TOX/2021/26

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

The potential effects that ginger and ginger supplements may have during pregnancy and lactation.

Background

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' (SACN, 2011a) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery.

2. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice. A provisional list of chemicals was proposed by SACN Members; however, this was subject to change following discussion by COT. A scoping paper was presented to the Committee (TOX/2020/45) to define the scope of the work from the toxicological safety perspective and also requesting their input on the selection of candidate chemicals or chemical classes that could be added or removed.

3. As part of this work, the Committee thought it would be useful to consider the use of dietary supplements during pregnancy. A discussion paper (TOX/2020/51) was presented reviewing the commonly used dietary supplements used during pregnancy. These were supplements that are not officially recommended by relevant authorities, but which are promoted by anecdotal evidence and unofficial sources as having various purported benefits.

4. 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 suggested ginger required further investigation, noting that both human and animal in vitro and in vivo data were available. Main areas of concern were general toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with drugs.

Introduction

5. Ginger (*Zingiber officinale*) is a flowering tropical plant originating in Southeast Asia and grown in warm climates including China, India, Africa and the Caribbean.

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 immune system-boosting properties and also for motion sickness and post-operative nausea and vomiting.

6. Ginger supplements are regarded as a “safe” by people looking for a natural alternative to natural alternative for the relief of morning sickness. Some adverse effects have been reported however, few specific safety studies specifically have been carried out in this area. Despite its extensive use among pregnant women, there is limited information on the safety of its use.

7. In the current paper, a literature search was conducted using Google Scholar, PubMed and Science Direct databases to identify studies detailing the use of ginger during pregnancy, using search terms including 'ginger supplement', 'ginger and pregnancy', and 'ginger and safety'. The search was centred on papers published between 2010 and 2020. Information was taken from the EMA's review of ginger and recently published reviews of ginger use during pregnancy.

8. Many of the studies found were centred on the efficacy of ginger as a remedy for post-operative, chemotherapy and pregnancy associated nausea and vomiting and few discussed safety aspects of ginger use during pregnancy and pregnancy outcomes.

9. 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 means exposure will also vary.

Uses

10. Ginger is commonly consumed in fresh root form, dried root powder, capsule (encapsulated dried powder) form, liquid extract, preserved in syrup or sugar and as a tea. Ginger is a common traditional treatment for prophylaxis of motion sickness, Digestive disorders, upset stomach and nausea[1]. In pregnancy it is most used in the treatment of pregnancy-related nausea (NHS). It has also been used as a dietary supplement and a traditional remedy in many cultures[2]. Ginger is included in the official pharmacopoeias of several western countries.

Constituents

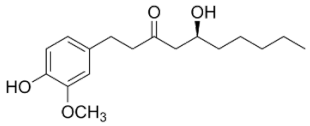
11. The ginger rhizome contains two main classes of constituents: the essential oils responsible for the aroma, and the main pungent principles, gingerols and

[1] https://www.nhs.uk/news/pregnancy-and-child/drugs-ginger-and-acupuncture-best-for-morning-sickness/
[2] https://www.webmd.com/vitamins-and-supplements/ginger-uses-and-risks

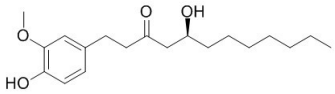
shogaols. Organic acids are also present in smaller amounts. Depending on area of cultivation, gingerols make up 4-7.5% of the pungent principles, the main one being 6-gingerol. Gingerols of other chain lengths are also present in smaller amounts.

12. Over 100 compounds have been identified, most of them 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). Relative amounts of the main principles and relative concentrations of gingerol to shogaol differ according to preparation and processing.

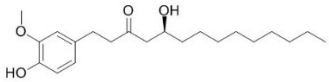
6, 8 and 10-Gingerol



6-Gingerol

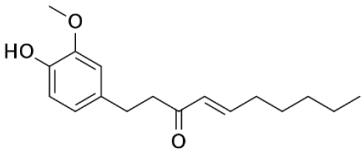


8-Gingerol



10-Gingerol

6-Shogaol



6-Shogaol

Essential oils

13. The major components of essential oils found in ginger include camphene, sabinene, α-curcumene, zingiberene, α-farnesene, β-sesquiphellandrene and geranial. The principle organic acids found in ginger include included citric, malic, oxalic, succinic, and tartaric acids. Animal models suggest one of the major components of ginger – 6-gingerol – is eliminated partially in the liver (Naora *et al.*, 1992).

