Statement on the Hepatotoxicity of Green Tea Catechins

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Introduction

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Authors: Food Standards Agency
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Committee on Toxicity

1. In 2017, following a series of reports of adverse effects associated with the consumption of green tea supplements, the European Commission requested the European Food Safety Authority (EFSA) to assess the available information on the safety of green tea catechins (GTCs) (principally epigallocatechin-3-gallate

(EGCG)) from all dietary sources including preparations such as food supplements and traditional infusions. The EFSA opinion, which was adopted in March 2018, was published in April 2018 (EFSA, 2018). At that time, and at the request of the Department of Health and Social Care (DHSC), who have the policy lead for food supplements in England, the Food Standards Agency's (FSA) Chemical Risk Assessment team reviewed the EFSA opinion informally and agreed with its conclusions.

2. These conclusions were "catechins from green tea infusion, prepared in a traditional way, and reconstituted drinks with an equivalent composition to traditional green tea infusions, are in general considered to be safe according to the presumption of safety approach provided the intake corresponds to reported intakes in European Member States. However, rare cases of liver injury have been reported after consumption of green tea infusions, most probably due to an idiosyncratic reaction. Based on the available data on the potential adverse effects of GTCs on the liver, the Panel concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG per day taken as a food supplement has been shown to induce a statistically significant increase of serum transaminases in treated subjects compared to control." (EFSA, 2018).

3. Following the adoption of the EFSA opinion, in December 2022, Commission Regulation (EU) 2022/2340 came into force which amended Annex III to Regulation (EC) No 1925/2006 as regards green tea extracts containing (-)-epigallocatechin-3-gallate. The Regulation set restrictions for an individual portion of a food to contain less than 800 mg of EGCG. In addition, the labels of all foods including food supplements containing EGCG at any level were required to include information on the maximum number of portions of the food for daily consumption, the content of EGCG per portion and warnings for consumers on appropriate use including a warning not to consume a daily amount of 800 mg EGCG or more.

4. The amendments to Regulation (EC) No 1925/2006 do not apply in Great Britain (GB). Under the Windsor Framework, the amendments in Regulation (EC) No 1925/2006 apply in respect of Northern Ireland. This is because Regulation (EC) No 1925/2006 is included in Annex 2 to the Windsor Framework.

5. The Nutrition Labelling Composition and Standards (NLCS) policy group has been set up under the NLCS provisional common framework, to maintain a consistent and co-ordinated policy approach across the UK (DHSC, 2020). The NLCS framework sets out arrangements for co-operation between officials in

DHSC, Food Standards Scotland (FSS) (representing Scottish Government), Welsh Government (WG) and the Food Standards Agency Northern Ireland (FSANI) with regard to NLCS policy.

6. All future policy proposals relating to nutrition are considered on a four-nation basis via the NLCS policy group, with the impact assessed on the UK as a whole not just each individual nation or Great Britain (GB). The risk assessment and risk management processes of amendments to legislation (including food supplements) in scope of the provisional NLCS framework includes seeking scientific evaluation from the relevant scientific advisory committee, where appropriate.

7. Following the publication of the EFSA opinion in 2018, the UK and European food supplements industry raised a number of concerns to DHSC regarding the potential risk management measures for including GTCs (EGCG) under Article 8 of Regulation (EC) 1925/2006. These concerns were also raised to the European Commission (EC).

8. On behalf of the UK, the NLCS have requested the FSA to evaluate whether the conclusions of the 2018 EFSA opinion are still applicable considering any new data that have become available since its adoption, to enable them to consider the next steps for risk management. The EFSA 2018 evaluation pertains to GTCs and the associated cases of probable idiosyncratic hepatotoxicity, rather than a safety assessment of either GTCs or green tea infusions and extracts more generally (EFSA, 2018).

9. Following the risk assessment (which includes the domestic scientific assessment) and risk management processes set out in the NLCS Framework, the NLCS policy group will provide advice to ministers on whether any restrictions in relation to the use of EGCG in foods are in the interests for the GB market.

10. This statement presents a summary of the key findings of the EFSA Opinion and provides an update on the state of science based on the literature since the EFSA Opinion was published in 2018 up to September 2022. To determine what new literature had become available since the publication of the EFSA opinion a literature search was undertaken, focused on the safety of GTCs, related to the safety of the use of green tea extracts (GTEs) and hepatotoxicity. Databases searched included PubMed, Google Scholar and LIVERTOX using ‘green tea extract’, ‘liver injury’ and ‘hepatotoxicity’ as search terms.

11. Previous discussion papers and drafts of the COT statement are detailed in Table 1 of Annex A.

Background

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Definitions

12. The terms ‘herbal infusions’ and ‘tea (*Camellia sinensis*; *C. sinensis*)’ as defined in Annex of Commission Regulation (EU) 2020/2040 refer to: herbal infusions (dried product) from flowers, leaves, herbs, roots and any other parts of the plant (in sachets or in bulk)/tea (*C. sinensis*) (dried product) from dried leaves, stalks and flowers (in sachets or in bulk) used for the preparation of herbal infusion (liquid product)/tea (liquid product) (UK Legislation, 2020).

13. The term ‘green tea extract’ refers to ‘herbal infusions’ which have been soaked in ethanol/water mixtures after which they have been concentrated to 40-50% solids (as powders or dry extracts) (UK Legislation, 2020).

Identity

14. Green tea, produced from the leaves of the *C. sinensis* plant, is a popular drink, consumed worldwide. Various reports on the health benefits of green tea on different types of cancer, liver and heart disease are available in the

literature. Many of these claimed beneficial effects are associated with a particular catechin, epigallocatechin-3-gallate (EGCG) (Chacko et al., 2010).

15. Catechins are polyphenolic compounds, and most of the polyphenols derived from green tea are catechins. GTCs are derived from the unfermented leaves and leaf buds of the tea plant, *C. sinensis*. Catechins constitute ~20% of the total flavonoids found in green tea (Sakata et al., 2013). Aqueous alcohol extraction of *C. sinensis* leaves concentrates levels of catechins and removes other components such as caffeine (*C. sinensis* has naturally occurring caffeine; Vuong & Roach, 2014).

16. As identified by EFSA, the most significant catechin associated with hepatotoxicity is epigallocatechin-3-gallate (EGCG) (EFSA, 2018).

17. A study by Bhagwat et al., reported that EGCG is present in dried leaves of green tea at around 7,400 mg per 100 g (limited sample number) (Bhagwat et al, 2011). Khan et al., 2006 have reported EGCG levels of 200-300 mg in a cup of brewed green tea. EGCG has been reported to form more than 50% of all GTC, representing ~16.5% of the water-extractable fraction of tea (Balentine et al., 1997). EGCG is present in green tea infusions but is found at a higher concentration in GTEs.

Toxic mode of action

18. The exact mechanism of GTE associated liver injury has not yet been fully elucidated. There is evidence that exposure to GTCs (specifically EGCG) can result in increased serum levels of the enzymes aspartate transaminase (AST) and alanine transaminase (ALT), which are biomarkers of liver toxicity (Gurley et al., 2022). For example, in a prospective study in post-menopausal women, raised ALT levels were found in 6.7% of treated subjects and in only 0.7% of the controls. Most instances of liver toxicity were mild but, only in the treated group, a few were serious (Acosta et al., 2022, further described in paragraph 117).

19. Shil et al., (2022) investigated the effects of two decaffeinated GTEs (dGTE) on oxidative stress, mitochondrial function and cell viability in HepG2 cells. dGTE1 was sourced from a food ingredient manufacturer and was an anhydrous capsulated powder standardised to 70% EGCG; each capsule provided a total 725 mg dGTE1, of which 400 mg was EGCG. dGTE2 was sourced directly from a supplement company and was also an anhydrous powder standardised to 98% polyphenols; each capsule provided 725 mg dGTE2, of which 326 mg was EGCG. Cells were exposed to dGTE concentrations ranging from 0.001 to 1000

μg/ml. dGTE1 was found to be protective against hydrogen peroxide-induced apoptosis and cell death by attenuating oxidative stress pathways. In contrast to dGTE2, which increased cellular and mitochondrial oxidative stress and apoptosis itself, and if anything, exacerbated that induced by hydrogen peroxide. The effects of dGTE1 resembled those of EGCG itself. The differences between the two dGTE preparations were attributed to the presence of constituents other than EGCG in dGTE2.

