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TOX/2026/26

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

Herb Induced Liver Injury

Introduction

1. Due to the increasing number of incidents relating to food supplements received by the Food Standards Agency (FSA), the FSA Secretariat have asked the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to review the information on the role of idiosyncratic Herb Induced Liver Injury (HILI) and to consider whether a COT position or stand-alone statement on idiosyncratic HILI would be required.
2. Consumption of food supplements containing botanicals appears to be increasing. They are widely available and they are often consumed in place of, or as a supplement to, conventional Western medicine, however, although often perceived as a safer alternative the safety profile is often not well characterised. As such there have been increasing reports of hepatotoxicity and liver injury that have been related to their consumption.
3. In 2002, the Committee on Safety of Medicines (CSM) concluded that the herbal ingredient, kava kava, could cause serious liver toxicity, stating that the precise mechanism by which such toxicity occurs is not understood and there are no clear predictors of this toxicity. The CSM therefore advised that the licensing authorisation for kava kava products be withdrawn and the use of kava kava in unlicensed medicines be prohibited. This led to the statutory Medicines for Human Use (Kava-kava) (Prohibition) Order 2002 (COT, 2002).

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4. Furthermore, in their 2024 statement on the hepatotoxicity of Green Tea Catechins, the COT concluded that although studies did not identify any effects of epigallocatechin gallate (EGCG) in humans at doses below 800 mg/day, the possibility cannot be excluded that a few individuals could still experience adverse effects below this dose due to an idiosyncratic reaction. In their 2024 statement on the potential risk to human health of turmeric and curcumin supplements, the COT identified that consumption of turmeric at the levels found in supplements, even at low concentrations (i.e., leading to exposures below the Acceptable Daily Intake (ADI) of 0 – 3 mg/kg bw) may pose a risk of adverse effects to the liver, due to an idiosyncratic response.

5. Therefore, this discussion paper provides an overview of HILI including information on what it is, current regulation of herbal dietary supplements in the UK, EU and globally, epidemiological evidence, aetiology, and current challenges to understanding with the aim of considering whether a COT statement on idiosyncratic HILI is required.

Background

6. The term ‘herbal dietary supplement’(HDS) is widely used in the literature as an umbrella term for a broad range of supplements that includes vitamins, minerals, traditional medicines, herbs, herbal preparations and some synthetic compounds. Regulatory authorities around the world frequently have their own definitions and while there is often overlap there is a lack of congruence (Thakkar *et al.*, 2020).

7. Under the Food Supplements (England) Regulations 2003, a “food supplement” is defined as any food whose purpose is to supplement the normal diet, and which is a concentrated source of a vitamin, mineral or other substance with a nutritional or physiological effect, alone or in combination, and is sold in dose form. The FSA guidance reflects this legislative definition and notes that food supplements may contain a wide range of ingredients, including vitamins, minerals, amino acids, essential fatty acids, fibre, plants

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and herbal extracts. Products placed on the market as food supplements are regulated as foods and must comply with general food law and applicable food supplements requirements; they are not medicinal products and should not be presented as preventing, treating or curing disease or as exerting a medicinal pharmacological, immunological or metabolic action. Botanical or plant-derived ingredients may therefore fall within the “other substances” limb of the food supplement definition where the product is marketed as a food, but products may fall within medicines legislation where their presentation, claims, composition or intended function brings them within the medicinal product regime (‘The Food Supplements (England) Regulations’, 2003).

8. This paper will address the entire evidence base, and it is worth noting that some of the herbs and botanicals discussed may fall outside of the FSA remit because they are not considered supplements, they are medicinal or they do not comply with supplements regulation.

9. Drug Induced Liver injury (DILI) and Herb induced liver injury (HILI) are not interchangeable terms, and DILI specifically refers to the liver injury seen following ingestion of medicinal products whereas HILI refers to liver injury observed following the ingestion of herbal and dietary supplements. However, in the absence of HILI specific monitoring programmes, HILI is often accounted for in studies monitoring DILI.

10. HILI can be classified as idiosyncratic or intrinsic. Intrinsic HILI is predictable and dose-dependent with high experimental reproducibility. Most cases of HILI are idiosyncratic, which conversely, is unpredictable with a low incidence in humans, is not clearly dose dependent and lacks experimental reproducibility. Idiosyncratic HILI is typically caused by herbs at therapeutic dosages through an idiosyncratic and thereby unpredictable reaction, which may be either metabolic or immunologic, as opposed to intrinsic HILI that develops from predictable reactions due to overdosed herbal products (Frenzel and Teschke, 2016).

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11. The incidence of HILI appears to be increasing globally, in the UK this has been attributed to an overall trend amongst UK consumers of aspiring to a healthier lifestyle, it was further suggested that the media has been integral in creating demand for fitness and healthier lifestyles, particularly social media, as consumers share their healthy lifestyles and aspire to the lifestyles they follow online (Food Standards Agency, 2018).

12. In the prospective study of drug induced liver injury from the NIH funded Drug Induced Liver Injury Network (DILIN), the proportion of cases during the 8 years of the study increased from 7 % in 2004/2005 to 19 % by 2010-2012 (Navarro *et al.*, 2017). In the Spanish DILI registry, the proportion of cases of liver injury that were attributed to HDS increased from 2 % in 2006 to 13 % in the period of 2010-2013 (Andrade *et al.*, 2005). While there are no population-based estimates for the frequency of HILI in the United Kingdom, there are estimates from a population-based study of DILI in Iceland which indicated that the overall incidence of DILI in 2011-2012 was 19 cases per 100,000 persons, as 16 % of those cases were attributed to HDS and it was therefore calculated that the incidence of HDS-related acute liver injury was 3 per 100,000 persons (Björnsson *et al.*, 2013).

13. Due to the variety of herbal supplements available for purchase both as individual ingredients and as mixtures, hepatotoxicity can present in a variety of different ways and affect all of the different cell types within the liver. The spectrum of injury can range from elevated enzyme levels which can be asymptomatic, to acute liver failure which is potentially fatal (Andrade *et al.*, 2019).

14. Frequently implicated herbal supplements include *Garcinia cambogia*, green tea, turmeric, ashwagandha and multi-ingredient supplements such as Herbalife and Hydroxycut, although this list is by no means exhaustive (Gurley, McGill and Koturbash, 2022). The reason for HDS consumption in Western countries is usually due to their purported benefits although they are also consumed as part of practices such as ayurveda and traditional Chinese

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medicine. In the 2018 report on Food Supplements Consumer Research, the top 5 reasons for taking supplements were cited as 'to maintain overall health', 'to improve overall health', 'to maintain my immune system', 'to give me energy' and 'to maintain my health as I get older' (n =990) (Food Standards Agency, 2018). It is particularly challenging to identify the hepatotoxic component of a HDS because even single herb HDS are not truly single ingredient as each plant extract is a diverse blend of individual phytochemicals, furthermore, many cases of HILI can be traced to formulations containing untested combinations of extracts and/ or phytochemicals. This complexity may be further increased by the variability in the plant part used, the extraction and preparation methods adopted, the phytochemical concentrations, and the possibility of adulteration, substitution or contamination of products. (Gurley, McGill and Koturbash, 2022).

15. The low incidence of HILI coupled with the limited knowledge of the biochemical pathways responsible for adverse effects makes it difficult to identify high-risk patients. Further study is required in order to understand the mechanisms behind HILI and any subsequent biomarkers which could be used as predictors of adverse outcomes and enable vulnerable populations to be described (Fontana *et al.*, 2009).

Current Regulations of Herbal Dietary Supplements: UK, EU and Globally

16. Herbal dietary supplements are used globally however, the types of supplements and the context in which they are used vary from country to country. There is similarly little consensus between countries on the terminology and definitions used to describe HDS and subsequently the regulatory framework. This lack of harmonisation may affect product classification, adverse event reporting, product quality requirements and how easily HILI cases can be compared between countries.

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Regulation in the USA

17. In the United States the Food and Drug Administration (FDA) is responsible for regulating dietary supplements under the Federal Food, Drug and Cosmetic Act (the FD&C Act) as amended by the Dietary Supplement Health and Education Act (DSHEA) of 1994. The FD&C Act defines a dietary supplement as “*a product, other than tobacco that are intended to supplement the diet and that contain one or more of the following dietary ingredients: a vitamin; a mineral; a herb or other botanical; an amino acid; a dietary substance, for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described previously.*”. Pre-marketing approval of dietary supplements is not required, however, it is the responsibility of the manufacturer to ensure that their product is safe; while there is no requirement to demonstrate efficacy of a particular product, supplements must not be marketed to diagnose, cure, mitigate, treat or prevent disease (‘Federal Food, Drug, and Cosmetic Act (FD&C Act)’, 2018; Thakkar *et al.*, 2020).

Regulation in Canada

18. Most dietary supplements are classified as natural health products (NHP) they are a subclass of medicine and are regulated by health Canada (HC). NHPs are regulated under the Natural Health Products Regulations (NHPR), enacted in 2004, and provide for site licensing requirements, good manufacturing practices, adverse reaction reporting, clinical trials, as well as labelling- including warnings and recall features. The manufacturer is required to provide evidence to demonstrate any health claim that is made on a product label (Thakkar *et al.*, 2020; ‘Guidance document: Supplemented Foods Regulations’, 2022).

Regulation in Australia

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19. In Australia dietary supplements are regulated under the Therapeutic Goods Act (TGA) 1989. The TGA regulates products both “classified as supplements” or “classified as medicines” and considers dietary supplements under this as “complementary medicine”. Some products fall within both aforementioned categories. The Australian government provides the Food-Medicine Interface Guidance Tool to characterise a product, for those products classified as supplements, some therapeutic claims can be made but the product must state on its label that the claims have not been evaluated under the TGA (‘Australian regulatory guidelines for complementary medicines’, 2018; Thakkar *et al.*, 2020).

