Meeting

Second Draft Statement on the Hepatotoxicity of Green Tea Catechins

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 (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 Department of Health and Social Care (DHSC) who have the policy lead for food supplements in England, the Food Standards Agency's Chemical Risk Assessment Unit reviewed the EFSA opinion 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."

3. Following the adoption of the EFSA opinion, the EU Commission are proposing amendments to EU legislation to restrict or prohibit the use of GTCs 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 4 of 2022 (EC, 2022a). This Retained EU regulation has yet to be updated since there are outstanding changes yet to be made by the European Parliament and Council (Retained EU Regulation (EC) No. 1925/2006 of the European Parliament and of the Council) (UK Legislation, 2006).

4. 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 GTCs (EGCG (–)-) under Article 8 of Regulation (EC) 1925/2006. These concerns were also raised to the European Commission (EC) (EC, 2021).

5. On behalf of the UK, the Nutrition Labelling Composition and Standards (NLCS) Common Framework have requested the FSA to evaluate whether the conclusions of the 2018 EFSA opinion are still applicable considering any new scientific data that have become available since its adoption, to enable them to consider the next steps for risk management. As the evaluation will cover the 2018 EFSA Opinion and any new scientific data, the FSA have requested that the COT undertake the assessment. 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).

6. The current draft statement presented in Annex A provides a summary of the key findings of the EFSA Opinion on the safety of GTCs. 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 September 2022, the findings of which are presented to the Committee for their consideration.

7. 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

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

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

b) Can the draft be cleared by Chair's action prior to publication?

Secretariat

February 2023

TOX/2023/05 Annex A

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 (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 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. 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."

3. Following the adoption of the EFSA opinion, the EU Commission are proposing amendments to EU legislation to restrict or prohibit the use of GTCs 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 were scheduled for 4 of 2022 (EC, 2022a). This Retained EU regulation has yet to beupdated since there are outstanding changes yet to be made by the European Parliament and Council (Retained EU Regulation (EC) No 1925/2006 of the European Parliament and of the Council).

4. 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 GTCs (EGCG (–)-) under Article 8 of Regulation (EC) 1925/2006. These concerns were also raised to the European Commission (EC).

5. 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 and Memorandums of Understanding 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).

6. All future policy proposals relating to:

- Nutrition and health claims made on foods;
- The addition of vitamins, minerals, and certain other substances to foods;
- The composition and labelling of food intended for infants and young children, food special medical purposes, and total diet replacement for weight control (‘Food Specific Groups’) and;
- The mandatory nutrition declaration (food labelling), including additional forms of expression and presentation in which it may be given.

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.

7. On behalf of the UK, the NLCS have requested the Food Standards Agency 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 GCTs or green tea infusions and extracts more generally (EFSA, 2018).

8. This statement presents a summary of the key findings of the EFSA Opinion and provides an updated state of science within the literature since the EFSA Opinion was published in 2018. To determine if any new literature had become available since the publication of the EFSA opinion a literature search was undertaken and 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.

Background

Definitions

9. The terms ‘herbal infusions’ and ‘tea (Camellia sinensis; C. sinensis)’ 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).

10. 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).

Identity

11. Green tea, produced from the leaves of the C. sinensis plant is a popular drink, consumed worldwide. GTCs are derived from the unfermented leaves and leaf buds of the tea plant, C. sinensis. 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 levels of catechins and removes other components such as caffeine (C. sinensis has naturally occurring caffeine; Vuong & Roach, 2014).

12. Catechins are polyphenolic compounds, and most of the polyphenols derived from green tea are catechins. As identified by EFSA, the most significant catechin associated with hepatotoxicity is epigallocatechin-3-gallate (EGCG (–)-) (EFSA, 2018). Therefore, as demonstrated in the literature reviewed in this statement, the dosage of EGCG (–)- has been investigated linking GTCs to hepatotoxicity. A study by Bhagwat et al. determined that EGCG (–)- is present in dried leaves of green tea at 7,380 mg per 100 g (Bhagwat et al, 2011). EGCG (–)- is present in green tea infusions, but is found at a higher concentration in GTEs.

Toxic mode of action

13. The exact mechanism of GTE associated liver injury remains to be fully elucidated. Data suggest that exposure to GTCs (specifically EGCG (–)-) can result in increased levels of the enzymes aspartate transaminase (AST) and alanine transaminase (ALT). In liver function blood tests, these enzymes are used as biomarkers of liver toxicity (Gurley et al., 2022).

14. EFSA note 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

15. Chemical analysis shows that green tea leaves contains several other constituents. 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 also be an effect of varying manufacturing processes, product shelf-life and storage conditions (Jafaar et al., 2017).

16. In other instances, for the broad term of GTE, the composition of this extract remains completely 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 (FSA, 2020).

