavouring with other Natural Flavourings.

Fentimans Ginger Beer	Drink	Fermented Ginger Root Extract (Water, Glucose Syrup, Ginger Root, Pear Juice Concentrate, Yeast); Natural Flavourings (Ginger, Lemon, Capsicum).
Cawston Press Apple & Ginger Juice	Juice	1% Ginger Extract.
Pukka Lemon Ginger & Manuka Tea	Tea	Ginger Root (32%).
Twinings Spiced Ginger Tea	Tea	Ginger Root* (70%), Liquorice Root* (15%), Cinnamon* (10%), Cloves* (5%).
No.1 Kombucha Ginger & Turmeric	Tea drink	Kombucha (Filtered Water, Cane Sugar*, Green Tea*, Live Kombucha Cultures), Ginger Juice* (1.5%), Ginger* (0.14%), Turmeric* (0.14%), Black Pepper*.
Teapigs Lemon & Ginger Tea Bags	Tea	Ginger (65%), Lemongrass, Lemon Peel (5%), Liquorice Root.
MOJU Ginger Juice Shot 60ml	Juice	17.2g fresh ginger root'. Apple, Ginger Root (25%), Lemon, Antioxidant: Ascorbic Acid.
Innocent Shots Ginger Kick, Kicking Ginger & Spicy Turmeric 100ml	Juice shot	Apple Juice (54%), Carrot Juice (15%), Ginger Juice (10%), Red Pepper Juice, Lemon Juice, Orange Juice, Jalapeño Pepper Juice, Turmeric Juice (0.2%), Vitamin D.
Plenish Organic Ginger Immunity Juice Shot	Juice shot	Apple, Ginger (20%), Lemon, Apple Cider Vinegar (7%), Acerola Cherry Powder.
Lo Bros Organic Kombucha Gut Shot Ginger	Juice shot	Carrot Juice* (30%), Orange Juice*, Ginger Juice* (25%), Kombucha (14%) (Filtered Water, Kombucha Culture*, Green Tea*, Oolong Tea*, Raw Sugar*), Lemon Juice Concentrate", Living Cultures.
Belvoir Ginger Beer	Drink	Carbonated Spring Water, Sugar, Lemon Juice from Concentrate, Fresh Root Ginger Infusion 2%, Pressed

		Ginger Juice, Ginger Extracts, Lemon Extract, Capsicum Extract.
Grace Tropical Rhythms Sorrell Ginger	Drink	Water, Sorrel Cordial (Water, Sugar, Sorrel Flower (3%), Acid: Citric Acid), Rum Flavouring, Natural Sorrel Powder (0.13%), Ginger Emulsion (Water, Ginger Flavouring (.006%), Acid: Citric Acid, Capsicum, Stabilisers: Acacia Gum, Ester Gum), Colour: E129.

Background Exposure from the diet

Exposure estimates based on the NDNS

4. Table 5 provides exposure estimates for women of childbearing age (16 - 49 years) from years 1 – 8 of the NDNS survey (Bates *et al*., 2014; 2016; Roberts *et al*., 2018). The NDNS (Bates *et al*., 2014; 2016; Roberts *et al*., 2018) does not provide data for pregnant or lactating women so while data is based on women of childbearing age, this data may not necessarily be representative of the maternal diet. The food group used for the exposure assessment consisted of all foods within the NDNS database which contained ginger (raw, powdered etc) except for alcoholic beverages. Mean chronic ginger exposure from the diet of women aged 16 - 49 years old was 0.0083 g/kg bw/day, and at a 97.5th percentile consumption was 0.058 g/kg bw/day.

5. Table 5 indicates the contribution of ginger to the diet of women aged 16-49 years is low, therefore, the main contributor to exposure for some could be from supplement use. This may vary however according to country of origin. For example, ginger is used more and in larger quantities in foods in Asian, African and Caribbean communities.

6. The NDNS does not provide data for pregnant women, therefore there would be uncertainty as to whether this give an accurate reflection of exposure during pregnancy, especially in women who will use ginger drinks and teas or foods such as ginger biscuits to alleviate symptoms of pregnancy associated sickness.

7. TOX/2021/26 demonstrated that the potential risks arising from exposure to ginger from food can be considered low compared to exposure from supplements, which are available at much higher doses due to the concentrated nature of supplements and shots.