Regulation in New Zealand

20. In New Zealand, dietary supplements are regulated under the Dietary Supplements Regulations 1985. While pre-market approval is not required, dietary supplements are intended to be taken orally at a specified dose stated on the product label and should not be intended for therapeutic purposes. The Supplemented Food Standard sets out requirements for products that are represented as foods but have been modified in some way or had substances added to them such as vitamins, minerals, herbals or other bioactive substances, so that they perform a physiological role and are defined by New Zealand Food Safety as “supplemented foods” (‘New Zealand Food (Supplemented Food) Standard 2016’, 2016; Thakkar *et al.*, 2020).

Regulation in the EU

21. In the EU, food supplements are regulated as food under Directive 2002/46/EC. They are intended to supplement the normal diet contributing to the maintenance of healthy tissues. A case-by-case approach is applied to assess the applicable legal framework so as to determine whether a product is a food supplement, a medicinal product, a traditional herbal medicinal product, or potentially a novel food, depending on its characteristics. A case-

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by-case approach is therefore advised. Food supplements do not require pre-market authorisation unless another regime applies, such as medicines legislation or novel food authorisation (EC, 2002).

22. Herbal Medicinal Products that are “Classified as Medicines” are regulated under EU medicinal law Directive 2004/24/EC. The safety, efficacy, and premarket authorisation of these products is handled by the European Medicines Agency (EMA) (EC, 2004; Thakkar *et al.*, 2020).

Regulation in the UK

23. Herbal products can be either sold as traditional herbal medicines (licensed by the Medicines and Healthcare Products Regulatory Agency (MHRA) or food supplements in the UK.

24. Herbal medicines require a traditional herbal registration (THR) from the MHRA. A THR is only granted if the medicine is used for minor health conditions where medical supervision is not required (such as a cold).

25. Food supplements are regulated in the UK under The Food Supplements (England) Regulations 2003, with equivalent regulations in Scotland, Wales and Northern Ireland and also need to comply with other relevant food law, including that they are deemed to be safe before they are placed onto the market. The Food Supplements Regulations specify compositional and labelling requirements for food supplements containing vitamins, minerals and other substances.

26. There are no specific compositional or purity criteria requirements for “other substances” such as botanicals and plants extracts set out in the legislation. However, manufacturers selling “other substances” in food supplements in Great Britain must ensure they comply with food supplements requirements and that they adhere to labelling requirements.

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27. Where risk assessment identifies potential safety concerns with a substance that is used in the manufacture of food, including food supplements, assimilated EC regulation 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods provides a potential mechanism to manage those risks, through Article 8 of Regulation (EC) No 1925/2006, including placing substances under scrutiny, restricting their use, or prohibiting their use where necessary to protect public health

28. Variability in botanical composition, ingredient concentration, product specifications and quality control is particularly relevant to HILI because it may complicate both safety assessment and attribution of liver injury to a specific product or ingredient.

World Health Organization Recommendations

29. The World health Organization (WHO) have acknowledged that the definitions and categorisations of herbal medicines vary greatly between countries and depending on the regulations applying to foods and medicines, a single plant may be categorised as a food, functional food, dietary supplement or herbal medicine depending on the country regulating it. As such the WHO has attempted global harmonisation of terminology and collated information on global regulations in order to develop international guidelines for herbal medicines in their 2005 report of National Policy on Traditional Medicine and Regulation of Herbal Medicines (World Health Organization, 2005). However, it is worth noting that as this report is now 21 years old and since its publication the regulatory landscape will have altered once again, not least, for example in GB as GB has since left the EU and is responsible for its own regulatory activity of supplements. In 2025 the WHO renewed their commitment to ensuring universal access to safe, effective, and people-centred traditional, complementary, and integrative medicine (TCIM) in their Global Traditional Medicine Strategy 2025–2034 (World Health Organization, 2025).

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Monitoring of HILI in the UK

30. Herbal medicines may be captured through MHRA pharmacovigilance routes, but many herbal dietary supplements regulated as foods may not be systematically monitored for adverse reactions, which is particularly relevant to the detection of HILI cases. The MHRA has set up the Herbal Medicines Advisory Committee (HMAC) to give advice on safety, quality and efficacy in relation to human use of:

- a) Herbal medicinal products eligible for registration under the simplified traditional use registration procedure set out in Part 7 of the Human Medicines Regulations 2012.
- b) Unlicensed herbal medicinal products (unless it is subject to an application for a marketing authorisation, product licence or a homeopathic certificate of registration) (UK Government, 2012).

31. The HMAC produces an annual report in which the committee details its review of reports of adverse reactions. However, it is stated that reports pertaining to products which are considered to be foods, devices, cosmetics, homeopathic products licenced medicines not considered to be herbal medicines and unlicensed products which contain non herbal ingredients are excluded. Therefore, it can be concluded that the data on adverse reactions to dietary supplements and products available without market authorisation or THR is not currently being formally captured at a government level (Herbal Medicines Advisory Committee, 2021).

32. Yellow Cards are occasionally received, reviewed and logged by the FSA. The reports include self-reports as well as reports from medical practitioners. Typically the FSA will review the circumstances of the report and try to determine whether the effects described could be attributed to the active in question, however, in many cases the information presented is incomplete (e.g the actual dose that the person was taking is not confirmed) and/or there

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are indications of confounding factors (such as people with underlying conditions who are on a number of other medicines/ people who report multiple supplement intake) therefore it is difficult at times to verify what is causing the effects reported.

Research Networks and Registries

33. Despite an increase in the reported numbers of consumers of herbal dietary supplements and anecdotal evidence to suggest an increase in herbal dietary supplement induced liver injury, there are few data that describe or quantifies the issue either in the UK or globally.

34. In recent years there have been a number of attempts to build prospective studies and registers of DILI that capture information such as prevalence, patient demographics, clinical presentation of injury, patient outcomes and suspected causative agents (Andrade *et al.*, 2005; Fontana *et al.*, 2009; Björnsson *et al.*, 2013; Devarbhavi *et al.*, 2021; Bessone *et al.*, 2025). However, while these databases do collect some information relating to cases of HILI there are no registers or studies specifically designed to capture this data. This poses a challenge as the level of detail required to understand the characteristics of HILI is lacking, for example, one of the key differences between DILI and HILI is that medical drugs are often well described pharmacologically and have a single active ingredient whereas dietary supplements, even if only extracted from a single plant, are complex mixtures of chemicals, making it even more challenging to attribute adverse liver effects to a single substance.

Causality Assessment Using Roussel Uclaf Causality Assessment Method (RUCAM)

35. The RUCAM scale, also known as the Council of International Organisations of Medical Sciences scale (CIOMS) is a standardised and

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weighted scoring system of predicting the likelihood of liver damage caused by a suspected drug or herbal supplement. The assessment of causality of HILI is the same as that is used for DILI (Nunes, Monteiro and Dos Santos, 2022). The scale assigns points in 7 different categories: (1) time to onset (+1 or +2); (2) course (-2, 0, +1, +2 or +3); (3) risk factors (2 scores: 0 or +1 each); (4) concomitant drugs (0, -1, -2 or -3); (5) nondrug causes of liver injury (-3, -2, 0, +1, or +2); (6) previous information on the hepatotoxicity of the drug (0, +1, or +2); and (7) response to rechallenge (-2, 0, +1, or +3). The individual points range from -3 to +3 and the total possible score ranges from -9 to +14. The final score categorises the likelihood of causality as follows: 0 or less indicate that the suspected agent is “excluded” as a cause; 1 to 2 that it is “unlikely”; 3 to 5 “possible”; 6 to 8 “probable”; and greater than 8, “highly probable” (National Institute of Diabetes and Digestive and Kidney Diseases, 2012).

36. Other methods of causality assessment are available, however, RUCAM is the one used in all of the studies described below.

HILI Case Classification

37. Hepatotoxicity case classification is essential to facilitate RUCAM assessment. 3 types of liver injury are considered: hepatocellular, cholestatic or mixed. Hepatocellular injury generally reflects predominant hepatocyte damage; cholestatic injury reflects cholangiocyte damage, impaired bile flow, or bile duct involvement, and mixed injury shows features of both. Classification is based upon the R ratio, calculated as ALT divided by its upper limit of normal (ULN), divided by ALP divided by its ULN “ $R = (ALT/ULN) \div (ALP/ULN)$ ”. The activity of both enzymes is measured at a time when liver injury is expected and is expressed as multiples of the upper limit of normal (ULN). Liver injury is hepatocellular if $R \geq 5$; liver injury is cholestatic if $R \leq 2$; and liver injury is mixed if $2 < R < 5$. As the liver enzyme elevations can evolve over time, the pattern of HILI is determined by the first set of

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laboratory tests available in relation to the clinical event (Frenzel and Teschke, 2016).

The Drug Induced Liver Injury Network (DILIN)

38. The DILIN was set up by the National Institutes of Health in order to conduct research to improve our understanding of the causes and outcomes of DILI in the United States. The purpose of DILIN is to collect and analyse cases of severe liver injury which have been suspected to have been caused by prescription drugs, over-the-counter drugs or alternative medicines such as herbal products and supplements.

39. The DILIN is currently running 2 registry studies: a retrospective study which aims to collate a nationwide registry of individuals with experience of liver injury caused by prescription drugs or herbal and dietary supplements and a prospective study which aims to establish a nationwide registry of people who have experienced liver injury within the past 6 months after taking prescription drugs or herbal and dietary supplements (Barnhar, 2025). The methodology of the prospective study and results to date are described below.