20. Shi et al., (2021) aimed to characterise the metabolic alterations induced by EGCG and the effects of dietary restriction in female C57BL/6J mice plasma using metabolomics. Mice were split into two groups and were fed either a free or fixed diet (50% of the average food intake, limited to <2 g each mouse per day) once daily for six days. On the final day, the mice in the free diet group were further divided into three groups (n=8/group): control, 400 mg EGCG/kg [bw] and 800 mg EGCG/kg [bw]. The mice in the fixed diet group were also divided into three groups (n=8/group): fixed diet group control, fixed diet with 400 mg EGCG/kg [bw] and fixed diet with 800 mg EGCG/kg [bw]. Note that the EGCG (>98% purity) treatment groups were dosed via intragastric administration. Further note that the doses were assumed to have been expressed per kg body weight; however, the methodology did not clarify this in detail. The results showed that EGCG induced enhanced lipid metabolism pathways, although EGCG did not cause liver injury at the doses used in animals that were not on a restricted diet. In mice that were under dietary restrictions, it was observed that EGCG caused dose-dependent hepatotoxicity and was associated with the overactivation of linoleic acid and arachidonic acid oxidation pathways, which increased the accumulation of pro-inflammatory lipid metabolites and thus contribute to liver injury.

21. Pandey et al., (2020) investigated the potential inhibition of human nicotinamide adenine dinucleotide phosphate-quinone oxidoreductase 1 (NQO1), an enzyme that plays a role in oxidative stress, by EGCG and its metabolites using a systematic computational approach. This included molecular docking, binding free energy calculations, and molecular dynamics simulations. It has been reported that *o*-quinone metabolites of gallic acid or EGCG are causative agents for the observed hepatotoxicity in humans. The binding free energy calculations showed that some EGCG metabolites exhibited strong predicted binding affinity to NQO1. The authors concluded that this may explain the observed idiosyncratic hepatotoxicity caused by the consumption of green tea and its constituents. However, the authors appreciate that there is a need for experimental validation of their results with appropriate biological methods. It is not clear any

hepatotoxicity resulting from the interactions described would be idiosyncratic.

22. GTCs have been reported to modulate epigenetic processes, such as DNA methylation, which play a significant role in cancer development. Yiannakopoulu (2015) published a review on the modulation of DNA methylation by GTCs. It was found that EGCG modulates DNA methylation by attenuating the effect of DNA methyltransferase 1 (DNMT1). However, the exact mechanism of DNMT1 inhibition is not fully understood. The potential mechanisms include (in)direct enzymatic inhibition, reduced DNMT1 expression and translation. The inhibition of DNMT1 is expected to prevent hypermethylation (thus, seen as a therapeutic action); however, in cases of severe reduction of DNMT activity, it may cause DNA hypomethylation, genomic instability and early development of cancers such as T-cell lymphomas and sarcomas (Eden et al., 2003; Gaudet et al., 2003).

23. Sergi (2020) reviewed the toxicity of EGCG in children. In general, EGCG demonstrated poor oral absorption, even at a daily intake corresponding to 8-16 cups of green tea. EGCG blood levels peak within 1.7 hours after consumption and it has a plasma half-life of ~5 hours (in healthy adults) (Lee *et al*., (2002); Chow *et al*., (2003)). EGCG toxicity observed at high concentrations was related to pro-oxidative properties attributed to the catechol structures (ortho-diphenols). These structures are able to form a superoxide anion radical ($O2^{-}$) from molecular oxygen using an electrophilic *o*-quinone functional group. The ester group in EGCG may also interact with a cell's lipid bi-layer membrane. The effects of EGCG on the mitochondria were also described. EGCG promoted decreased reactive oxygen species (ROS) production on low doses, but increased ROS formation on high doses. EGCG seemingly caused damage to the outer mitochondrial membrane and uncoupling of oxidative phosphorylation in permeabilized hepatocytes. Sergi concluded that the use of green tea polyphenols (including EGCG) should not be considered for use in children because of the potential adverse effect on immature or fast-developing liver cells.

24. Bedrood et al., (2018) performed a review on the toxicological effects of *Camellia sinensis* (green tea). The most important side effects of green tea and its constituents (e.g., polyphenols) to have been reported were hepatotoxicity and gastrointestinal disorders especially when consumed on an empty stomach. Inhibitory effects on metabolising enzymes and intestinal absorption as well as nervous system stimulatory effects were also reported. Green tea and its main components were not major teratogenic, mutagenic or carcinogenic substances. It was noted by the authors, that there are limited data on using green tea and its

components during pregnancy, and that they should be used with caution during pregnancy, breast-feeding and in susceptible people. In addition, green tea and its components show a wide variety of drug-interactions, and consideration should be taken when co-administrating with drugs.

25. James et al., (2018) examined the hepatotoxic effects of EGCG in C57BL/6J mice and evaluated changes in hepatic antioxidant response and mitochondria structure and function. Mice (n=11-18 per group) were dosed with EGCG (93% pure at up to 750 mg/kg) once daily for 3 days via intragastric administration. Hepatic inflammation, necrosis and haemorrhage were observed. Hepatotoxicity was associated with increased oxidative stress and decreased superoxide dismutase and glutathione peroxidase levels. The authors concluded that their data indicate the mitochondria may be a target for EGCG, and that the inhibition of mitochondria function/antioxidant response may be important for the hepatotoxicity of bolus exposure to EGCG.

26. The above studies are summarised in Table 1 in Annex B.

27. EFSA noted that rare cases of liver injury have been reported after consumption of green tea infusions, most probably due to an idiosyncratic reaction. Overall, the EFSA Panel noted that the number of human cases with hepatotoxicity associated with green tea infusions is extremely low when compared to the large number of consumers of green tea infusions (EFSA, 2018).

Chemical characterisation

28. Chemical analysis shows that green tea leaves contain several other constituents in addition to catechins. Some of these constituents, such as caffeine, could alter the toxicological profile of catechins. The difference in constituents and/or concentration levels of catechins observed may be due to varying growth conditions, manufacturing processes, product shelf-life and storage conditions (Jafaar et al., 2017).

29. In other instances, for the broad term of GTE, the composition of this extract remains unknown. In 2020, an FSA survey detected the presence of pyrrolizidine alkaloids (PAs) in 11 out of 55 samples from *C. sinensis,* typically at levels of <500 µg per kg, most likely due to co-harvesting with PA producing plants (FSA, 2020).

30. PAs can result in hepatotoxicity following both acute and chronic exposure (COT, 2008; EFSA, 2017). The toxicity of PAs is almost exclusively

associated with their metabolites forming DNA adducts. Pyrroles can penetrate the nucleus and react with DNA leading to the formation of DNA cross-links and DNA-protein cross-links. In the liver, they can pass to the adjacent space of Disse and into the sinusoidal lumen, where they interact with sinusoidal cells.

31. The adverse toxicological effects and potency of PAs can be considered an uncertainty when assessing the possible hepatotoxicity of GTCs (in either green tea infusions or GTEs in supplements), as they can lead to similar hepatotoxicity endpoints, and therefore uncertainty exists as to what degree of hepatotoxicity is caused by PAs as compared to GTCs. However, the COT noted that the primary effect of PAs in the liver is most often characterised by hepatic veno-occlusive disease. Hence, there are differences in the hepatopathology profile observed with PAs and GTCs. This would suggest that any contribution of PAs is more likely to be synergistic than as an alternative hepatotoxin. PAs are discussed in more detail in paragraphs 68 - 79.

32. Green tea has also been shown to contain residues of pesticides and contaminants such as mycotoxins and heavy metals (Abd El-Aty et al., 2014). These substances are usually subject to regulatory limits, or not detectable following leaching into an infusion or manufacture of GTEs (for use in supplements).

Previous evaluations

International Agency for Research on Cancer

33. The International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence to conclude on the carcinogenicity in humans from tea drinking. There was also inadequate evidence to conclude on the carcinogenicity in experimental animals exposed to tea. Overall, IARC concluded that tea, which included green tea, is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1991).

United States Pharmacopeia

34. In 2007, the United States Pharmacopeia (USP) Dietary Supplement Information Expert Committee assigned a warning statement for GTE, based on reports of liver injury, which was later removed in 2009, following the review of additional information and stakeholder comments (USP, 2009). More recently, the USP has included a cautionary labeling requirement in its powdered decaffeinated

green tea extract monograph: “Do not take on an empty stomach. Take with food. Do not use if you have a liver problem and discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes).” (Oketch-Rabah et al., 2020).

European Medicines Agency

35. The European Medicines Agency (EMA) identified contraindications for use of green tea herbal infusions, those being: hypersensitivity to the active substance(s), gastric and duodenal ulcers, cardiovascular disorders such as hypertension and arrhythmia and hyperthyroidism. Overdose was considered in the context of caffeine content and can lead to restlessness, tremor, and elevated excitability (quantities corresponding to more than 300 mg of caffeine or 5 cups of tea as a beverage). Green tea dried extracts were involved in some cases of hepatoxicity and gave rise to safety concerns. Hepatotoxicity is related to high doses of herbal preparations (up to 35% of catechins) and the cytotoxicity of EGCG exhibited at these levels (EMA, 2013).

European Food Safety Authority

36. An evaluation was carried out by EFSA (EFSA, 2018) on the safety of GTCs. The evaluation focused on GTCs and the associated cases of probable idiosyncratic hepatotoxicity. It was not a general safety assessment of either GTCs or green tea infusions and extracts. The EFSA opinion is summarised in the next section.