8. The Committee highlighted that assumptions would have to be made on how many products, such as ginger shots, were consumed per day. The Committee noted that, as it is commonly understood that ginger suppresses morning sickness, it could not be ruled out that pregnant women would be using the supplements in this way. Diet plus supplement exposure would need to be considered, as well as diet plus shots depending on the exposure period of concern.

Consumption of ginger from food sources

9. The FSA Exposure team have sourced information on Ginger intake in women of childbearing age from food. Due to the limited information on consumption amounts of supplements and drinks in pregnant women, exposure was estimated based on the compositional information and usage information in widely available supplements and information on concentrated drinks. Full details of the ginger sources are given in Table 1 - 4.

Table 5: Estimated ginger exposures from a variety of sources in women aged 16 – 49 years old.

Commodity	**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 chronic exposure* (g/day)**	**Mean chronic exposure* (g/kg bw/day)**	**97.5th percentile chronic exposure* (g/day)**	**97.5th percentile chronic exposure* g/kg bw/day**
Food[a]	NA	NA	1.7	0.026	11	0.16	0.55	0.0083	3.4	0.058
Drinks (Including tea and shots) [b1,b]	0.5 - 32.5	0.0071 - 0.46	NA	NA	NA	NA	NA	NA	NA	NA
Supplements [c]	0.010 - 24	0.00014 - 0.34	NA	NA	NA	NA	NA	NA	NA	NA

[1]This 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.

10. Table 5 provides exposure estimates for women of childbearing age - (16 - 49 years) 1 from years 1 – 8 of the NDNS survey (Bates *et al*., 2014; 2016; Roberts *et al*., 2018). The NDNS (Bates *et al*., 2014; 2016; Roberts *et al*., 2018) does not provide data for pregnant or lactating women so while data is based on women of childbearing age, this data may not necessarily be representative of the maternal diet. The food groups used for the exposure assessment consisted of all foods within the NDNS database which contained ginger (raw, powdered etc) except for alcoholic beverages. Mean acute ginger exposure from the diet of women aged 16-49 years old was 0.026 g/kg bw/day, and at a 97.5th percentile consumption was 0.16 g/kg bw/day. The corresponding mean and 97.5th percentile chronic exposure was 0.0083 and 0.058 g/kg bw/day. The upper value of the range of exposure from drinks and supplements was over double those estimated from 97.5th percentile acute consumption from food.

11. As the NDNS does not provide data for pregnant women, there would be uncertainty as to whether the data in Table 1 are an accurate reflection of consumption during pregnancy. This uncertainty also extends to data presented for drinks and supplements, as the patten of consumption during pregnancy to alleviate symptoms of sickness is unknown.

Further Information

Table 6: Ginger content in shots, teas and other drinks**.**

Shots	**Notes**
Ginger Shot | Pret A Manger	Contains 25% ginger in 110 ml shot, equivalent to 27.5 g fresh ginger.
Innocent Shots Ginger Kick, Kicking Ginger & Spicy Turmeric 100ml	Contains 10% ginger juice in 100 ml shot, equivalent to 10 g fresh ginger.
Hot Shot | Pret A Manger	Contains 2.5% ginger in 110 ml, equivalent to 2.75 g fresh ginger.
James White Drinks Organic Xtra Ginger Zinger Shot 70ml	Contains 26% organic ginger juice in 70 ml, equivalent to 18.2 g fresh ginger.
James White Drinks Organic Xtra Ginger Zinger Shot	Contains 40% organic ginger juice in 70 ml, equivalent to 28 g of fresh ginger.
MOJU Ginger Shots (12x60ml)	Contains 17.2 g of ginger in a 60 ml shot.
BumbleZest Ginger Turmeric Drink	Contains 16% ginger juice in 60 ml shot, equivalent to 9.6 g of fresh ginger.
Teas	**Notes**
Myrtle & Maude - Morning Sickness Herbal Tea - Peppermint & Ginger for Nausea Relief	Contains 25% ginger in each tea bag. Assuming that each bag is approximately 2 g, they will contain 0.5 g of dried ginger.