17. PAs can result in hepatotoxicity at both acute and chronic exposure (COT, 2008; EFSA, 2017). The toxicity of PAs is almost exclusively associated with their metabolites forming DNA adducts (e.g., 2,3-dihydro-1H-pyrrolizine protein). Pyroles can also penetrate the nucleus and react with DNA causing the formation

of DNA cross-links and DNA-protein cross-links. In the liver, they can pass to the adjacent Dissé space and into the sinusoidal lumen, where they interact with sinusoidal cells.

18. The adverse toxicological effects and potency of PAs can be considered an uncertainty when assessing it in conjunction with GTCs (in either green tea infusions or GTEs in supplements), as they are evaluated via similar hepatotoxicity endpoints, and therefore uncertainty exists in what degree of hepatotoxicity is caused by PAs vs GTCs. PAs are discussed in more detail in paragraphs 50-60.

19. Green tea has also been shown to contain contaminants such as pesticides, mycotoxins and heavy metals (Abd El-Aty et al., 2014). These contaminants are usually under regulatory limits, or not detectable following leaching into an infusion or manufacture of GTEs (for use in supplements). PAs are also subject to regulatory limits under Retained EU Regulation (EC) No. 2020/2040 (UK Legislation, 2020).

Previous evaluations

20. 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 carcinogenixity in experimental animals exposed to tea. Overall, IARC concluded that tea is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1991).

21. In 2007, the United States Pharmacopeia (USP) Dietary Supplement Information Expert Committee assigned a warning statement for GTE, which was later removed in 2008, following the review of additional information and stakeholder comments (USP, 2009).

22. The European Medicines Agency (EMA) identified contraindications for use of green teaherbal 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 reason for safety concerns. Hepatotoxicity is related with high doses of herbal preparations (elevated percentages of caffeine at 5-10% and

up to 35% on catechins) and the cytotoxicity of EGCG exhibited at these levels (EMA, 2013).

23. An evaluation was carried out by EFSA (EFSA, 2018) on the safety of GTCs. As mentioned in paragraph 8, 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.

Summary of the EFSA Opinion

24. 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). Metabolism of tea flavanols addressed in the EFSA opinion is based on data presented by the Norwegian Institute of Public Health (NIPH) (NIPH, 2015).

25. 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.

26. Generally, catechin metabolism follows the same pathway in mice, rats and humans this is due to 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.

27. 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.

28. The 2017 United States pharmacopoeia; however, 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

29. 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). Exposure in pregnant women, breastfeeding infants or children was not available, and therefore could not be considered. Therefore, the Panel estimated chronic exposure to EGCG for the following population groups: infants, toddlers, children, adolescents, adults and the elderly.

30. 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.

31. 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 dietary administration of GTCs (using a safety factor of 100).

32. 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 genotype but these were not found to contribute to 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).

Key studies

Intervention studies:

33. A total of 49 intervention studies were evaluated on green tea preparations, which included green tea infusions (4 studies) and GTEs (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 (–)- 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, 64% EGCG (–)- (Dostal et al., 2015, Yu et al., 2017) to pure EGCG (Ullmann et al., 2004).

34. 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.

35. 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.

36. 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 increase following rechallenge, suggesting a correlation between exposure to GTE and liver effects.

37. 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.”

Human case reports of liver toxicity

38. 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, fall outside the remit of the Panel and the scope of the current mandate and thus, were not considered.

39. 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 EGCGC (–)- 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).

40. 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.

41. 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.

42. 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).

43. 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. The EFSA Panel concluded that many of the cases of liver injury were as a result of idiosyncratic reactions.

44. 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

45. 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 different observed effects. 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).

46. 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 determined to be 500 mg GTE/kg bw per day – equivalent to 242 mg EGCG/kg bw per day (Chan et al., 2010).

47. In a study on fasted and non-fasted dogs treated with Polyphenon E (GTE) containing 63.3–64.8% EGC), 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 per day, which was 10 times lower than the NOAEL identified in fed dogs (Kapetanovic et al., 2009).

48. 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 (n=9) or fed (n=3) dogs. Severe toxicity, mainly in the gastro-intestinal tract was observed in fasted dogs, administered GTEs in capsules at doses of 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).

49. 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 per day (NTP, 2016).

Pyrrolizidine alkaloids

50. 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.

51. 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).

52. 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 in a child after 2 weeks exposure and lethality in a 2-month infant after 4 days exposure.

FSA survey of PAs in certain foodstuffs

53. In 2014, the FSA carried out research 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 therefore 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).

54. 55 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 SEQ Table1 – 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	n/a	1	n/a	LOQ – 1,170
Herbal infusions	70	35	9	12	8	4	2	LOQ - 52,508*
Plant-based supplements	48[#]	5	2	3	n/a	n/a	n/a	LOQ – 344

Honeys	54	35	29	6	n/a	n/a	n/a	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.

55. As it is evident that PAs are 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.

56. 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).