DILIN Prospective Study (Fontana et al., 2009)

40. The primary aim of the prospective study was to identify cases of confirmed DILI in order to collect epidemiological data and biological samples for future mechanistic studies.

Methods

41. Eligible patients were referred by a medical provider or self-referred. The DILI must have been attributable to one or more prescription drugs, over-the-counter medicines or herbal products. Subjects were placed in one of two categories- either 'standard DILI' with no known liver disease prior to starting

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the suspected medication or 'liver DILI' if the patient had known liver disease (such as chronic hepatitis B, chronic hepatitis C or fatty liver disease) before the onset of DILI. Patients underwent an initial baseline visit at which point a complete medical history, physical examination and medication history was taken. The type of liver injury was then classified as hepatocellular, cholestatic or mixed by an R ratio as described in paragraph 36. Further immunological and viral tests were performed to look for liver disease markers, and a cross-sectional imaging study was undertaken. For those with known liver disease, detailed information of prior disease status, viral load and treatments was collected. All patients provided urine and whole blood samples.

42. Exclusion criteria included known or suspected paracetamol overdose, history of bone marrow or liver transplant prior to DILI onset or pre-existing immune mediated liver disease.

43. Patients were reviewed at 6-month intervals at which point the presence of chronic DILI could be determined. Chronic DILI was defined as one of the following: (i) for subjects with normal or unknown baseline liver biochemistries, a serum aspartate aminotransferase (AST), ALT, international normalised ratio (INR) or total bilirubin that was persistently elevated on two separate occasions; (ii) for liver DILI subjects, a serum AST, ALT, ALP, INR or total bilirubin level that exceeded 1.25 times the baseline value on two separate occasions; (iii) any evidence of portal hypertension such as ascites on imaging, varices on upper endoscopy or clinical evidence of hepatic encephalopathy; (iv) any histological evidence of persistent liver injury at least 6 months after DILI onset; or (v) any radiological evidence of chronic liver disease such as ascites, hepatomegaly, nodular liver or intra-abdominal varices. Subjects with preexisting chronic Hepatitis B or Hepatitis C infection, liver transplant recipients since the baseline visit and patients with cirrhosis or clinical evidence of portal hypertension before starting the suspect medication were excluded from the chronic DILI protocol.

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44. Subjects determined to have chronic DILI were reviewed again at 12- and 24-month intervals.

45. Because DILI is a clinical diagnosis of exclusion, a formal and standardised approach to causality assessment was established. Causality was assessed in 2 ways, firstly with RUCAM for cases of idiosyncratic liver injury and secondly by 'expert consensus'. For expert consensus, a DILIN causality committee was established.

46. To ensure causality assessment by expert opinion was objective, definitions were developed for each causality level which included three elements: (i) a percentage likelihood that the drug caused the liver injury (>95%, 75–95%, 50–74%, 25–49% and <25%); (ii) standard legal terms to help define the weight of the evidence for causality (i.e. 'beyond a reasonable doubt', 'clear and convincing evidence' and 'the preponderance of evidence'); and (iii) a set of criteria describing the clinical features that match the known timing and pattern of injury. When the DILIN causality scores of the assigned reviewers did not agree, the case was discussed by the entire Committee via teleconference wherein a final consensus score was assigned. Finally, the severity of the DILI episode was categorised on a scale of 1–5.

47. When a minimum of 15 standard DILI cases due to a single medication were enrolled, three age-matched control subjects per case were identified to test for differences in clinical risk factors. A minimum of 15 cases was required to have adequate power (i.e. 80%) to detect a difference in a risk factor with a prevalence of 20% in the control subjects that is strongly associated with DILI and had an odds ratio of 12 or greater.

Results

48. In an analysis of features and outcomes of 899 patients with DILI, it was found that liver injury could ultimately be attributed to one or more of 190 different agents; 754 cases were due to prescription drugs, and 145 cases were found to be due to HDS. HDS were the second most commonly

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implicated group, but most individual HDS agents were not implicated more than once and thus no single HDS was in the top 25 most implicated (Chalasani *et al.*, 2015).

49. The proportion of DILI cases caused by HDS (excluding AAS) was shown to have increased during the 8 years of the study from 5% in 2004–2005 to 13% by 2010–2012 peaking at 14 % in the 2013-2014 period.

50. In a 2017 follow up report specifically looking at herbal and dietary supplements the DILIN authors analysed the specific agents attributed to cases of liver injury. It was found that 35 % of HDS- related liver injury was linked to the consumption of body building agents with patients presenting with clinical signs associated with anabolic steroids. The authors commented that as anabolic steroids are largely synthetic derivatives of testosterone and are added illegally to products and without prescription, they are perhaps better considered ‘agents of abuse’ rather than HDS. The remaining 65 % liver injury cases could be attributed to 116 different products.

51. The majority of these products contained more than one ingredient and were complex mixtures sold under commercial brand names such as ‘Slimquick’, ‘Herbalife’ and ‘Hydroxycut’. These products typically contained up to 20 different ingredients and label information regarding concentration was rare, therefore, attributing liver injury to a single agent in these cases was extremely challenging. However, it was found that in 24 instances (including 15 attributed to multi-ingredient supplements) green tea was listed as a component and considered to be the causative agent (Navarro *et al.*, 2017). It was further noted that individuals frequently reported consuming more than one product at a time and sometimes concomitantly with conventional medications, therefore pinpointing specific causative agents was not always possible.

52. Demographic data of patients with HDS attributed liver injury showed that individuals had an average age of 47 years and were more likely to be female (65 % vs 35 % male).

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53. When assessing liver injury outcomes, the authors found that individuals with non-bodybuilding HDS attributed liver injury had a statistically significant higher proportion of cases rated severe based upon their DILIN score than individuals with liver injury due to conventional medication. ($p=0.02$). Furthermore, liver transplantation was also required more frequently among the non-bodybuilding HDS liver injury cases (13 % vs 3 % respectively, $p<0.001$) and this difference remained statistically significant even after adjusting the data for clinical and demographic variables. In total 13 patients required a liver transplant, the mean age was 56 years (range 27- 73 years), all were female and 69 % were white. 3 patients ultimately died and 2 of the 3 deaths were attributed to liver injury (the remaining death was a due to a complication of an endoscopic procedure). In terms of the biochemical characteristics, it was found that patients with injury from non-bodybuilding HDS had higher mean ALT and AST values (1019 U/L and 815 U/L respectively) and intermediate mean ALP and bilirubin levels (212 U/L and 7.5 mg/dL respectively) compared to patients with conventional medication induced injury where intermediate elevation of ALT and AST was observed (505 U/L and 319 U/L respectively) and high Alk P (value not reported) (Navarro *et al.*, 2014).

54. The study authors concluded that injury was most commonly observed in women which broadly reflects the demographic of HDS consumers. The typical pattern of injury was hepatocellular, similar to acute hepatitis, and predisposed more serious outcomes than liver injury attributed to conventional medicine (Chalasani *et al.*, 2015). It was stated that while the results demonstrate the capacity of HDS products to cause injury, identifying the ingredient responsible was often not possible. It was suggested that the only effective approach to identifying specific agents would be complete separation of products into their constituent ingredients followed by *in-vitro* and *in-vivo* evaluation, this approach, however, would be costly and time-consuming. The authors considered that a more pragmatic suggestion may be to improve the regulation regarding labelling of products including ingredients and

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concentrations, so that frequently implicated ingredients could be identified and their toxicology studied (Navarro *et al.*, 2014). Non-bodybuilding HDS-related liver injury is often hepatocellular, commonly linked to multi-ingredient products, difficult to attribute to one ingredient, and may sometimes be more severe than conventional medicine-related DILI.

The Prospective European Drug Induced Liver Injury Registry (pro-Euro-DILI) (Björnsson *et al.*, 2023)

55. The Pro-Euro-DILI was a European-wide prospective registry of patients with DILI established in 2016. It was established to determine the most common causes of DILI, clinical features and prognosis of individuals with liver injury in the United Kingdom, Spain, Germany, Switzerland, Portugal and Iceland. No previous multi-national study has been undertaken in Europe.

56. The study period was 2016- 2021, 246 individuals were deemed to be DILI cases and a further 100 individuals were included as non-DILI acute liver injury controls. The remaining 100 individuals were excluded due to an inconclusive diagnosis, not fulfilling the DILI criteria at the time of first extraction or 'other reasons'.

57. Patients presenting with liver injury, which was suspected to be caused by prescription drugs, over-the-counter medications or HDS were identified for recruitment into the study. Eligible participants were male or female aged 18 years or over and who presented with the acute manifestations of liver injury. The inclusion criteria were described as follows: (1) to have exposure to drugs including any prescription drug, over-the-counter drug, recreational drug, herbal remedies or dietary supplements prior to the onset of liver injury; (2) to meet one of the following analytical thresholds at enrolment (day 0) and at the first sample collection visit (which in most cases was at the enrolment day): ALT ≥ 5 times the ULN, ALP ≥ 2 times ULN, or ALT ≥ 3 times ULN plus bilirubin exceeding 2x ULN; (3) absence of other known causes of liver injury after detailed investigations, that can explain the acute liver injury. Patients with

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acute exacerbation/ decompensation of known chronic liver disease that could explain the acute event were excluded. Patients found to have a virus known to cause hepatitis (for example, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus) were classified as non-DILI acute liver controls. DILI severity was graded as mild, moderate, severe or fatal/ liver transplantation. Cases were routinely followed up until resolution of the acute event, transplantation or death. The causal relationship between the event and the suspected agent was assessed using the RUCAM scale (as described in paragraph 34) and the ultimate decision on whether the case was considered a DILI case was by expert judgement.