Pukka Lemon, Ginger and Manuka Honey 20 Herbal Tea Sachets 40g	Each tea bag contains ginger root 32%. Assuming each bag is 2 g, they will contain 0.64 g of dried ginger.
Twinings Lemon & Ginger 20 Tea Bags	Each tea bag contains 37% ginger root. Assuming each bag is 2 g, they will contain 0.74 g of dried ginger.
Pukka Organic Ginger, Galangal & Golden Turmeric Tea Bags	Contains 52% ginger root. For a 2 g tea bag, this is equivalent to1 g of dried ginger.
Twinings Spiced Ginger 20 Tea Bags	Contains 70% ginger root. For a 2 g tea bag, this is equivalent to 1.4 g of dried ginger root.
Lemon & Ginger | Herbal Tea | teapigs	Contains 65% ginger. For a 2 g tea bag, this is equivalent to 1.3 g of dried ginger.
Other drinks	**Notes**
Ginger Kombucha | Pret A Manger	Contains 2.2% ginger in 250 ml, equivalent to 5.5 g fresh ginger.
Belvoir Fruit Farms Ginger Cordial	Contains 11% fresh root ginger infusion and 2% pressed ginger juice in a 500 ml product. This is equivalent to 65 g fresh ginger and 32.5 g in a 250 ml serving.
Pure Pret Sparkling Ginger Beer | Pret A Manger	Contains 1% ginger juice in 330 ml, equivalent to 3.3 g of fresh ginger.

Please note the different forms of ginger (i.e., gingerols, ginger extract, dried ginger root, fresh ginger) which may not be directly comparable.

Table 7: Consumption of ginger from supplements.

Supplement	Maternal supplement ?	Form of ginger	Recommended dose per person/day	Daily Consumption (g/kg bw)*	Notes
Seven Seas Pregnancy - 28 tablets	Yes	Ginger extract 10 mg	0.010 g	0.00014	NA
Boots Pregnancy Essential Vitamins | 90 Tablets	Yes	Ginger root extract 58.5 mg	0.05 9g	0.00084	NA
Boots Naturals Ginger | 60 Tablets	No	Dried ginger root 1.2 g	1.2 g	0.017	NA
Boots Pharmaceutical	No	Ginger Root	0.35 g extract	0.005	NA

s DIGESTION SUPPORT TRAVEL with added Ginger 30 Capsules		Extract to 345 mg and Ginger root - 750 mg	+ 0.75 g ginger root	+ 0.011	
Good n Natural Ginger Root Capsules 550mg | Holland & Barrett	No	Ginger root	1.1 g	0.016	2 capsules daily
Ginger 3000mg Tablets – Supplemented	No	Ginger extract	6.0 g	0.085	NA
Solgar Ginger Root Extract (60 Veg Caps)	No	Ginger root powder + Ginger root extract	0.15 g + 0.30 g	0.0021 + 0.0043	NA
GINGER 250mg 120 Vegetarian Capsules by BIOVEA	No	Ginger root	0.75 g	0.011	NA
Jarrow Formulas Ginger (100 Capsules)	No	Ginger root concentrate	1.5 g	0.021	NA
High Strength Ginger Root Capsules | Nature's Best	No	24 mg gingerols equivalent to 14.4 g fresh ginger	14.4 g	0.20	NA
Ginger 12000mg x 120 Tablets | Nausea - Stomach Settler - Aids Digestion |	No	Ginger extract 600 mg equivalent to 12 g fresh ginger-	24 g	0.34	1-2 capsules a day

Neulife Health & Fitness					
Lifeplan Ginger Root 1000mg 90 Tablets	No	Ginger Extract (equiv. herb powder 1000 mg) 50 mg	2 g	0.028	2 tablets/day

*Consumption per body weight based on recommended dose rounded to 2 significant figures.

is calculated from the daily recommended intake and the average body weight of women aged 16- 49 years (70.3kg).

^Indicates whether the supplement is marketed specifically to pregnant or breastfeeding women.

Please note the different forms of ginger (i.e., gingerols, ginger extract, dried ginger root, fresh ginger) which may not be directly comparable.

This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

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TOX/2024/44 Annex C

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

Annex D: Red ginger

Red ginger (Zingiber officinale var. rubrum)

Background

1. A recent review (Zhang et al., 2022) on red ginger (also known as *Zingiber officinale var. rubrum* and Alpinia purpurata) summarises the constituents found in red ginger and its potential medical uses. This review does not describe the use of red ginger during pregnancy. The major bioactive compounds in red ginger are vanilloids and based on the chemistry of the side chain they are divided into groups including gingerols and shogaols. (Zhang et al., 2022).

2. Ghasemzadeh et al. reported that the total number of phenolic and flavonoids in red ginger is higher than in common ginger (Ghasemzadeh et al., 2010). Several studies compare red ginger and white ginger and at the same concentrations red ginger is able to elicit stronger effects for the given end point. (See section: Studies comparing red ginger and common ginger) The visual difference is shown in Figure 1.