Toxicity

14. Ginger is classified as 'Generally Recognised as Safe' (GRAS) by the FDA however few specific studies have been carried out to evaluate the safety of ginger use during pregnancy and lactation. Recently, the Finnish Food Authority has 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 [3]. It was noted that the concentrates contained harmful

[3] https://www.ruokavirasto.fi/globalassets/henkiloasiakkaat/tietoa-elintarvikkeista/turvallisen-kayton-ohjeet/18.10.ruokavirasto-taulukko1eng_saavutettava.pdf

substances and safe consumption levels were unknown. 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).

15. Ginger has been reported to cause heartburn (Vutyavanich *et al*., 2001, Chittumma *et al*., 2007 abstract only), exacerbate lower gastrointestinal tract conditions such as irritable bowel syndrome and duodenal ulcer, hypotension and there is a theoretical possibility of cardiac arrhythmias associated with ginger use (Tiran 2012). Very large doses of 6 g are reported to possibly lead to gastric irritation and loss of protective gastric mucosa (Supu *et al*., 2018).

Health based guidance values

16. There are currently no health-based guidance values (HBGV) with respect to ginger use during pregnancy and no consensus on the safe dosage of ginger. The UK Teratology Information Service (UKTIS) have concluded that while exposure to ginger would not usually be regarded as grounds for termination or additional monitoring during pregnancy, other factors could affect the overall risk outcome and this is something that would take place on an individual basis[4].

Toxicity studies

Cytotoxicity

17. The cytotoxicity of ginger has been investigated with varied results. Plengsuriyakarn *et al*. examined cytotoxicity in Cholangiocarcinoma (CCA) cell line 6 (CL-6), hepatocarcinoma (HepG2) and normal human renal epithelium (HRE) models using calcein-AM release and Hoechst 33342 assays. Median inhibitory concentration, (IC_{50}) and value for cytotoxicity of the crude ethanolic extract of ginger were 10.95 and 53.15, µg/ml respectively.

18. Zaeoung *et al.* (2005) reported that the IC_{50} of ginger was higher than 39.2 µg/ml against breast (MCF7) and colon (LS174T) cell lines. Abudayyak *et al*. found the aqueous and methanol extracts of ginger exhibited no cytotoxic activity when assessed using an MTT test in rat kidney, NRK-52E cell line. The chloroform extract resulted in a IC_{50} value of 9.08 mg/mL (2015).

[4] https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-GINGER-IN-PREGNANCY/

Mutagenicity

19. Nakamura & 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 the 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.

20. In another Ames assay, an ethanol extract of ginger (Soudamini *et al.* 1995) and an essential oil from ginger (Sivaswami *et al*. 1991) demonstrated mutagenic activity in *S. typhimurium* strains TA 100 and TA 1535 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 TA 100 and TA 1838 with metabolic activation by rat liver S9 fraction, while zingerone did not display mutagenic effects (Nagabhushan *et al*. 1987).

21. Abudayyak *et al*. found the aqueous ginger extract exhibited mutagenic activity when assessed using the Ames assay on S. typhimurium TA98 (-S9) strains. no activity was observed in the chloroform and methanol extracts (2015).

Animal studies

Acute toxicity

22. An acute toxicity study carried out by Malik and Sharma on male Wistar rats showed no signs of toxicity or mortality (2011). The animals were administered doses of 250, 500 and 1000 mg/kg 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 lyophilised ginger powder (5000 mg/kg).

23. Plengsuriyakarn *et al*. also examined acute and subacute toxicity in hamsters. Sixty hamsters (nine groups of 5 male and 5 female) were fed either 1000, 3000 or 5000 mg/kg bw ethanolic ginger extract, resuspended in a distilled water-Tween-80, mixture 4:1, v:v, by oral gavage and observed for 14 days (acute toxicity) or 30 days (subacute toxicity). The group concluded an absence of any toxicity at maximum dose of 5 g/kg bw during the investigation period.

Short term repeat dose studies

24. 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. It was only at the highest dose tested (2000 mg/kg), that 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.

25. 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).

26. Jeena *et al*., 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 (2011). No mortality was observed. No unusual changes in behaviour or locomotor activity was 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.

27. 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 was no significant changes in hepatic function parameters such as alkaline phosphatase, total protein, albumin, and globulin content.

Reproductive and developmental toxicity

28. Reproductive and developmental toxicity has also 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 via their drinking water - during days 6 to 15. 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 results of this study suggest that in utero exposure to ginger tea results in early embryonic loss and increased growth in surviving foetuses.

