Statements

The safety of green tea catechins- first draft statement

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Background

1. In 2017, following a series of reports of adverse effects as a result of 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 (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 Department of Health and Social Care (DHSC) who have the policy lead for food supplements in England, the FSA CRAU team reviewed the EFSA opinion informally and agreed with its conclusions.

2. Following the adoption of the EFSA opinion, the EU Commission are proposing amendments to EU legislation to restrict or prohibit the use of green tea catechins to ensure that foods containing these substances are safe for human consumption. The proposed risk management measures could include prohibiting the substance, restricting the permitted dose, or placing it under Community scrutiny for a period of time under Article 8 of Regulation (EC) 1925/2006. These measures are scheduled for Quarter 1 of 2022.

3. In addition, following the publication of the EFSA opinion, in 2019 the UK and European food supplements industry raised a number of concerns to DHSC regarding the potential risk management measures for including green tea catechins (EGCG) under Article 8 of Regulation (EC) 1925/2006. These concerns were also raised to the European Commission (EC).

4. On behalf of the UK, the NLCS have asked 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. This evaluation of the 2018 EFSA opinion pertains to green tea catechins and the associated cases of probable idiosyncratic hepatotoxicity, rather than a safety assessment of either green tea catechins or green tea infusions and extracts more generally.

5. The current draft statement presents a summary of the key findings of the EFSA Opinion on the safety of green tea catechins. To determine if any new literature had become available since the publication of the EFSA opinion, related to the safety of the use of green tea extracts and hepatotoxicity, a literature search was conducted from 2018 to the present, the findings of which are presented to the Committee for their consideration. Databases searched included PubMed, Google Scholar and LIVERTOX. Search terms used included ‘Green tea extract’, ‘liver injury’ and ‘hepatotoxicity’. Two papers (Hu et al., 2018; and Fallah et al., 2022) were identified as of potential interest to the COT and are described in more detail in the statement in Annex A.

Questions for the Committee

6. The Committee are asked to consider the following question:

a) Does the Committee have any comments on the structure or content of the draft Statement?

Secretariat

September 2022

Annex A to TOX/2022/51

Introduction

1. In 2017, following a series of reports of adverse effects as a result of 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 (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

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4. The Nutrition Labelling Composition and Standards (NLCS) common framework (which has been developed to maintain a consistent and co-ordinated policy approach across the UK) 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 (NLCS, 2020).

5. All future policy proposals relating to nutrition are therefore 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 in scope of the provisional NLCS framework includes seeking scientific evaluation from the relevant scientific advisory committee where appropriate.

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7. The current draft statement presents a summary of the key findings of the EFSA Opinion. To determine if any new literature had become available since the publication of the EFSA opinion on the safety of green tea catechins, related to the safety of the use of green tea extracts and hepatotoxicity, a search was conducted from 2018 to the present, the findings of which are presented to the Committee for their consideration. Databases searched included PubMed, Google Scholar and LIVERTOX. Search terms used included ‘Green tea extract’, ‘liver injury’ and ‘hepatotoxicity’. Two papers (Hu et al., 2018; and Fallah et al., 2022) were identified as of potential interest to the COT and are described in more detail in paragraphs 52 and 53.

Background

8. Catechins are polyphenolic compounds derived from green tea, the most significant being epigallocatechin-3-gallate (ECGC). Data suggest that exposure to green tea catechins can result in increased levels of the enzymes aspartate transaminase (AST) and alanine transaminase (ALT), indicating liver damage. The weight loss supplement Exolise, containing green tea extract as well as 5-10% caffeine, has been associated with liver failure in a number of case reports. The assessment of green tea catechins is complicated by the fact that catechins present in green tea infusions do not appear to pose a risk. It is thought that this is due to catechin doses in green tea infusions being lower than that of green tea extract in supplements or the extraction/manufacturing process affecting the properties of catechins in green tea extract in supplements.