37. In 2018, following a series of reports of adverse effects as a result of the intake of GTE supplements, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) considered the possible association between the consumption of EGCG (the major catechin present in green tea) and hepatotoxicity (EFSA, 2018). Information on the metabolism of tea flavanols addressed in the EFSA opinion is based on data presented by the Norwegian Institute of Public Health (NIPH) (NIPH, 2015).

38. When comparing studies, the EFSA Panel considered supplements in terms of EGCG content, the principle catechin in green tea. EGCG has been shown to be more cytotoxic than both epigallocatechin (EGC) and epicatechin-3-gallate (ECG) in primary rat hepatocytes (Schmidt et al., 2005; Galati et al., 2006). It was noted that in some cases, EGCG was the only catechin for which content was reported.

39. The EFSA Panel observed that generally, catechin metabolism follows the same pathway in mice, rats and humans based on the similarities in circulating, hepatic and intestinal metabolites observed in the plasma. Overall, animal models are generally predictive of catechin toxicokinetics in humans; however, due to other factors that affect toxicokinetics, there may be different outcomes. For example, GTCs are known to bind to dietary components such as proteins leading to a possible decrease in bioavailability of both catechins and dietary components, such as proteins and thus decreasing the free concentration available for absorption. Fasting was demonstrated to result in increased toxicity, probably due, in part, to a higher bioavailability of GTCs and reduced hepatic glycogen levels (which may be due to less binding of catechins to dietary proteins). Animal experiments suggest the liver is the primary target organ for toxicity.

40. The EFSA Panel noted that there were no specifications for the preparation of green tea as a food or food supplements in the EU Regulations and no monographs were held in the current edition of the European Pharmacopoeia. The Panel also noted the absence of a maximum limit for pyrrolizidine alkaloids in green tea preparation in food supplements.

41. However, the EFSA Opinion did note that the 2017 United States pharmacopoeia, provided specifications for 'Powdered decaffeinated Green Tea Extract' for use in green tea supplements, with the following definition: Powdered decaffeinated GTE is prepared from young unfermented leaves and the leaf buds of C. sinensis (L.) Kuntze (Family Theaceae) [syn, Thea sinesis L.] using suitable solvents such as alcohol, methanol, acetone, water, or mixtures of these solvents; the caffeine has been removed. The ratio of the starting crude plant material to powdered decaffeinated GTE is 6:1 to 10:1. It contains no less than 60% of polyphenols, calculated as (−)-epigallocatechin-3-O-gallate, no less than 40.0% of (−)-epigallocatechin-3-O-gallate, and no more than 0.1% of caffeine, all calculated on the anhydrous basis (USP-NF, 2023).

Toxicological data

42. As part of their assessment, EFSA reviewed literature studies, monographs and risk assessment reports available up to January 2018 following a public call for data (no data were received from interested parties on the levels of catechins in GTEs used for the manufacturing of food supplements). The risk assessment was carried out according to the EFSA Guidance on safety assessment of botanicals and botanical preparations intended for use as

ingredients in food supplements (EFSA, 2009). The Panel estimated chronic exposure to EGCG for the following population groups: infants, toddlers, children, adolescents, adults and the elderly.

43. In a peer reviewed publication based on human and animal data, a tolerable upper intake level (TUL) of 300 mg per day of EGCG was proposed by Yates et al., (2017) based on separate data from animals and in healthy human adults, respectively. An acceptable daily intake (ADI) of 4.6 mg/kg bw per day, derived from toxicity data, was proposed.

44. In a safety assessment of GTE supplements, Dekant et al., (2017) proposed a TUL of EGCG of 300 mg per person, based on clinical trials not reporting any liver effects (using a two-fold safety margin), and No Observed Adverse Effect Levels (NOAELs) from animal studies of dietary administration of GTCs (using a safety factor of 100).

45. There was evidence that intake of doses above 800 mg of EGCG per day over a duration of 4 months or longer led to elevations in ALT and AST levels in less than 10% of the general population (EFSA, 2018). Intense exercise can also increase serum ALT levels, and GTE supplements are often used in conjunction with other supplements by gym users, with the combined effect being unknown. In a smaller section of the general population (5.1%), doses of 843 mg EGCG per day over the course of a year, resulted in more serious effects on liver function. Additional factors contributing to hepatotoxicity were investigated, such as alcohol consumption, concomitant use of medicines and catechol-*O*-methyltransferase (COMT) genotype but these were not found to influence the hepatotoxicity. This effect was particularly noted in individuals with a higher body mass index, who were more likely to take weight loss supplements containing GTEs (Dostal et al., 2015; Yu et al., 2017).

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Key studies described by EFSA in their Opinion

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Intervention studies

46. The EFSA Panel evaluated a total of 49 intervention studies on green tea preparations, which included green tea infusions (4 studies) and GTEs (45 studies). No intervention studies in pregnant women, breastfeeding infants or children were identified. Following a review of the 49 studies evaluated, 9 studies reported elevated liver transaminases. However, two of the studies considered did not include a control group and were thus excluded. In the 7 remaining studies showing a higher incidence of abnormal liver parameters, doses of EGCG were 800 mg or above. The total number of treated participants receiving doses at or above 800 mg EGCG per day in the studies was 724. Of the reviewed studies, six covered a duration of between 4 and 12 months. Reported EGCG content in catechin extracts used ranged from 56 – 72% in Polyphenon E a decaffeinated extract of green tea containing 64% EGCG (Dostal et al., 2015, Yu et al., 2017) to pure EGCG (Ullmann et al., 2004).

47. Of the studies that reported no effects on liver parameters (26 studies: 1 used infusion, and 25 used extracts), the EGCG doses ranged from 10 to 857 mg per day ranging over a period of 10 days to 12 months. Of the studies using GTEs, 14 of the studies were at a dose of 316 mg EGCG per day or less (n=756 subjects) and 377 mg – 800 mg EGCG per day in 4 studies.

48. The COT considered that despite the weighting of data, with most studies using 300 mg dosage of EGCG per day or less, it is sufficient to show that the use of green tea herbal infusions is relatively safe compared to GTEs.

49. 756 subjects across 29 studies treated with GTEs at levels of 316 mg EGCG per day or less, exhibited no elevation in serum transaminase levels. The

EFSA Panel noted that in many cases, elevated transaminase levels returned to normal after dechallenge and increased following rechallenge, suggesting a relationship between exposure to GTE and liver effects.

50. With regard to the consumption of GTCs from herbal infusions, the EFSA Panel noted “The sparse data on green tea exposure from traditional green tea infusions and noted that there was no evidence of elevated ALT levels at a consumption of green tea infusion of ≥ 5 cups per day or containing 700 mg EGCG (–)- per day.” Elsewhere in the EFSA Opinion (pp.44), it is clarified that in order to consume 700 mg EGCG from green tea infusions, the consumption would be greater than or equal to 5 cups of green tea per day.

Human case reports of liver toxicity

51. The EFSA ANS Panel considered reports on the association of GTEs (in supplements) with hepatotoxicity, noting that many studies were focused on the purported beneficial effects of green tea on the liver. Such studies were outside the remit of the Panel and the scope of the mandate for the Opinion in question and thus, were not considered.

52. Several cases of liver toxicity were reported with the use of weight loss supplements containing GTE. In 2003, the weight loss supplement Exolise® was withdrawn from the market following 13 cases of hepatotoxicity (Sarma et al., 2008; Mazzanti et al., 2009, 2015; Navarro et al., 2017). The GTC EGCG was extracted using 80% ethanol (as an extraction agent) and standardised to 25% EGCG. The supplement also contained 5-10% caffeine. The recommended dose was two capsules twice a day, corresponding to the equivalent of 375 mg EGCG (ESCO, 2009). Liver toxicity was estimated to occur in one case per 100,000 boxes sold and appeared on average after 50 days of use (Sarma et al., 2008). The COT noted that a daily dose corresponding to 375 mg EGCG is somewhat lower than the ‘safe’ limit of 800 mg described by EFSA.

53. In 2009, fat burner supplement Hydroxycut® was withdrawn from the market, following 23 cases of hepatotoxicity reported to the US FDA (Livertox, 2012). Prior to 2009, Hydroxycut® formulations contained GTE, as well as caffeine, and ephedra.

54. SLIMQUICK® weight loss products, of which some contain GTE, have also been linked to six cases of acute liver injury between 2007 and 2011 (Zheng et al., 2016). Furthermore, some SLIMQUICK® products have caffeine content through the ingredients: guarana and yerba mate.

55. The presence of additional ingredients, in combination with GTEs further complicates the interpretation of data and the ability to attribute observed adverse effects to a specific chemical. A study found that 40% of herbal and dietary supplements linked to hepatotoxicity, contained catechins despite not identifying them as an ingredient (Navarro et al., 2013).