29. Hosseini *et al.* investigated the effect of ethanolic ginger extract on serum testosterone, LH and FSH as well effect on spermatogenic cell lines in male mature offspring rats (2015, abstract only). In this study, 72 female rats, sorted into 9 groups were orally administered of alcoholic extract of ginger at doses of 50, 100 and 200 mg/kg bw, during their neonatal and perinatal periods versus saline as a control. Following puberty, LH, FSH, cell numbers of Sertoli, spermatogonia, spermatocyte 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 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."

30. 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 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.

31. 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 the ginger treated group, suggesting that maternal administration of ginger during mid pregnancy resulted in reduced maternal weight gain and increased embryonic loss without affecting the postnatal growth and physical maturation of the surviving offspring.

32. ElMazoudy and Attia (2018) investigated the effect of powdered dried ginger root on the oestrus cycle and implantation in female mice. ICR mice, orally dosed at 250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract. These were investigated in four different experiments: the main study of outcomes (treatment for 90 days and throughout mating and gestation), a 35-day treatment study evaluating effects on the oestrous cycle. The third and fourth intended antifertility and abortifacient loss (20 days treatment). In the main study, the dams were sacrificed on gestation day 20. One mortality was recorded in the 100mg/kg bw/d group on gestation day 18 and two mortalities in the 2000 mg/kg bw/d group at day 16. There was also a significant reduction in body weight change in these two dose groups compared to the control group; however, food consumption was comparable.

33. In the study investigating the oestrus cycle, a significant reduction in the numbers of oestrus cycles was observed at the highest dose group, 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 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 group. Implantation failure was also increased by 36% compared to the control group and pre-implantation loss at this dose group was also 16.59% higher than the control group. The authors considered that this may reflect a dose-depend antifertility (anti-implantation) effect.

34. Regarding fertility and developmental outcomes, the female copulation index was significantly reduced at 2000 and 1000 mg/kg bw/d groups, 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 were lower than the other treated and control groups. An increase in fetal resorption and post implantation loss was also seen at 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 at 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.

35. 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 in damaged ova follicular nuclei were non-visible. 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 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 highest NOAEL to be 500 mg/kg bw.

Human studies - exposures in pregnancy

36. In their 2003 review of interventions for nausea and vomiting in early pregnancy, Jewell and Young concluded that ginger shows no evidence of teratogenicity in infants (Jewell and Young, 2003). 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. This review was based on systematic literature searches until the end of December 2017. Most of the studies included in this review have already been included in the current paper.

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 focuses on the reported effects rather than statistical significance, therefore more details on studies reporting more serious effects are given below.

37. In a double-blind randomised crossover trial, 27 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 (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.

38. 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 both 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.

39. An observational study in humans examined pregnant women who took ginger in their first trimester and compared them to 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 2500 g and the ginger group had 8 sets of twins.

40. 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. Three spontaneous abortions were observed in the group receiving ginger compared to those in the placebo group. 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 abortions in the group taking 75 mg B6 daily for 3 weeks (2004).

41. Ensiyeh *et al*, investigated the effectiveness of ginger versus B6 for treatment of NVP (2009) in women before 17 weeks' gestation. 70 women were randomised to receive either ginger at a dose of 1 g per day or B6 and 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 condition.

Lactation

42. With respect to lactation, the focus of available studies 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. Ginger has reportedly been used as a galactagogue in Turkey and parts of Asia (Laxmay *et al.*, 2011, Kaygusuz *et al.*, 2021), and has been demonstrated to possibly enhance milk production in women who had vaginal births (Dilokthornsakul *et al*., 2021), though the mechanism for this effect is unclear. Overall, ginger has not previously been considered a galactagogue for pregnant women.

Effect on Cytochrome P450 Enzymes and Herb-Drug Interactions

43. Qiu *et al.* (2015) investigated 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 cytochrome 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.

44. These results could potentially be significant in pregnant women on medication, who are using ginger as a remedy for nausea in the early stages of pregnancy.

In vitro studies

45. Ginger extracts and the major components thereof - 6-gingerol (6G), 8-gingerol (8G), 10-gingerol (10G) and 6-shogaol (6S) - were investigated and shown to have an inhibitory effect on CYP isoenzymes in *in vitro* models by various groups (Kimura *et al*., 2010; Kim *et al*., 2012; Mukkavill *et al*., 2014).