58. As with DILIN the primary focus of the registry is conventional medicine, however, HDS cases were monitored but considered as a single group. The report is lacking in the granular detail of individual implicated ingredients. Furthermore, supplementary information to the report showed that, unlike the DILIN study, the implicated HDS agents did not distinguish between steroids and other HDS. There were 18 causative agents in total, 5 of which were anabolic androgenic steroids (AAS). Excluding AAS, only Iberogast (a mixture of herbs intended to relieve the symptoms of irritable bowel syndrome) was identified more than once (n=2). The remaining products were predominantly for the purpose of weight loss. Green tea extract was the only single herb agent listed.

59. 7.3 % of cases in the registry were attributed to HDS (either alone or in combination with conventional medicines). This proportion is lower than in the DILIN study (16 %). Additionally, HDS was the second most common group after antibacterials, whereas in the Pro-Euro-DILI study it was the fifth most common group (including AAS). The hepatocellular pattern of liver injury predominated and was observed in 50 % to 80 % of cases depending on the subgroup of agent implicated. Exact figures for hepatocellular liver injury observed from HDS is not available.

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60. The Pro-Euro-DILI study found no difference in age, sex and pattern of liver injury between DILI cases and non-DILI cases. Overall, the Pro-Euro-DILI registry provides useful European context, but the limited HILI-specific detail and lack of granular product-level information make it difficult to identify the contribution of specific herbal products or ingredients.

Incidence, Presentation, and Outcomes in Patients with Drug-Induced Liver Injury in the General Population of Iceland (Björnsson et al., 2013)

61. Little is known about the incidence rate of DILI or HILI within the general population in the UK or Europe, one of the only prospective studies found to address incidence as well as liver injury presentation and patient outcomes was a prospective study in Iceland.

62. All physicians in Iceland received a letter concerning the initiation of the prospective study and its purpose; they were encouraged to report all suspected patients older than 15 with liver injury suspected to be caused by drugs or HDS. Data were collected from 96 individuals diagnosed with DILI in Iceland from 2010 to 2011.

63. Liver injury classification was defined using an R ratio as described in paragraph 36. Causality was assessed using RUCAM (as described in paragraph 34).

64. The incidence of DILI was calculated assuming 100% ascertainment of cases and a population of 251,860 at the start of 2011 (based on the official figures of the population of Iceland of individuals 15 years and older). The crude annual incidence during the study period was therefore determined to be 19.1 cases per 100,000 inhabitants.

65. HDS were implicated in 16 % (n=15) of liver injury cases. Therefore, this suggested an incidence rate of HDS-related acute liver injury of 3 cases per 100,000 inhabitants. Of the 15 individuals with HILI, 33 % (n=5) of the cases were associated with Herbalife products. Herbalife products were the only

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supplements to be implicated more than once. Green tea extract was found to be the active ingredient in 27 % (n=4) of the supplements including 2 of the Herbalife products. Although the number of HDS-related cases was small, the estimated incidence and the relative contribution of individual products should be interpreted with caution.

Other Registries

Spanish DILI Registry (*Andrade et al., 2005*)

66. A Spanish Registry of DILI was set up in 1994 and ran until 2016. A total of 856 cases were reported to the registry, and this included 32 cases that were attributed to HDS (4 %). The method of determining classification of liver injury was by R ratio as previously described (paragraph 36). Severity was classified as mild, severe or fatal. AAS were considered as a separate category to HDS.

67. HDS represented the sixth highest category in terms of frequency in 2016. It was found that the proportion of all DILI caused by HDS increased steadily over the study period, ranging from 2 % to 6 %. Furthermore, it was found that the majority of liver injury cases were attributed to multi-ingredient products (63 %) and 37 % of cases due to single-ingredient products. The most frequently occurring single herb ingredient was green tea (*Camellia sinensis*) and was implicated in 25 % of HILI cases. Herbalife products were the most frequently implicated multi-ingredient product and were implicated in 19 % of HILI cases. The pattern of liver injury observed was hepatocellular in 94 % of HILI cases. 63 % of HILI patients were women. The study authors stated that these findings suggest that HILI is often hepatocellular and frequently associated with multi-ingredient products, with green tea and Herbalife products repeatedly identified (*Andrade et al., 2005*).

Latin DILI (*Bessone et al., 2025*)

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68. The LATINDILI Network Is comprised of Argentina, Uruguay, Chile, Mexico, Paraguay, Brazil, Ecuador, Peru, Venezuela and Colombia. Between 2011 and 2019, 367 cases of DILI were reported to the LATINDILI Network.

69. The pattern of liver injury was determined using a similar method to that previously described (paragraph 36), briefly, ALT and ALP activity was expressed as a multiple of the upper limit of normal to calculate the ratio of ALT/ALP from the first available blood test after DILI recognition.

70. HDS hepatotoxicity cases were classified as mild, moderate, severe, or fatal/liver transplantation on the basis of the DILI severity classification and causality was assessed using the RUCAM score.

71. 8 % of these cases (n=29) were attributed to HDS and represented the third largest cause of hepatotoxicity in this registry. Natural products were classified as single or multi-ingredient HDS. Bodybuilding dietary supplements containing AAS were evaluated separately.

72. The most frequently attributed causative agents in HDS hepatotoxicity were *Camellia sinensis*, followed by Herbalife products. Garcinia cambogia represented the third most frequent cause, interestingly, however, all cases attributed to *G cambogia* were reported from Argentina, which the authors suggested could be due to a greater use of the plant in this geographical area (Bessone *et al.*, 2022).

73. Hepatocellular damage was more frequently reported than cholestatic in all groups but was more frequently found in HDS-related liver injury compared to liver injury from conventional medicines (83% vs 62%). The HDS hepatotoxicity cases showed greater severity than conventional medicines induced liver injury, with an elevated number of severe and fatal/liver transplantation cases (21% vs 12%).

[Indian DILI](#) (Devarbhavi *et al.*, 2021)

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74. A prospective study of DILI in India was conducted from 2013 to 2018; 1288 patients were recruited of which it was found that 13.9 % experienced liver injury associated with complementary and alternative medicines (CAM). The diagnosis of DILI and its severity were made based on criteria adopted by international DILI Expert Working Group (Aithal *et al.*, 2011). Causality assessment was carried out using the RUCAM model.

75. Cholestatic liver injury was more frequently reported than hepatocellular or mixed (42.8 % vs 29.7 % vs. 27.4 %). Liver injury was more severe in HILI associated with CAM than with conventional medicines and was more likely to be seen in men than women (51 % vs 49 %). The case record form did not have the provision to capture individual drug or component details, so it was not possible to determine individual CAM products responsible for HILI.

76. These findings contrast with the previously mentioned Western registry data, where HILI was more often hepatocellular and more frequently reported in women, suggesting that geographical variations in CAM use, product details and reporting practices may influence the observed HILI profile.

Androgenic Anabolic Steroids

77. While sometimes classed as a dietary supplement, AAS are often illicit compounds used as agents of abuse rather than dietary supplements. Additionally, they have a separate and distinct profile of liver injury compared to HDS. Therefore, while mentioned in the registries above, where the HDS data has separated them out this has been indicated and where they haven't, it is worth reiterating that AAS may mask the profile and characteristics of non-AAS HILI. AAS will also not be discussed further in this paper for these reasons.

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Summary

78. Many similarities were observed between the studies that can inform the profile of HILI and draw out differences between HILI and DILI. HILI predominantly affects women as was seen in the Americas and Europe. This was not mirrored in India where men were predominantly affected. This may be due to the different reasons for consumption of HDS with weight loss being frequently cited across Western regions and more widespread practise of alternative medicine such as ayurveda in India. Interestingly, a further difference in the Indian DILI study cholestatic pattern of liver injury was more frequently observed than hepatocellular which is not mirrored in the DILIN, LATINDILI or Pro-Euro-DILI network studies. In fact, hepatocellular injury was observed in up to 94 % of HILI cases in the Spanish Registry. A summary of the different registries is presented in Table 1.

79. The most frequently implicated agents for HILI were broadly similar across studies where product-level information was recorded. Multi-ingredient supplements were more frequently mentioned than single herb products and Herbalife products were among the most frequently implicated multi-ingredient products in studies where this level of information was indicated. Where the ingredients of Herbalife products were assessed, green tea (*Camellia sinensis*) was identified, supporting the observation that green tea was one of the most frequently implicated single products across the studies.

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Table 1. Summary of research networks and registries

Registry	DILI Patients (n)	HDS cases (%)	Most common pattern of injury	Implicated products	Causality assessment	Demographic	AAS separated
DILIN	899	16	Hepatocellular	Multi-ingredient products (e.g. Herbalife, Hydroxycut), Green tea	RUCAM	65 % F 35 % M	Y
Pro-Euro-DILI	246	7	Hepatocellular	Iberogast (multi-ingredient), Green tea	RUCAM	57 % F 43 % M	N
Icelandic	96	16	Hepatocellular	Herbalife, Green tea	RUCAM	56 % F 44 % M	Not stated
Spanish	856	4	Hepatocellular	Multi-ingredient products (Herbalife), green tea	RUCAM	63 % F 37 % M	Y
LATIN DILI	367	8	Hepatocellular	Green tea, Herbalife, <i>G cambogia</i>	RUCAM	66 % F 34 % M	Y
Indian	1288	14	Cholestatic	Not captured	RUCAM	49 % F 51 % M	Not captured

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Weight Loss Supplements

80. Weight loss supplements are indicated by the authors of all the registers and studies listed in Table 1 as being the most frequent HDS associated with cases of HILI. Additional case studies found in the literature linked with the only products (Herbalife and Hydroxycut) mentioned in all of the registers and using larger numbers of patients, are listed below.