56. There was large variability in dose, composition, duration of exposure to GTE and incidence of hepatotoxicity as a result of consumption of green tea products, where doses ranged from three cups of green tea herbal infusions to 1,800 mg GTE per day. The EFSA Panel concluded that cases of hepatotoxicity associated with the consumption of green tea herbal infusions were very low. However, the COT noted that eight of 22 cases of hepatotoxicity from exclusive use of green tea products were reported to occur after consumption of green tea infusion. The EFSA Panel concluded that many of the cases of liver injury were as a result of idiosyncratic reactions.

57. Overall, in terms of human studies, the COT considered the “safe” limit of 800 mg per day defined by EFSA is realistic. However, the Committee recognised that there were a number of unknowns and uncertainties as discussed in the EFSA Opinion (see Uncertainties section).

Data from animal studies

58. Animal studies indicate that the liver is the target organ for EGCG toxicity in mice as demonstrated by higher incidences of elevated ALT levels and liver toxicity following high oral bolus doses or parenteral administration. The method of administration of green extract tea gives rise to differences in the magnitude of the effects observed. Daily oral bolus doses of 750 mg/kg bw EGCG (2 doses/day for up to 7 days) induced hepatotoxicity in mice, whereas doses of 100 mg/kg EGCG administered intraperitoneally were enough to induce liver injury (Lambert *et al.*, 2010).

59. In a 14-week toxicity study (n=10/sex/group) in which rats were administered a GTE (ethanol:water extraction of green tea leaves, resulting in an EGCG content of 48.4%) by oral gavage, 5 days/week, the NOAEL for liver toxicity was 500 mg GTE/kg bw per day – equivalent to 242 mg EGCG/kg bw per day (Chan et al., 2010).

60. In a study on fasted dogs treated with Polyphenon E (GTE) containing 63.3–64.8% EGC, animals were administered 0, 200, 500 and 1,000 mg/kg bw per day in gelatine capsules (equivalent to approximately 0, 128, 320 and 640 mg/kg

bw per day of EGCG) on an empty stomach. The study was terminated early (after 6.5 months instead of the intended 9-month period), due to extensive morbidity and mortality in all treated groups. Hepatic centrilobular necrosis and chronic active inflammation with infiltration of neutrophils and mononuclear cells were reported in the liver together with brown intracytoplasmic pigment in Kupffer cells (not described in relation to dose).

61. In a follow-up 13-week study in fed and fasted dogs receiving 200 mg/kg bw per day of Polyphenon E, corresponding to 128 mg EGCG/kg bw per day, increased levels of ALT were observed in one fasted dog and increased levels of AST was observed in another of the dogs. No effects on liver parameters were observed in fed dogs. Fasted dogs showed mild liver damage (haematopoiesis and presence of pigmented macrophages), whereas no changes were observed in the livers of fed dogs. Exposure (in terms of the area under the curve (AUC) and maximum concentration values (Cmax)) to EGCG was considerably lower in fed dogs than in fasted ones at the end of the 13-week period, which might explain, at least in part, the difference in toxicity in the fasted state (Kapetanovic et al., 2009).

62. In a 13-week study in dogs, an EGCG preparation (80% EGCG) was administered by capsule at doses of 0, 50, 150 and 500 mg/kg bw per day (corresponding to 0, 40, 120 or 400 mg EGCG/kg bw per day) to groups of fasted male and female animals (Isbrucker et al., 2006). Three dogs in the high-dose and two in the intermediate-dose group died or had to be terminated prematurely for humane reasons. Serum bilirubin levels were elevated in all high-dose animals, and some of these animals had increased ALT and AST values. The NOAEL was 50 mg/kg bw per day (equivalent to 40 mg/kg bw per day of EGCG).

63. In a second, 13-week study reported in the same paper (Isbrucker et al., 2006), groups of fed male and female dogs received capsules containing re-crystallized EGCG (91.8% purity) at doses of 0, 50, 300, or 500 mg/kg bw per day. No adverse effects were observed in any dose group. The NOAEL was therefore 500 mg/kg bw per day, the highest dose tested. This paper also showed that there was an appreciable increase in systemic exposure to EGCG in the fasted animals compared to that in the fed ones. Therefore, the NOAEL in fasted dogs was 10 times lower than the NOAEL identified in fed dogs.

64. A commentary was provided by Wu *et al.*, as mentioned in the EFSA Opinion (pp. 50). Wu *et al.*, (2011) pointed out that the estimated AUC was lower at the NOAEL in fasted dogs (9.2 and 12.1 µg h/mL in female and male, respectively) than at the NOAEL in fed dogs (39.9 and 88.3 µg h/mL in female and

male, respectively). In their commentary, they pointed out, that if the biological exposure is the primary factor for toxicity, the NOAEL exposure levels should be similar to one another when studies are conducted in the same species. Based on this argument, they speculated that fasting had increased the susceptibility of target organ systems to the effects of green tea extract. The EFSA Panel considered that an additional component contributing to increased susceptibility to EGCG in fasted dogs could be due to reduced hepatic glycogen.

65. Animal and human studies were considered in terms of other systemic end points. In the 13-week follow-up to the above study by Kapetanovic et al. (2009) , where one dose of 200 mg/kg bw per day of Polyphenon E, corresponding to 128 mg EGCG/kg bw per day was given to fasted (n=9; lots A, B and C; 3/lot) or fed (n=3, lot A) male dogs, severe toxicity, mainly in the gastro-intestinal tract, was observed in fasted dogs, whereas no adverse effects were observed in fed dogs. Additional observations in the fasted animals included vomiting, mild diarrhoea and/or red material in the faeces. No such signs were observed in the fed animals (Kapetanovic et al., 2009).

66. Based on histopathological effects (no clinical chemistry was performed in the study) in the liver in male and female rats, the Panel identified a possible NOAEL of 145 mg EGCG/kg bw per day (administered by gavage, 5 days/week, for 14 weeks and up to 105 weeks). Based on liver effects in male mice only, the NOAEL identified was 48.4 mg EGCG/kg bw per day (NTP, 2016).

67. The COT were of the opinion that EGCG appears to be directly hepatotoxic, at least in experimental animals, with limited evidence in humans, but there is also evidence for idiosyncratic liver toxicity in humans. The relationship with dose is more obvious with animals than humans.

Pyrrolizidine alkaloids

68. Pyrrolizidine alkaloids (PA) are known hepatotoxicants, as well as genotoxic and carcinogenic (COT, 2008; EFSA, 2017), and their contamination has also been suggested as a contributing factor to the hepatotoxic potential of green tea. This is thought to be the result of the co-harvesting of PA-producing plants.

69. It is thought that 1,2-unsaturated PAs can be activated by CYP enzymes, namely CYP3A4, to form hepatotoxic reaction products (EFSA, 2011, 2016, 2017; Stegelmeier et al., 2016, Robertson and Stevens, 2017).

70. PAs have been well documented to induce acute liver toxicity. However, as noted above, this is most often hepatic veno-occlusive disease, which differs

somewhat from the pathology profile observed with GTCs. The lowest dose of PA known to induce acute/short-term effects in human poisoning cases is 1– 3 mg/kg bw per day, based on the onset of hepatic veno-occlusive disease in a child after 2 weeks exposure and lethality in a 2-month infant after 4 days exposure.

Statement on the Hepatotoxicity of Green Tea Catechins

FSA survey of PAs in certain foodstuffs

In this guide

71. In 2014, in response to the EFSA Panel's 2011 recommendation that 'ongoing efforts should be made to collect analytical data on occurrence of PAs in relevant food and feed commodities [to inform future safety evaluations]' (EFSA, 2011), the FSA commissioned a survey to measure the levels of PA in teas, herbal infusions, plant-based food supplements and honey (FSA, 2014). The data collected as part of this survey were submitted to EFSA for their 2017 evaluation (summarised in the following paragraphs).

72. Fifty-five samples of tea from C. sinensis (common black and green teas), 70 samples of herbal infusions, 45 samples of plant-based supplements and 54 samples of honey were analysed in this study. The samples were purchased from a range of national supermarkets, smaller retailers, health/natural/organic food stores and UK internet/mail order retailers between February and March 2014.

The analytical results for PAs (detected by liquid chromatography with tandem mass spectrometry) are presented in Table 1.

Table 1– Analytical results of the FSA pyrrolizidine alkaloids survey in teas, herbal infusions, plant-based foods and honey carried out in 2014 (FSA, 2014).

Type of tea	Total no. of samples	No. of samples in which PAs were detected	0-100 (µg/kg)	100-500 (µg/kg)	500-1,000 (µg/kg)	1,000 – 3,000 (µg/kg)	>3,000 (µg/kg)	Range (µg/kg)
Teas (black, green and Earl Grey)	55	11	6	4	Not detected.	1	Not detected.	< LOQ – 1,170
Herbal infusions	70	35	9	12	8	4	2	< LOQ - 52,508*
Plant-based supplements	48#	5	2	3	Not detected.	Not detected.	Not detected.	< LOQ – 344
Honeys	54	35	29	6	Not detected.	Not detected.	Not detected.	< LOQ – 251

Abbreviations: LOQ – Limit of quantification.