3. The consumption of red ginger in the diet is not common due to the difference in taste when compared common ginger. Red ginger has a strong aroma and more distinctive heat and spiciness than common ginger. Red ginger is more commonly used for health applications. Red ginger extract tablets are a purported to have anti-inflammatory and anti-nausea effects.

4. The availability of red ginger in the UK is mostly ecommerce as a root powder and appears to have a greater presence in the US currently than in the UK. It cannot be ruled out that it would be available to purchase from Asian markets/grocery stores but there is no evidence of this. Red ginger root can be purchased online for the cultivation of the plant but appears difficult to grow in the UK climate.

5. Marketing is targeted in some instances at pregnant women (dried root extract capsule and powder) for morning sickness and inflammation/pain. There is literature describing its use to manage pain and wound healing post-partum. (Fikriyani, 2023).

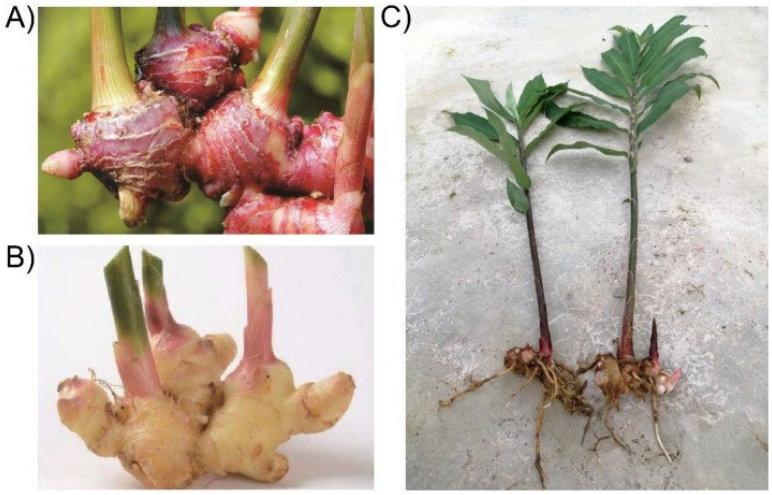

Figure 1: Photographs of (A) Red ginger *(Zingiber officinale var. rubrum),* (B) common ginger, and (C) whole plant of *Zingiber officinale var. rubrum.*

Biological activity

6. In traditional medicine, red ginger is used for treating headaches, indigestion, nausea, vomiting, and cancer. In addition, it is widely used to treat autoimmune diseases (psoriasis), hypertension, hypercholesteremia, hyperuricemia and bacterial infections. (Zhang et al., 2022).

Studies related to pregnancy

7. Hutabarat presents a study which aimed to analyse red ginger extract on reducing blood pressure among pregnant women with gestational hypertension. (Hutabarat et al., 2020) Thirty-four patients were recruited and divided into an experimental and control group. The experimental group received antihypertensive drugs plus red ginger extract at a dose of 500 mg for 14 days and the control group was given antihypertensive drugs with a placebo. There was a significant decrease in blood pressure. The paper is limited to the effects of interest, and no mention of adverse or unexpected effects.

Studies comparing red ginger to common ginger

8. Malondialdehyde (MDA) is the end-product of lipid peroxidation and is used as a biomarker to measure the level of oxidative stress in an organism. A study carried out by Obah compares the protective properties of two varieties of red and common ginger Fe^{2+} induced lipid peroxidation in rat brain *in vitro*. (Oboh et al.,

2012) Incubation of the brain tissue homogenate in the presence of Fe caused a significant increase in the malondialdehyde (MDA) contents of the brain. The aqueous extract from both varieties of ginger caused a significant decrease in the MDA concentration of the brain in a dose-dependent manner. The aqueous extract of red ginger had a significantly higher inhibitory effect on both Fe2+-induced lipid peroxidation than that of common ginger. The higher inhibitory effect of red ginger could be attributed to its significantly higher phytochemical content.

9. The aim of a study carried out by Handayani was to determine the antibacterial effectiveness of red ginger extract compared to common ginger extract in S*treptococcus mutans in vitro*. (Handayani et al., 2018) Red ginger extract and white ginger extract had an antibacterial effect on *Streptococcus mutans.* Red ginger extract at concentration of 60% has greater antibacterial effect against *Streptococcus mutans* compared to white ginger extract.