81. Herbalife supplements are marketed for multiple purposes including weight management, energy and fitness. Hepatotoxicity, suspected to be associated with these supplements, was initially suspected in two separate cases from Switzerland and Israel. An additional case study was later reported in Spain.

Switzerland (*Schoepfer et al., 2007*)

82. Ten cases were identified in Switzerland between 1998 and 2004 following a systematic survey in public Swiss hospitals and subsequent causality assessment. The predominant clinical symptoms of the patients were fatigue, loss of appetite and jaundice. No patient exhibited signs of either allergy or extra-hepatic disease. None of the patients were taking other medication with known hepatotoxic potential. All patients had taken Herbalife products for the purpose of weight reduction and had reportedly taken the manufacturer's recommended dose. Almost all patients were taking several Herbalife products at the same time. Hepatic necrosis, marked lymphocytic and eosinophilic infiltration, and mild to moderate cholestasis were observed in five patients and one patient ultimately required a liver transplant. The liver enzyme pattern was hepatocellular in nine patients and mixed hepatocellular/cholestatic in one patient. Ultimately, the prognosis was favourable following cessation of intake.

83. One of the ten cases did not present in the same way as the others, showing sinusoidal obstruction syndrome which is a well-known side effect of pyrrolizidine alkaloids. Pyrrolizidine alkaloids can be found in products

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containing *Heliotropium*, *Senecio*, *Symphytum* and *Crotalaria* species. It is worth noting that the effects of pyrrolizidine alkaloids are well established and while they cause liver injury it is not typically idiosyncratic.

84. The study authors indicated that determination of the toxic agent was challenging because the retrospective nature of the study meant that none of the consumed products were available for analysis. Similarly, the company was not forthcoming with revealing the composition of their products and furthermore, it seems that the company prepares the products differently in different countries. Despite this, the study authors have hypothesised that likely candidates could include *ephedra sinica* (also known as ma huang) which has been used for centuries and is reported to be present in many products including Herbalife.

Israel (*Elinav et al., 2007*)

85. In a case series from Israel, 12 cases of unexplained acute liver injury associated with Herbalife consumption were identified. Acute liver injury was diagnosed on average after 11.9 ± 11.1 months of Herbalife consumption. Patients were screened for co-medication and were evaluated as negative for other causes of hepatic injury. Patients presented with symptoms including fatigue, jaundice, and weight loss. Liver biopsies from four cases showed that liver injury was predominantly hepatocellular, with lobular disarray, ballooning degeneration of hepatocytes, focal mild steatosis, spotty necrosis and extensive inflammation with Kupffer cell hypertrophy and hyperplasia.

86. Hepatitis resolved completely in 11 of the 12 patients following cessation of consumption. One patient developed fulminant hepatic failure and died following complications of liver transplantation; however, this patient also had underlying hepatitis B infection.

87. The causal association between consumption of Herbalife products and acute liver injury in this case series of 12 patients is suggested by the

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exposure to Herbalife products, the negative evaluation of other causes and the fact that cessation was associated with normalisation of liver enzymes.

88. The study authors indicated that the patients were identified in a short period of time (months rather than years) and therefore it could not be ruled out that hepatotoxicity was caused by inadvertent contamination of one specific batch. It was added that while there were similarities between the Swiss and the Israeli cases, the histopathological manifestations were not identical. However, it is known that products are produced slightly differently in different countries and different dosages or combinations could have been consumed.

89. The mechanism of liver injury was not established, but the presence of plasma-cell-rich infiltrates in some biopsies and transient positivity for anti-nuclear (ANA) and or anti-smooth muscle (ASMA) in some patients may suggest a possible immune-mediated mechanism.

Spain (*Manso et al., 2011*)

90. A case series of 20 patients in Spain further suggested the potential for Herbalife products to be associated with liver injury. Where specific product consumption information was available it was noted that 11 of the patients were taking between two and nine Herbalife products and one patient had taken only one Herbalife product. Patients were screened for co-medication and causality assessment yielded a score of 'possible' in 3 patients, 'conditional' in 3 patients and 'unlikely' in 3 patients. This highlights the difficulty of attributing liver injury to a single product or ingredient. The prognosis was favourable in 17 patients, unknown in 2 and the remaining patient developed cirrhosis.

91. The authors indicated that the analysis of the components of Herbalife products (where available) revealed the presence of green tea and aloe vera, both of which have previously been associated with potential liver injury.

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92. Hydroxycut is a range of supplement products which are marketed for weight loss, including actions related to boosting metabolism and fat burning. In 2004, dietary supplements containing ephedrine alkaloids were banned by the FDA and listed as “dietary supplements that present a significant or unreasonable risk” under the Federal Food, Drug, and Cosmetic Act (Food and Drug Administration, HHS, 2004). Following this, Hydroxycut products were reformulated. Separately, in 2009, the FDA warned consumers to stop using certain Hydroxycut products following 23 reports of serious liver-related adverse events, including jaundice, elevated liver enzymes, liver damage requiring transplantation and one death. Subsequent cases of liver injury were still reported despite reformulation (FDA, 2009).

93. In the UK, the sale and supply of botanicals containing Ephedra are controlled under the Medicines (Retail Sale or Supply of Herbal Plants Remedies) Order, 1977 and they are not considered to be food products. Ephedrine products are classified as pharmacy medicines and are required to be sold under the supervision of a pharmacist, this is due to concerns that ephedrine and pseudoephedrine can be extracted from over-the-counter medicines for use in the illegal manufacture of the Class A drug, methylamphetamine (Royal Pharmaceutical Society, 2014).

94. The example of ephedrine illustrates how different botanical compounds are defined differently and regulated differently across the world.

COT Advice

Kava Kava

(COT, 2002, 2005)

95. Kava-kava, also known as kava, is an herbal ingredient derived from the plant, *Piper methysticum*, a member of the pepper family, which is native to

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many Pacific islands. The leaves and root of the plant are used in herbal preparations as tablets, capsules, tinctures and drops. These products are largely considered medicinal, however some products are sold as foods such as teas.

96. In July 2002, the Food Standards Agency requested urgent advice on the herbal preparation kava kava following a series of reports of serious hepatotoxicity in kava kava users including deaths and several cases requiring liver transplants. The reports occurred mainly in Germany but also in Switzerland, the US and UK. In December 2001, the Medicines Control Agency (MCA) and the Food Standards Agency advised against consumption of kava kava and urged the voluntary withdrawal of medicinal and food products from the market, pending a definitive safety assessment.

97. The Committee on Safety of Medicines (CSM) assessed the 68 detailed case reports of kava kava associated liver toxicity. The CSM concluded that kava kava could cause serious liver toxicity, although the precise mechanism by which such toxicity occurs was not understood and there were no clear predictors of this toxicity. The CSM considered that the risks of kava kava products outweighed the benefits and therefore, they advised that the licensing authorisation for kava kava products be withdrawn and the use of kava kava in unlicensed medicines be prohibited. This led to the statutory [Medicines for Human Use \(Kava-kava\) \(Prohibition\) Order 2002](#), which officially came into force on January 13, 2003.

98. The risk assessment, as agreed by the COT Chairman concluded:

- It is not possible to conclude that the hepatotoxicity is dose dependent nor can we exclude an immune mediated toxicity for which dose would not be relevant.
- There is evidence to suggest that hepatotoxicity can occur in users of the traditional kava kava preparations as well as in users of kava kava supplements.

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- There are no data to compare the effects of extraction in hot liquid on the composition of the kava kava. Thus, we are not able to determine if kava kava containing tea-bags result in exposures comparable to traditional or solvent extracted kava kava preparations.
- In the absence of a clear understanding of the hepatotoxicity, including its mechanism and relevant patient and exposure characteristics, it is not possible to exclude hepatotoxicity arising from food uses of kava kava.
- The information provided since December 2001 provides further evidence that consumption of kava kava may cause hepatotoxicity

99. In February 2005, the FSA consulted with stakeholders to assess whether any further information had emerged on kava kava. The COT was invited to consider whether the new information altered its previous conclusions.

100. The COT considered that the new data were not sufficient to demonstrate the safety of food products containing kava-kava particularly considering the severe nature of the hepatotoxicity linked with kava kava consumption. It was also agreed that, because the hepatotoxicity appeared to be an idiosyncratic reaction, it would be extremely difficult to predict or to propose a suitable animal model.

101. Overall, COT Members concluded that the new data did not warrant a change in their previous advice. More information would be needed on the mechanism of hepatotoxicity before it would be possible to propose further research to establish a safe usage of kava-kava in foods.

Green Tea Catechins

(COT, 2024a)

102. In 2017, following a series of reports of adverse effects associated with the consumption of green tea supplements, the European Commission (EC)

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requested the European Food Safety Authority (EFSA) to assess the available information on the safety of green tea catechins (GTCs), the key constituent of these supplements (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) *et al.*, 2018).

103. EFSA concluded that GTCs from green tea infusions prepared in a traditional way are generally considered to be safe; however, rare cases of liver damage/injury (i.e. hepatotoxicity) have been reported in those who had used GTC supplements containing EGCG. EFSA concluded that it was not possible to identify an EGCG dose from GTCs that could be considered safe. In the clinical trials that were reviewed, there was no evidence of hepatotoxicity below 800 mg of EGCG/ per day for up to 12 months. However, hepatotoxicity was reported for one specific product containing 375 mg EGCG. Doses over 800 mg EGCG/day, were shown to increase the levels of liver enzymes that indicate liver injury, compared to control subjects.