Identity

9. Green tea, produced from the leaves of the Camellia sinensis plant is a popular drink, consumed worldwide. Green tea catechins are derived from the unfermented leaves and leaf buds of the tea plant, C. sinensis (L.) Kuntze. Catechins are the major group of polyphenols that constitute ~20% of the total flavonoids found in green tea (Sakata et al., 2013). Aqueous alcohol extraction of C. sinensis leaves concentrates these catechins and removes other components such as caffeine.

Chemical Characterisation

10. Chemical analysis shows that green tea contains several constituents. Some of these constituents, such as caffeine, could alter the toxicological profile. In other instances, for the broad term of green tea extract, the composition of this

extract remains completely unknown.

11. Pyrrolizidine Alkaloids (PAs) were detected in 11 out of 55 samples from Camelia sinensis, typically at levels of 500 ug/kg (El-Aty et al., 2014). PAs can be considered an uncertainty when assessing green tea catechins, as PAs can result in hepatotoxicity at both acute and chronic exposure (COT, 2008; EFSA, 2017). PAs are discussed in more detail in paragraphs 32-36. Green tea has also been shown to contain contaminants such as pesticides, mycotoxins and heavy metals (El-Aty et al, 2014). These contaminants are usually under regulatory limits, or not detectable following leaching into an infusion.

Previous evaluations

12. The European Medicines Agency (EMA) identified contraindications for use of green tea leaves, those being: hypersensitivity to the active substance(s), gastric and duodenal ulcers, cardiovascular disorders such as hypertension and arrhythmia and hyperthyroidism (European Medicines Agency, 2013b). Overdose was considered in the context of caffeine content.

13. The International Agency for Research on Cancer (IARC) concluded that there was insufficient evidence to suggest carcinogenicity (IARC, 1991). In 2007 the USP Dietary Supplement Information Expert Committee assigned a warning statement for green tea extract, which was later removed.

14. An evaluation was carried out by EFSA (EFSA, 2018) on the safety of gren tea catechins. As mentioned in paragraph 5, the evaluation focussed on green tea catechins and the associated cases of probable idiosyncratic hepatotoxicity. It was not a general safety assessment of either green tea catechins or green tea infusions and extracts. The EFSA opinion is summarised in the next section.

Summary of the EFSA Opinion

15. In 2018, following a series of reports of adverse effects as a result of the intake of green tea supplements, the EFSA Panel on “Food Additives and Nutrient Sources added to Food (ANS)” considered the possible association between the consumption of (-)-epigallocatechin-3-gallate (EGCG), the most relevant catechin in green tea, and hepatotoxicity. A link to the EFSA opinion is provided in Annex B. Metabolism of tea flavanols addressed in the EFSA statement is based on data presented by the Norwegian Institute of Public Health (NIPH) (NIPH et al, 2015).

16. 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.

17. Generally, catechin metabolism follows the same pathway in mice, rats and humans, however there may be different outcomes. Overall, animal models are generally predictive of catechin toxicokinetics in humans. Green tea catechins 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. Fasting was demonstrated to result in increased toxicity, presumably due to increased bioavailability of green tea catechins and reduced hepatic glycogen levels. Furthermore, fasting is known to reduce liver glutathione (GSH) levels, which is important to consider when considering human case studies as hepatotoxicity may also deplete GSH levels. Animal experiments suggest the liver is the primary target for toxicity.

18. The 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 2017 United States pharmacopoeia however, provided specifications for ‘Powdered decaffeinated Green Tea Extract’ for use in green tea supplements. The panel also noted the absence of a maximum limit for pyrrolizidine alkaloids in green tea preparation in food supplements.

Toxicological data

19. 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. 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 Scientific Committee, 2009b). Exposure in pregnant women, breastfeeding infants or children was not available, and therefore could not be considered.