Studies on male reproduction

10. Aprilia carried out a study in mice which aimed to determine the effect of administering red ginger ethanol extract of on the sperm quality of mice exposed to MSG.(Aprilia et al., 2024) This study used male mice which were randomly divided into groups of 5: (control), MSG 4 mg/g bw and MSG 4 mg/g bw and Z. officinale extract 0.4 mg/g bw, and all extracts were administered orally for 30 days. Red ginger extract at a dose of 0.4 mg/g body weight proves to be effective in increasing the quality of spermatozoa exposed to MSG. The toxicity of red ginger and MSG was not assessed.

11. A study looking at the effects of red ginger on testicular function in rats was carried out by Sutyarso. (Sutyarso et al., 2016) Using a randomised trial design 24 male rats were split into four groups consisting of 6 rats. Group 1 received 1ml of distilled water; group 2 given 500 mg/kg of ginger extract; group 3 treated with 500 mg/kg of the extract and 0.5 mg/kg zinc sulfate; and group 4 fed with 500 mg/kg of extract and 1 mg/kg of zinc. Testosterone levels increased in the ginger extract group and this is enhanced with the coadministration of zinc.

Studies on antibacterial properties

12. See above for study comparing anti-bacterial testing of red vs common ginger.

13. An antimicrobial study showed that red ginger ethanol extract can inhibit the growth of *Salmonela thypi*, *Staphylococcus epidermidis*, and *Streptococcus mutans* at a concentration of 500 µg/mL, while *Pseudomonas aeruginosa* at a concentration of 250 µg/mL. (Juariah et al., 2023) Further observation of bacterial cell leakage

showed that the higher the red ginger ethanol extract concentration, the higher the bacterial cell leakage.

14. A separate study claimed limited antimicrobial activity of red ginger extract when compared to oil and concluded that red ginger extract did not not inhibit bacterial activity, whereas red ginger essential oil at a concentration of 100% provided inhibition of the growth of *E. coli* and *S. aureus* bacteria. (Kapelle et al., 2024) The paper commented on the significant difference in constituents of the two test items.

15. There are several studies in addition to the ones described which claim antimicrobial effects of red ginger.

Studies on blood glucose

16. A study was carried out to determine the effect of the dried red ginger powder on fasting blood glucose (FBG) and 2-hour postprandial blood glucose patients with type 2 diabetes mellitus. (Almasdy et al., 2022) 33 patients divided into two groups: the control group and the treatment group. Exclusion criteria included pregnant and lactating mothers. The treatment group received 3g of red ginger powder per day with standard medicines while the control group received a standard drug without red ginger powder. Dried red ginger powder at a dose of 3 grams per day, significantly affected the decline in fasting blood glucose. Dried red ginger powder 3 grams a day, did not influence the 2-hour postprandial blood glucose (diet was not controlled and this may have had an effect).

17. This study discussed adverse effects which would be considered self-limiting. The article states “the use of dried red ginger powder 3 x 2 capsules daily after every meal for a month showed that no adverse events reported by patient’s irritation. Irritation of the stomach is the major side effects that have been reported by previous researchers. Other side effects that arise during the study were diarrhoea though only 2 of 16 patients who received treatment. Ginger can increase intestinal peristalsis thus estimated diarrhoea in patients caused by it. In addition, some patients also feel a headache, burning sensation in the throat. This reaction causes one patient withdrew from the study on the second day of use. Yet another patient recognizes that this reaction only occurs in the first three days of drug consumption capsule that researchers provide. Then the reaction goes away by itself after 3-7 days of use”. Note that no references are given for these “major side effects” and that these statements may be referring to common ginger. No other studies found referred to any adverse effects as a result of red ginger administration.

18. A study on mice by Dewi aimed to determine the effectiveness of Red Ginger extract against decreasing blood glucose levels. (Dewi & Jumain, 2023) This study was conducted using alloxane as a diabetes inducer, Na CMC 1% as a negative

control, glibenclamide as a positive control, and red ginger extract doses of 2 %, 5 % and 7 % orally for 7 days in 5 groups of male mice test animals. It was concluded that the administration of red ginger extract has been shown to significantly reduce blood glucose levels in alloxane-induced mice at concentrations of 2%,5% and 7% (most effective) ($p < 0.05$).