104. Following the adoption of the EFSA opinion, the EU Commission restricted EGCG to a maximum level of 800 mg/ day.

105. In 2024, the COT reviewed the literature on the potential of concentrated green tea extract (GTE) supplements to cause liver toxicity which had been published since the 2018 EFSA opinion and assessed whether the data would affect the conclusions drawn by EFSA.

106. The COT noted that these cases of liver damage were due to reactions that are unusual and/or unique to an individual and are related to an individual's genetic makeup. These are called "idiosyncratic" reactions, which are rare, unpredictable, and not reproducible in animals. Development of these reactions can vary markedly among individuals with dose and duration of consumption of supplements containing GTCs. The individual may not know they are susceptible before taking a supplement. This possibility of an unexpected idiosyncratic response cannot be ruled out when using such supplements.

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107. In the studies reviewed, there was large variability in dose, composition, duration of exposure to GTE and incidence of liver toxicity as a result of consumption of green tea products. The EFSA Panel had concluded that many of the cases of liver injury were as a result of idiosyncratic reactions. Following their review of the literature, the COT agreed.

108. Overall, the COT concluded that there were no new data to suggest that EFSA's conclusion, that 800 mg/day EGCG was probably safe, is inappropriate. Although no new studies identified any effects of EGCG in humans at doses below 800 mg/day, the possibility cannot be excluded that a few individuals could still experience adverse effects below this dose due to an idiosyncratic reaction (COT, 2024a).

Turmeric

(COT, 2024b)

109. Turmeric is the common name for the rhizome (underground stem) of *Curcuma longa* L (Linnaeus), a perennial herb cultivated in tropical and subtropical regions of the world. India is the largest producer of turmeric, supplying over 90 % of the world's demand (Olojede *et al.*, 2009).

110. Due to its claimed health benefits, the consumption of curcumin/turmeric supplements is increasingly popular. However, in recent years there have been a number of reports of hepatotoxicity linked to the consumption of these supplements.

111. In 2019, following incidents of adverse events related to consumption of raw and powdered turmeric and its supplements and uncertainties surrounding the composition and possible contamination of these commodities, the FSA asked the COT to comment on the risk to human

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health from turmeric, in particular it's chemical curcuminoid components, consumed in various forms, which include supplements.

112. Using the 2010 and the 2014 EFSA dietary exposures, consumption of turmeric/curcumin as part of the diet from its use as a food additive or as a spice generally leads to exposures that are within the dietary ADI of 0 – 3 mg/kg bw. However, when consumed in high quantities such as for its purported health benefits, or via the intake of supplements, occasional exceedances of the ADI can occur.

113. The Committee reviewed all available data regarding recent reports of hepatotoxicity and concluded that, despite the limited data, there was reasonable evidence for a link to turmeric consumption because the effects occurred upon challenge and were reversed after withdrawal. The signs were consistent with an idiosyncratic reaction. The presence of contaminants (e.g. heavy metals) as the reason for the recent incidents of hepatotoxicity was considered unlikely.

114. The Committee indicated that, in rare individuals, consumption of turmeric at the levels found in supplements, even at low concentrations (i.e., leading to exposures below the ADI) may pose a risk of adverse effects to the liver, due to an idiosyncratic response. Individuals prone to this response may be genetically susceptible, for example, those carrying the HLA-B*35:01 allele. However, the individual would not know they were susceptible before taking a supplement. This possibility of an unexpected idiosyncratic response should be considered when providing guidance on the use of such supplements.

Ashwagandha

115. Due to an increasing number of incidents relating to food supplements containing ashwagandha received by the FSA between February 2021 and December 2024, FSA Policy teams asked that the COT to review the safety of

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ashwagandha supplements and if possible, determine a safe level of intake based on the available evidence. This work is ongoing.

116. Ashwagandha containing supplements have been linked with five cases of liver injury, three were collected in Iceland between 2017- 2018 and two were identified in the DILIN in 2016. The liver injury was typically cholestatic or mixed with severe jaundice and pruritus, but self-limited with liver tests normalising in 1-5 months. The case reports are mixed with some noting that co-medication with potentially hepatotoxic prescription medications was not identified (Björnsson *et al.*, 2020).

Aetiology and Pathophysiological mechanisms of HILI

117. The idiosyncratic nature of most HILI cases means that specific mechanisms of liver injury are challenging to determine, responses are not dose dependent and attempts to model effects in laboratory studies are hampered by a lack of reproducibility. Diagnosis is one of exclusion as the clinical presentation of HILI is often similar to a number of other conditions, it has been shown that liver injury can present in a vast number of ways and affect all cells present in the liver and biliary tree. Injury can range from mild asymptomatic liver enzyme elevation to acute or chronic hepatitis, acute and chronic cholangitis, steatosis, vascular lesions and even cirrhosis and liver failure (Andrade *et al.*, 2019). Understanding causality is further complicated by the fact that there is a vast myriad of potential botanical products and mixtures thereof and HDS may be sold with labels that do not identify full lists of ingredients or ingredient concentrations.

118. Nevertheless evidence has emerged that susceptibility to certain botanicals such as green tea, *Garcinia cambogia* and turmeric may be immune mediated due to the presence of the HLA-B*35:01 allele (Li *et al.*, 2019, p. 01; Hoofnagle *et al.*, 2021, p. 01; Vuppalandhi *et al.*, 2022; Halegoua-DeMarzio *et al.*, 2023).

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HLA-B*35:01 Allele

HLA-B*35:01 and Green Tea-Induced Liver Injury (Line et al., 2023)

119. Green tea is one of the most frequently consumed beverages world-wide and has been used for centuries without known adverse effects, however, it is a frequently listed component of multi-ingredient products and has been implicated in instances of liver injury. Most reports of hepatotoxicity have implicated GTE supplements, rather than green tea consumed as a traditional beverage, it is also worth noting that GTE products can be highly variable in their composition and manufacture, including catechin content, EGCG content, caffeine content, extraction method, preparation, dose and formulation. Green tea extracts are processed from the leaves of *Camellia sinensis*, they contain concentrated polyphonic catechins and have other components such as caffeine removed. The most common catechin in green tea is (EGCG) and it is EGCG that is believed to be responsible for liver injury.

120. One of the aims of DILIN was to study and characterize the frequency, risk factors, clinical features, outcomes, and pathogenesis of green tea-associated liver injury. The patients enrolled in the DILIN study who consented for genetic research had high resolution Class I and II HLA sequencing done on DNA extracted from whole blood to investigate associations of HILI and HLA. Two disease control groups were used: (1) patients enrolled in DILIN with liver injury related to dietary supplements without green tea and (2) patients with liver injury attributed to conventional drugs. For population controls, the Illumina genotype data from the Electronic Medical Record and Genomics Study (eMERGE) network were used.

121. 272 cases in the DILIN register that were judged to be probable, highly likely or definite cases of HDS related drug induced liver injury. A review of the product labels for the products associated with these cases for mention of green tea or associated catechins identified 70 patients as possibly having taken at least one product containing green tea. Green tea accounted for 15

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% of HDS related liver injury and 3 % of all cases of liver injury in the DILIN register.

122. The primary implicated product was GTE, and this was found in single ingredient products in 20 % of cases and multi-ingredient products in 80 % of cases. Where a multi-ingredient product was implicated, there were typically between 4 and 60 total active ingredients. Only 17 products had labels that provided the dose of GTE per serving. Total daily dose ranged from 50 to 2,000 mg. Interestingly, there was no clear correlation between the severity score and peak bilirubin levels with the estimated daily intake. Chemical analyses of 16 available products indicated that catechins were detectable in all but 1 product, with levels ranging from 6.6 to 384 mg. The product without detectable catechins was labelled as containing green tea but without concentration.

123. Clinical chemistry found that 95 % of green tea associated HILI was hepatocellular and none were cholestatic, interestingly this is not the pattern seen with other HDS cases or those due to medicinal drugs which included more cholestatic (22 % and 24 %) and mixed cases (25 % and 23 %) respectively.

124. Liver biopsies were available for 15 (38 %) patients and found an acute hepatitis-like pattern in 12 patients, 4 of which showed mild cholestasis.

125. HLA testing was performed on 36 of the 38 patients who were judged to have definite, highly likely or probably green tea related liver injury as well as 17 possible and 12 unlikely cases, 192 control cases taking other HDS and 1113 cases attributed to conventional drugs. These subjects were compared to 15,094 controls from eMERGE.

126. Among the green tea cases, 26 had at least one copy of the HLA-B*35:01 allele, resulting in a carrier frequency of 72 % (95% CI = 58% to 87%). This is a rate up to 7-fold higher than in patients without green tea HDS related liver injury (15%: 95% CI = 10% to 20%), conventional drug

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related liver injury (12%: 95% CI = 10% to 14%) and the eMERGE derived population controls (11%: 95% CI = 10.5% to 11.5%). Furthermore, when breaking down the individual green tea related cases it was seen that the carrier frequency was higher in the patients judged to have definite or highly likely green tea related HILI (91 %) compared to probably cases (64 %) and possible or unlikely cases (24 %) ($p < 0.001$). It should be noted that HLA-B*35:01 might be a potential susceptibility factor rather than a definitive predictor of green tea-related HILI, as not all the allele carriers will develop liver injury, and not all cases occur in the allele carriers.