57. The samples used in this report were collected in early 2014 and should no longer 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

58. 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 value of 237 µg/kg bw 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 bw per day resulted in Margin of Exposure values varying from 98,750 to 2,838 in adult consumers (EFSA, 2017). The reference point of 237 µg/kg was calculated for riddelliine, a specific PA, and a range of 237-548 µg/kg BMDL10 – benchmark dose upper limit that results in 10% extra above background (BMDU10) was calculated using a control group and five different doses with a measured endpoint of hemangiosarcoma.

59. 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).

60. The EFSA Panel concluded, that whilst the levels of 1,2-unsaturated PAs present in green tea products were not sufficiently high enough 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

61. The EFSA Panel considered several uncertainties with respect to exposures, biological and toxicological effects. These are detailed in the EFSA opinion 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.

62. In addition, due to the limited dose-response data after daily EGCG exposures of up to 800 mg/day, 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 GTEts; 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

63. 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; 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 (as mentioned in paragraph 19, PAs are also subject to regulatory limits under Retained EU Regulation (EC) No. 2020/2040).
- 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

64. 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 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’, ‘liver injury’ and ‘hepatotoxicity’.

Alert systems

65. 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. 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 shows the supplement contains 972 mg green tea leaves (C. sinensis L.) standardised to ECCG 30% per two tablet serving/day (New Nordic, 2022).

66. 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, which implies that some of the reports may have been from exposure to EGCG present in such produicts. 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, shows a total of 9 serious hepatobiliary disorders (n= 5 cholestasis and jaundice, n=2 hepatocellular damage and hepatitis (not elsewhere classified as A, B or C), n=1 hepatic enzymes and function abnormalities an, n=1 hepatic failure and associated disorders) (MHRA, 2022).

Animal studies

67. 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 (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.

68. 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).

69. 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. 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 response (Cho and Uetrecht, 2017).

70. 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. Female PD-1-/- mice treated with anti-CTLA-4 antibody and GTE 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 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).

71. Rojo et al., (2020) investigated the combined toxicity of green tea polyphenols present in Polyphenon 60® with Sambucus ribosome-inactivating lectin (RIL) ebulin. Swiss female mice were administered one dose via oral gavage of Polyphenon 60®, either in isolation (n=7) 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 (n=11). Polyphenon 60® contains (-) epicatechin-3-gallate (21.0%), (-) epicatechin (7.3%), (-) epigallocatechin (7.9%), and EGCG (29.2%).

72. 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%. Visual examination showed darkened areas in the internal organs, presumed to be due to bleeding. It is thought that GTEs 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

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

74. 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 was 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.

75. 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, it was believed to be due to Hydroxycut. Laboratory tests showed leucocytosis with a white blood cell count of 24 x 103/µl (4.4-10.5 x 103/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.

76. 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.

77. 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) per 1,400 mg. The exact amounts are not individually specific as it is considered a proprietary blend. The patient had been using the supplement daily for one month; consuming half tea spoon dissolved in pomegranate juice (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.

78. 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 painless jaundice and a weight loss of 25% bodyweight, 4 weeks after cessation of supplementation. The patient was found to have the following concentrations: AST at 2,179 IU/L, ALT at 3,016 IU/L, an 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.

Literature studies

79. 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 of 2019 showed no new reports other than those considered by EFSA in their 2018 opinion (Grewal and Ahmad, 2019).

80. 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.

81. Fallah et al., 2022 analysed cross-sectional data from the 2009–2014 United States National Health and Nutrition Examination Survey. 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.

82. 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. Their review showed a correlation between the occurrence of severe hepatotoxicity and the consumption of GTEs. The recognised factors contributing to hepatotoxicity include concentration of catechins in GTE-containing products, the 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.

83. 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.

84. Another study investigating cases of GTE related DILI, showed GTEs – alone and as part of a multi component supplement, as a major 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 EGCG per serving ranged from 0 – 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).

85. 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).

86. 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 whom to compare directly, and the study had used historical data, from a potentially different study design, for the comparison.

87. 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 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 confounding factors, such as caffeine may have on tolerance of GTE.

COT Conclusions

88. 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.

89. Data from human studies remains less consistent, 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 caffeine and PAs, to hepatotoxicity.

90. 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.

91. 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. Although no studies identified any effects of EGCG at doses below 800 mg/day, the possibility cannot be excluded that sensitive populations could still experience adverse effects. Additional data is required for more informed guidance, as a NOAEL or HBGV cannot currently be established for green tea or EGCG.

COT Statement XX/2023

February 2023

Abbreviations

ADI	Acceptable daily intake
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase

AST	Aspartate aminotransferase
BMDL10	Benchmark dose lower confidence limit for 10% below background
BMDU	Benchmark dose upper confidence limit for 10% extra above background
DILI	Drug-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
IARC	International Agency for Research on Cancer
IDILI	Idiosyncratic drug-induced liver injury
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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