Other studies

19. A study carried out by Devia to determine the effect of the consumption of red ginger stew on dysmenorrhea in high school adolescents. (Rahayu et al., 2018) The process in formulating the red ginger stew included 15 mg of red ginger boiled with 400 ml of water reducing to 200 ml then add. This is administered as a drink to participants. The quasi-experiment with non-equivalent control group design was carried out by purposive sampling on 54 respondents. It was concluded that consumption of red ginger stew (Zingiber Officinale var. Rubrum) reduced the symptoms of dysmenorrhea. There is no information on dosing and results are obtained from questionnaires which did not request the reporting of adverse effects.

20. An *in vitro* study was carried out to determine the inhibitory activity of red ginger rhizome infusion on the rate of prostaglandin production. (Fikri et al., 2016) This research was conducted by colorimetric COX Inhibitor Screening Assay method. The rate of prostaglandin formation by red ginger infusion in COX-1 was slower than COX-2. Inhibitory strength of red ginger infusion in COX-1 and COX-2 is weaker than acetosal (aspirin).

21. A study carried out by Sarmoko aimed to determine the effect of red ginger extract as a co-chemotherapy agent with 5-fluorouracil (5-FU) on WiDr colon adenocarcinoma cells using an MTT assay. (Sarmoko et al., 2020) It was concluded that, red ginger extract increases the cytotoxic activity of 5-FU, therefore it acts as a nutraceutical agent in the treatment of colon cancer. Red ginger alone reduced cell viability when compared to the control group at all concentrations.

22. Research has shown that red ginger plants growing in different places or locations have different tolerances which leads to differing content in their constituent metabolites. This was demonstrated by Febriani by determining the LC50 of 3 different red ginger methanolic extracts in zebra fish. (Febriani et al., 2023) The LC50 differed relative to location from which the plant was harvested.

23. Nirvana *et al.* present a study on the anti-hypercholesterolemia activity of red ginger. (Nirvana et al., 2020) In this study 25 rats were divided into 5 treatment groups receiving 0, 200, 350, or 500 mg/kg bw red ginger extract or simvastatin 7.2 mg/kg bw. Before the treatment rats were induced a on a high fat diet. The treatment of red ginger extract and simvastatin were carried out for 2 weeks. The results of *in vivo* test showed that red ginger extract had a significant effect on lipid profile and

body weight changes in hyperlipidemia rats at a dose of 200 mg/kg bw and was comparable to the positive control of simvastatin. Data was only presented on the lipid profile and body weight of the animals with no discussion on the higher dose groups.

24. An *in vitro* model of epidermal inflammation indicated that red ginger extract (chloroform) samples directly inhibited keratinocyte proliferation and the production of IL-20 and IL-8, both are key psoriasis-promoting cytokines. (Nordin et al., 2013) The author stated that the experiments showed that the two identified compounds (6-shogaol and 1-dehydro-6-gingerdione) from the active fraction of the red ginger extract effectively inhibited nitric oxide (NO) and prostaglandin E2 (PGE2) production.

25. Razali evaluated vasorelaxant and vasoconstriction effects of red ginger extract on live rats and isolated aortic rings of spontaneously hypertensive rats (SHRs). (Razali et al., 2020) This demonstrated that red ginger extract (petroleum ether) when dosed at 250 mg/kg body weight per day may exert an antihypertensive effect in the SHR model. Possible active compounds that contribute to the vasorelaxant effects are 6-gingerol, 8-gingerol and 6-shogaol.

26. Treatment with gentamicin can lead to cell membrane damage and the release of SGOT and SGPT. This increase can be measured in serum. A study demonstrated that red ginger ethanol extract can inhibit the increase in SGOT levels in white rats induced by Gentamicin 80 mg/kg BW with an effective dose of 400 mg/kg BW and can inhibit the increase in SGPT levels in white rats induced by Gentamicin 80 mg/kg BW with an effective dose of 200 mg/kg BW. (Humairo et al., 2024).

Summary

27. There is limited evidence to suggest that red ginger is commonly purchased or consumed in the UK. Health claims relating to red ginger reference the benefits of consuming red ginger for emesis and pain during and following pregnancy however studies in this area are primarily from hospital obstetrics settings in Asia (largely Indonesia) where red ginger is grown and readily available. Studies carried out in primarily in Indonesia and Malaysia comment on the frequent and common use of red ginger for medicinal purposes.

28. There is limited toxicological data available on red ginger and studies looking at the medicinal potential of red ginger do not assess or comment on effects outside of those of interest. There are some examples of comparisons or red vs common ginger on toxicological literature. In these studies, red ginger has an enhanced effect when compared to common ginger. This demonstrates that the constituent profile of the two differ.

This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

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