127. *In vitro*, EGCG has been shown to be immunogenic in HLA-B*35:01 positive and HLA-B*35:01 negative donors. Peripheral blood mononuclear cells and T-cells from healthy donors showed statistically significant ($p < 0.0001$), dose dependent, proliferation in response to EGCG treatment (1-50 μM). The study also indicated that EGCG-specific T-cell clones (TCC) were identified in 2 healthy donors positive for the HLA-B*35:01 allele. Secretion of Granzyme B was detected in all TCC profiled indicating involvement of cytotoxic T-cell responses, it was therefore hypothesised that this mechanism could be induced in GTE related liver injury. It should be noted, however, that the observations were made in a small number of samples (only 4 HLA-B*35:01 positive subjects and 4 non- HLA typed subjects) and similar studies would need to be replicated in a larger sample size to fully understand the mechanisms. Similarly, while TCC were observed in 2 donors positive for the risk allele, this was not studied in donors negative for the risk allele so comparisons cannot be made. The relevance of the concentrations tested compared to real-world HDS consumption levels is also an uncertainty.

128. Other studies in rodent models of GTE associated liver injury, that have generally focussed on direct hepatotoxicity have suggested a potential mitochondrial toxicity as a mechanism of action mediated through reactive oxygen species production. It is worth noting, however, that these studies often use high doses, far higher than would be expected to be consumed by humans in the form of HDS. Furthermore, such toxicity would be more likely

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to be as a result of intrinsic HILI, and the clinical features of green tea associated liver injury suggest that it is idiosyncratic (Elbling *et al.*, 2005).

Polygonum Multiflorum

129. *Polygonum multiflorum* (PM) is a well-known traditional Chinese medicine that is used for purported nourishing effects on the liver and kidney. It has a long history of consumption in China and is used in dietary supplements across Asia, America and Europe. An investigation by Li *et al.* (2019) aimed to identify the genetic basis of susceptibility to PM-induced liver injury in a study of Han-Chinese patients. The major histocompatibility complex (MHC) regions of 11 patients with PM-DILI were sequenced, and all human leukocyte antigen (HLA)–type frequencies were compared to the Han-MHC database. It was found that 13 of 15 (86.7%) PM-DILI patients carried HLAB*35:01, whereas only 4 of 33 (12.1%) other DILI patients and 5 of 99 (5.1%) Han population controls carried the allele. The results suggested that HLA B*35:01 was a strong risk factor for PM-DILI compared to other DILI and population controls (PM-DILI versus other DILI, OR, 77.9; 95% CI, 9.9-614.8; $P = 3.6 \times 10^{-5}$; and PM-DILI versus population, OR, 131.7; 95% CI, 19.7-879.0; $P = 4.7 \times 10^{-7}$ (Li *et al.*, 2019).

Garcinia Cambogia

130. *Garcinia Cambogia* is a plant that is native to India and Southeast Asia. The rind of the plant contains a chemical called hydroxycitric acid (HCA). HCA is purported to decrease appetite and *therefore G Cambogia* and HCA are usually consumed in HDS for the purposes of weight loss. Vuppalanchi *et al.* (2022) investigated the DILIN register for cases of liver injury from *G cambogia* consumption. Of the 1418 patients enrolled from 2004 to 2018, 22 cases of liver injury were identified- from *G cambogia* alone (n=5), in combination with green tea (n= 16) or in combination with ashwagandha (n =1). A control group consisted of 57 patients with liver injury from HDS containing green tea without *G cambogia* and 103 patients from other HDS. It

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was found that the presence of HLA-B*35:01 allele was significantly higher in the *G cambogia* containing HDS (55%) compared with patients with liver injury because of other HDS (19%). The carriage frequency of the HLA-B*35:01 allele was significantly higher in the *G cambogia* alone cases (60 %) than the other HDS (19 %) (odds ratio, 5.1; 1.7–15.6; P= .0018) and the conventional drug group (12 %) (odds ratio, 8.8; 3.4–23.2; P = 2.55 x10⁻⁶), respectively (Vuppalanchi *et al.*, 2022).

Turmeric

131. Turmeric is a widely used herbal product derived from the roots of *Curcuma longa*, a perennial plant belonging to the ginger family. Curcuminoids such as curcumin found in the rhizomes of the plant, are believed to be the active compounds. Halegoua-DeMarzio *et al.* (2023) investigated the DILIN register for cases of liver injury from turmeric consumption. 10 patients were found, enrolled between 2011 and 2017 (Halegoua-DeMarzio *et al.*, 2023).

132. All 10 patients underwent HLA sequencing, and 7 were found to carry HLA-B*35:01 resulting in a carrier frequency of 70 %. The small sample size did not permit further analysis. However, it adds additional evidence to the idea that the presence of the HLA-B*35:01 allele is a potential risk factor for susceptibility to liver injury from HDS (Halegoua-DeMarzio *et al.*, 2023).

Potential Mechanism of Liver Injury

133. The consequences of the HLA-B*35:01 phenotype are unclear. HLA allotypes are the key molecules of MHC class I, the group of proteins which present epitopes to cytotoxic T-cells and are associated with inflammatory, autoimmune-like diseases rather than protective immunity phenotypes in infectious disease (Chessman *et al.*, 2008). HLA-B*35:01 has previously been associated with hypersensitivity responses in patients taking the anti-viral nevirapine, linked to the activation of CD8+ and CD4+ T-cells and a similar

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mechanism has therefore been postulated for the liver injury seen with PM (Li *et al.*, 2019).

134. Although further work is required to fully elucidate mechanisms of hepatotoxicity, studies of liver injury associated with consumption of green tea, *G cambogia* and PM indicate that presence of the HLA-B*35:01 allele may be a risk factor associated with liver injury for some herbal compounds and could potentially provide a susceptibility marker that may support causality assessment, rather than a standalone diagnostic biomarker.

Challenges in Addressing HILI

Regulatory Challenges

135. There are a number of regulatory challenges that complicate the understanding and monitoring of HILI. As previously mentioned, the lack of alignment on the nomenclature of botanicals and definitions of supplements illustrates the difficulty faced in compiling data particularly when more than one regulatory body is involved- a single plant may be categorised as a food, a dietary supplement or a herbal medicine for example.

136. At present, there is no effective, UK-specific, system available for the reporting and monitoring of adverse effects from the consumption of food supplements containing botanicals. The MHRA collects data through the Yellow Card Scheme on products classified as herbal medicines, but this may not capture products regulated as foods. There are a number of registers available that are prospectively recruiting patients that meet the criteria of idiosyncratic liver injury. However, none of the available registers specifically focus on HILI, the main focus being DILI from conventional medicine. Furthermore, none of the registers are UK based and while some information is available in the European Prospective DILI study, it is limited and does not give the full picture of HILI in the UK (Ekor, 2014).

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137. Companies do not necessarily need to apply for a pre-market authorisation of their product. This means that product specifications which strictly determine the purity and concentration of the components of a supplement are not necessarily required. As a result, it may be more difficult to determine whether HDS could potentially contain unlabelled ingredients or may be substituted or adulterated with alternative ingredients or be unintentionally contaminated with chemicals such as heavy metals where quality controls are inadequate. In addition to this, downstream processes can also potentially compromise the final product, without the need to meet product specifications, manufacturers may be unaware of the origins of their source ingredients and pre-processing methods (Navarro *et al.*, 2017). Nonetheless, manufacturers are still required to exercise due diligence in Great Britain (GB) under The Food Safety Act 1990 which states that a business has a due diligence defence if:

- (a) That the commission of the offence was due to an act or default of another person who was not under his control, or to reliance on information supplied by such a person;
- (b) That he carried out all such checks of the food in question as were reasonable in all the circumstances, or that it was reasonable in all the circumstances for him to rely on checks carried out by the person who supplied the food to him; and
- (c) That he did not know and had no reason to suspect at the time of the commission of the alleged offence that his act or omission would amount to an offence under the relevant provision ('The Food Safety Act', 1990).

138. Health based guidance values are scientifically derived limits that indicate the amount of a substance in food or water that can be consumed safely over a specific period without posing a health risk. They are usually set based upon dose-dependent population effects. The idiosyncratic nature of

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HILI means that this process becomes difficult as it is challenging to predict who will experience liver injury, the severity of the liver injury or the dose at which it will occur in order to determine a safe level of exposure.

Chemical Analytical Identification

139. One of the key issues with understanding HILI is the identification of the botanical compound, ingredient or probable contaminant responsible for the observed liver injury. This is partly due to the vast array of potential botanical compounds and a lack of standardised reference database of these compounds. Reliable methods for chemical characterisation and quantification are available, for example, high-performance liquid chromatography followed by detection such as UV or mass spectrometry can provide a unique chemical 'fingerprint' of a botanical compound. However, a disadvantage of this technique is the need to calibrate the method using pure reference marker compounds, in situations where these are unavailable, the necessary quality control cannot be built into the method (Navarro *et al.*, 2017).

140. From a regulatory perspective, *in vitro* and *in vivo* testing may be required for novel ingredients in order to determine the potential of a product to cause cellular or organ toxicity. The current protocols for toxicity testing are best suited to individual chemical compounds. If a positive result for toxicity is observed from testing of a complex mixture it can often be challenging to determine the individual active agent responsible for the effects observed (Navarro *et al.*, 2017).

Quality Control of Ingredients

141. Food manufacturers are expected to exercise due diligence under The Food Safety Act 1990; however, variable regulation means that there is the potential for less stringent controls on source materials and ingredients, this could result in downstream and upstream effects on the final product. For

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example, manufacturers may be unaware of the origins of the ingredients or any pre-processing that has occurred with those ingredients. As a consequence, it is possible that contaminants, such as heavy metals, may be unintentionally introduced into the final product. Similarly, supplements may be adulterated or completely substituted with cheaper alternative ingredients that are subsequently not described on the product label. Further labelling issues may also arise from incomplete ingredient lists, incorrect ingredient identification or inaccurate labelling of ingredients' concentrations (Navarro *et al.*, 2019).