20. In a peer reviewed publication based on human and animal data, a tolerable upper intake level (TUL) of 300 mg/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/day, derived from

toxicity data, was proposed. In a safety assessment of green tea supplements, Dekant et al (2017) proposed a TUL of EGCG of 300 mg/person, based on clinical trials not reporting any liver effects (using a two-fold safety margin), and NOAELs from animal studies dietary administration of green tea catechins (using a safety factor of 100).

21. 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 population (EFSA, 2018). Intense exercise can also increase serum ALT levels, and green tea supplements are often used in conjunction with other supplements by gym users, with the combined effect being unknown. In a smaller section of the population (5.1%), doses of 843 mg EGCG/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 contribute to hepatotoxicity. This effect was particularly noted in individuals with a higher body mass index (BMI), who were more likely to take weight loss supplements containing green tea extracts (Dostal et al., 2015; Yu et al., 2017).

Key studies

Intervention studies:

22. A total of 49 intervention studies were evaluated on green tea preparations, which included green tea infusions (4 studies) and green tea extracts (45 studies). 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. Of 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/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, 64% EGCG (Dostal et al. 2015, Yu et al. 2017) to pure EGCG (Ullmann et al. 2004).

23. Of the studies that reported no effects on liver parameters (26 studies – 1 infusion, 25 extracts), the EGCG doses ranged from 10 mg to 857 mg/day ranging over a period of 10 days to 12 months. Of the studies using green tea extracts, 14 of the studies were at a dose of 316 mg EGCG/day or less (756

subjects) and 377 mg – 800 mg EGCG/day in 4 studies. The COT considered that despite the weighting of data, with most studies using 300mg dosage of EGCG/day or less, it is sufficient to show that the use of green tea infusions is relatively safe compared to green tea extracts.

24. 756 subjects across 29 studies treated with green tea extracts at levels of 316 mg EGCG/day or less, exhibited no elevation in serum transaminase levels. The panel noted that in many cases, elevated transaminase levels, returned to normal after dechallenge and increase following rechallenge, suggesting a correlation between exposure to green tea extract and liver effects.

25. With regard to the consumption of green tea catechins from infusions, the 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/day.”

Human case reports of liver toxicity

26. The EFSA ANS Panel considered reports on the association of green tea extracts with hepatotoxicity, noting that many studies were focused on the purported beneficial effects of green tea on the liver.

27. Several cases of liver toxicity were reported with the use of weight loss supplements containing green tea extract. 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 supplement, consisting of 375 mg of a green tea extract, 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).

28. 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 green tea extract as well as caffeine and ephedra. SLIMQUICK® weight loss products, of which some contain green tea extract, 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.

The presence of additional ingredients, in addition to green tea extracts further complicates the interpretation of data and the ability to attribute observed 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).

29. There was a large variability in dose, composition of the green tea extract and duration of treatment and incidence of hepatotoxicity as a result of consumption of green tea products, where doses ranged from three cups of green tea infusion to 1800 mg green tea extract/day. The Panel concluded that cases of hepatotoxicity associated with the consumption of green tea infusions were very low. The panel also concluded that many of the cases of liver injury were as a result of idiosyncratic reactions. Overall, in terms of human studies, the COT considered the “safe” limit of 800mg 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.

Data from animal studies

30. 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 extraction of green tea gives rise to different observed effects. Daily oral bolus doses of 750 mg/kg bw EGCG (2 doses/day) induced hepatotoxicity in mice, whereas doses of 100 mg/kg EGCG administered intraperitoneally were enough to induce liver injury (Lambert et al., 2010).

31. In a 14-week toxicity study (10 males and 10 females per group) in which rats were administered a green tea extract (ethanol:water extraction of green tea leaves, resulting in an EGCG content of 48.4%) by oral gavage, 5 days per week, the lowest no observed adverse effect level (NOAEL) for liver toxicity was determined to be 500 mg green tea extract/kg bw per day – equivalent to 242 mg EGCG/kg bw/day (Chan et al., 2010).