*The highest levels were from borage and comfrey infusions which are known to contain high levels of PAs.

#Three of the samples could not be tested.

73. As it was evident that PAs were present in teas and herbal infusions as a result of contamination from PA containing weeds, more rigorous quality control and good agricultural practices including better weed control, harvesting and

processing are being put in place to minimize PA levels.

74. The FSA has been working with the producers of teas, herbal infusions, plant-based supplements, and honey in identifying measures that will reduce levels of PAs in these foods. The Food Business Operators (FBOs) have identified and implemented good agricultural practices in the growing and harvesting of the plant material used in the production of these products. FBOs have shown that subsequent testing, since 2014 when this work was carried out, of these foods has indicated that the mitigatory measures have been successful in reducing the levels of PAs. The FSA will continue to monitor the levels of PAs in food (FSA, 2014).

75. The samples used in this report were collected in early 2014 and should not be considered representative of what is available on the market now. The findings of this report have led to positive changes in agricultural practices and recent industry results continue to show a reduction in PA levels. The results have been fed into the EFSA dataset and have been used in discussions on managing the risks associated with the presence of PAs in food and feed at European level (FSA, 2020).

EFSA 2017 PAs evaluation

76. In 2017, the EFSA CONTAM Panel established a new reference point for PAs, based on the increase in incidence of liver hemangiosarcoma in female rats. The reference point of 237 µg/kg (benchmark dose lower confidence limit for 10% extra tumour incidence above background (BMDL10) with a was calculated for riddelliine, a specific PA, with a BMDU10) of 548 µg/kg (benchmark dose upper limit), using a control group and five different doses with a measured endpoint of hemangiosarcoma.

77. The EFSA CONTAM Panel concluded that there is a possible concern for human health related to the exposure to PAs, in particular for frequent and high consumers of tea and herbal infusions. Specifically, for green tea, exposure levels calculated from various data sets compared to the reference point of 237 µg/kg bw per day resulted in margin of exposure (MOE) values varying from 98,750 to 2,838 in adult consumers (EFSA, 2017). An MOE of <10,000 is of potential concern.

78. Furthermore, the EFSA CONTAM Panel noted that “consumption of food supplements based on PA-producing plants could result in exposure levels too close (i.e., 100 times lower) to the range of doses known to cause severe

acute/short term toxicity” (EFSA, 2017).

79. The EFSA Panel concluded, that whilst the levels of 1,2-unsaturated PAs present in green tea products were not sufficiently high to be responsible for non-neoplastic hepatotoxicity alone, their presence in green tea products could not be ruled out as a contributing factor (EFSA, 2017).

Uncertainties

80. The EFSA Panel considered several uncertainties with respect to exposures, biological and toxicological effects. These are detailed in the EFSA opinion (EFSA, 2018), and include considerations such as natural variation in chemical composition (due to plant variety, growing environment, season, age of leaves and manufacturing conditions), and the potential presence of hepatotoxic contaminants such as PAs.

81. In addition, due to the limited dose-response data after daily EGCG exposures of up to 800 mg/day in humans, there is uncertainty regarding the starting point for the derivation of a health-based guidance value for the general population. There is an uncertainty as to whether serious liver effects may develop after long-term use of GTEs; and the mechanism(s) leading to both the dose-dependent hepatotoxicity of EGCG and the mechanism(s) leading to idiosyncratic hepatotoxicity to EGCG (EFSA, 2018).

EFSA discussion and conclusion

82. EFSA concluded that catechins from green tea prepared in the traditional way of infusion, or reconstituted drinks giving the equivalent composition of catechins as that of green tea infusions, were, in general, safe; however, the Panel at the time were unable to determine a dose of EGCG from GTEs that would be considered safe. The EFSA Panel made the following recommendations:

- Studies to be carried out determining a dose-response of hepatotoxicity of GTCs and examine inter and intra species variability.
- As pyrrolizidine alkaloids in green tea preparations including food supplements could contribute to hepatotoxicity, maximum limits should be established.
- Labelling of green tea products (particularly food supplements), should include catechin content and EGCG proportion.

New reports and studies published since the EFSA 2018 Opinion

In this guide

83. To determine what new data had become available since the publication of the EFSA Opinion that might be relevant to the safety of the use of GTEs and hepatotoxicity, a literature search was conducted spanning the duration of 2018 to September 2022. Databases searched included PubMed, Google Scholar and LIVERTOX. Search terms used included (green tea extract and hepatotoxicity); (green tea extract and liver toxicity); (“green tea” and hepatotoxicity); (“green tea” and liver damage); (epigallocatechin-3-gallate OR EGCG) AND hepatotoxicity).

Alert systems

84. The EU Rapid Alert for Food and Feed (RASFF Portal) is a tool that provides information on public health warnings issued by food safety authorities and food companies. It also provides the latest information on food recall notices. The search in RASFF using the relevant search criteria filters returned one notification. In 2020, Denmark raised a RASFF for epigallocatechin gallate in GTE from Sweden (RASFF Notification 2020.2658). The dietary supplement ‘Chili burn’

was withdrawn following the Danish Veterinary and Food Administration's assessment that found the product to be harmful to health due to its content of EGCG (RASFF, 2020). Further information on this case was unavailable but an internet search showed the supplement contains 972 mg green tea leaves (*C. sinensis L*.) standardised to ECCG 30% per two tablet serving/day (New Nordic, 2022).

85. The UK Medicines and Healthcare products Regulatory Agency (MHRA) has a Yellow Card Scheme that allows reporting of adverse or suspected side effects to medicines, vaccines, e-cigarettes, medical device incidents, defective or falsified (fake) products to ensure safe and effective use (MHRA, 2023). The Yellow Card database has an 'Interactive Drug Analysis Profile' for *C. sinensis*, and though not explicit records for EGCG, multiple brand names that are targeted as weight loss supplements were noted. This implies that some of the reports may have been from exposure to EGCG present in such products. From January 2018 – November 2022 (when reports were last processed), 8 serious (excluding fatal) and 3 non-serious reports were recorded; however, none of these reported hepatobiliary disorders. Previous reports from January 2002 – December 2017, showed a total of 9 serious hepatobiliary disorders (n=5 cholestasis and jaundice, n=2 hepatocellular damage and hepatitis (not classified as A, B or C), n=1 hepatic enzymes and function abnormalities an, n=1 hepatic failure and associated disorders) (MHRA, 2022). The COT noted that the reports on the database may be subject to recall bias.

In vitro studies

86. Zhao et al., (2022) performed a review on the phytochemistry, pharmacology, and toxicology of green tea (*Camellia sinensis*). Many of the papers cited in this review have been detailed elsewhere. However, a study by Furukawa et al., (2003), not cited in EFSA (2018), who investigated whether EGCG could cause oxidative damage to *in vitro* bovine thymus DNA under the action of metal ions and H2O2-induced oxidative stress, was summarised. It was previously found that EGCG promoted the formation of 8-oxo deoxyguanosine, characteristic of oxidative damage to DNA that is associated with mutations and cancer (Shibutani et al., 1991). Furukawa et al., (2003) confirmed this finding together with indications of oxidative damage to DNA induced by EGCG in vitro.

87. In another study by Bertram et al., (2003) EGCG was found to cause DNA damage in both human lymphocytes and Nalm6 cells in a dose dependent manner. Furthermore, when the maximum dose of EGCG was 100 µm, the

survival rate of both cell lines decreased by 25% and 50%, respectively.

88. These studies are summarised in Table 2 in Annex B.

Animal studies

89. Cho et al., (2021) investigated the effects of GTEs on idiosyncratic drug-induced liver injury (IDILI) in murine models. Male and female wild type and PD-1-/- (C57BL/6 strain) mice, which respond to a number of other IDILI agents (n=3-4 per dose group) were administered a green tea fat burner supplement containing 150 mg EGCG per capsule at a dose of 250 mg or 500 mg/kg bw per day orally over a 6-week period.

90. PD-1-/- mice lack exons 2-3 of the programmed cell death 1 (Pdcd1) gene. Therefore, PD-1-/- mice do not express the PD-1 protein, which is typically located on the surface of T-Cells and B-Cells. It is involved in the regulation of T-cell function during immunity and tolerance. More specifically, PD-1 has been demonstrated to exhibit a role in anti-tumour immunity. Due to a lack of PD-1 expression, PD-1-/- mice display an increased infiltration of inflammatory cells in models of atherosclerosis, allograft vascular disease, encephalomyelitis, cardiomyopathy, and sepsis (The Jackson Laboratory, 2022).

91. PD-1-/- mice received anti-CTLA-4 antibody intraperitoneally at a dose of 300 µg on days -3 and -1 prior to the commencement of treatment and then weekly to sustain CTLA-4 inhibition. CTLA-4 (CD152) is an immune checkpoint protein which downregulates immune response. Anti-CTLA-4 antibody is used to block immune checkpoints and impair immune tolerance. This treatment was used as it is believed that the mechanism of IDILI is mediated through the immune system (Cho and Uetrecht, 2017).