142. Without knowing the exact composition of a supplement, it may not be possible to elucidate the causative agents of liver injury.

Diagnostic and Clinical

143. Diagnosis of HILI is currently a diagnosis of exclusion and currently relies on a compatible history, a substance with a known record of causing liver injury and the exclusion of other causes (Navarro *et al.*, 2017). Supplement consumption can often be a missing detail in patient history. Many patients do not link their illness with their consumption of HDS as their reason for HDS consumption is the promotion of health and they are therefore presumed to be safe. HILI is often mistaken for other conditions particularly because the symptoms are so broad.

144. Traditional biochemical endpoints such as ALT/ AST and total bilirubin can be useful evidence of liver injury; however, they do not characterise the degree of liver injury and provide limited insight into the mechanisms causing the liver injury. Finally, there is no guarantee that alterations in these biochemical markers are not caused by other non-hepatic factors. If HDS consumption is not recorded, doctors may also miss the possibility of herb/ drug interactions if the patient is taking concomitant medications. Similarly, if a patient has an underlying condition, HILI may be exacerbated. It is, therefore,

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important that any patient suspected of idiosyncratic liver injury has a thorough history taken including any supplement use (Gurley, McGill and Koturbash, 2022).

Assessment of Causality

145. As the diagnosis of HILI is complex, physicians often rely on assessment algorithms alongside their expert clinical judgement. One of the most frequently used, and the one used in all of the registrars described above, is RUCAM. The scoring system has been criticised for not being suitable for assessment of HILI as accurate scores for all categories are difficult to attribute due to lack of available information on the HDS such as the ultimate causative agent as well as a lack of knowledge of individual active ingredients' hepatotoxic potential. As a result, inaccurate scores often result and causality can be either under- or overestimated (García-Cortés *et al.*, 2011).

Greater Celandine

146. The example of Greater Celandine (GC) illustrates how causality can be underestimated as a result of using a scoring system that is suited to conventional medicines rather than HDS.

147. GC extracts can contain more than 20 ingredients, including various isoquinolones which are known to be biologically active such as: chelerythrine, chelidone, isochelidone, sanguinarine, berberine, coptisine, dihydrocoptisine, stylopine, and protopine. While GC hepatotoxicity appears to follow a typical HILI pattern, a specific causal ingredient has not yet been identified (Teschke, Frenzel, *et al.*, 2012).

148. Teschke *et al.* (2012) evaluated 21 published cases plus 22 regulatory cases representing a total of 43 patients for causality assessment following GC intake using the RUCAM (CIOMS) scale. Among the 43 cases causality for GC was judged to be possible, unlikely, or excluded in a total of 27 cases and highly probable or probable in the remaining 16. The highly probable or

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probable cases were used to characterise GC hepatotoxicity as a distinct liver disease. It was noted that confounding variables reduced causality levels for GC in reported cases of liver injury, but there was, however, striking evidence for HILI by GC with high causality gradings.

149. When the laboratory, pathogenetic, and clinical classifications were combined, it was found that GC has a hepatocellular pattern of injury based upon an idiosyncratic reaction possibly caused by a metabolic aberration.

150. However, as many of the compounds that make up GC extract do not have supporting experimental hepatotoxicity *in vivo* data, a single causative agent for HILI has yet to be established. Furthermore, this lack of knowledge of the chemistry of GC means that additional future cases of GC induced HILI may be underestimated as scores for causative agent during the RUCAM assessment cannot be fulfilled (Teschke, Frenzel, *et al.*, 2012; Teschke, Glass, *et al.*, 2012).

Future Directions

Towards Improved Regulatory Harmonisation

151. In 2005 the WHO collated information on the global regulation of herbal medicines with the aim of developing unified international guidelines (World Health Organization, 2005). This project remains incomplete, however, in their Global Traditional Medicine Strategy 2025–2034, the WHO renewed their commitment to ensuring universal access to safe, effective, and people-centred traditional, complementary, and integrative medicine (TCIM) (World Health Organization, 2025). Their strategy for achieving this includes set goals, guiding principles, and four strategic objectives, all supported by actionable directions for Member States, partners, stakeholders, and WHO. One of the key objectives from a regulatory standpoint is to support the provision of safe and effective TCIM through appropriate regulatory mechanisms. In order to achieve this the objective is supported by actionable directions for stakeholder and the WHO. For the WHO these are as follows:

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- Develop standards for herbal medicines in the form of the International Herbal Pharmacopoeia and other such documents.
- Develop, update and disseminate guidelines, technical documents and tools to support TCIM regulatory mechanisms, including pharmacovigilance.
- Develop standardized terminologies and an international classification of TCIM products.
- Enhance the WHO International Regulatory Cooperation on Herbal Medicines network.

152. In the EU efforts have been made towards harmonisation. In 2009 EFSA published guidelines on the safety assessment of botanical products and preparations (EFSA Scientific Committee, 2009). Additionally, in 2025, EFSA released the Database of Compendium of botanicals that is available on the EU Open Data Portal (<http://data.europa.eu/euodp/data/dataset/efsa-botanicalcompendium>). The EFSA Compendium of Botanicals is an open-source database of plant species that are reported to contain naturally occurring substances of potential concern for human and animal health. The database does not conclude on the safety of the listed plant species but aims to help with the safety assessment of botanicals and botanical preparations by facilitating hazard identification (EFSA Scientific Committee, 2025).

Towards Improved Hazard Identification

153. A promising tool for testing HDS is high throughput screening using *in vitro* assays, an example being those included in the Tox21 Program ([Tox21 – Toxicology in the 21st Century](#)). Tox21 is an initiative involving a partnership of the National Center for Advancing Translational Sciences (NCATS, NIH), National Institute of Environmental Health Sciences (NIEHS, NIH), the Environmental Protection Agency (EPA) and the FDA. The goals of Tox21 are to develop methods to rapidly and efficiently evaluate the safety of commercial chemicals, pesticides, food additives and contaminants, and

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medical products. The goals of Tox21 are to (1) identify mechanisms of chemically induced biological activity; (2) prioritize chemicals for more extensive testing; and (3) develop more relevant and predictive models of in vivo toxicological responses. The Tox21 programme has so far screened thousands of single chemicals, as well as some mixtures (Navarro *et al.*, 2017).

154. Developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), LiverTox is another tool available to clinicians, researchers, and the general public that can be used as an information source for up-to-date, evidence-based, comprehensive, and unbiased information about DILI, prescription drugs, over-the-counter drugs, and herbs and food supplements (Nunes, Monteiro and Dos Santos, 2022).

Conclusions

155. Consumption of HDS is increasing in the UK and globally. While efforts have been made around the world to establish registers of liver injury to better understand the causes and mechanisms behind HILI each region has a different profile of HDS consumption in part dependent upon on the individual reasons for consumption. In Europe and the US, it appears that most HDS are primarily taken for the purposes of weight loss and as such multi-ingredient products are of particular concern. However, it can often be difficult to understand the wider picture and make comparisons between registers because of a lack of harmonisation when describing different botanicals and their components due to variation in nomenclature. This is further compounded by difficulty in identifying the individual parts of the plants being consumed, the variable concentrations of bioactives in these different parts and the effects of different extractions methods. Variable regulatory requirements and quality-control standards can also lead to mislabelling of ingredients which further complicates identification of causative agents. However, what is also clear is that there is a lack of UK specific data

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regarding HILI cases associated with HDS intake. Without UK specific information it is not possible to know the scale of the issue or the key drivers behind it.

Questions on which the views of the Committee are sought

Members are invited to consider the following questions:

- i) Do members want to see any follow up action to this discussion paper?
- ii) If no further action is required, do members want to see a stand-alone statement on idiosyncratic HILI?

Secretariat

July 2026

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List of Abbreviations and Technical terms

AAS	Anabolic Androgenic Steroids
ADI	Acceptable Daily Intake
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear
ASMA	Anti-smooth muscle
AST	Aspartate Aminotransferase
CAM	Complementary and Alternative Medicines
CI	Confidence Interval
CIOMS	Council of International Organisations of Medical Sciences scale
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CSM	Committee on Safety of Medicines
DILI	Drug Induced Liver Injury
DILIN	Drug Induced Liver Injury Network
DSHEA	Dietary Supplement Health and Education Act
EC	European Commission
EFSA	European Food Safety Authority
EGCG	Epigallocatechin gallate
EMA	European Medicines Agency
eMERGE	Electronic Medical Record and Genomics Study
EU	European union
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug and Cosmetic Act
FSA	Food Standards Agency
GB	Great Britain

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GC	Greater Celandine
GTC	Green Tea Catechins
GTE	Green Tea Extract
HC	Health Canada
HCA	Hydroxycitric Acid
HDS	Herbal Dietary Supplement
HILI	Herb Induced Liver Injury
HMAC	Herbal Medicines Advisory Committee
INR	International Normalised Ratio
MHRA	Medicines and Healthcare Products Regulatory Agency
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
MCA	Medicines Control Agency
MHC	Major Histocompatibility Complex
PM	Polygonum multiflorum
Pro-Euro-DILI	Pro-European-Drug Induced Liver Injury
RUCAM	Roussel Uclaf Causality Assessment Method
TCC	T-cell Clones
TCIM	Traditional, Complementary, and Integrative Medicine
TGA	Therapeutic Goods Act
THR	Traditional Herbal Registration
UK	United Kingdom
ULN	Upper Limit of Normal
WHO	World Health Organisation