Animal studies

46. A study into the effect of ginger on the pharmacokinetics of metronidazole was studied 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.

47. 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 hr following oral administration of 10 mL/kg 50% ginger juice or water. Pre-treatment with ginger juice was found to significantly increase tacrolimus blood concentrations compared to those pre-treated with water or orange juice.

48. The possible herb-drug interaction of ginger crude extract 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).

49. Single administration of ginger crude extract showed 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 exhibited a significantly reduction in the N-FBGL 26.3% and 25.1% respectively after 4.5 hours, compared to glibenclamide alone which exhibited a 7.9% reduction.

50. 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

51. 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.
52. With regards to the relevance of such effects in pregnancy, literature reports 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).

53. The implications and clinical significance of the anti-platelet activity of ginger exposure during different stages of pregnancy remain undetermined.

In vitro studies

54. Srivastava reported an effect of ginger extracts on *in vitro* platelet aggregation (1986). 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.

55. The effect of an aqueous ginger extract on platelet thromboxane-B_2 (TBX_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 thromboxane-B_2 levels when compared to saline-treated control groups but doses at 500 mg/kg significantly reduced TBX_2 levels in serum.

56. 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 TXB2 levels in control rats that had received saline. 50 mg/kg of ginger administered orally resulted in serum PGE_2 levels being significantly reduced however, 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

57. 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*.

58. 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 prices and tea from ginger powder. Following treatment with vitamin K, the patient's INR and PTT returned to within therapeutic range.

59. 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 ginger and 10 mg nifedipine in combination and 1 g ginger and 75 mg ASA in combination daily for one week each following a washout period (7 days following ASA administration, 10 days thereafter).

60. 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 were 79.8%, 75.2%, 69.3% respectively.

61. 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 prior after taking a 48 mg ginger supplement daily. A week following cessation of the ginger supplement, the INR declined to 2.6.

62. 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 in 150 ml of boiling water once daily vs. 4 g twice daily for five consecutive days. 4 g of ginger powder administered daily resulted in reduced platelet aggregation in subjects using epinephrine only. Platelet aggregation inhibition was also found to be higher in women using arachidonic acid.

Effects on blood pressure

63. Ghayur and Gilani (2005) reported that a crude extract of ginger induced a dose-dependent (0.3–3 mg/kg) fall in arterial blood pressure of anesthetized Sprague-Dawley rats (2005). In Guinea pig paired atria, the crude extract exhibited cardio-depressant activity on the rate and force of spontaneous contractions. In rabbit thoracic aorta preparation, the crude extract relaxed the phenylephrine induced vascular contraction at a dose 10 times higher than that required against K^+-induced contraction (80 mM).

64. Ca^{2+} channel-blocking (CCB) activity was confirmed when the crude extract shifted the Ca^{2+} dose–response curves to the right similar to the effect of 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 at a dose 14 times less than that required for relaxing the PE-induced contraction. 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 the 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.

Exposure

65. 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.

66. Many ginger supplements 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).

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 10mg	1 tablet a day.
Seven Seas Pregnancy Plus Follow-On	Tablet, capsule	Ginger extract 10mg	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 150mg, Standardised Ginger (Zingiber officinale) Root Powdered Extract (5% ginger gingerols) 300mg	1-2 capsules daily
Solgar	Capsules	Ginger (Zingiber officinale) Root Powder 500mg. Ginger (Zingiber officinale) Root Powdered Extract (4:1) 5mg.	1-3 capsules daily
Swanson	Capsules	Ginger Root 540 mg	2 capsules daily
Bio Health	Capsules	Ginger Root 500mg	-
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 14,400mg (provided by 120mg of a 120:1 extract) providing 24mg 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 12,000mg (20:1) standardised to 600mg 12,000mg	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 400mg	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

67. 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	-	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

Consumption estimates based on the NDNS

68. Table 5 provides consumption estimates was 49 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 group used for the consumption assessment consisted of all foods within the NDNS database which contained ginger (raw, powdered etc) except for alcoholic beverages. Mean chronic ginger consumption 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.

Table 5: Estimated chronic consumption for ginger in women aged 16 – 49 years old (Bates *et al*., 2014; 2016; Roberts *et al*., 2018)

Consumers (n)	**Chronic consumption***		**Respondents in population group (n)**
	Mean (g/kg bw/day)	**97.5th Percentile (g/kg bw/day)**	
1308	0.0083	0.058	1874

*Rounded to 2 s.f.

69. 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.

70. 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.