32. In a study on fasted and non-fasted dogs treated with Polyphenon E (green tea extract containing 63.3–64.8% EGCG), fasted dogs 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) 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). Increased levels of ALT were observed in one dog and increased levels of AST was observed in another of the fasted dogs. No effects on liver parameters were observed in fed dogs. The NOAEL in fasted dogs was 40 mg EGCG/kg bw/day, which was 10 times lower than the NOAEL identified in fed dogs (Kapetanovic et al., 2009).

33. Animal and human studies were considered in terms of other systemic end points. A 13-week follow-up to the above study was carried out, 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 (9 dogs) or fed (3 dogs) dogs. Severe toxicity, mainly in the gastro-intestinal tract was observed in fasted dogs, administered green tea extracts in capsules at doses 200 mg/kg bw per day of Polyphenon E, which were non-toxic to fed dogs. Observed effects included vomiting, mild diarrhoea and/or red material in the faeces (Kapetanovic et al., 2009).

34. Based on histopathological effects (no clinical chemistry was performed in this 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 would be 48.4 mg EGCG/kg bw/ day (NTP, 2016).

Pyrrolizidine alkaloids

35. Pyrrolizidine alkaloids (PA) are known hepatotoxicants (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.

36. It is thought that 1,2-unsaturated PAs can be activated by CYP450 enzymes, namely CYP3A4, to form hepatotoxic reaction products (EFSA, 2011, 2016, 2017; Stegelmeier et al., 2016, Robertson and Stevens, 2017).

37. PAs have been well documented to induce acute liver toxicity. 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 (HVOD) in a child after 2 weeks exposure and lethality in a 2-month infant after 4 days exposure.

38. In 2017, as part of their evaluation of PAs, the EFSA CONTAM panel established a new Reference Point for PAs, based on the increase in incidence of liver hemangiosarcoma in female rats. The value of 237 µg/kg body weight per day was based on a benchmark dose lower confidence limit for 10% (BMDL10) to assess the carcinogenic risks of PA and concluded that there is a possible concern for human health related to the exposure to PA, 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 body weight per day resulted in Margin of Exposure (MOE) values varying from 98,750 to 2,838 in adult consumers. (EFSA, 2017)

39. Furthermore, the CONTAM Panel noted that “consumption of food supplements based on PA-producing plants could result in exposure levels causing acute/short-term toxicity” (EFSA, 2017).

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

Uncertainties

41. The panel considered several uncertainties with respect to exposures, biological and toxicological effects. These are detailed in the EFSA opinion (2018), and include considerations such as natural variation in chemical composition, and the potential presence of hepatotoxic contaminants.

EFSA conclusions and discussion

42. EFSA concluded that catechins from green tea prepared in the traditional way of infusion, or reconstituted drinks giving the equivalent composition of catechins as green tea infusions were, in general, safe. EFSA (2018) were however unable to determine a dose of EGCG from green tea extracts that would be considered safe. The panel made the following recommendations:

- Studies to be carried out determining a dose-response of hepatotoxicity of green tea catechins 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

43. To determine whether any new data have become available since the publication of the EFSA opinion, that might be relevant to the safety of the use of green tea extracts and hepatotoxicity, a literature search was conducted spanning the duration of 2018 to the present. Databases searched included PubMed, Google Scholar and LIVERTOX. Search terms used included ‘Green tea extract’, ‘liver injury’ and ‘hepatotoxicity’.

44. The 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. In 2020, Sweden raised a RASFF for Epigallocatechin gallate in green tea extract from Sweden (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 (2017). Further information on this case was unavailable but an internet search shows the supplement contains 972 mg green tea leaves (Camellia sinensis L.) standardised to ECCG 30% per two tablet serving.