92. In male and female wild type mice, GTE administered at doses of 250 mg/kg or 500 mg/kg did not result in a significant elevation of ALT levels over the 6-week treatment period. In female PD-1-/- mice treated with anti-CTLA-4 antibody and GTE at a dose of 500 mg/kg, GTE induced a delayed onset increase in serum ALT levels and an increase in CD8+ T cells. Male PD-1-/- mice exhibited a smaller increase in ALT on day 7, which was less consistent over time. Additionally, in female PD-1-/- mice an increase in cytotoxic T cells was observed following both dose levels of GTE. No evidence of liver injury was observed in wild type mice and the effect was less pronounced in male PD-1-/- mice (Cho et al., 2021).

93. Rojo et al., (2020) investigated the combined toxicity of green tea polyphenols present in Polyphenon 60® with the ribosome-inactivating lectin (RIL) ebulin f from dwarf elder (Sambucus ebulin) fruits.

94. The combined treatment resulted in a reduction in mouse survival by 70% with darkened areas in the internal organs, presumed to be due to bleeding. It is thought that GTEs enhance the apoptotic effect of ebulin f. (Rojo et al., 2020). The COT were of the opinion that the relevance of these findings to the effects of consumption of green tea or its extracts is questionable.

95. There is some suggestion that interaction between GTE and caffeine may also influence hepatotoxicity. In a study of the hepatotoxic potential of decaffeinated GTE (containing 180 mg EGCG/capsule; total sum of catechins 255 mg) in lean B6C3F1 mice, Gurley et al., (2019) demonstrated no significant alterations to their liver tissue following administration of decaffeinated GTE. Male B6C3F1/J mice were administered decaffeinated GTE at doses of either 1x (equivalent of 1.5 mg total catechins delivered in 300 µL of gavage solution), 3x (4.5 mg total catechins) or 10x (15 mg total catechins) mouse equivalent doses (MED) by gavage, for up to two weeks (Monday-Friday). However, there was no group receiving a caffeinated preparation with which to compare directly, and the study used historical data from a different study design, for comparison.

96. In acute toxicity studies (24 hours post dosing, liver tissue samples were collected), significant decreases in bodyweight were observed in the mice given 10x MED. Liver to bodyweight ratio was slightly decreased in all groups. Clinical biochemistry showed a two-fold increase in ALT, which was considered insignificant and ~20% increase in AST following administration of 1x MED decaffeinated GTE. Investigation into sub-acute toxicity following 2 weeks (Mon-Fri) of daily gavage with either 1x, 3x or 10x MED decaffeinated GTE showed no changes in liver to bodyweight ratio. No changes were observed in serum parameters except for an ~30% increase in ALP in mice administered 1x MED decaffeinated GTE. These findings agree with previous reports where no liver injury was observed at doses of ~750 mg/kg bw per day (Isomura et al, 2015; Isbrucker, 2006), suggesting further studies are needed to elucidate the effect that confounding factors, such as caffeine, may have on tolerance of GTE.

97. El-Bakry et al., (2017) (not referenced in the EFSA, 2018 Opinion) performed a study that aimed to address the effect of a therapeutic dose of GTE on the liver, evaluate the potential hepatoprotection of GTE against paracetamol overdose-induced hepatotoxicity, assess the regenerative capacity of the liver after discontinuation of treatments and explore the mechanisms underlying these

effects. The latter two objectives will not be summarised in this summary. The GTE tablets were obtained as a dietary supplement (known as Multi-treat), each table contains 300 mg GTE (30% polyphenol). Adult male albino rats (strain not specified) were divided into six groups (n=9/group): control, paracetamol (2 g/kg, orally for one week), GTE (8.5 mg/kg, orally for one month), paracetamol followed by GTE, paracetamol recovery (for one month) and paracetamol followed by GTE recovery (for one month). Administration of paracetamol or GTE resulted in biochemical and histopathological alterations that indicated hepatotoxicity including augmented concentrations of AST and ALT, hepatocellular necrosis and degeneration, congestion, haemorrhage, inflammation, and fibrosis.

98. Ramachandran et al., (2016) (not referenced in the EFSA, 2018 Opinion) carried out a study to estimate the maximum tolerated non-toxic dose of pure EGCG (100% purity) in adult female Swiss albino mice. Three experiments were carried out:

i. Animals were grouped into the following experimental groups (n = 5 per group); control (0), 217, 67.8, 21.1 and 6.6 EGCG mg/kg/day and dosed (100 µL) through oral gavage, for 14 consecutive days followed by 14 days of observation without treatment (total of 28-day study);

ii. Animals were grouped into (n = 5 per group); control (0), 108, 67.8, 21.1 and 6.6 EGCG mg/kg/day and dosed (100 µL) either through oral or intraperitoneal (i.p.) route of administration for 14 consecutive days followed by immediate termination after 24 h of the last dose (total of 14-day study) and;

iii. Animals were grouped into (n = 5 per group); control (0), 67.8, 21.1 and 6.6 mg/kg/day and dosed (100 µL) through i.p. route of administration, for 14 consecutive days followed by 14 days of observation without treatment (total of 28-day study).

99. Dose- and administration route-dependent hepatotoxic effects were observed, especially for the i.p. treated groups, where the EGCG serum lipid profile increased in parallel to hepatotoxicity. The 14-day tolerable dose of EGCG was established as 21.1 and 67.8 EGCG mg/kg bw/day for i.p. and oral routes, respectively. The authors noted that, EGCG induced effects in both treatment groups were reversible 14 days following cessation of treatment.

100. These studies are summarised in Table 3 in Annex B.

Human data on liver toxicity

Case reports

101. A number of new studies based on human data have been reported in the literature since the EFSA (2018) opinion was published.

102. Percevault et al., (2022) presented two case reports of green tea and hepatotoxicity. The first concerned a 48-year-old-woman (with no significant medical history except nephrolithiasis) presenting with symptoms suggestive of gastroenteritis. She was admitted and upon questioning she had drunk ~1.5 L of green tea a day for five years. She was also taking royal jelly with magnesium twice a day for 3 months. Her AST and ALT levels reached 8 times the upper limit of the normal range (ULN). The patient's condition rapidly worsened and she underwent a liver transplant for fulminant hepatitis (a rare syndrome of necrosis of the liver parenchyma and a decrease in liver size).

103. The second case involved a 28-year-old woman who had no previous medical history but was hospitalized for abdominal pain associated with elevated AST (greater than 100 times the ULN) and ALT (greater than 200 times the ULN). Her regular medications included an etonogestrel contraceptive, which had been implanted for two years. She also took a dietary supplement (ANACA3+®, Nutralvia, Mougins, France) composed of artichoke, carob, cola, guarana, curcuma, cichorium intybus, caffeine, zinc, ascophyllum, and green tea leaf powder (160 mg). The dose was four capsules per day for one year, as recommended. The patient discontinued supplementation. Liver function normalised over 1 month after the beginning of symptoms despite the contraceptive implant not being removed. The authors concluded that hepatotoxicity is more commonly reported from consumption of GTE than of green tea infusions. However, the authors noted that high consumption of green tea infusion over a long period can also lead to liver damage. Furthermore, the authors noted that toxicity was observed to be more frequent when green tea is consumed with other herbal or dietary supplements (Percevault et al., 2022).

104. Assis et al., (2022) performed a pooled analysis of case reports that described the clinical cases of dietary supplement-induced liver injury (DSILI) and herb-induced liver injury (HILI). They further identified the main products involved and the clinical outcomes related to them. Nineteen cases of liver injury were reported for the consumption of green tea. Most cases were in "middle-aged women and adults", with a predominance of hepatocellular lesions.

105. In 2021, a news article detailed the case of a 47-year-old man who developed DILI following years of taking GTE (brand was not disclosed and

therefore, the Secretariat could not ascertain whether the extract comprised catechins or EGCG) and concomitantly taking energy booster and “immunotherapy support” supplements also containing unspecified but large amounts of GTE (AZ Big Media, 2021). The article details that the patient is now recovering and illustrates the prevailing issue of DILI linked to supplement use and the fact that different supplements contain varying amounts of GTEs as part of proprietary blends.

106. Woo et al., (2021) reported the highlights from recent literature (September 2019 to March 2021) on DSILI and HILI, which included GTE. In this, a review conducted of human cases determined the median intake of 720 mg/day of EGCG for at least two weeks was related to liver injury. It was also found that over-the-counter GTE supplements contain EGCG concentrations from 45 - 1,575 mg/day. The bioavailability of EGCG increases in a fasting state, increasing serum concentrations at lower consumed dosages. The reported GTE-related hepatotoxicity in the majority of cases were acute hepatitis with a hepatocellular injury pattern (Oketch-Rabah et al., 2020; described further in paragraph 123).