Risk characterisation

71. There is a high uncertainty regarding the risk of consuming ginger drinks and particularly, concentrated ginger ‘shots’, which can contain as much as 27 g of raw, pressed ginger root per serving. Some marketed supplements provide limited

composition information, which adds further uncertainty of the exact exposure to the various components of ginger. It is considered likely that in addition to exposure from food and the use of supplements, people may consume ginger in tea or juice form to alleviate nausea and vomiting or symptoms of illnesses such as colds, potentially increasing risk.

72. Based on the available data, ginger showed some mutagenicity in TA 100, TA 1535, and T 98 strains, but this is low compared with established mutagens. Ginger is not shown to be mutagenic in vivo. Ginger showed no signs of acute or sub-acute toxicity in vivo at maximum levels of 5000 mg/kg bw, but studies show it may affect serum ALT and AST levels at does above 200 mg/kg. From the available studies it appears that ginger exposure could affect hormonal levels in animals thus interfering with reproduction, fertility and resulting in early embryonic loss. Furthermore, there is indication in utero exposure or exposure to ginger during breastfeeding indirectly affected hormonal levels and spermatogenesis in male animals.

73. It is not possible to fully characterise the risks associated with ginger use in pregnancy, due to the lack of safety data available and the varied study results to date. It has been considered that these varied results are attributed to the volatility of the principle compounds of ginger commonly reviewed - gingerols and shogaols. There is currently limited toxicological information available for the use of ginger during pregnancy. Among the variety of ginger supplements commercially available, there is a large variability in their composition, which also adds uncertainty regarding their use during pregnancy.

Conclusions

74. Ginger (*Zingiber officinale*) is the rhizome of the ginger plant, originating from in Southeast Asia. Ginger 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 immune system-boosting properties and also for motion sickness and post-operative nausea and vomiting.

75. Ginger supplements are regarded as a “safe” by people looking for a natural alternative for the relief of morning sickness. Some adverse effects have been reported however, few specific safety studies have been carried out in this area.

76. 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, containing large amounts of pressed ginger, are increasingly becoming popular. The variability in the composition of these supplements adds uncertainty on the amount of ginger actually being consumed.

77. The lack of safety and toxicological information available on ginger use in pregnancy make it difficult to fully characterise the risks. From the available studies it

appears that ginger exposure could affect hormonal levels in female animals thus interfering with reproduction, fertility and resulting in early embryonic loss. Furthermore, there is indication that *in utero* exposure or exposure to ginger during breastfeeding indirectly affected hormonal levels and spermatogenesis in male animals. These are indications based on limited studies and although some authors have speculated on the mode of action of ginger, it has not been fully elucidated. Human epidemiological studies have not reported comparable effects and the effects of *in utero* exposure to ginger in humans are unknown.

Questions for the committee

Members are asked to comment on

a) The effects of ginger in animal studies
b) The effects of ginger in humans?
c) Based on the available information, is the Committee able to identify a point of departure to be used in the risk assessment of ginger?
d) Any other comments on this paper.

Secretariat
April 2021

Abbreviations

µg/kg bw/d -	Micrograms per kilogram bodyweight per day
AA -	arachidonic acid
ADMET -	Absorption, distribution, metabolism, excretion, and toxicity
ADI -	Acceptable daily intake
ADP -	adenosine diphosphate
ALT -	Alanine Aminotransferase
AM -	Acetoxymethyl
ASA -	Acetylsalicylic acid
AST -	Aspartate Aminotransferase
BGL	Blood glucose level
CCB -	Ca^{2+} channel-blocking
COT -	Committee on Toxicity
CYP	Cytochrome P450
EFSA -	Scientific Committee on Food and the European Food Safety Authority
EMA -	European Medicines Agency
GCE -	Ginger crude extract
GRAS -	Generally recognised as safe
HBGV -	health-based guidance values
INR -	International normalized ratio
L-NAME -	N_{ω}-nitro-L-arginine methyl ester hydrochloride
mg -	Milligram
mg/kg bw/d -	Milligrams per kilogram bodyweight per day
MHRA -	Medicines and Healthcare Products Regulatory Agency
NDNS -	The National Diet and Nutrition Survey
PE -	Phenylephrine
PGE_2 -	Prostaglandin-E_2
PTT -	Partial thromboplastin time
SACN -	Scientific Advisory Committee on Nutrition
STZ -	Streptozotocin
TBX_2 -	Thromboxane-B_2
UKTIS -	UK Teratology Information Service

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