45. A recent news article detailed the case of a 47-year-old man who developed DILI following years of taking green tea extract and concomitantly taking energy booster and “immunotherapy support” supplements also containing unspecified but large amounts of green tea extract (AZ Big Media, 2021). The article details that the patient is now recovering and illustrates the prevailing issue of drug induced liver injury linked to supplement use and the fact that different supplements contain varying amounts of green tea extracts as part of proprietary blends.

Animal studies

46. Cho et al (2021) investigated the effects of green tea extracts on idiosyncratic drug-induced liver injury (IDILI) in murine models. Male and female wild type and PD-$1^{-/-}$ (C57BL/6 strain) mice were administered a green tea fat burner supplement containing 150 mg EGCG/capsule at a dose of 250 mg or 500 mg/kg per day orally over a 6-week period.

47. PD-1-/- mice lack exons 2-3 of the programmed cell death 1 (Pdcd1) gene. PD-1 is an inhibitory cell surface receptor involved in the regulation of T-cell function during immunity and tolerance. 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).

48. 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 thus weekly to sustain CTLA-4 inhibition. Anti-CTLA-4 antibody is used to impair immune tolerance which is documented to be the major immune response to a drug that can cause IDILI (Cho and Uetrecht, 2017).

49. In male and female wild type mice, green tea extract 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. Female PD-$1^{-/-}$ mice treated with anti-CTLA-4 antibody and green tea extract at a dose of 500 mg/kg 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 green tea extract. 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).

50. Rojo et al (2020), whilst investigating the combined toxicity of green tea polyphenols with Sambucus ribosome-inactivating lectin (RIL) ebulin, found orally administered Polyphenon 60® extract from green tea, in combination with 5 mg/kg bw ebulin f, administered intraperitoneally, resulted in a reduction in mouse survival by 70%. Swiss female mice were administered one oral dose (p.o.) of Polyphenon 60, either in isolation or with an intraperitoneal treatment of 2.5 mg/kg bw of ebulin f administered as solution in 0.1-M phosphate-buffered saline, pH 7.4. Visual examination showed darkened areas in the internal organs, presumed to be due to bleeding. It is thought that green tea extracts enhance the apoptotic effect of ebulin f. Neither independent oral administration of Polyphenon 60 nor intraperitoneal administration of 2.5 mg/kg body weight ebulin f triggered lethal toxicity, however, lethality appeared 2 days after the combined treatment and reached more than 50% after 10 days. Rojo et al. (2020).

Human data on Liver toxicity

Case reports

51. A number of new studies based on human data have emerged since the EFSA opinion was published. Teschke and Xuan (2019), re-analysed cases of suspected liver injury associated with green tea extract (GTE) published from 1999 to 11 June 2019 and categorised the cases into three groups: “idiosyncratic” or “intrinsic herb induced liver injury” or “liver adaptation”. 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.

52. In 2020, a case report was published detailing a case of supplement 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 drug induced liver injury, it was believed to be due to Hydroxycut. Laboratory tests showed leucocytosis with a white blood cell count of 24 x 10^3/ul (4.4-10.5 10^3/ul), severe transaminitis with concentrations (normal range in brackets) of alanine aminotransferase (ALT) at 2399 U/L (4-51 U/L), aspartate aminotransferase (AST) at 4040 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 (INR) of 1.4 (0.8-1.2). Following cessation of Hydroxycut use, ALT and AST reduced to 189 and 61 U/L, respectively. The specific product used by the patient was not specified and therefore the quantity (if any) of green tea extract present unknown. Several products exist under the name Hydroxycut, previous formulations have been listed to contain 91 mg per 2 capsule serving of green tea extract (as camellia sinensis leaf) (Kaswala et al, 2014). The specific ingredient responsible for acute liver injury was not identified but it was considered that green tea extract was a causative agent in acute liver injury.