107. Ballotin et al., (2021) identified herbal products associated with HILI and described the type of lesion associated with each product. In this, 90 patients (mean age 44, m = 22, f = 68) reported HILI due to consumption of GTE. This was most common in the USA (32.5%), Spain (19.1%) and Japan (14.6%). The main symptoms were jaundice, fatigue, nausea, and abdominal pain. The HILI patterns were mainly hepatocellular (78.8%), cholestatic (9.6%) and mixed (8%). As for the clinical outcome, 91.7% of patients recovered, 1.1% sustained chronic effects and 7% died.

108. In 2020, a case report was published detailing a case of supplement (i.e., drug) induced liver injury following the use of weight loss supplement, Hydroxycut (Khetpal et al., 2020). A 22-year-old obese female, who presented with chest pain, fatigue and shortness of breath, was diagnosed with DILI, which was believed to be due to Hydroxycut. Laboratory tests showed leucocytosis with a white blood cell count of 24 x 10^3/µl (4.4-10.5 x 10^3/µl), severe transaminitis with concentrations (normal range in brackets) of ALT at 2,399 U/L (4-51 U/L), AST at 4,040 U/L (5-46 U/L), alkaline phosphatase at 72 U/L (40-129 U/L), total bilirubin at 0.6 mg/dl (0.1-1.5 mg/dl), and an International Normalized Ratio of 1.4 (0.8-1.2). Following cessation of Hydroxycut use, ALT and AST reduced to 189 and 61 U/L, respectively. Several products exist under the name Hydroxycut; previous formulations have been listed to contain 91 mg per 2 capsules serving of GTE (as *C. sinensis* leaf) (Kaswala et al., 2014). The specific ingredient responsible for

acute liver injury was not identified since the specific product used by the patient was unknown, however, it was considered that GTE was a causative agent in acute liver injury.

109. D’Agostino et al., (2019) published a case of severe hepatitis related to the consumption of green tea in a 2-year-old child. The child was found to be allergic to milk and the mother replaced this with green tea infusions. Before hospital admission, the child presented acute otitis, which was treated with amoxicillin for 7 days. The child also presented with rash and diarrhoea for 5 days and a fever that persisted for 10 days. A laboratory test showed levels of ALT of 400 mg/dL, and thus was admitted to accident and emergency in the hepatology centre. The patient presented an elevation of AST and ALT enzymes with a maximum value of 2,200 and 1,600 uL/L, respectively. At the time of questioning, the mother stated that the child would only take green tea infusions, and these were given to him at a rate of 2-3 cups per day for 5 months. Each cup provided 80-106 mg of polyphenols, equivalent to 36-47.7 g of polyphenols in 5 months. The final presumptive diagnosis was severe acute hepatitis secondary to green tea infusion toxicity. The family was recommended to stop providing the child with green tea infusions. Four days after, a significant decrease in ALT and AST levels were observed, and levels returned to normal after 3 months.

110. Teschke and Xuan (2019), re-analysed cases of suspected liver injury associated with GTE published from 1999 to 11 June 2019 and categorised the cases into three groups: “idiosyncratic” or “intrinsic herb induced liver injury (HILI)” or “liver adaptation”. Although the mechanistic steps leading to liver injury have not been elucidated, there is evidence that GTE may cause idiosyncratic HILI in susceptible users as well as intrinsic HILI that is dose dependent. Liver adaptation may also develop, characterised by changes in levels of ALT (<5 times the normal upper limit) and/or alkaline phosphatase (ALP) (<2 times the normal upper limit). The authors concluded that the benefit-risk assessment was negative and thus the use of GTE cannot be recommended, but they did not recommended restrictions for the use of green tea beverages.

111. Surapaneni et al., (2018) reported a case of a 50-year-old woman who presented with constriction around the common bile duct, elevated AST levels of 1,657 U/L and an ALT level of 1,170 U/L following the use of an over-the-counter supplement (Vital Stem™). Vital Stem™ claims to contain stem cell enhancing blend (L-leucine, blueberry powder, GTE, L-carnosine and Vitamin D3). The exact amounts are not individually specified as it is considered a proprietary blend. The patient had been using the supplement daily for one month; consuming half a

teaspoon full dissolved in pomegranate juice (the recommended serving is 3.9 g in ~350 mL water (The Longevity Study, 2017)). After excluding other potential causes of acute liver injury, it was suspected the patient's severe hepatic necrosis was due to GTE in the supplement. No further information was given on when the patient ceased using the treatment, but the patient's symptoms were said to have improved following treatment with prednisolone.

112. Popovic et al., (2018) reported on the case of a 21-year-old man who had developed acute hepatitis following the concurrent use of both a weight loss and a fat burning supplement over an 8-week period. The patient was reported to have taken 3 capsules of Evlution Nutrition Lean Mode Stimulant-Free Weight Loss Supplement™ twice per day, containing 250 mg green tea leaf extract (EGCG content unknown) and 2 capsules of Evlution Nutrition Trans4orm Thermogenic Fat Burner™ twice per day, containing 500 mg GTE (standard minimum 50% EGCG). The patient exhibited a weight loss of 25% bodyweight. Four weeks after cessation of supplementation, the patient presented with painless jaundice and was found to have the following concentrations: AST at 2,179 IU/L, ALT at 3,016 IU/L, and ALP at 260 IU/L, and a total bilirubin at 148 µmol/L. It was noted that the weight loss supplement also contained *Garcinia cambogia*, a supplement widely promoted for weight loss, which has also been reported to cause hepatotoxicity (Corey et al., 2016), which, according to the authors, may have had a synergistic effect.

113. Gavrić et al., (2018) provided a case series of fat burner induced acute liver injury observed in four patients. Liver injury was associated with consumption of various commercially available fat burners including GTE (from *Camellia sinensis*). In one case, a 52-year-old woman consumed a product containing GTE (unknown concentration of EGCG) and presented with hepatitic and cholestatic idiosyncratic liver injury. In another case, a 57-year-old woman consumed Chili burn; a commercial product containing 486 mg green tea leaves and other constituents for 10 weeks, altogether she had consumed 85 pills, and presented with hepatitis idiosyncratic liver injury. Five years later, the same woman now (62-years-old) consuming SlimCut; a commercial product containing green tea leaf extract containing 45% EGCG for one month, consuming 60 pills in total presented with the same type of liver injury at the previous admission.

114. The above studies are summarised in Table 4 in Annex B.

Other literature studies

115. A small number of new papers detailing human studies on GTEs had been published since 2018. Grewal and Ahmad's review on drug induced liver injury and dietary supplements spanning the period to 2019 showed no new reports other than those considered by EFSA in their 2018 opinion (Grewal and Ahmad, 2019).

116. In a paper identified after the cut-off date for the literature search, Siblini et al., (2023) assessed the hepatic safety of EGCG in reproductive aged women. Uterine fibroids are the most common cause of unexplained infertility in reproductive-aged women. There was some evidence that EGCG can shrink uterine fibroids from prior preclinical and clinical studies. Thirty-nine women aged ≥18 to ≤40 years old, with or without uterine fibroids were split into three groups: 800 mg of EGCG daily alone, 800 mg of EGCG daily with clomiphene citrate 100 mg for 5 days, or 800 mg of EGCG daily with letrozole 5 mg for 5 days. No subject demonstrated signs of DILI and no subject showed serum folate level outside the normal range. Hence, the authors concluded that their data suggests that a daily dose of 800 mg of EGCG alone or in combination with clomiphene citrate or letrozole (for 5 days) is well-tolerated and is not associated with liver toxicity or folate deficiency in reproductive-aged women.

117. Acosta et al., (2022) investigated the influence of COMT and uridine 5'-diphospho-glucuronosyltransferase 1A4 (UGT1A4) genotypes on changes in liver injury biomarkers, AST and ALT in response to long-term, high-dose GTE supplementation among post-menopausal women (n=1,075) in the Minnesota Green Tea Trial, which was a large double-blind, placebo-controlled trial. Participants were given a high dose of GTE (843 mg/day EGCG) or placebo capsules for 12 months. Analysis of covariance was performed to examine changes in AST and ALT ratios at 3-monthly intervals of the study period. Clinically relevant serum transaminase elevations were found with 6-9 months of high dose of GTE supplementation amongst menopausal women with the UGT1A4 heterozygous genotype. There were too few subjects homozygous for the affected allele to analyse.

118. Fallah et al., (2022) analysed cross-sectional data from the 2009–2014 United States National Health and Nutrition Examination Survey (NHANES). It investigated the association between green tea infusions and GTE supplement consumption and abnormal liver biomarkers – increased levels of bilirubin, gamma- glutamyl transferase, ALT, AST, and/or ALP. It demonstrated that green tea consumption significantly reduced the probability of having one or more abnormal liver biomarkers. However, GTE supplement consumption had no

significant effect.

