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 The dietary supplement ‘Chili burn’ was withdrawn following the Danish Veterinary and Food Administration’s assessment that found the product to be harmful to health due to its content of EGCG (RASFF, 2020).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).