53. Surapaneni et al (2018) reported a case of a 50-year-old woman who presented with constriction around the common bile duct, elevated aspartate aminotransferase (AST) levels of 1657 U/L and an alanine aminotransferase level of 1170 U/L following the use of an over-the-counter supplement (Vital Stem). The patient had been using the supplement for one month and after excluding other potential causes of acute liver injury, it was suspected the patient’s severe hepatic necrosis was due to green tea extract in the supplement. Ingredients listed include green tea extract of unknown amounts, L-leucine, blueberry fruit and L-carnosine per 1400mg. 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.

54. 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 (2018). 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 and 2 capsules of Evlution Nutrition Trans4orm Thermogenic Fat Burner™ twice per day, containing 500 mg green tea extract. The patient exhibited painless jaundice and a weight loss of 25% bodyweight, 4 weeks after cessation of supplementation. patient was found to have an aspartate aminotransferase (AST) of 2179 IU/L, an alanine aminotransferase (ALT) of 3016 IU/L, an alkaline phosphatase (ALP) of 260 IU/L, and a total bilirubin of 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.

Literature studies

55. A small number of new literature papers detailing human studies on green tea were published since 2018. Grewal and Ahmad's review on drug induced liver injury and dietary supplements spanning the period of 2019 showed no new reports other than those considered by EFSA in their 2018 opinion. Hu et al. (2018) also reviewed the safety of green tea extract consumption though, their search covered literature up to 2016.

56. In 2018, and too recent to be published in the EFSA opinion, Hu et al 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 (OSL) of 704 mg EGCG/day was proposed for human consumption when ingested periodically, such as in tea preparations.

57. A recently published study analyses cross-sectional data from the 2009–2014 United States National Health and Nutrition Examination Survey (U.S. NHANES). It investigated the association between green tea and green tea

supplement consumption and abnormal liver biomarkers - increased levels of bilirubin, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) (Fallah et al, 2022). It demonstrated that green tea consumption significantly reduced the probability of having one or more abnormal liver biomarkers. However, green tea supplement consumption had no significant effect.

58. Oketch-Rabah et al (2020) conducted an update to their United states Pharmacopoeia review of the hepatotoxicity of green tea extracts spanning June 2008 to September 2017. Their review showed a correlation between the occurrence of severe hepatotoxicity and the consumption of green tea extracts. Recognised factors contributing to hepatotoxicity include concentration of catechins in green tea extract-containing products, the bolus dose ingested provided by different dosage forms, animal studies and whether the GTE is ingested in a fasted or fed state.

59. 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 drug-induced liver injury (DILI) (Bessone et al, 2021). Of a total of 29 cases of DILI, attributed to herbal supplements, 8 cases were reportedly linked to green tea 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.

60. Another study investigating cases of green tea related drug-induced liver injury showed green tea - either alone as an extract and as part of a multi component supplement - as a major cause of supplement related liver injury (Hoofnagle et al, 2020). The study, which found that of 1414 patients enrolled on the United States Drug-Induced Liver Injury Network, 40 cases of liver injury were attributed to green tea consumption. Patients ranged in age from 17 to 69 years, with a median age at time of onset = 40 and symptoms developed between 15 to 448 days (median = 72). 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 alanine and aminotransferase levels. In three 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 green tea extract (median = 800 mg) from the 17 products that supplied information on green tea extract content.

61. Green tea–related liver injury was found to be strongly associated with the HLA B*35:01 allele. Human leukocyte antigen (HLA) testing carried out on 36 patients defined as ‘definite, highly likely, or probable’ green tea–related liver injury 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.

62. There is some suggestion that interaction between green tea extract and caffeine may also influence hepatotoxicity. In a study of the hepatotoxic potential of decaffeinated green tea extract in lean B6C3F1 mice, Gurley et al. (2019) demonstrated no significant alterations to their liver tissue following administration of decaffeinated green tea extracts. Male B6C3F1/J mice were administered decaffeinated green tea extract 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 whom to compare directly, and the study had used historical data, from a potentially different study design, for the comparison.