119. A study on herbal and dietary supplement-induced liver injury in Latin America between 2011 to 2019, found green tea was a frequently reported cause of DILI (Bessone et al., 2021). Of a total of 29 cases of DILI, attributed to herbal supplements, 8 cases were reportedly linked to GTE containing supplements – 7 of which were weight loss supplements and 1 an energy support supplement. The composition of the supplements in review were not detailed but three of the cases involved concomitant use of medicines including a prednisone, thalidomide, mirtazapine, clonazepam, amitriptyline and levopromazine mixture, and Equisetum arvense and hibiscus in the cases that presented with hypertransaminasemia (elevated transaminase levels). Duration of treatment ranged between 15 and 175 days, with a latency period of between 7 and 175 days.

120. Another study investigating cases of GTE related DILI, showed GTEs - alone and as part of a multi component supplement, as a cause of supplement related liver injury. The study, which found that of 1,414 patients enrolled on the United States Drug-Induced Liver Injury Network, 40 cases of liver injury (3%) were directly attributed to green tea consumption of which sixteen products were linked to GTE induced liver injury, the catechins per serving ranged from 6.6 – 384 mg, whilst the EGCG per serving ranged from 1.6 – 219 mg. Patients ranged in age from 17 to 69 years, with a median age at time of onset of 40 years and symptoms developed between 15 to 448 days (median = 72 days). In 8 cases, the primary implicated product was green tea and in 32 cases a multi-ingredient supplement was implicated. Liver injury was typically hepatocellular, seen in 95% of cases, with marked increases in serum ALT and AST concentrations. In 3 instances, liver injury recurred following re-exposure to the green tea product with a shorter onset time. Nine patients were also found to be taking two green tea-containing supplements concomitantly. Total estimated daily doses ranged from 50 mg to 2,000 mg GTE (median = 800 mg) from the 17 products that supplied information on GTE content (Hoofnagle et al., 2021).

121. Green tea–related liver injury was found to be strongly associated with the human leukocyte antigen (HLA) B*35:01 allele. HLA testing carried out on 36 patients defined as ‘definite, highly likely, or probable’ green tea–related liver injury cases, found 26 patients had at least one copy of the HLA-B* 35:01 allele – a carrier frequency of 72% (95% confidence interval [CI] = 58-87). This rate was 5-to 7-fold higher than in control groups, also suggesting an immunologic aetiology (Hoofnagle et al., 2021).

122. Deka et al., (2020) compared the effects of two green tea processing techniques orthodox and curl, tear and crush (CTC) and the effect on quality parameters and sensory profiles. A risk assessment was also carried out to determine the level of EGCG that is free from the risk of hepatotoxicity. The results showed that CTC green tea infusions has 7.1% more EGCG than infusions prepared form orthodox green tea. The risk assessment showed that daily consumption of five cups (10 g) of green tea results in an EGCG level that is free from the risk of hepatotoxicity.

123. Oketch-Rabah et al., (2020) conducted an update to their United states Pharmacopoeia review of the hepatotoxicity of GTEs spanning June 2008 to September 2017. The systematic review involved 204 human clinical research studies, 126 animal studies of GTEs, 51 published case report articles reporting 75 individual cases associated with GTE intake. The human cases reviewed involved use of GTE from 500 to 3,000 mg per day (equating to ~250 to 1,800 EGCG mg per day). Their review showed a correlation between the occurrence of severe hepatotoxicity and the consumption of GTEs. However, no evidence was found for the involvement of hepatotoxic solvent residues, pesticide residues, PAs, and elemental impurities in GTE-induced liver injury. The recognised factors contributing to hepatotoxicity include concentration of catechins in GTE-containing products, the repeated oral consumption of bolus dose ingested provided by different dosage forms, and as observed from animal studies whether the GTE is ingested in a fasted or fed state (when consumed during fasting the bioavailability of catechins, specifically EGCG, significantly increased). The published adverse event case reports associated with hepatotoxicity of EGCG covered a range of doses from 140 to 1,000 mg per day, thus substantial interindividual variability is apparent.

124. Levin et al. (2018) investigated the safety and efficacy of EGCG in multiple system atrophy by performing a randomized, double-blind, parallel group, placebo-controlled clinical trial at 12 specialist centres in Germany. Participants (n=47 and 45 in EGCG and placebo groups, respectively) were given one hard gelatin capsule (containing either 400 mg EGCG or mannitol) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks. After 48 weeks, all patients underwent a 4-week wash-out period. Four patients in the EGCG group and two in the placebo group died. Two patients in the EGCG group had to stop treatment because of hepatotoxicity. The authors concluded that 48 weeks of EGCG treatment did not modify disease progression in patients with multiple system atrophy. EGCG was overall well tolerated but was associated with hepatotoxic effects in some

patients (n=8), and thus doses of more than 1,200 mg should not be used.

125. Hu et al., (2018) performed a systematic review of published toxicology and human intervention studies to assess the risk to human health from green tea consumption. Supporting findings of previous studies, high level doses of catechins resulted in adverse events and hepatotoxicity in a dose dependent manner. However, the review demonstrated that the dosing method was critical, and that a large bolus dose caused an increased frequency of adverse events compared to ingestion through food and drink. Therefore, an observed safe level of 704 mg EGCG per day was proposed for human consumption when ingested periodically, such as in tea preparations. Whilst it was suggested that a safe intake level of EGCG for green tea preparations ingested as a bolus dose was 33 mg per day.

126. Hassan & Fontana (2018) reported liver injuries associated with the use of herbal and dietary supplements by amateur and professional athletes. Such products were broadly classed into two main categories: supplements used for their anabolic effect (for bodybuilding) and those used for energy enhancement and/or weight loss. GTE was classed as the latter and the reported DSILI were acute hepatocellular injury, acute liver failure and autoimmune histology. The authors noted that it is not possible to determine the exact amount of GTE in each supplement, but liver injury is suspected to occur up to exposure levels at much higher than that of green tea consumption alone.

127. Roytman et al., (2018) performed a review on botanicals including GTE and hepatotoxicity. They referenced the first study that the DILI Network published, which evaluated the potential impact of GTE or catechins on hepatotoxicity in documented HDILI cases. No statistically significant association between the presence of catechin or the dose consumed and liver injury causality score, severity or pattern of liver injury was found. However, the publication highlighted the issues faced with product labelling, where 40% of the dietary supplements containing catechins did not list/declare them on the label, whilst some that listed them did not contain any GTE following chemical analysis (Navarro et al., 2013; as described in paragraph 55).

Statement on the Hepatotoxicity of Green Tea Catechins

COT Conclusions

In this guide

128. The aim of this statement was to assess whether any new literature had been published on the hepatotoxic potential of GTEs since the adoption of the EFSA opinion on GTCs in 2018, that would affect the conclusions drawn by EFSA.

129. Data from human studies remain inconsistent, with incidences of hepatotoxicity occurring at a variety of doses, formulations and treatment duration. Recent evidence suggests this hepatotoxicity may be a result of individual idiosyncratic responses. The human data also suggest that it can prove difficult to determine the amounts of GTE (and thus EGCG) present in the supplements taken. Furthermore, there remains uncertainty in the extent of the contribution of other compounds, that may be present in the same GTE formulation such as PAs, to hepatotoxicity.

130. While some new studies have become available, it appears further studies are needed to elucidate factors contributing to potential green tea induced hepatotoxicity, which it seems may at least in part, be idiosyncratic, and be affected by multiple factors including genetic factors, nutrient and fasting state, and possibly general liver health.

131. Additional information on the nature of the idiosyncratic response, susceptibility factors and on the incidence of affected individuals, would be required to enable more informed guidance to be given by the Committee.

132. Overall, the COT concluded that there are no new data to suggest that EFSA's conclusion, that 800 mg/day EGCG was probably safe, is inappropriate. Although no new studies identified any effects of EGCG in humans at doses below 800 mg/day, the possibility cannot be excluded that sensitive individuals could still experience adverse effects below this dose due to an idiosyncratic reaction.

COT Statement 08/2024

November 2024

Statement on the Hepatotoxicity of Green Tea Catechins

Abbreviations

In this guide

ADI	Acceptable daily intake
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase

AST	Aspartate aminotransferase
AUC	Area under the curve
BMDL10	Benchmark dose lower confidence limit for 10% above background
BMDU10	Benchmark dose upper confidence limit for 10% above background
Cmax	Maximum concentration
DILI	Drug-induced liver injury
DSILI	Dietary supplement-induced liver injury
EFSA ANS	Panel on Food Additives and Nutrient Sources Added to Food
EGCG	(-)- Epigallocatechin-3-gallate
EMA	European Medicines Agency
ESCO	EFSA Scientific Cooperation
GTC	Green tea catechin
GTE	Green tea extract
HILI	Herb-induced liver injury
IARC	International Agency for Research on Cancer
IDILI	Idiosyncratic drug-induced liver injury

i.p.	intraperitoneal
LOQ	Limit of quantification
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
PA	Pyrrolizidine alkaloids
US FDA	United States Food and Drug Administration
USP-NF	United States Pharmacopeia National Formulary

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