63. In acute toxicity studies, 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 green tea extract. Investigation into sub-acute toxicity following 2 weeks (Mon-Fri) of daily gavage with either 1x, 3x or 10x MED decaffeinated green tea extract 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 green tea extract. These findings agree with previous reports where no liver injury was observed at doses of ~750 mg/kg bw/day (Isomura et al, 2015, Isbrucker, 2006), suggesting further studies are needed to elucidate the effect confounding factors, such as caffeine may have on tolerance of green tea extract.

COT Conclusions

64. The aim of this paper was to assess whether any new literature had been published on the hepatotoxic potential of green tea extracts since the adoption of the EFSA opinion on green tea catechins in 2018, that would affect the conclusions drawn by EFSA. 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 be affected by multiple factors including genetic factors, idiosyncrasy and possibly general liver health.

65. Data from human studies remains less consistent, with incidences of hepatotoxicity occurring at a variety of doses, formulations and treatment duration. The human data also suggest that it can prove difficult to determine the amounts of GTE (and thus EGCG) present in the supplements taken.

66. Overall, there is no additional new data to suggest that EFSA's conclusion, that 800 mg/day EGCG was probably safe, is no longer appropriate. Based on both the previous and additional data, it has still not been possible to identify a NOAEL for green tea extract or for EGCG.

Secretariat

September 2022

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Abbreviations

ADI	acceptable daily intake
ADME	Absorption, distribution, metabolism and excretion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASP	aspartate aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice per day (bis in die)
BMDL10	dose lower confidence limit for 10%

BMI	body mass index
C (+)-	catechin
CAS	Chemical Abstracts Service
CG (+)-	catechin-3-gallate
CI	confidence interval
COMT	catechol-O-methyltransferase
CSFII	Continuous Survey of Food Intakes by Individuals
DILI	drug-induced liver injury
EC (–)-	epicatechin
ECG (-)-	epicatechin-3-gallate
EFSA ANS	Panel on Food Additives and Nutrient Sources Added to Food
EGC (–)-	epigallocatechin
EGCG (–)-	epigallocatechin-3-gallate
EMA	European Medicines Agency
ESCO	EFSA Scientific Cooperation
GC (+)-	gallocatechin

GCG (–)-	gallocatechin-3-gallate
GGT	gamma-glutamyl transferase
GTC	green tea catechin
GTE	green tea extract
GTP	glutamyl transpeptidase
HCC	hepatocellular carcinoma
HPLC/MS	high performance liquid chromatography/mass spectrometry
HVOD	hepatic veno-occlusive disease
IARC	International Agency for Research on Cancer
IDILI	idiosyncratic drug-induced liver injury
IUPAC	International Union of Pure and Applied Chemistry
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LC–MS	liquid chromatography–mass spectrometry
LD50	lethal dose, median
LLOQ	lower limit of quantification

LOD	limit of detection
LOQ	limit of quantification
MOE	margin of exposure
MOS	margin of safety
MRT	Mean Residence Time
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NSAIDs	non-steroidal anti-inflammatory drug
OECD	Organisation for Economic Co-operation and Development
PAH	polycyclic aromatic hydrocarbon
PA	pyrrolizidine alkaloids
P.O.	per os “by mouth”

ROS	reactive oxygen species
SID	once per day (singular in die)
ULN	upper limits of normal
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia

Keywords

Adverse effects

Adverse reactions

Camellia sinensis

Catechins

Catechins hepatotoxicity

Catechins Liver toxicity

Catechins toxicity

Epigallocatechin gallate

EGCG

Green tea catechins

Green tea extract

Green tea supplement

Green tea supplement safety

Hepatotoxicity

Herb induced liver injury (HILI)

Liver injury

Liver damage

Polyphenols

Toxicity

Safety

Annex B to TOX/2021/51

The EFSA Scientific opinion on the safety of green tea catechins can be found below:

Scientific opinion on the safety of green tea catechins (wiley.com).

Secretariat

September 2022